SYNTHETIC STUDIES TOWARDS TAMIFLU AND BIOTIN

A THESIS

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IN

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BY

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MARCH 2014

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Synthetic studies towards Tamiflu and Biotin."*** *submitted by Mr. Prakash N. Chavan was carried out by him under my supervision at CSIR-National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.*

March, 2014

CSIR-National Chemical Laboratory

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Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **"*Synthetic studies towards Tamiflu and Biotin.*"** submitted for Ph. D. degree to the University of Pune has been carried out at CSIR-National Chemical Laboratory, under the supervision of Dr. Subhash P. Chavan. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

March, 2014 Prakash N. Chavan

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Dedicated

To

BABA and (late) AAI

Acknowledgements

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PRAKASH NARSING CHAVAN, CSIR-NCL, PUNE

Contents

Chapter 2: Aziridine based synthetic strategies

Section 1: Introduction to aziridine

Section 2: Lactone based strategy towards Tamiflu and shortest synthesis of major building block of mitomycinoids

General Remarks

1. All the melting points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each section refer to that section only.
3. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualised by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recoreded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Abbreviations

Ac	Acetyl
ADD	(Azodicarbonyl)dipiperidine
AIBN	2,2-Azobis(isobutyronitrile)
^{t}Am	*tertiary* amyl
Ar	Aryl
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane-dimthyl sulfide
Bn	Benzyl
BnBr	Benzyl bromide
Boc	*tertiary* butoxy carbonyl
Bu	Butyl
*s*Bu	*secondary* butyl
*t*Bu	*tertiary*-butyl
CAL	Candida antarctica lipase
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
*m*CPBA	*meta*-chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane

DEPT	Distortionless Enhancement by Polarization Transfer
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
dppf	(Bis-diphenylphosphino)ferrocenyl
Et	Ethyl
g	gram(s)
GABA	Gamma-aminobutyric acid
h	hour(s)
IPA	Isopropyl alcohol
IR	Infra red
HMPA	hexamethylphosphoramide
Hz	Hertz
KHMDS	Potassium hexamethyl disilazide
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
LICA	Lithium isopropyl cyclohexylamide
MAD	Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
Me	Methyl
min	minute(s)
mL	mililitres
Mp	Melting point
Ms	methanesulfonyl
MVK	Methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMO	*N*-methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate
PDC	Pyridinium dichromate
PEG	Polyethylene glycol
PHMS	Poly(hydromethylysiloxane)
PLE	Pig liver esterase
PMP	*para*-methoxyphenyl
PPA	Polyphosphoric acid
PTAB	Phenyl trimethylammonium tribromide
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-toluene sulfonic acid
r t	room temperature
TBAB	Tetrabutyl ammonium bromide
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulfate
TBAI	Tetrabutyl ammonium iodide
TBSOTf	*tert*-butyldimethylsilyl triflate
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
Triton-B	Benzyltrimethylammonium hydroxide

ABSTRACT

The thesis entitled, **"Synthetic Studies towards Tamiflu and Biotin"** is divided into three chapters. Chapter one deals with the introduction and synthetic studies towards Tamiflu. The second chapter deals with introduction of aziridine and aziridine based synthetic strategies. The third chapter deals with introduction of Biotin and synthetic studies towards Biotin.

Chapter 1: Synthetic studies towards Tamiflu.

Section 1: Introduction to Tamiflu

The present section describes introduction and literature review on synthetic approaches for the tamiflu (Oseltamivir phosphate).

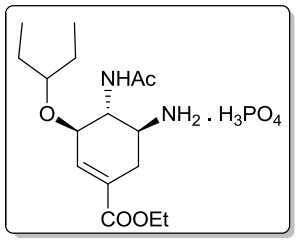
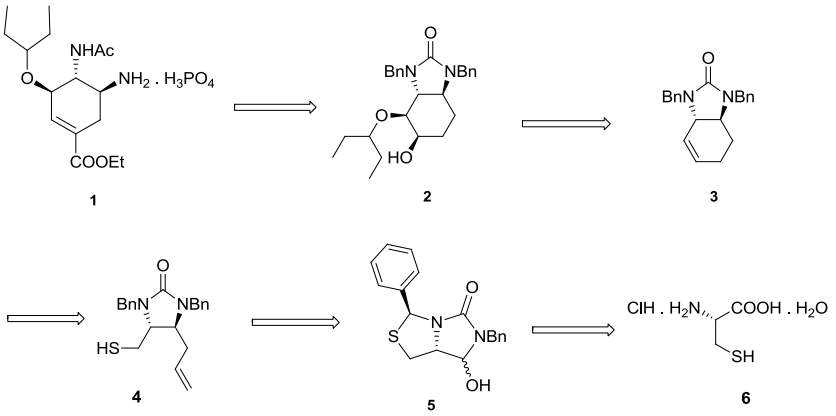


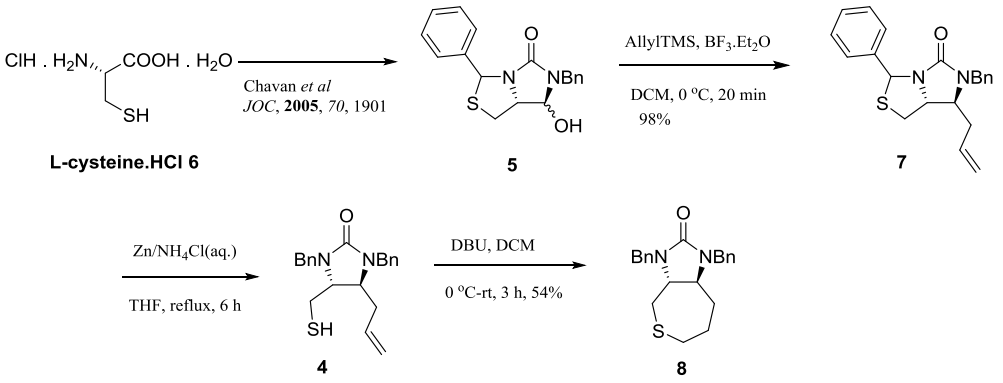
Fig 1: Tamiflu **1**

Section 2: Attempted synthesis towards Tamiflu.



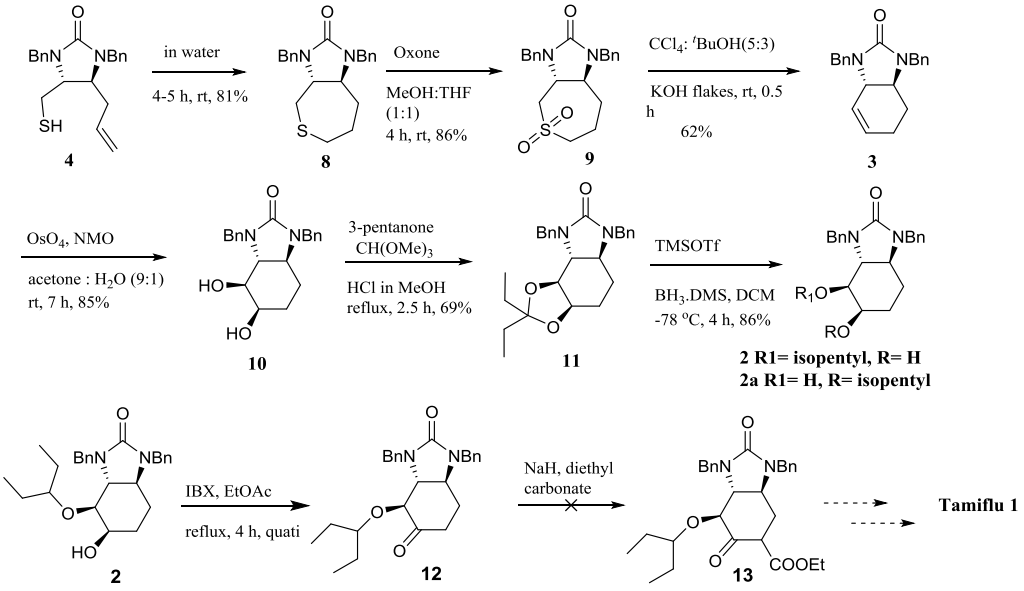
Scheme 1: Retrosynthesis for Tamiflu employing stereospecific amidoalkylation protocol

This section describes the attempted synthesis of Tamiflu **1** using stereospecific amidoalkylation of imidazothiazolone and Ramberg-Backlund reaction as the key reactions. The retrosyntheic analysis was planned which is described in Scheme 1.



Scheme 2: Synthesis of sulfide **8**

The compound **5** was subjected for stereospecific amidoalkylation protocol followed by *C-S* cleavage leading to thiol **4**. Thiol **4** under DBU condition afforded cyclic sulfide **8** in 54% low yield (Scheme 2).

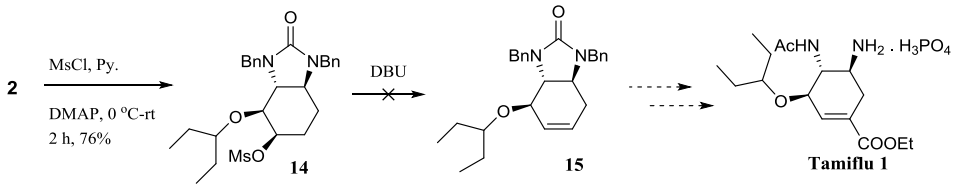


Scheme 3: Stereospecific amidoalkylation protocol based attempt for Tamiflu **1** synthesis

The yield of reaction was improved by stirring thiol **4** in water to afford sulfide **8** in 81% yield. Sulfide **8** was oxidized to sulfone **9** by oxone, which when subjected to Ramberg-

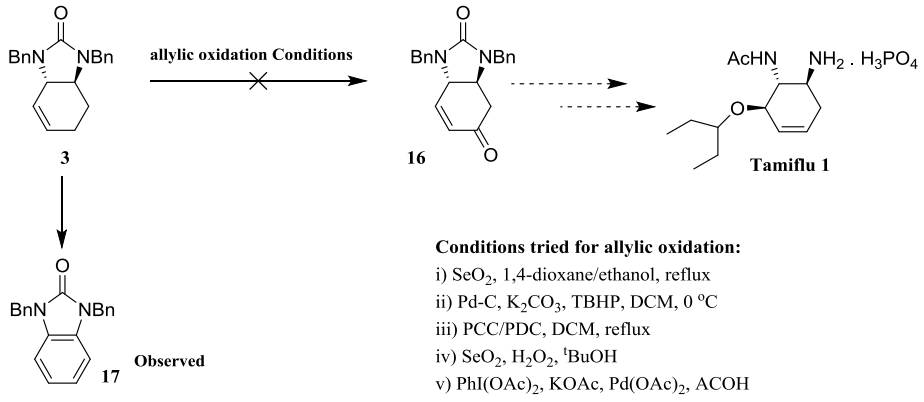
Backlund conditions furnished cyclohexene **3** in 62% yield. Cyclohexene **3** on dihydroxylation afforded diol **10**, which was converted to pentaniod acetal **11** using 3-pentanone, trimethyl orthoformate in HCl/MeOH afforded pentaniod acetal **11** in 69% yield. Pentaniod acetal **11** was treated with BH_3.DMS/TMSOTf to afford regioisomeric ethers **2:2a** in 1:1 ratio. Desired hydroxy compound **2** was oxidized to ketone **12** using IBX. Attempts were failed to obtain compound **13** from ketone **12** (Scheme 3).

An alternate strategy was planned starting from alcohol **2**. Accordingly, alcohol **2** was converted into its mesylate **14** using mesyl chloride, cat DMAP and pyridine to furnish mesylate **14** in 76% yield. Next task was to obtain olefin **15**. Accordingly, mesylate **14** was subjected to DBU treatment but it failed to afford the desired olefin **15** (Scheme 4).



Scheme 4: Mesylate **14** based strategy for Tamiflu **1**

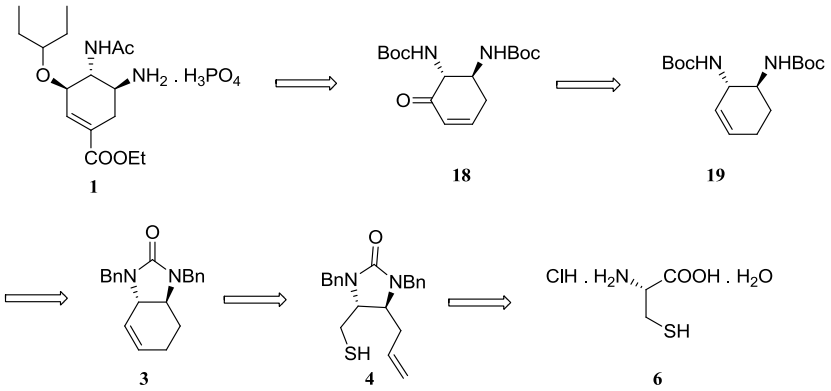
After failure to convert the mesylate **14** into olefin **15**, an alternative strategy was planned for Tamiflu **1** synthesis from cyclohexene **3**. Accordingly cyclohexene **3** was subjected under different allylic oxidation conditions like SeO_2, Pd-C/TBHP, PCC, PDC, SeO_2/H_2O_2 and $PhI(OAc)_2/Pd(OAc)_2$ which lead to aromatized urea **17** (Scheme 5).



Scheme 5: Allylic oxidation attempt for Tamiflu

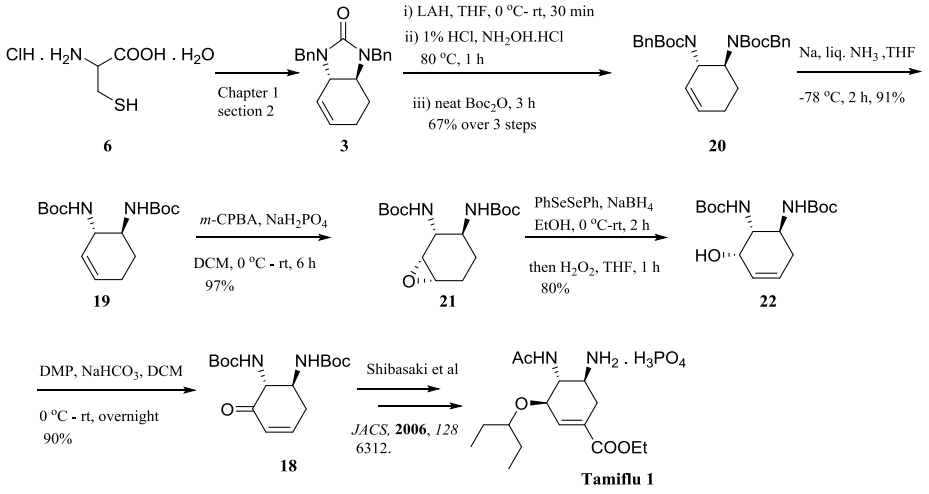
Section 3: Formal synthesis of Tamiflu employing stereospecific amidoalkylation and Ramberg-Backlund reaction.

This section describes the formal synthetic approach towards Tamiflu **1** based on Ramberg-Backlund reaction. The retrosynthesis for Tamiflu **1** is shown in Scheme 6.



Scheme 6: Retrosynthesis for Tamiflu **1** based on Ramberg-Backlund reaction

According to retrosynthetic analysis thiol **4** was converted to cyclohexene **3** which is discussed in Chapter 1 Section 2. Generally cyclic ureas are chemically inert to basic as well as acidic conditions. But fruitfully it was possible to successfully hydrolyze urea **3** *via* LAH reduction followed by hydrolysis in 1% HCl/$NH_2OH.HCl$ and resultant crude diamine was protected as carbamate derivative using neat Boc anhydride to furnish compound **20** in 67% yield over 3 steps.

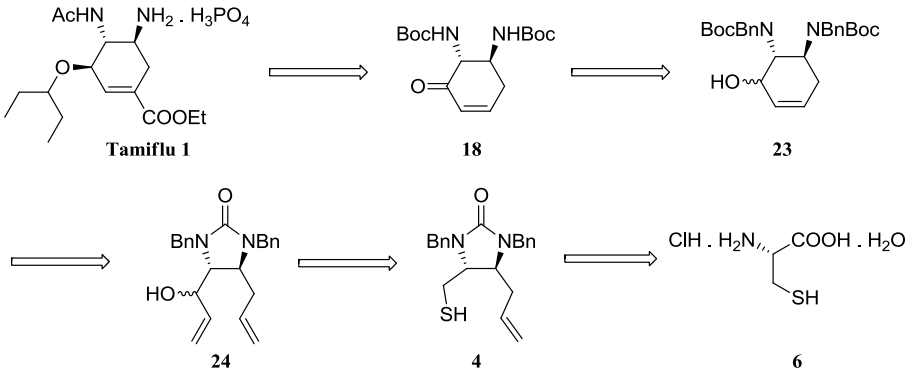


Scheme 7: Synthesis of Enone **18**

Having succeeded to hydrolyze urea **3** to vicinal *trans* diamine **20**, next task was to synthesise unsaturated ketone **18**. Accordingly diboc derivative **20** on Birch reduction followed by epoxidation using *m*-CPBA gave stereospecific epoxide **21** which was fully characterized by NOSEY mult and single crystal X-ray analysis. Epoxide **21** under Sharpless-Reich protocol was rearranged to afford allylic alcohol **22** followed by DMP oxidation afforded enone **18** well known intermediate for tamiflu **1** synthesis by Shibasaki *et al* (Scheme 7).

Section 4: Formal synthesis of Tamiflu employing stereospecific amidoalkylation protocol and ring closing metathesis (RCM)

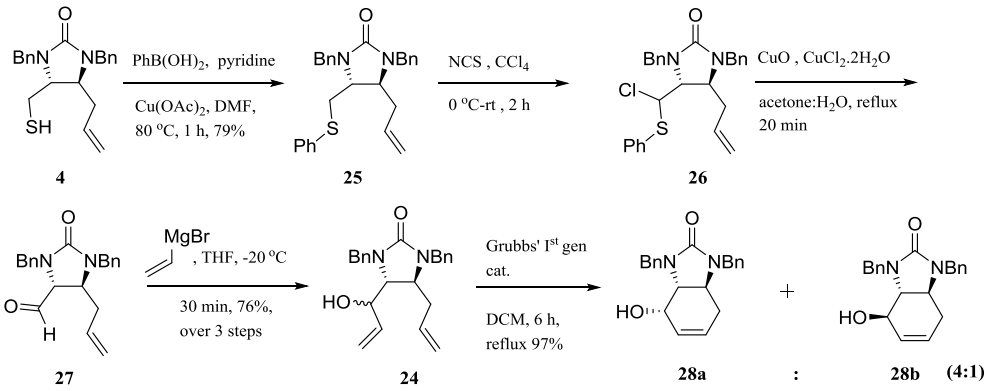
This section describes the formal synthetic approach towards Tamiflu using stereospecific amidoalkylation protocol and ring closing metathesis (RCM). The retroanalysis for Tamiflu synthesis is outlined in Scheme 8.



Scheme 8: Retrosynthesis for Tamiflu based on RCM

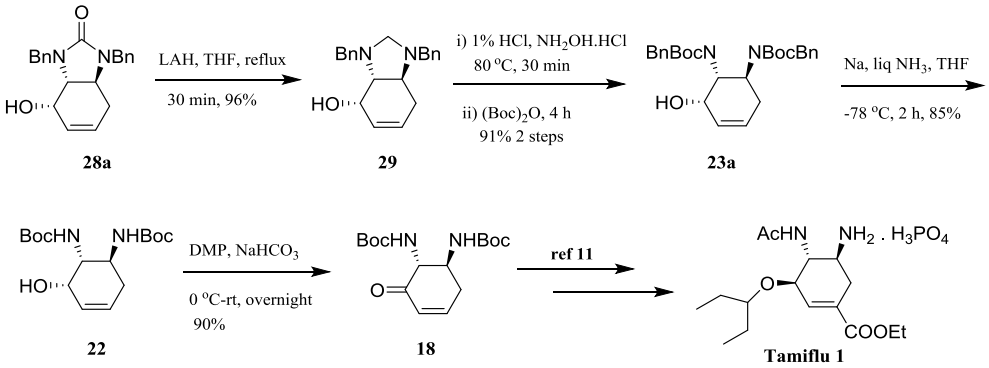
Accordingly, thiol **4** was treated with phenyl boronic acid, $Cu(OAc)_2$ and pyridine to afford phenyl sulfide **25**. The next task was to obtain RCM precursor **24**. Accordingly sulfide **25** was treated with NCS followed by treatment of $CuCl_2.H_2O/CuO$ led to aldehyde **27**, which on vinyl magnesium bromide addition afforded **24** in 76 % yield over 3 steps. The diastereomeric mixture **24** on RCM using Grubbs' Ist gen. catalyst afforded alcohol **28a**:**28b** in 4:1 ratio in 97% yield (Scheme 9).

Having cyclohexene skeleton of the Tamiflu with desired diamine in *trans* fashion, next task was to obtain enone **18**. Accordingly compound **28a** was subjected to LAH reduction, led to the diamine **29** which was hydrolyzed in 1% HCl to afford diamine.



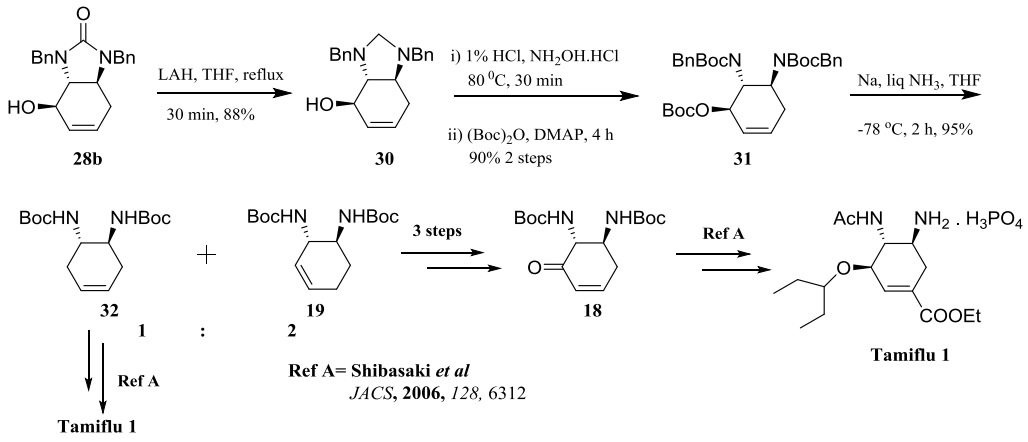
Scheme 9: Synthesis of allylic alcohol **28a** and **28b**

Resultant diamine without purification was masked as carbamate derivative using neat $(Boc)_2O$ to furnish diboc derivative **23a** in good yield. Further diboc **23a** was subjected for chemoselective debenzylation under Birch reduction conditions to afford allylic alcohol **22**. Conversion of **22** to enone **18** is discussed in Chapter 1 Section 3 (Scheme 10).



Scheme 10: Synthesis of Enone **18** from **28a**

Similarly other diastereomer **28b** was subjected for LAH reduction gave amine **30**, which was hydrolyzed using 1% $HClNH_2OH.HCl$ to diamine and resultant diamine on treatment with $(Boc)_2O$/DMAP provided triboc derivative **31**.Triboc **31** on Birch reduction conditions provided **32** and **19** in ratio 1:2 respectively. The **32** is reported foe tamiflu **1** by Shibasaki *et al* where as transformation of diboc **19** to enone **18** is discussed in Chapter 1 Section 2 (Scheme 11).



Scheme 11: Synthesis of Enone **18** from **28b**

Chapter 2: Aziridine based synthetic strategies

Section 1: Introduction to aziridine

The present section describes the introduction, synthetic methods of aziridines and its chemical application in natural product synthesis.

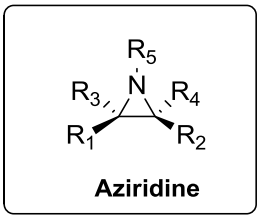
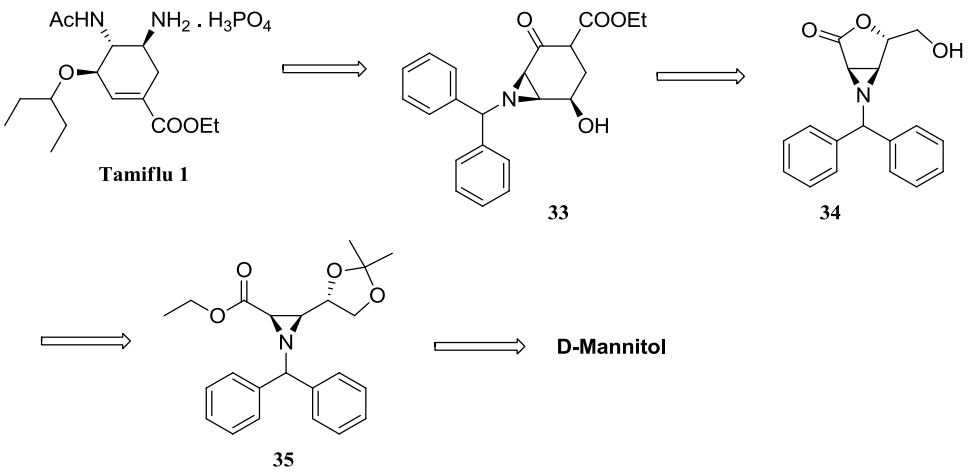


Fig 2: Aziridines

Section 2: Lactone based strategy towards Tamiflu and shortest synthesis of major building block of mitomycinoids.

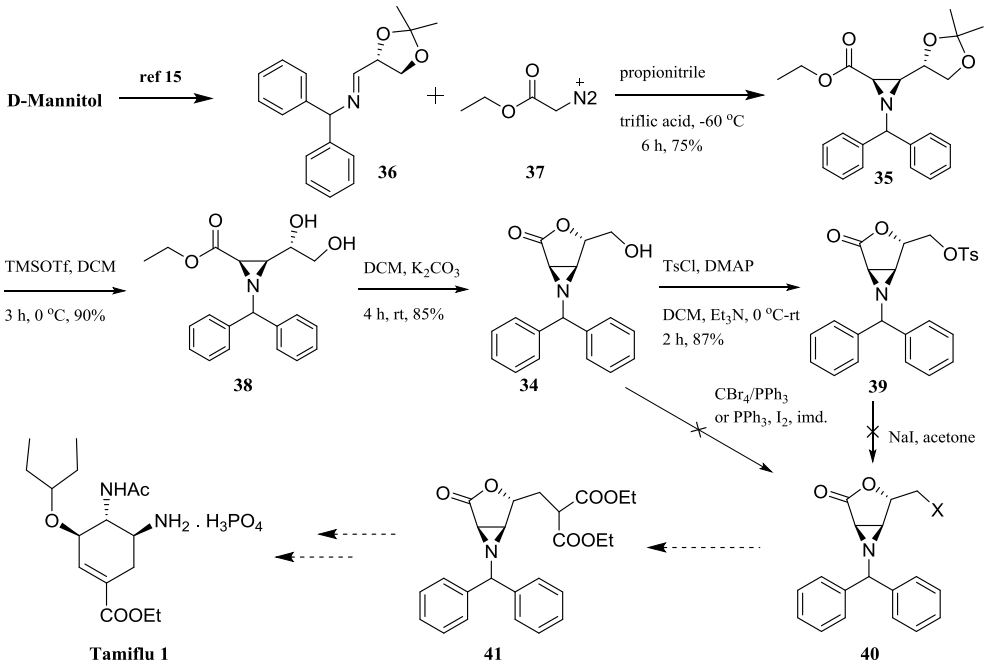
This section describes the attempted synthesis of Tamiflu **1** starting from D-mannitol. The retrosynthetic analysis for Tamiflu **1** is described in Scheme 12.

According to retrosynthetic analysis *cis*-aziridine **35** which was prepared from D-mannitol using reported procedure. The *cis*-aziridine **35** subjected for acetonide deprotection using TMSOTf in dry DCM at 0 ^{o}C to afford dihydroxy compound **38**, which on treatment with K_2CO_3 in DCM gave exclusively five membered lactone **34** in



Scheme 12: Retrosynthetic analysis for Tamiflu starting from D-mannitol

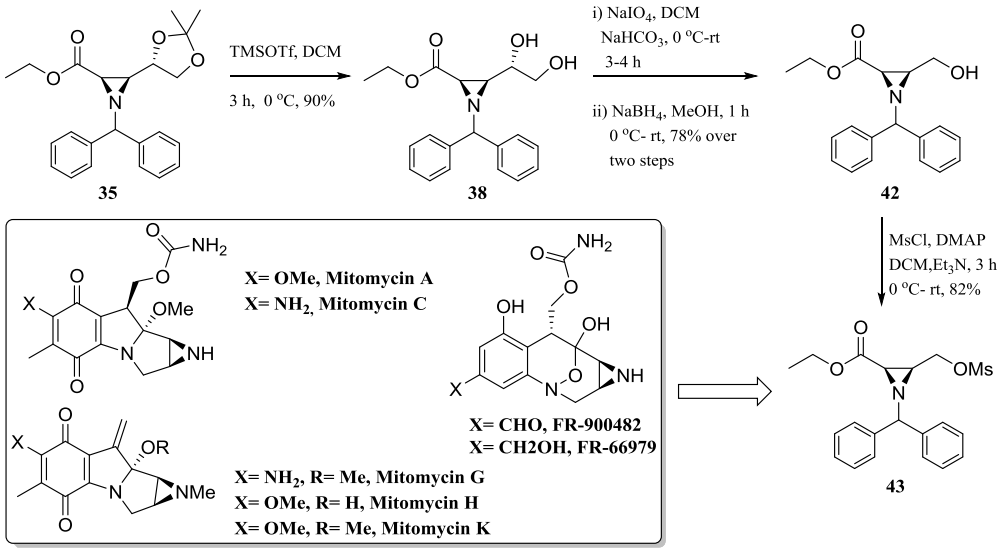
85% yield.



Scheme 13: Synthesis of lactone **34** and attempts to explore it for Tamiflu **1**

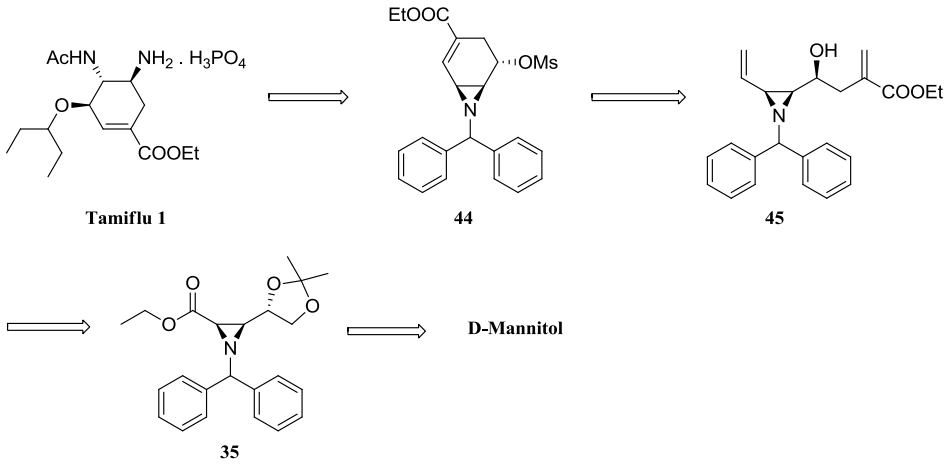
After successfully synthesizing crucial intermediate lactone **34**, next task was to obtain the compound **41**. Accordingly lactone **34** was subjected under Appel conditions, but failed to furnish the desired halides. So lactone **34** was subjected for tosylation to furnish tosylate **39**, which on NaI treatment failed to afford **40** (Scheme 13).

With the *cis*-aziridine **35** compound in hand, to synthesis of **43** was planned as a major building of the mitomycinoids family. Accordingly dihydroxy **38** on oxidative cleavage with $NaIO_4$ afforded aldehyde followed by $NaBH_4$ reduction provided alcohol **42**. The hydroxy **42** on mesylation gave mesylate **43** in 82% yield (Scheme 14).



Scheme 14: Synthesis of mesylate **43** major building block of mitomycinoids

Section 3: Formal synthesis of Tamiflu using *cis*-aziridine as the key precursor and RCM.

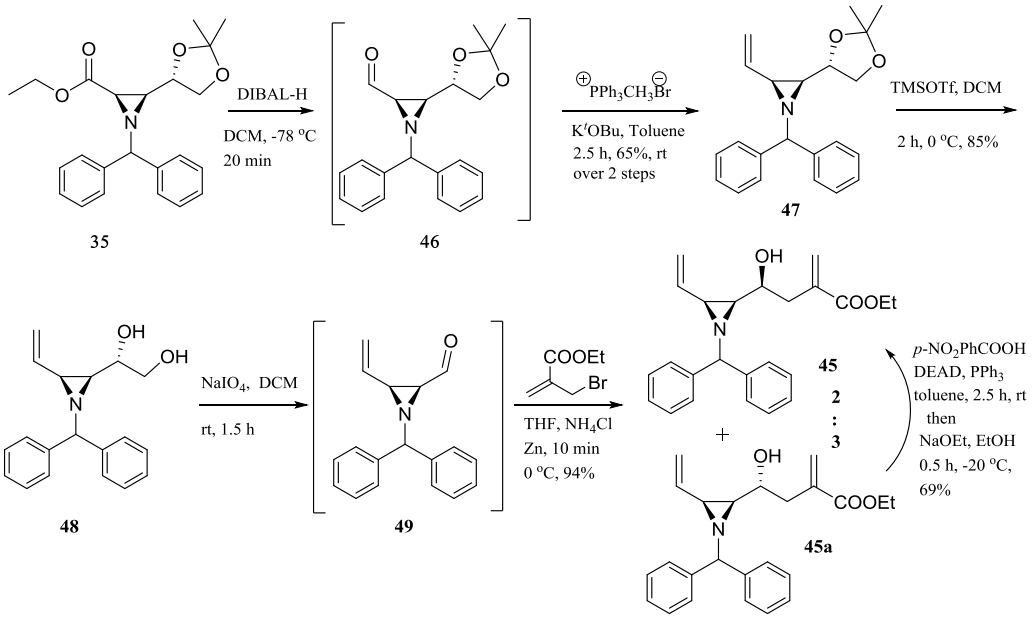


Scheme 15: Retrosynthetic analysis for Tamiflu based on *cis* –aziridine **35**

The present section describes formal synthesis of Tamiflu starting from *cis*- aziridine **35**

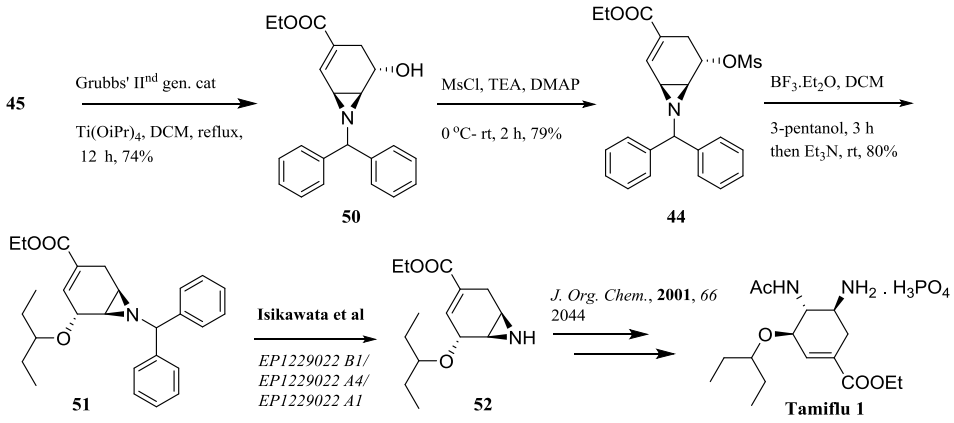
as the key precursor and ring closing metathesis (RCM). The retroanalysis is outlined in Scheme 15.

Accordingly aziridine **35** was reduced to aldehyde **46** using DIBAL-H to afford aldehyde **46**. The crude aldehyde **46** on Wittig olefination gave olefin **47**. Olefin **47** was treated with TMSOTf to afford diol **48**, which on $NaIO_4$ cleavage provided aldehyde **49**. The crude aldehyde **49** on Barbier addition of bromo-methacrylate/Zn afforded **45:45a** in 2:3 ratio respectively. The undesired diastereomer **45a** was readily converted into desired isomer **45** using Mitsunobu conditions followed by basic hydrolysis (Scheme 16).



Scheme 16 Synthesis of RCM precursor **45**

Having the RCM precursor **45** in hand it was subjected to RCM reaction by refluxing in DCM with Grubbs' IInd gen. catalyst/Ti (i-PrO)$_4$, gave alcohol **50**. Alcohol **50** was converted to its mesylate **44** using MsCl/TEA in 79% yield. The spectral data of mesylate **44** was in well agreement with the reported data by Ishiwata *et al*. Finally mesylate **44** was treated with $BF_3.Et_2O$/3-pentanol to furnish aziridine **51** in 80% yield. The spectral data of **51** was fully in agreement with the data reported in the literature (Scheme 17).



Scheme 17: Synthesis of intermediate **51**

Chapter 3: Synthetic studies towards Biotin

Section 1: Introduction to Biotin

This section described the introduction and review on reported synthetic strategies for Biotin.

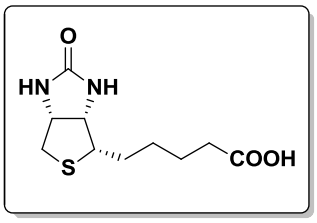
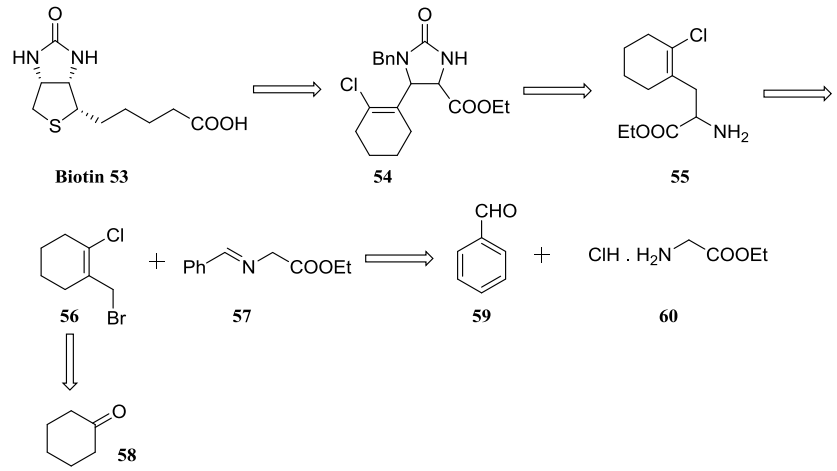


Fig 3: Biotin **53**

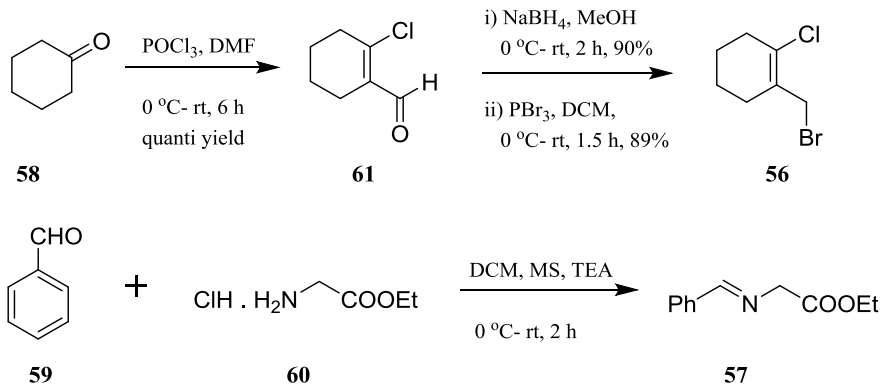
Section 2: *C*-alkylation strategy towards Biotin.

This section describes the *C*-alkylation strategy towards Biotin, the retrosynthetic analysis shown as per Scheme 18.

Accordingly synthesis began with *C*-alkylation of bromide **56** and imine **57** (which was prepared from cyclohexanone **58** and glycinate ester hydrochloride salt **60** as described in Scheme 19) in 10% NaOH and $TBAHSO_4$ as PTC gave compound **62**, which was directly subjected for hydrolysis in conc. HCl afforded amine **55**. The crude amine **55** on treating with benzyl isocyanate afforded urea **63** in 70% over three steps.

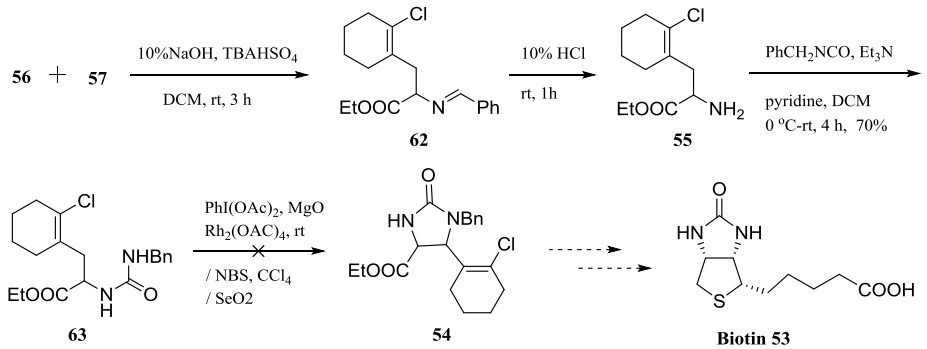


Scheme 18: *C*-alkylation based retrosynthetic analysis for Biotin **53**



Scheme 19: Synthesis of bromide **56** and imine **57**

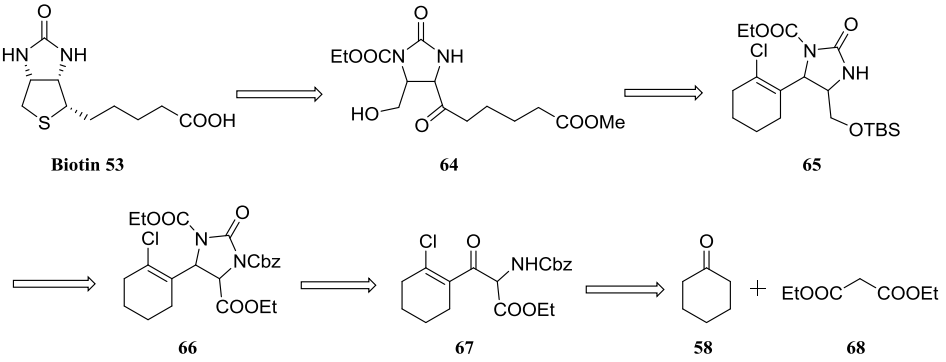
The next task was to obtain cyclic urea **54**. Accordingly acyclic urea **63** was subjected under different reaction conditions like $Rh_2(OAc)_4$/$PhI(OAc)_2$, NBS/AIBN and SeO_2. All these attempts led to complex reaction mass (Scheme 20).



Scheme 20: Synthesis of urea **63** and attempts to explore it for Biotin **53**

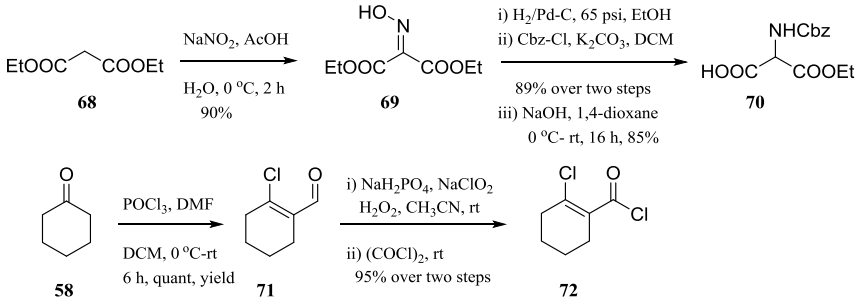
Section 3: Formal synthesis of Biotin: $MgCl_2/Et_3N$ mediated coupling and Mitsunobu reaction.

The present section describes the formal synthesis of Biotin employing the $MgCl_2/Et_3N$ mediated coupling and Mitsunobu reaction as the key steps. The retrosynthetic analysis is highlighted in Scheme 21.



Scheme 21: Retrosynthetic analysis for Biotin **53**

According to retrosynthetic analysis, the synthesis of Biotin began with coupling of the acid **70** and acyl chloride **72** (which was prepared from diethyl malonate **68** and cyclohexanone **58** respectively as shown in Scheme 22) by using $MgCl_2/Et_3N$ to furnish

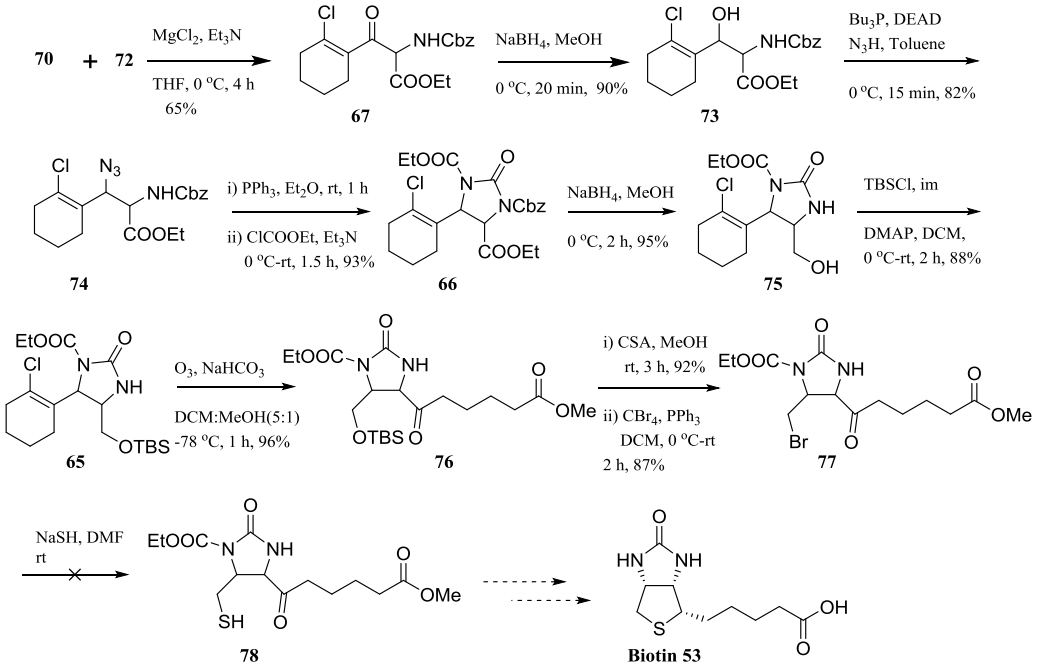


Scheme 22: Synthesis of acid **70** and acyl chloride **72**

β-keto ester **67**. *β*-Keto ester **67** on chemoselective reduction with $NaBH_4$ to afford *β*-hydroxy ester **73**, which on the Mitsunobu inversion using N_3H gave azide **74** in 82% yield. The azide **74** on Staudinger reduction followed by ethylchoroformate/TEA treatment provided urea **66** in 93% yield.

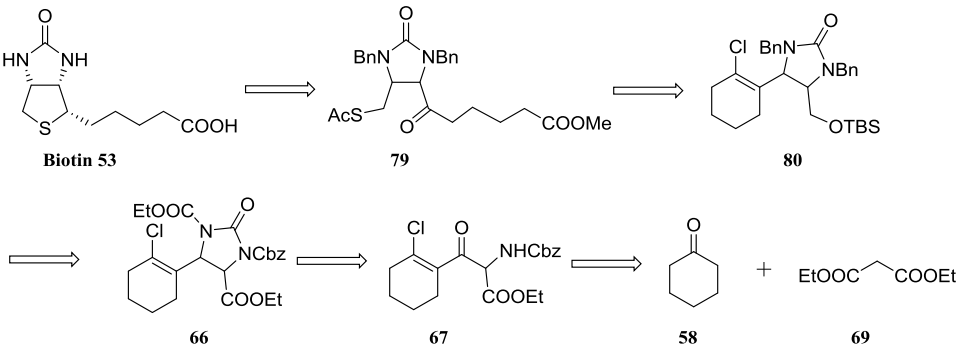
After having urea **66** in hand, the ester functionality was reduced to alcohol **75** followed

by TBS protection with TBSCl furnished compound **65** in 88% yield. The compound **65** on ozonolysis provided ketone ester **76**. The TBS deprotection of **76** was carried out by using CSA/MeOH followed by treatment with CBr_4 afforded bromide **77**. Bromide **77** was subjected for thiol **78** substitution under different reaction conditions but unfortunately it ended up in uncharacterized reaction mass (Scheme 23).



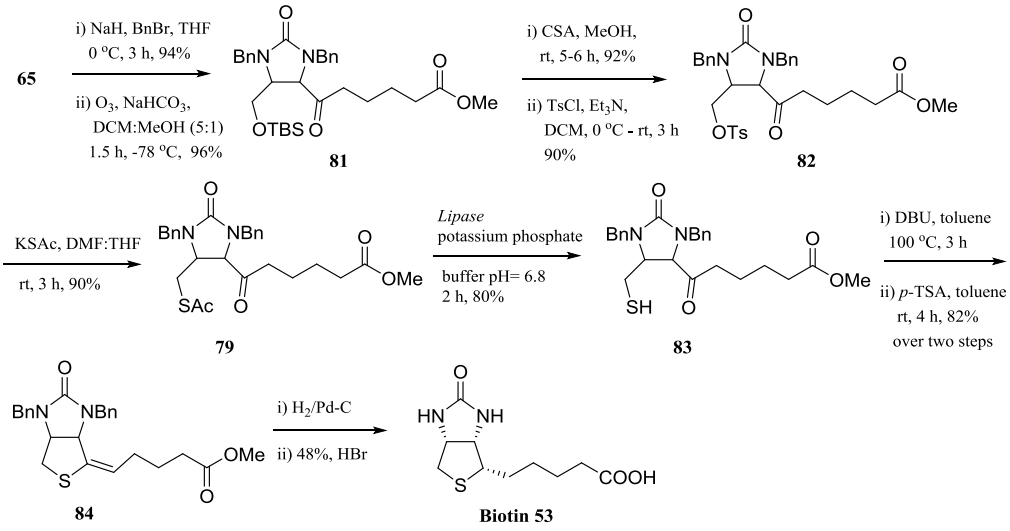
Scheme 23: Attempt towards synthesis of thiol **78**

The retrosynthetic plan was revised for Biotin **53** synthesis which is summarized in Scheme 24.



Scheme 24: Revised retrosynthetic analysis for Biotin **53**

According to retroanalysis urea **65** was treated with benzyl bromide/NaH to afford dibenzyl urea which on ozonolysis furnished into keto ester **81**. Next task was to access thioacetate **79**. Accordingly **81** was subjected to TBS deprotection using CSA followed by tosylation gave tosylate **82** in 90% yield. The tosylate **82** was treated with KSAc in DMF:THF to afford thioacetate **79** in 90% yield. The hydrolysis of thioacetate **79** was carried out using lipase strain to furnish the thiol **83** in 80% yield. The thiol **83** was cyclized to known intermediate **84** *via* base mediated cyclisation using DBU as the base followed by hydroxy elimination was carried out with *p*-TSA to furnish olefin **84** in 82% over two steps. Using usual reported procedure reported elsewhere and from this lab olefin **84** can be converted into Biotin **53** (Scheme 25). This constitutes a formal synthesis of biotin.



Scheme 25: Synthesis of intermediate **84**

Chapter 1

Synthetic studies towards Tamiflu

Section 1

Introduction to Tamiflu

1.1 Introduction of Tamiflu

1.1.1 Introduction

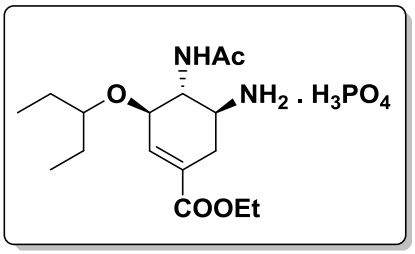


Fig 1 Tamiflu

C. U. Kim, W. Lew and X. Chen from Gilead Science (US) have discovered oseltamivir in 1995[1] and along with F. Hoffmann-La Roche Ltd. the drug was commercially launched in 1999 as its phosphoric acid salt.[2] Oseltamivir phosphate is marketed under trade name Tamiflu® which is an antiviral drug.

Tamiflu is a white crystalline solid with chemical name (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester phosphate with chemical formula $C_{16}H_{31}N_2O_8P$. It is prodrug, a relatively inactive chemical form, which is well absorbed by gastrointestinal track and hydrolyzed to its carboxylate active form. It is the first orally active neuraminidase inhibitor which is used to treat both influenza A virus and influenza B virus due to its good bioavailability. It is generally administrated in capsules form or as suspension to the infected patient within 36-48 h after flu infection. Tamiflu may slow the spread of influenza (flu) virus by stopping sialic acid complex cutting from its host cell.

Influenza[3]

Influenza is commonly known as “the flu” and it is caused by RNA virus of the *Orthomyxiviridae* family. It infects birds and mammals. Generally it affects all age groups, mostly in the young children and old people due to their weak immune system. It spreads through air by cough, sneezes and also by the direct contact with bird dropping,

nasal secretions or contact with contaminated surface. The seasonal influenza pandemics led to hospitalization of the millions and death of thousands of people. In twentieth century three historical influenza pandemics have threaten public health worldwide (Spanish flu in 1918, Asian flu in 1957, and Hong Kong flu in 1968).

There are three types of influenza A, B and C, which are RNA viruses. There are subtypes of influenza A virus on the basis of glycoprotein present on the cell surface of the virus. The surface of the influenza virus includes two types of glycoprotein *i.e.* hemagglutinin (H) and neuraminidase (N). The type A influenza virus is additionally having M2 protein channel which is absent in type B and C influenza virus. Influenza is a viral agent that causes mortality and morbidity due to annual epidemics and unpredictable pandemics, such as the pandemic in 1918 (Spanish flu), 1957 (Asian), 1968 (Hong Kong) and 2009 (swine flu). The influenza pandemics in 1918 is estimated to have killed kill 20 to 40 million people worldwide.[3]

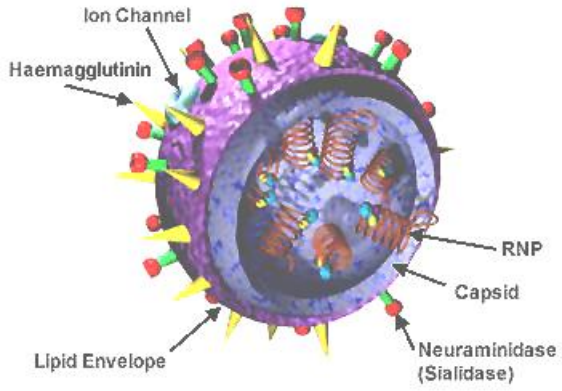


Fig 2: Structure of an influenza virus

Epidemics and pandemics

Influenza is specifically related with respiratory illness which leads to hospitalization and death of aged people. Every year global impact of influenza epidemics are believed to be 3-5 million illnesses and 300000-500000 death cases. The person more than 65 years of age, children below 2 year and person who has medicinal conditions faces more

complication from the influenza. Every 1 to 2 years new epidemic arises by mutation within glycoprotein hemagglutinin (HA) and neuraminidase (NA) at the selected point in influenza A. These permanent and small changes in the antigenicity of the influenza are termed "antigenic drift" and are the basis of the occurrence of the influenza epidemics. The new variants are able to evade human cells so that there is no lasting immunity against the virus, neither after natural infection nor after vaccination.

The pandemics are the rare events and which occurs every 10 to 50 years. Their documentation has been made since from the 16th century (in last 400 years), almost 31 pandemics are recorded. In the twentieth century, three influenza pandemics occurred. In 1918 (the Spanish flu) caused by H1N1 virus of the avian origin, in 1957 (Asian flu) by H2N2 and in 1968 (Hong Kong flu) by H3N2 viruses containing genes from the avain virus. The recent pandemic in 2009 (United states) was caused by H5N1 virus. The major changes in the antigenicity of an influenza virus are called an "antigenic shift". There are no prevention techniques available against the influenza pandemics, which spread around the globe in successive waves. The new viral strains will eventually reach everywhere and within the period of few years, will infect every human being. As unpredictable as pandemics, unpredictable is the virus itself. Nothing is known about the next pathogenic potential of the viral strains. The next pandemics could be the relatively benign as it was in 1957 and 1968 or truly malignant as was observed in 1918. The cause of the next pandemic, its rate of spreading, which age groups are at the high risks and how many lives will be killed are unpredictable. It is wise to plan and imagine for facing such unknown threats. For the global threats, the strategy must be global but it will become tricky the planet is divided into hundreds of nations. Dealing with nations and their leaders is like dealing with children in a nursery. In this difficult context, the WHO is performing an amazing job.

1.1.2 Pharmacology of Zanamivir and Oseltamivir phosphate[4]

The primary prevention method of influenza is through vaccination. However, vaccine production takes near about 6-8 months and its effectiveness is limited up to 18 months

and main limitation is that it should be administrated at least four months before the viral infection. The influenza virus is mutating each year so there is need to produce the new vaccine every year. The main drawback of the newly prepared vaccine is, it doesn't show the prolonged effect against seasonal flu. Thus an alternative to vaccination, antiviral and neuraminidase inhibitors could be employed to combat influenza.

For the drug development it is necessary to understand the mode of viral infection of the influenza. Hemagglutinin (H) is the surface glycoprotein of the virus which binds to the sialic acid receptor present on cell surface and it mediates the entry of virus into the target cell. In the cell virus gets replicated to form progeny virus particle called virion. To release virions from infected cell it is must to break sialic acid-hemagglutinin covalent binding. The neuraminidase is another glycoprotein, which cleaves the sialic acid residue from the newly created virions to avoid the virion's aggregation, which would otherwise make them ineffective to attack new cells. Also neuraminidase facilitated the spreading of the virus through the mucus of the respiratory tract (fig 2).[5] Drug designing and

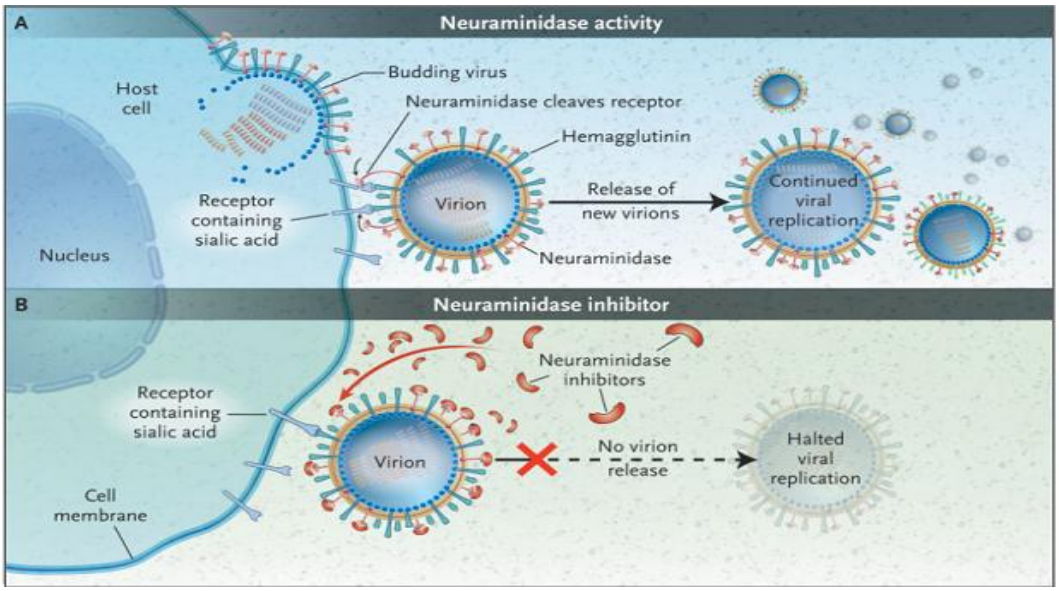


Fig 3: Panel **A** shows the action of neuraminidase & panel **B** shows role of neuraminidase inhibitors

development must target to block the active site of the neuraminidase glycoprotein. First reported example of this type of molecule is 2-deoxy-2,3-dehydro-*N*- acetylneuraminic

acid (DANA) in 1974. In 1980s X-ray structure of the neuraminidase A, B and their complexes with sialic acid helped to understand the functional groups and the active site for the structure based drug designing on the viral flu. Extensive study of the transition state of neuraminidase action led to discovery of Zanamivir (GSK's Relenza®, marketed in July 1999) and Oseltamivir phosphate (Gilead's Tamiflu®, launched in the market in October 1999). Those are structurally very similar as compared to sialic acid, only difference is of hydroxyl group at 4th position on ring which was replaced with basic group guanidine and amino respectively. Those were designed as mimic of oxocarbonium intermediate transition state, which on enzymatic hydrolysis gives sialic acid. Zanamivir and Oseltamivir phosphate binds to the active site of neuraminidase and which lead prevent the sialic acid complex cleavage and as a result they inhibit the release and spreading of virus totally (shown in fig 3).

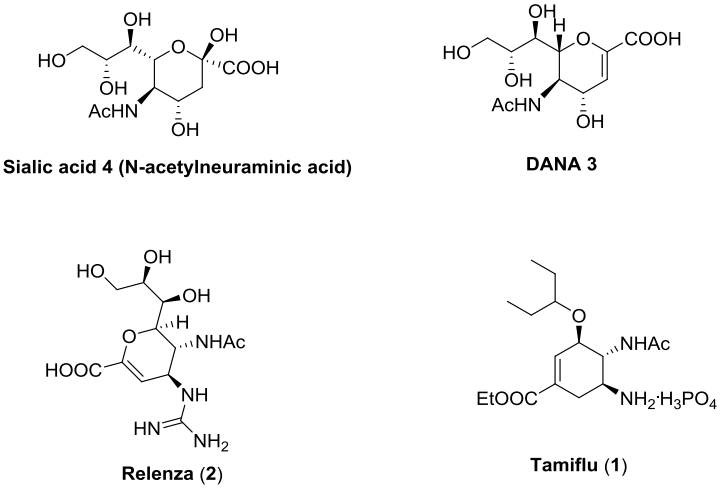


Fig 4: Structure of sialic acid and neuraminidase inhibitors

Zanamivir has low bioavailability and it is administrated by inhalation as a dry powder. Through the inhaler it is directly delivered to the respiratory tract. Zanamivir is concentrated in respiratory tract but only 10-20% active compound reaches to the lung, which results into low bioavailability. Drug concentration in the respiratory tract is estimated to be more than 1000 times of its 50% inhibitory concentration for

neuraminidase and its effects start within 10 seconds. But the main drawback of the Zanamivir (Relenza®) is, it can cause problem in patients who have respiratory disease.

The discovery of the oseltamivir came as the result of a search of less polar 3-pentanol side chain as replacement of polar glycerol side chain group present in the DANA or Zanamivir to prepare an orally active drug. The double bond in tamiflu increases its potency while water soluble phosphate salt and ethyl ester group, the less polar side chain increases drug lipid solubility. Oseltamivir phosphate is administered as a capsule or powder in liquid suspension with good oral bioavailability. The ester group of oseltamivir phosphate is hydrolyzed *in vivo* into oseltamivir carboxylate, which is active form therefore, it is considered as the prodrug. It is recommended as the best choice as influenza drug due its effectiveness against the both H5N1 and H1N1 viral strains. Tamiflu is available as capsules containing 30 mg, 45 mg or 75 mg of oseltamivir for oral use while as a powder for oral suspension, which when constituted with water as directed contains 6mg/ml oseltamivir base. Along with active ingredient, each capsule contains talc, croscacamellose sodium, red iron oxide, pregelatinized starch and povidone K30. And the oral suspension powder contains sorbitol, monosodium citrate, xanthan gum, TiO_2, sodium benzoate, tutti-frutti flavoring and saccharin sodium. The drug is administered orally at a dose of 75 mg twice a day. It should be administered to the patient within 36-48 h after detection of the symptoms of influenza.[6] It is readily absorbed from the gastrointestinal tract and converted to its the active carboxylate form. The half life of the drug is 6-10 hours; primarily it is excreted through kidney. Thus it can achieve high level in plasma and can act outside the respiratory tract as well as. To date zanamivir and oseltamivir phosphate are the only two drugs approved to fight influenza.

1.1.3 Literature review

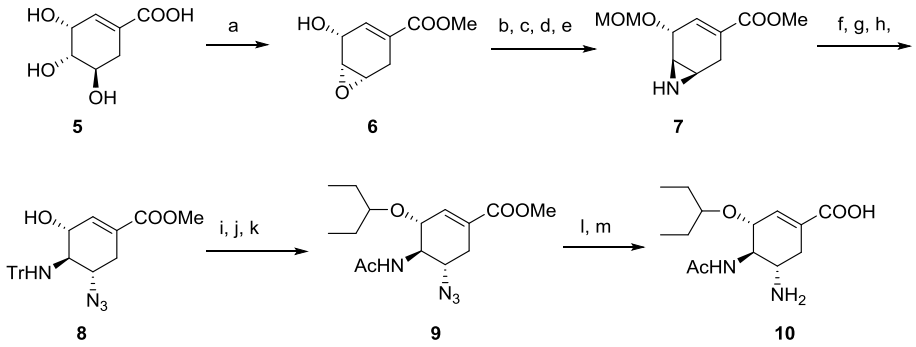
There is continuous threat to human as well as other animal health worldwide from the influenza viral infection. Due to crucial role of tamiflu against both influenza A and B viral strains, the synthetic communities have reported elegant efforts towards the synthesis of tamiflu. Various syntheses of tamiflu are known in the literature by several routes, which include (-)-shikimic acid, quinic acid and other chiral materials as starting

material, some people also reported the asymmetric methodology-based strategy. Some of the reported synthetic developments are described in this section.

Gilead's 1st approach (*J. Am. Chem. Soc.* **1997**, *119*, 681)[1a]

Gilead scientists first time identified oseltamivir **10** for development, but the ethyl ester prodrug oseltamivir phosphate **1** was in due course chosen as the clinical candidate based on its potent *in vitro* and *in vivo* activities and its good oral bioavailability. The synthesis of oseltamivir **10** began with (-)-shikimic acid **5**, which already contains required cyclohexane system which is described in the Scheme 1.

The (-)-shikimic acid **5** was converted to epoxide **6** using reported protocol. The alcohol **6** was protected as MOM derivative, followed by epoxide opening with NaN_3 and mesylation in MsCl/TEA and azide reduction under Staudinger conditions to furnish the aziridine compound **7**. The aziridine **7** was opened with NaN_3, MOM deprotection followed by the amine protection carried out with trityl chloride to afford compound **8**. The mesylation of azide **8** resulted into aziridine formation, which was opened with 3-pentanol/ $BF_3.Et_2O$ and resultant amine was protected as its acetyl derivative to provide **9**. Azide reduction of azide **9** and ester hydrolysis led to oseltamivir **10**.



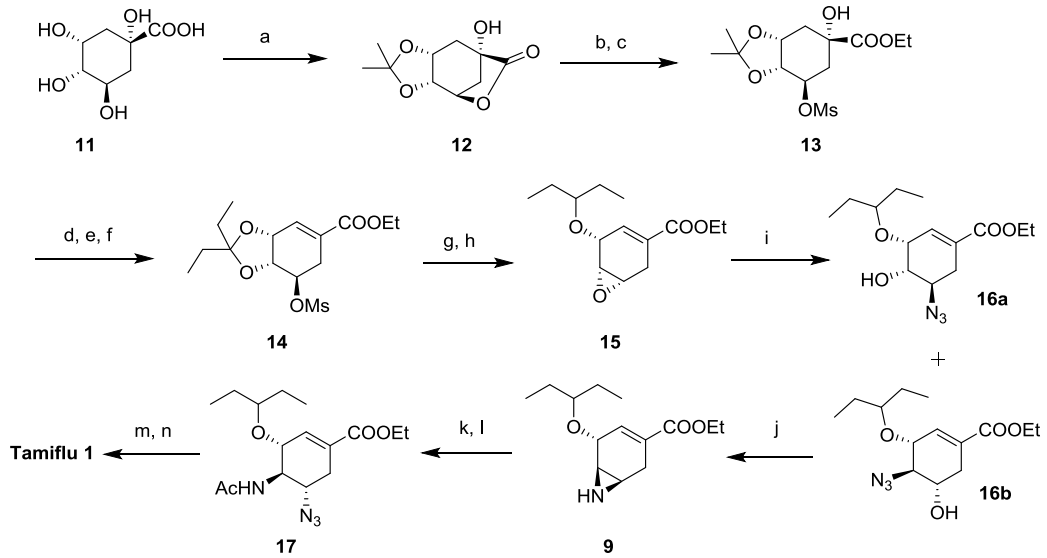
Scheme 1

Reagents and conditions: *(a) ref* ***1c****; (b) $MeOCH_2Cl$, DIPEA, DCM, reflux, 3.5 h, 97%; (c) NaN_3, NH_4Cl, $MeOH/H_2O$, reflux, 15 h, 86%; (d) $MeSO_2Cl$, TEA, DCM, 0 ^oC to rt, 15 min, 99%; (e) (i) PPh_3, THF, 0 ^oC to rt, 3 h; (ii) TEA, H_2O, rt, 12 h, 78%; (f) NaN_3,*

NH_4Cl, DMF, 65-70 ^oC, 21 h, 77%; (g) HCl, MeOH, rt, 4 h, 99%; (h) TrCl, TEA, H_2O, 0 ^oC to rt, 3 h; (i) $MeSO_2Cl$, TEA, DCM, 0 ^oC to rt, 22 h, 86% (2 steps); (j) $BF_3.OEt_2$, 3-pentanol, 70-75 ^oC, 2 h; (k) Ac_2O, DMAP, pyridine, rt, 18 h, 69% (2 steps); (l) PPh_3, THF/H_2O, 50 ^oC, 10 h, 90%; (m) (i) KOH, THF, rt, 40 min; (ii) Dowex 50WX8, 75%.

Gilead's II approach (*J. Org. Chem.* **1998**, *63*, 4545)[7a]

The availability of (-)-shikimic acid **5** is very low and its cost is too high. So for the large scale production of the tamiflu **1** alternative strategy was developed by Gilead science from the (-)-quinic acid **11** which is outlined in Scheme 2. The quinic acid **11** was converted to the lactone **12** by known literature procedure.[7b] The lactone **12** was hydrolyzed with NaOEt/ethanol followed by treatment with mesyl chloride condition ended mesylate **13**, which on reaction with SO_2Cl_2, $Pd(PPh_3)_4$ followed by treatment with 3-pentanone/$HClO_4$ afforded compound **14** in 30% yield from quinic acid. The compound **14** was treated with TMSOTf/BH_3DMS conditions followed by $KHCO_3$ treatment afforded epoxide **15**. The epoxide **15** thus obtained was opened with NaN_3 to furnish regioisomeric mixture **16a**:**16b** in 10:1 ratio. Azido alcohols **16a** and **16b** were



Scheme 2

Reagents and conditions: *(a) 2,2-dimethoxypropane, p-TsOH, acetone reflux; (b)*

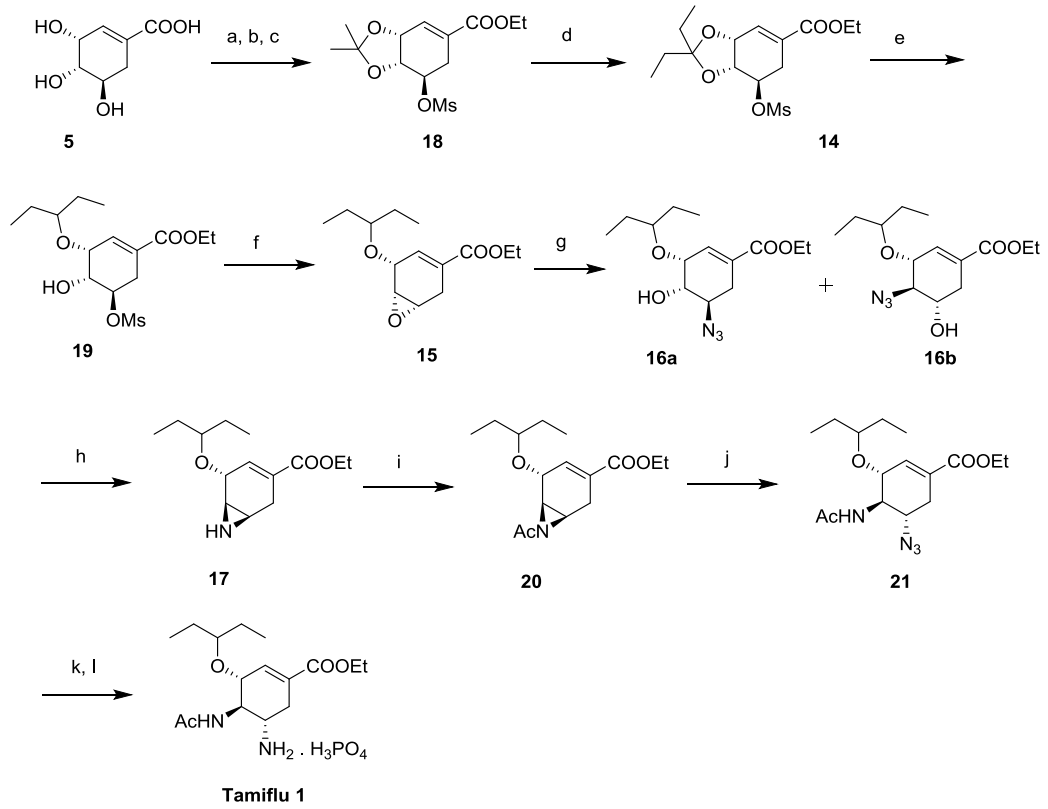
NaOEt, EtOH, 2 h; (c) MsCl, TEA, DCM, 0 - 5 ^{o}C, 1.5 h, 69% (three steps); (d) $SOCl_2$, py, DCM, -20 to -30 ^{o}C; (e) mixture, pyrrolidine, $Pd(PPh_3)_4$, EtOAc, 35 ^{o}C, 3.5 h, 30%; (f) 3-pentanone, $HClO_4$, 40 ^{o}C, 25 mmHg, 95%; (g) TMSOTf, BH_3.DMS, DCM, -10 to -20 ^{o}C, 45 min, 75%; (h) $KHCO_3$, EtOH/H_2O, 55-65 ^{o}C, 1 h, 96%; (i) NaN_3, NH_4Cl, EtOH/H_2O, 70-75 ^{o}C, 12-18 h, ***16a*** *:* ***16b*** *ratio 10:1, 85%; (j) Me_3P, MeCN, <38 ^{o}C, 2 h, 97%; (k) NaN_3, NH_4Cl, DMF, 70-80 ^{o}C, 12-18 h; (l) Ac_2O, $NaHCO_3$, hexane/DCM, 1 h, 44% (2 steps); (m) H_2 (1 atm.), Ra-Ni, EtOH, 10-16 h; (n) H_3PO_4, EtOH, 55-65 ^{o}C to 0 ^{o}C, 3-24 h, 71% (2 steps).*

subjected to Staudinger reduction conditions to provide aziridine **17**, which was opened with NaN_3 and the resultant amine was protected as its acetyl derivative in Ac_2O to give azide **9**. The azide **9** was reduced with Ra-Ni followed by phosphate salt formation which was carried out in H_3PO_4 to furnish oseltamivir phosphate **1**.

Roche's industrial process (*Org. Process Res. De*v. **1999**, *3*, 266**)**[2]

This industrial manufacturing process is based on the first synthesis of oseltamivir **10** from the (-)-shikimic acid **5** and (-)-quinic acid **11** by Gilead science. The (-)-shikimic acid strategy was improved by the Hoffmann-la Roche, which is used for industrial scale manufacturing of tamiflu is summarized in Scheme 3.

The (-)-shikimic acid **5** subjected to esterification and acetonide protection followed by treatment with mesyl chloride/trimethyl amine conditions furnished the corresponding mesyl compound **18**. The acetonide deprotection and pentanide protection in one pot using 3-pentanone and cat. triflic acid led to pentanide **14**. The pentanide **14** was treated with $TiCl_4$/trimethyl silane to afford compound **19** which on basic treatment gave epoxide **15**. Epoxide **15** was opened with NaN_3 and subjected to Staudinger reduction to furnish compound **17**. Compound 17 was protected as its acetyl derivative with acetic anhydride to afford aziridine **20**, which was subjected for aziridine opening with NaN_3 to give azide **21**. The azide **21** was reduced with Bu_3P followed by H_3PO_4 treatment to provide oseltamivir phosphate **1**.



Scheme 3

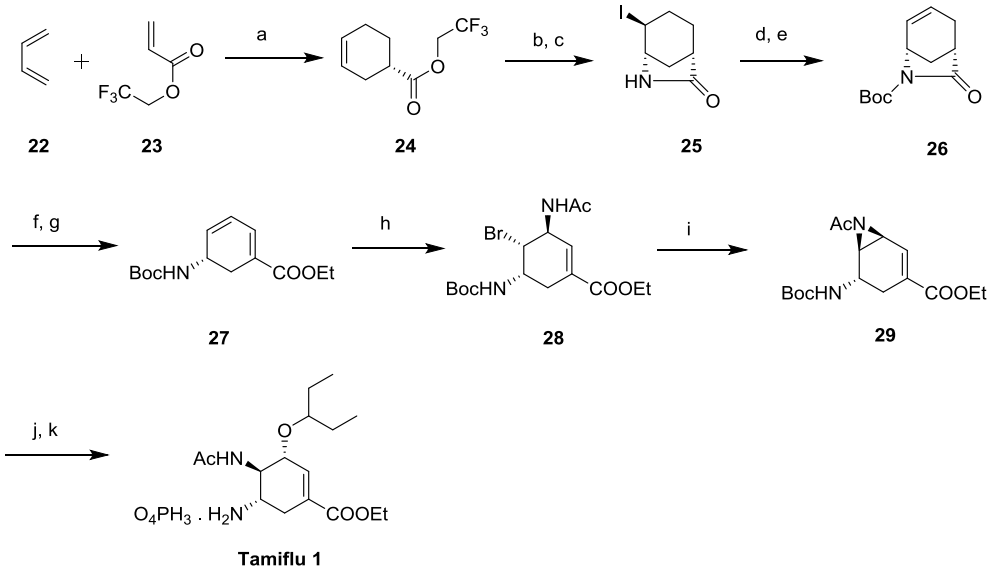
Reagents and conditions: *(a) EtOH, $SOCl_2$, reflux, 3 h; (b) $Me_2C(OMe)_2$, TsOH, EtOAc, 150-200 mbar, <35 ^oC, 4 h; (c) MsCl, Et_3N, EtOAc; (d) 3-Pentanone (excess), cat. TsOH, EtOAc, 40 ^oC, 100 mbar; (e) $TiCl_4$, Et_3SiH, DCM, -34 ^oC, 2-6 h; (f) $NaHCO_3$, EtOH; (g) NH_4Cl, NaN_3, EtOH/H_2O, 60-65 ^oC; (h) PPh_3, Et_3N, MsOH, DMSO, 50 ^oC, 1 h; (i) Ac_2O, Bu_2O, 0-25 ^oC; (j) NaN_3, H_2SO_4, DMSO, 35 ^oC, 4 h; (k) Bu_3P, AcOH, EtOH/H_2O, 5-20 ^oC; (l) H_3PO_4, EtOH, 50-20 ^oC.*

Corey's approach (*J. Am. Chem. Soc.* **2006**, *128*, 6310**)**[8a]

As the substitute for the (-)-shikimic acid **5**, Corey *et al* have reported synthesis of the tamiflu **1** using Diels-Alder cycloaddition in asymmetric fashion as described in Scheme 4.

The asymmetric cycloaddition reaction was carried out between butadiene **22** and

acrylate **23** in presence of the CBS catalyst to furnish cycloadduct **24**.[8b] The lactam **25** was derived from cyclohexene **24** on treatement with ammonia followed by the reaction with TMSOTf and iodine. The iodo lactam **25** on Boc protection with boc anhydride and on refluxing with DBU gave olefin **26**. The allylic bromination of compound **26** was achieved by treatement with NBS followed by reaction with the Cs_2CO_3 to afford diene **27**. The diene **27** was on reaction with $SnBr_2$ and *N*-chloroacetamide furnished bromo-ester **28**, which on treatment with KHMDS afforded aziridine **29**. The aziridine **29** on opening with 3-pentanol in the presence of $Cu(OTf)_2$ followed by H_3PO_4 mediated boc deprotection and phosphate salt formation furnished final compound **1**.

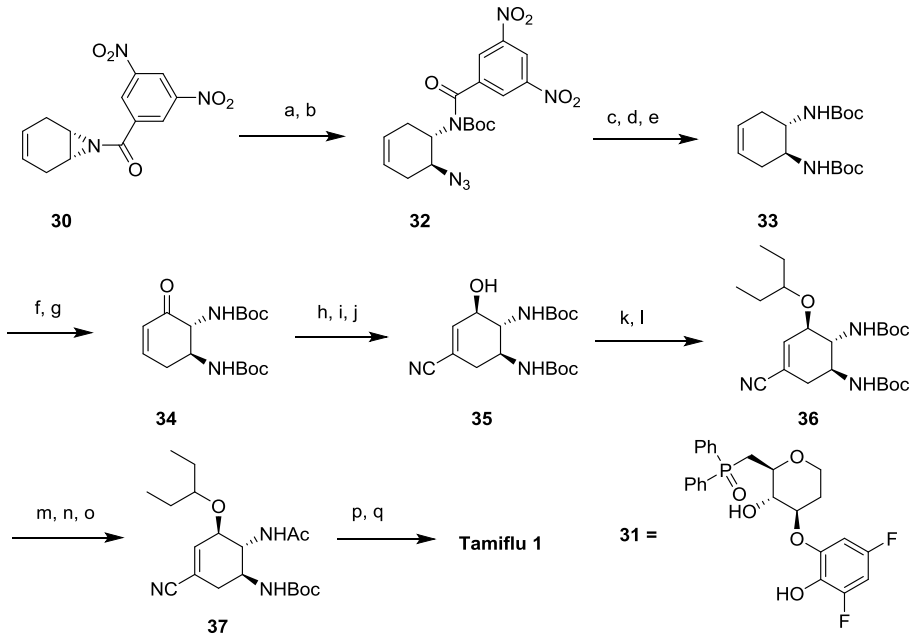


Scheme 4

Reagents and conditions: *(a) CBS cat., neat, 23 ^oC, 30 h, 97%, > 97% ee; (b) NH_3, CF_3CH_2OH, 40 ^oC, 5 h, 100%; (c) (i) TMSOTf, TEA, pentane; (ii) I_2, Et_2O/THF, 2 h, 84%; (d) $(Boc)_2O$, TEA, DMAP, DCM, 4 h, 99%; (e) DBU, THF, reflux, 12 h, 96%; (f) NBS, AIBN (cat.), CCl_4, reflux, 2 h, 95%; (g) Cs_2CO_3, EtOH, 25 min, 100%; (h) $SnBr_2$ (5 mol%), N-chloroacetamide, MeCN, -40 ^oC, 4 h, 75%; (i) n-Bu_4NBr, KHMDS, DME, -20 ^oC, 10 min, 82%; (j) $Cu(OTf)_2$ (cat.), 3-pentanol, 0 ^oC, 12 h, 61%; (k) H_3PO_4, EtOH.*

Shibasaki's 1st approach (*J. Am. Chem. Soc.* ***2006****, 128, 6312*)[9]

The first approach of Shibasaki *et al* towards tamiflu **1** is based on the asymmetric opening of the meso-aziridine **30** using $TMSN_3$ which is described in the Scheme 5. The synthesis was initiated with aziridine **30** opening to azide **32** using yttrium catalyst with $TMSN_3$ followed by treatment with boc anhydride to afford compound **32**. The C_2 symmetric olefin **33** was obtained from azide **32** by benzoyl deprotection, Staudinger reduction followed by the protection with boc anhydride. Olefin **33** on allylic oxidation with SeO_2/DMP gave a mixture which was treated with DMP to furnish unsaturated ketone **34**. Further, ketone **34** was subjected to the 1, 4 addition of TMSCN in presence of the $Ni(COD)_2$ as the catalyst followed by treatement with NBS and stereoselective reduction using L-seletride to furnish alcohol **35**. Alcohol **35** was subjected to Mitsunobu conditions followed by reaction with 3-pentanol/$BF_3.Et_2O$ to afford compound **36**. The boc deprotection and selective protection of sterically less hindered amine with $(Boc)_2O$ and second amino group with acetic anhydride provided compound **37**, which on heating with ethanolic HCl followed by H_3PO_4 treatment led to oseltamivir phosphate **1**.



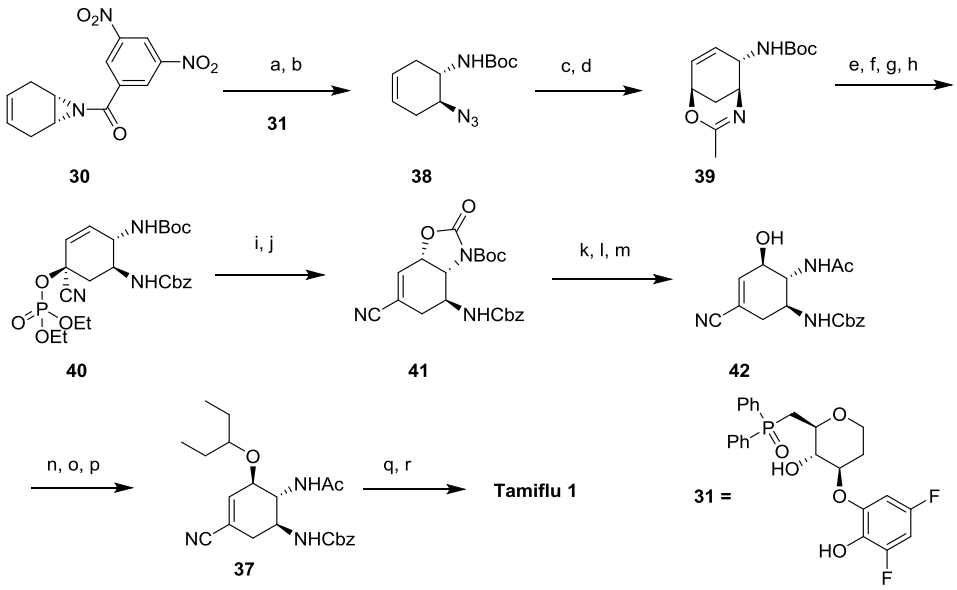
Scheme 5

Reagents and conditions: *(a) (i) $Y(OiPr)_3$ (1 mol%), **31** (2 mol%), $TMSN_3$, CH_3CH_2CN,*

2,6-dimethylphenol (1 eq.), rt, 12 h, 94%; (ii) recrystallized from iPrOH, 72%; (b) Boc_2O (1.5 equiv), DMAP (0.5 equiv), CH_3CN, rt, 3 h; (c) 4 M NaOH, rt, 2 h, 98% (2 steps); (d) Ph_3P (1.1 equiv), CH_3CN, 50 °C, 3 h; H_2O, 40 °C, 2 h; (e) Boc_2O (2 equiv), Et_3N (5 equiv), DCM, rt, 2 h, 90% (2 steps); (f) SeO_2 (1 equiv), DMP (1.5 equiv), dioxane, 80 °C, 12 h; (g) DMP (1.5 equiv), DCM, 4 °C, 68% (2 steps); recrystallized from iPr_2O-hexane, >99% ee, 62%; (h) $Ni(COD)_2$ (10 mol %), COD (10 mol %), TMSCN (3 equiv), THF, 60 °C, 65 h; (i) (i) NBS (1.05 equiv), THF, 20 min; (ii) Et_3N (14 equiv), 4 °C, 40 min; (j) $LiAlH(OtBu)_3$ (5 equiv), THF, 4 °C, 30 min, 60% (>20:1) (3 steps); (k) DEAD (2.5 equiv), Ph_3P (2.5 equiv), THF, 4 °C, 1 h, 87%; (l) 3-Pentanol, $BF_3.OEt_2$ (1.5 equiv), 4 °C, 1 h, 52%; (m) TFA (20 equiv), DCM, 4 °C to rt, 3 h; (n) Boc_2O (1.1 equiv), Et_3N (5 equiv), DCM, 4 °C, 30 min, 63% (2 steps); (o) Ac_2O (2 equiv), DMAP (0.5 equiv), py, rt, 1 h, 84%; (p) (i) 4.2 M HCl-EtOH, 60 °C, 4 h;(ii) H_2O, 4 °C, 3 h, 53%; (q) 85% H_3PO_4 (1 equiv), EtOH; cryst, 50%.

Kanai and Shibasaki approach (*Org. Lett.* **2007**, *9*, 259-262**)**[10a]

Kanai and Shibasaki have reported the meso-aziridine desymmetrization based approach to tamiflu **1**, which is described in Scheme 6. The synthesis for tamiflu began from enantiomerically pure azide **38**, which was synthesized using reported procedure. The compound **38** was reduced under Staudinger conditions followed by treatment with acetic anhydride to give amide, which was converted to compound **39** *via* reaction with NIS and further treatment with DBU. The compound **39** was subjected to Cbz protection, acetate hydrolysis to alcohol, followed by DMP oxidation to provide enone and cyanophosphorylation to give cyano compound **40**. Thermal allylic rearrangement of **40** was carried out at 150 ^{o}C followed by boc protection to afford compound **41**. The carbamate hydrolysis of **41** followed by oxidation and L-selectride reduction gave alcohol **42**. The alcohol **42** was subjected to Mitsunobu conditions followed by aziridine opening with 3-pentanol provided compound **37** and following known protocol[10b] compound **37** was converted into the oseltamivir phosphate **1**.



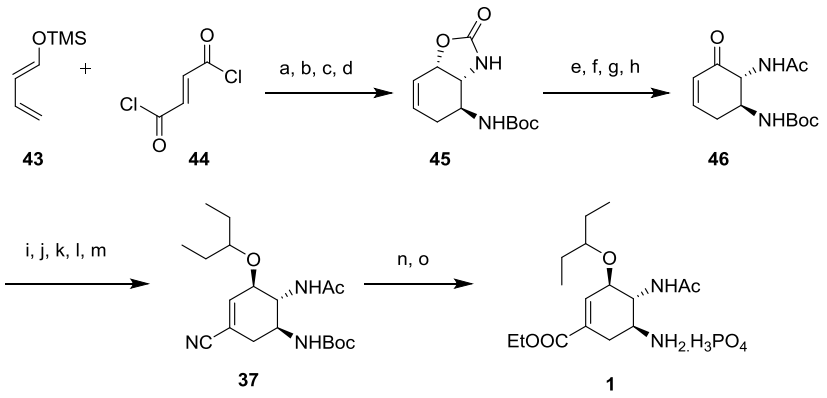
Scheme 6

Reagents and conditions: *(a) $Y(OiPr)_3$ (1 mol%), **31** (2 mol%), $TMSN_3$, CH_3CH_2CN, 2,6-dimethylphenol (1 eq.), rt, 12 h, 94%; (b) Boc_2O, DMAP, 4M NaOH aq., 98%; (c) (i) PPh_3, H_2O; (ii) Ac_2O, py, 99% (2 steps); (d) (i) NIS; (ii) DBU; (e) CbzCl, $NaHCO_3$, DCM-H_2O, 85% (3 steps); (f) K_2CO_3, MeOH, 99%; (g) DMP, DCM, 96%; (h) $(EtO)_2POCN$, LiCN, dr = 20:1; (i) Toluene, 150 ^oC, 3 h (sealed tube); (j) Boc_2O, DMAP, py, 72% (3 steps); (k) Cs_2CO_3 (10 mol %), MeOH, 97%; (l) DMP, DCM, 94%. (m) $LiAlH(OtBu)_3$, 91%; (n) DEAD, PPh_3, toluene, 87%; (o) 3-Pentanol, $BF_3.Et_2O$, 51%; (p) (i) TFA; (ii) Ac_2O, Et_3N, 81% (2 steps); (q) HCl, EtOH, NH_3 aq., 74%; (r) H_3PO_4, cryst.*

Shibasaki's 2nd approach (*Tetrahedron Letters* **2007**, *48*, 1403-1407**)**[11]

Shibasaki *et al* have described another approach towards tamiflu **1** employing Diels-Alder reaction as described in Scheme 27. The synthesis began with cycloaddition of diene **43** and dienophile **44** to give cycloadduct which was treated with $TMSN_3$ followed by acidic TMS deprotection and refluxing in *t*-BuOH to furnish carbamate **45**. The carbamate **45** was hydrolyzed with LiOH, resultant amine was acetylated with acetic anhydride followed by oxidation using isobutyric anhydride/DMSO conditions led to compound **46** in 54% yield over four steps. The conversion of enone **46** to cyano

cyclohexene **37** was achieved *via* TMSCN/Ni(COD)$_2$ mediated Michael addition, α-bromination with NBS followed by elimination with TEA and L-selectride mediated reduction of ketone, aziridine formation under Mitsunobu condition, and aziridine opening with 3-pentanol/BF_3.Et_2O. In the one pot ethanolysis of compound **37** to ester followed by *N*-Boc deprotection in acid led to amine and the resultant amine on H_3PO_4 treatment gave tamiflu **1**.



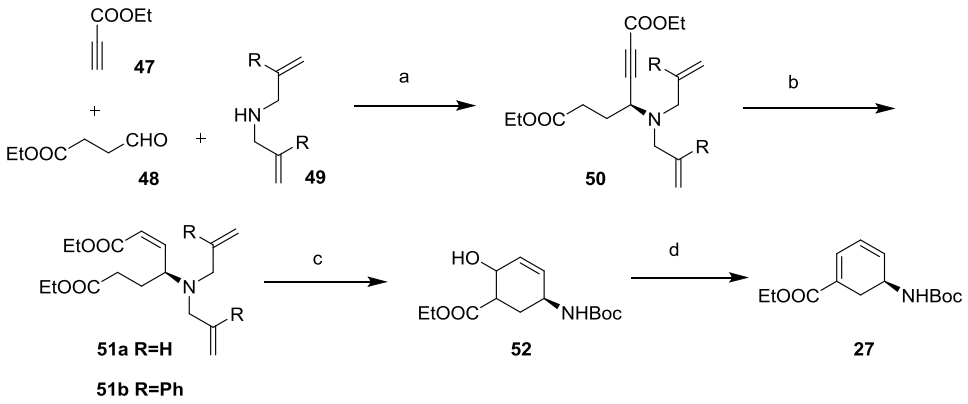
Scheme 7

Reagents and conditions: *(a) THF, rt, 2 h; (b) $TMSN_3$, DMAP, rt, 2 h; (c) 1N HCl, rt, 10 min, 55% (3 steps); (d) ^tBuOH, reflux; (e) LiOH; (f) Ac_2O, TEA; (g) Isobutaric anhydride, DMSO, 53% (4 steps); (h) Chiral HPLC; (i)TMSCN, Ni(cod)$_2$ (50 mol%), COD (50 mol%); (j) (i) NBS, (ii) TEA; (k) LiAl(O^tBu)$_3$H, 44% (3 steps); (l) DEAD, PPh_3, 66%; (m) 3-Pentanol, BF_3.Et_2O, 56%; (n) HCl, EtOH, 60%; (o) H_3PO_4, cryst.*

Shibasaki's 3rd approach (*J. Org. Chem.* **2013**, *78*, 4019**)**[12a]

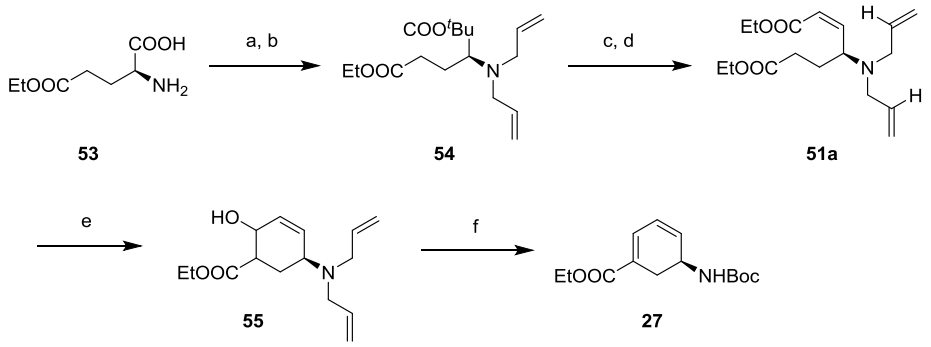
Recently Shibasaki and coworkers have developed two independent methods to access the synthetic precursor **27** of oseltamivir phosphate earlier reported by Corey *et al*. In first strategy, copper-catalyzed asymmetric three component reaction of terminal alkyne **47**, aldehyde **48** and secondary amine **49** to afford compound **50** was employed. The alkyne **50** was reduced to *Z*-alkene using a poisoned Pd-catalysed reduction condition using Trost method.[12b] Di-ester **51a** was converted into compound **52** using proper reaction sequence. The compound **52** was subjected to mesylation and subsequent DBU

elimination to give diene compound **27** (Scheme 8A).



Scheme 8A

Reagents and conditions: *(a) $CuBr_2$ (10 mol %), (S,S)- Ph-Py box (20 mol %),* ***47*** *(2 equiv),* ***48*** *(1 equiv),* ***49*** *(2 equiv), MS 4Å, toluene, -15 or 0 ^oC, 24 h; (b) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $P(o\text{-}tol)_3$ (10 mol %), $(Me_2HSi)_2O$ (1 equiv), AcOH (1 equiv), toluene, 45 or 40 ^oC, 19 or 24 h; (c) (i) LHMDS (3 equiv), THF, -40 ^oC, 1 h; (ii) $NaBH_4$ (2 equiv), MeOH, -20 ^oC, 30 min; (iii) $Pd(PPh_3)_4$ (10 mol %), N,N-dimethylbarbituric acid (6 equiv), DCM, rt, 1 h; (iv) Boc_2O (5 equiv), $NaHCO_3$ aq, CH_3CN, rt, 1 h, yield 55% for 4 steps; (d) MsCl (1.1 equiv), Et_3N (2 equiv), DCM, 4 ^oC, 10 min; DBU (3.1 equiv), DCM, rt, 1 h, 87% for 2 steps.*



Scheme 8B

Reagents and Conditions: *(a) 60% $HClO_4$ (1.1 equiv), t-BuOAc (excess), rt, 2 d, 77%; (b) allyl bromide (6 equiv), $NaHCO_3$ (4 equiv), EtOH, reflux, 24 h, yield 84%; (c) HCO_2H (excess), 80 ^oC, 1 h; $ClCO_2Et$ (3 equiv), Et_3N (5 equiv), THF, -10 ^oC, 15 min,*

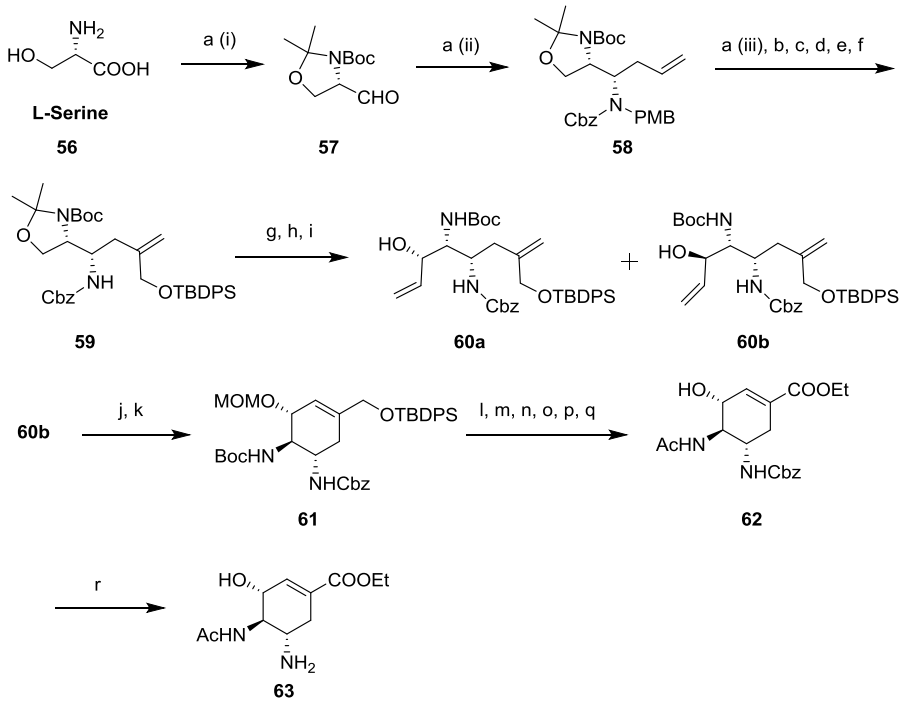
then $NaBH_4$ (6 equiv), MeOH, 0 ^oC, 30 min, yield 80% for 2 steps; (d) SO_3·pyridine (4 equiv), Et_3N (3.6 equiv), DMSO, 0 ^oC, 2 h; $(CF_3CH_2O)_2P(CO)CH_2CO_2Et$ (1.1 equiv), 18-crown-6 (5 equiv), KHMDS (1.2 equiv), THF, -78 ^oC, 2 h, yield 80% for 2 steps; (e) LHMDS (3 equiv), THF, -40 ^oC, 1 h; $NaBH_4$ (2 equiv), MeOH, -20 ^oC, 30 min; $Pd(PPh_3)_4$ (10 mol %), N,N dimethylbarbituric acid (6 equiv), DCM, rt, 1 h; Boc_2O (5 equiv), CH_3CN, rt, 1 h, yield 55% for 4 steps; (f) MsCl (1.1 equiv), Et_3N (2 equiv), DCM, 4 ^oC, 10 min; DBU (3 equiv), rt, 1 h, 87% for 2 steps.

The second strategy commenced with commercially available L-glutamic acid, which was masked as *t*-butyl ester **53** followed by the allyl groups introduced to amino group to give di-allyl compound **54**. The *cis*-unsaturated ester **51a** was derived from the compound **54** *via* ester reduction to alcohol by mixed-anhydride formation and $NaBH_4$ treatment, oxidation of alcohol to corresponding aldehyde followed by *Z*-olefination.[12c] Subsequently, compound **51a** under the similar reaction sequence developed for the first strategy, led to the desired Corey's intermediate **27** (Scheme 8B).

Yao's approach (*J. Org. Chem.* **2006**, *71*, 5365-5368**)**[13a]

Yao and coworkers have reported synthesis of oseltamivir starting from L-serine **56** as the starting material, which is described in the Scheme 9 utilizing ring closing metathesis (RCM) as key step. The Garnier aldehyde **57** was obtained from the L-serine **56** and it was converted to olefin **58** using reported procedure.[13b-d] Olefin **58** was converted to compound **59** *via* dihydroxylation, Cbz and PMB deprotection, primary hydroxy protection to its TBDPS ether and oxidation of 2-hydroxy to ketone, followed by Wittig olefination. The compound **59** was subjected for *N*-*O* acetal deprotection with catalytic $BiBr_3$ and oxidation of primary hydroxy group to aldehyde by Swern oxidation conditions; followed by vinylmagnesium bromide addition in presence of $ZnCl_2$ to give compound **60b** as major product.[13e] The diene **60b** was subjected to MOM ether protection followed by ring closing metathesis using Grubbs' Ist generation catalyst to furnish cyclohexene **61**. The unsaturated ester **62** was derived from the cyclohexene **61** by TBDPS ether deprotection, PCC oxidation to aldehyde, followed by Pinic oxidation and esterification of acid using EtOH/EDCI/HOBT coupling conditions and *N*-Boc

deprotection was carried out in acidic condition to afford amine. The resultant amine was protected with acetyl chloride to afford alcohol **62**. The Cbz- deprotection of alcohol was carried out using $Pd(OAc)_2$ catalysed reduction to give intermediate **63**.

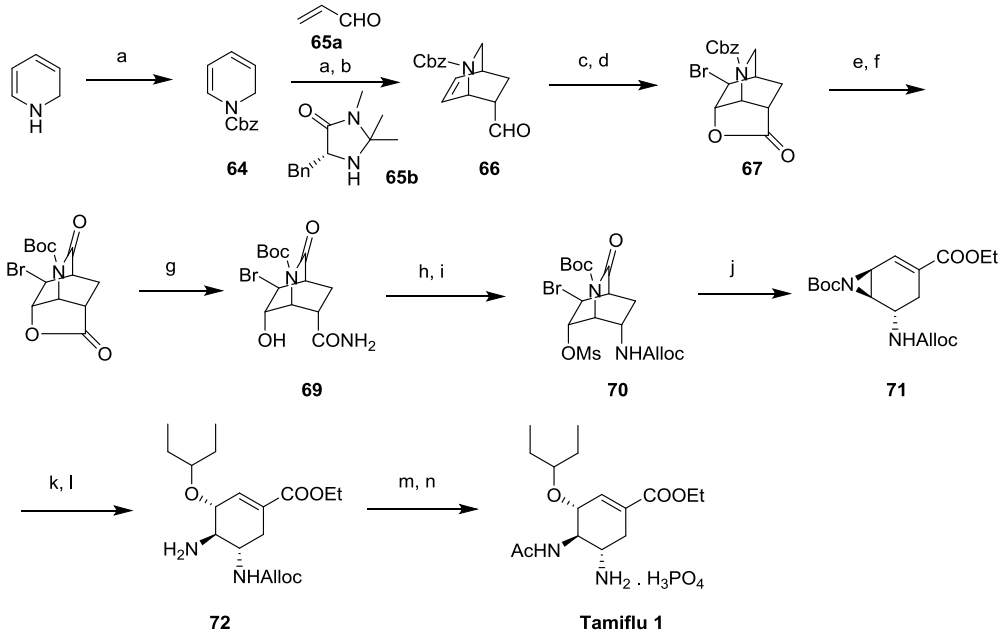


Scheme 9

Reagents and conditions: *(a) (i) ref 13d; (ii) ref 13e; (iii) OsO_4, NMO, acetone/water 5:1, 89%; (b) H_2, Pd/C, MeOH, 35 ^oC; (c) CbzCl, $NaHCO_3$, H_2O/EtOAc (v/v = 1:1), 86% (2 steps); (d) TBDPSCl, imid, DCM, rt, 96%; (e) $(COCl)_2$, DMSO, DCM, TEA, -78 ^oC; (f) PPh_3CH_3Br, n-BuLi, THF, 86% (2 steps); (g) $BiBr_3$, MeCN, rt, 89%; (h) $(COCl)_2$, DMSO, DCM, TEA, -78 ^oC; (i) VinylMgBr (3 eq.), $ZnBr_2$ (1 eq.), THF, -78 ^oC to -30 ^oC,* ***60a*** *(56%) +* ***60b*** *(19%); (j) MOMCl, DIPEA, TEA, 98%. (k) Grubbs-Hoveyda catalyst (10 mol %), DCM, rt, 98%; (l) TBAF, THF, rt, 96%. (m) PCC, 4 Å MS, DCM, rt; (n) $NaClO_2$, K_2HPO_4, 2, 3-dimethylbuta-1,3-diene, t-BuOH/THF/H_2O (v/v/v 1:1:1), 10 ^oC to rt, 88% (2 steps); (o) EtOH, HOBT, EDCl, DIPEA, DCM, rt, 85%; (p) 5% HCl/EtOH, 0 ^oC, to rt; (q) AcCl, Na_2CO_3, EtOH, 0 ^oC to rt, 83% (2 steps); (r) $Pd(OAc)_2$, Et_3SiH, TEA, DCM, 0 ^oC to rt, 92%.*

Fukuyama's approach (*Angew. Chem. Int. Ed.* **2007**, *46*, 5734**)**[14a]

Fukuyama and co-workers from the Tokyo University have reported the synthesis of the oseltamivir phosphate **1** which is highlighted in Scheme 10. Pyridine was reduced with $NaBH_4$ and resultant amine protected with Cbz-Cl followed by the asymmetric cycloaddition of diene **64** and dienophile **65a** in presence of MacMillan's catalyst[14b] **65b** furnished mixture of aldehyde **66**. The mixture of aldehyde **66** without purification was oxidized to acid using Kraus conditions to give mixture of the acid. The resultant acid on bromolactonisation and recrystallization afforded lactone **67**. The lactone **67** on Cbz deprotection followed by protection with boc anhydride and oxidation with $RuO_2/NaIO_4$



Scheme 10

Reagents and conditions: *(a) $NaBH_4$, CbzCl, MeOH, -50 to -35 ^oC, 1 h; (b) Acrolein (**65a**), **65b** (100 mol%), MeCN, H_2O, rt, 12 h; (c) $NaClO_2$, $NaHPO_4.{}_2H_2O$, 2-methyl-2-butene, t-BuOH, H_2O, 0 ^oC rt, 1 h; (d) Br_2, $NaHCO_3$, DCM, H_2O, rt, 26% (4 steps); (e) H_2, Pd/C, EtOH, THF, Boc_2O rt, 2 h, 92%; (f) $RuO_2.nH_2O$ (10 mol %), $NaIO_4$, DCE, H_2O, 80 ^oC, 1.5 h, 86%; (g) NH_3, t-BuOH, THF, 0 ^oC, 95%; (h) MsCl, TEA, DCM, rt, 1 h, 91%; (i) Allylic alcohol, $PhI(OAc)_2$, mol. sieves (4 Å), toluene, 60 ^oC, 10 h, 88%; (j)*

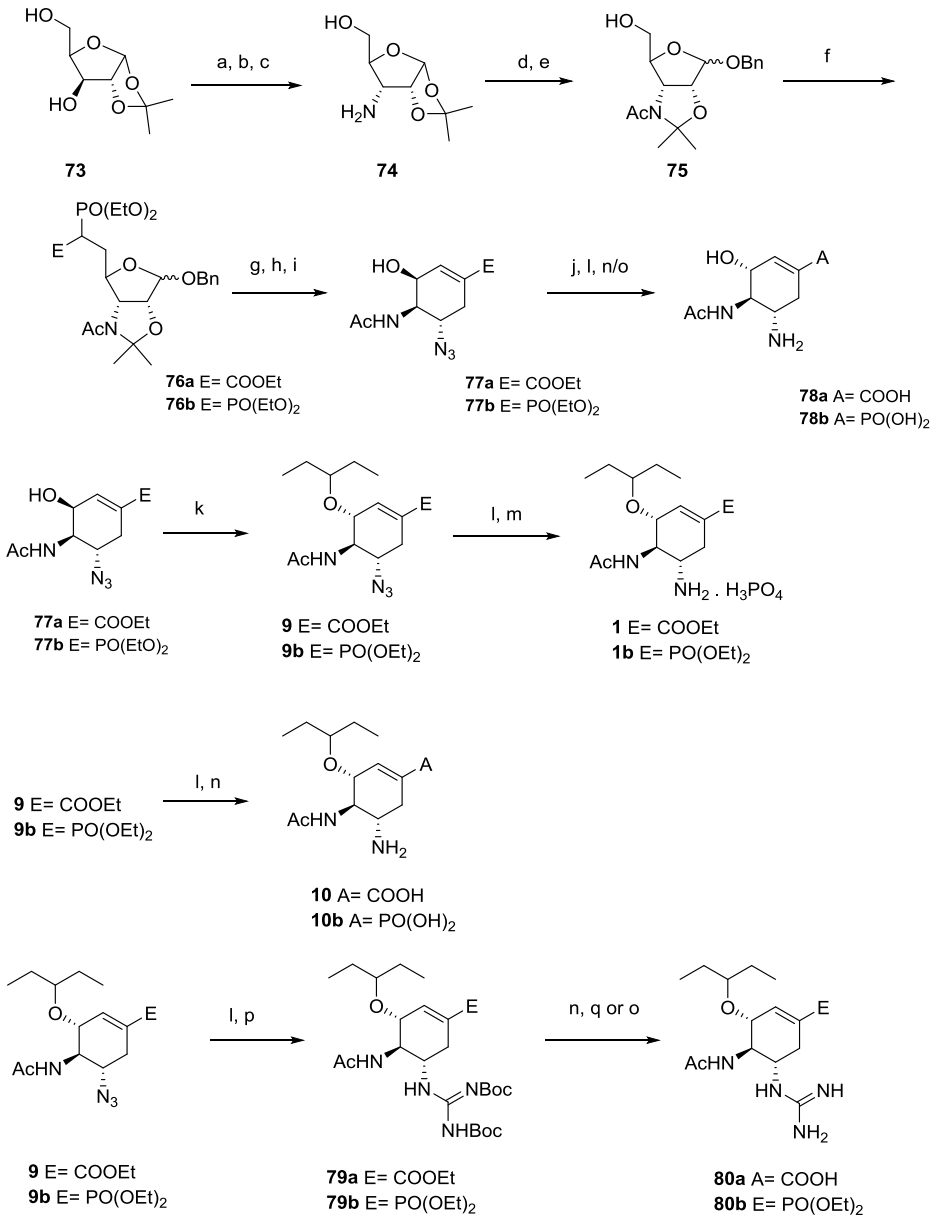
NaOEt, EtOH, 0 ^{o}C, 87%; (k) 3-Pentanol, $BF_3.Et_2O$, -20 ^{o}C, 62%; (l) TFA, DCM, 0 ^{o}C to rt; (m) Ac_2O, py, 88% (2 steps); (n) (i) Pd/C, PPh_3, 1,3-dimethylbarbituric acid, EtOH, reflux, 40 min; (ii) H_3PO_4, 76% (2 steps).

afforded the imide **68**. The imide **68** was reacted with ammonia to give compound **69**, which on mesylation and Hofmann rearrangement in presence of iodobenzene diacetate/allylic alcohol furnished carbamate **70**.[14c] The carbamate **70** was hydrolyzed in NaOEt/EtOH wherein it underwent HBr elimination and subsequently aziridine formation to provide aziridine **71**. The aziridine **71** was opened with 3-pentanol, followed by boc deprotection to give amine **72** and resultant amine **72** was acylated with acetic anhydride followed metallic reduction and H_3PO_4 treatment to furnish oseltamivir phosphate **1**.

Fang's approach (*J. Am. Chem. Soc.* ***2007****, 129, 11892*)[15a]

Fang and coworkers reported synthesis of tamiflu **1** from the D-xylose as starting material and provides phosphonate as congeners for the biological study as a bioisoetere for the carboxylate group in drug design. The compound **73** was obtained from the D-xylose by using the reported procedure,[15b] which on pivolyl protection and PDC oxidation led to ketone. The resultant ketone was treated with $NH_2OH.HCl$ followed by the LAH reduction to afford amino alcohol **74**. The amine **74** was acylated and on further treatment with benzyl alcohol in acidic condition and protection with DMP gave mixture of anomer **75**. The alcohol **75** was triflated, displaced with diethoxy phosphonoacetate/ tetraethyl methylene-*bis*-(phosphonate) followed by the intramolecular Horner-Wadsworth-Emmons, reaction to afford compounds **76a** and **76b** respectively. On reduction and Mitsunobu conditions[15c] followed by the acidic treatment, compounds **76a** and **76b** provided corresponding azides **77a** and **77b** respectively. The azides **77a** and **77b** were converted to **78a** and **78b** respectively following functional group transformations. The compounds **77a** and **77b** were subjected to the reaction with 3-pentyl trichoroacetamide for iso-pentyl introduction to afford **9** and **9b** respectively. The azides **9** and **9b** were subjected for reduction and then resultant amines were converted to

phosphate salt using H_3PO_4 to give **1** and **1b** respectively while azides **9** and **9b** on reduction followed by basic hydrolysis provided **10** and **10b** respectively.



Scheme 11

Reagents and conditions: *(a) Me_3CCOCl, pyridine, 0 ^oC, 8 h; 89%; (b)(i) PDC, Ac_2O, reflux, 1.5 h; (ii) $HONH_2$-HCl, pyridine, 60 ^oC, 24 h; 82%; (c) $LiAlH_4$, THF, 0 ^oC, then*

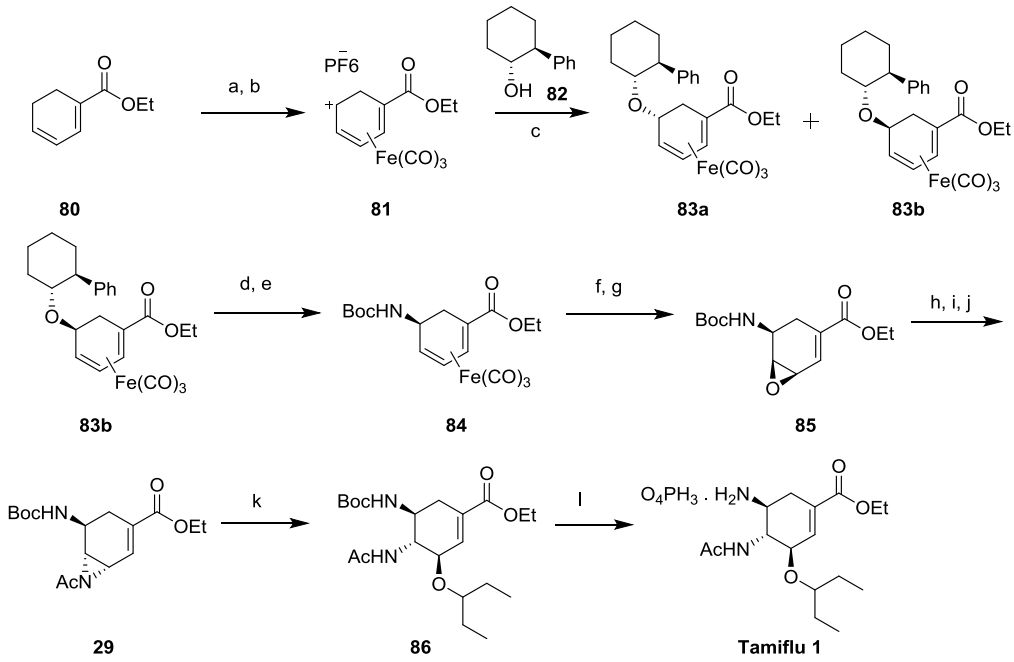
*reflux 1.5 h; 88%; (d) Ac_2O, pyridine, 25 ^oC, 3 h; HCl/1,4-dioxane (4 M), BnOH, toluene, 0-25 ^oC, 24 h; 85%; (e) 2, 2-Dimethoxypropane, toluene, catalyst p-TsOH, 80 ^oC, 4 h; 90%; (f) Tf_2O, pyridine, DCM, -15 ^oC, 2 h; $EtO_2CCH_2PO(OEt)_2$ or $H_2C[PO(OEt)_2]_2$, NaH, catalyst 15-crown-5, DMF, 25 ^oC, 24 h; 80% for **76a** and 73% for **76b**; (g) **76a**, H_2, Pd/C, EtOH, 25 ^oC, 24 h; NaH, THF, 25 ^oC, 1 h, 83%; or **76b**, NaOEt, EtOH, 25 ^oC, 5 h, 80%; (h) $(PhO)_2PON_3$, (i-Pr)N=C=N(i- Pr), PPh_3, THF, 25 ^oC, 48 h; (i) HCl, EtOH, reflux, 1 h; 83% for **77a** and 74% for **77b**; (j) Tf_2O, pyridine, DCM, -15 to -10 ^oC, 2 h; KNO_2, 18- crown-6, DMF, 40 ^oC, 24 h; 70% for **10a** and 71% for **10b**; (k) $Cl_3CC(=NH)OCHEt_2$, CF_3SO_3H, DCM, 25 ^oC, 24 h; 78% for **9** and 82% for **9b**; (l) H_2, Lindlar catalyst, EtOH, 25 ^oC, 16 h; 85% for **1b**; (m) H_3PO_4, EtOH, 40 ^oC, 1 h; 91% for **1**; (n) KOH, THF/H_2O, 0-25 ^oC, 1 h; 88% for **10** and 81% for **57a**; (o) TMSBr, $CHCl_3$, 25 ^oC, 24 h; aqueous NH_4HCO_3, lyophilization; 85% for **3** (as the ammonium salt), 72% for **80b** and 75% for **78b**; (p) N,N'-Bis(tert-butoxycarbonyl)thiourea, $HgCl_2$, Et_3N, DMF, 0-25 ^oC, 10-16 h; 78% for **79a** and 58% for **79b**; (q) TFA, DCM, 0 ^oC, 1 h; 88% for **80a**.*

The azides **9** and **9b** were reduced to corresponding amine and further treatment with *N, N'*-bis(*tert*-butoxycarbonyl)thiourea/$HgCl_2$ to afford **79a** and **79b** respectively, which were subjected for basic hydrolysis and boc deprotection with TFA to afford compounds **80a** and **80b** (Scheme 11).

Kann's approach (*Chem. Commun.* **2007**, 3183**)**[16a]

Kann's approach is based on the cationic iron carbonyl chemistry; the attractive chemistry of cationic complexes, which has ability to react with wide variety of the nucleophiles for C-C and C-X bond formation.[16b] The diene ester **80** was treated with di-iron nona-carbonyl followed by hydrogen abstraction with Ph_3CPF_6 to afford salt **81**. The resolution of the salt **81** was carried out by treating with chiral alcohol to provide diastereomeric mixture of **83a** and **83b** which were separated by PPTLC. The desired alcohol **83b** was converted to the urethane **84** on treatment with Boc-amine, which was decomposed with H_2O_2 and NaOH and followed by epoxidation of rich electronic double

bond to afford the epoxide **85**. The epoxide **85** was opened with NaN_3, hydroxy group was mesylated and subjected to Staudinger conditions to reduce azide and protection of resultant amine with acetic anhydride to give aziridine **29**. The opening of aziridine **29** was done using $Cu(OTf)_2$ followed by acidic treatment to provide the oseltamivir phosphate **1** (Scheme 12).



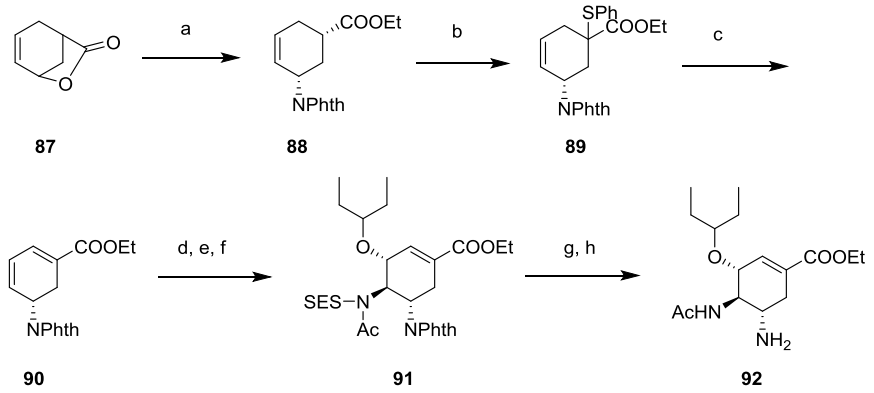
Scheme 12

Reagents and conditions: *(a) $Fe_2(CO)_9$, toluene, 55 ^oC, 86%; (b) Ph_3CPF_6, DCM, rt, 94%; (c)* ***82****, (i-Pr)$_2$NEt, DCM, 0 ^oC, 75%; (d) HPF_6, Et_2O, 0 ^oC, 94%; (e) BOC-NH_2, (i-Pr)$_2$NEt, DCM, 0 ^oC, 86%; (f) H_2O_2, NaOH, EtOH, 0 ^oC, 95%; (g) m-CPBA, DCM, -70 ^oC to rt, 95%; (h) NaN_3, DME/EtOH/H_2O, NH_4Cl, 0 ^oC, 95%; (i) MsCl, TEA, DCM, 0 ^oC, 68%; (j) (i) PPh_3, TEA, THF/H_2O, rt; (ii) Ac_2O, py, DCM, 0 ^oC, 65%; (k) $Cu(OTf)_2$, 3-pentanol, 0 ^oC, 48%; (l) ref 8a.*

Trost's approach (*Angew. Chem., Int. Ed.* **2008**, *47*, 3759**)**[17]

Trost and coworkers have reported shortest synthetic route for oseltamivir phosphate **1** so far using palladium catalyzed asymmetric allylic alkylation, desymmetrization and

rodium catalysed aziridination as shown in Scheme 13. The synthesis was started with the desymmetrization of the commercially available lactone **87** using trimethylsilylphthalimide as the nucleophile using palladium catalyst and Trost ligand followed by TMS group cleavage and esterification to furnish compound **88**. The compound **88** on treatment with $PhSSO_2Ph$ afforded the 1:1 mixture of the diastereomer of the thioester **89**, which was oxidized followed by elimination with DBU to furnish diene **90**. The diene **90** was treated with $[Rh_2(esp)_2]$, PhI $(OOCCMe_3)_4$ and $SESNH_2$ as nitrene source, followed by aziridine opening with $BF_3.Et_2O$/3-pentanol and acetylation to afford compound **91**. The compound **91** was subjected for SES group deprotection using TBAF and finally phthalimide group deprotection with NH_2NH_2 completed synthesis of oseltamivir free base **92** only in 8 steps with 30% overall yield.



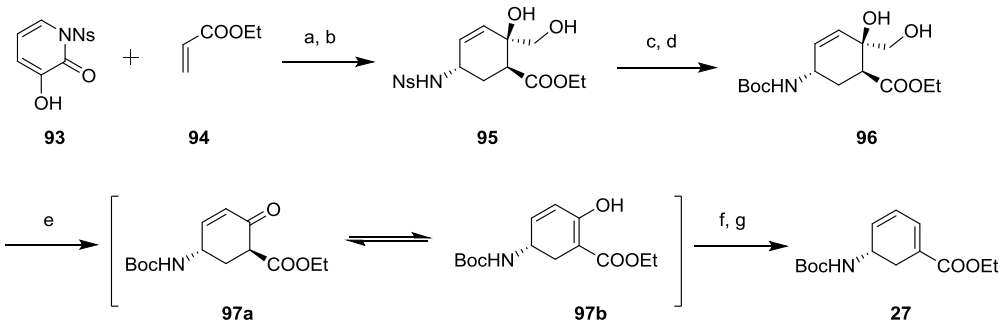
Scheme 13

Reagents and conditions: *(a) (i) Trimethylsilylphthalimide, $[(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2]$ (2.5 mol%), Trost ligand, THF, 40 ^oC; (ii) $TsOH.H_2O$, EtOH, reflux, 84%, 98% ee; (b) $PhSSO_2Ph$, KHMDS, THF; (c) (i) m-CPBA, $NaHCO_3$; (ii) DBU, toluene; (d) Du Bois rhodium catalyst, $SESNH_2$, $PhI(O_2CtBu)_2$, $[Rh_2(esp)_2]$, MgO, PhCl; (e) 3-Pentanol, $BF_3.Et_2O$, 75 ^oC, 65%; (f) Ac_2O, DMAP, py, MW, 1 h, 84%; (g) TBAF, THF, rt, 95%; (h) N_2H_4, EtOH, 68 ^oC, 100%.*

Okamura's approach (*Org. Lett.* **2008**, *10*, 815**)**[18]

Okamura and co-workers at Kagoshima University in Japan have reported a short

racemic synthesis of Corey's intermediate **27** which is summarized in Scheme 14. The synthesis started with base catalysed cycloaddition between pyridone **93** and ethyl acrylate **94** to give cycloadduct which on $NaBH_4$ reduction furnished cyclohexene **95**. The nosyl deprotection of **95** with thiophenol/K_3CO_3 and protection of the crude amine with boc anhydride furnished boc **96**. Diol **96** was cleaved with $NaIO_4$ followed by reduction to alcohol, which was mesylated using mesyl chloride in Et_3N as the base provided compound **27**.



Scheme 14

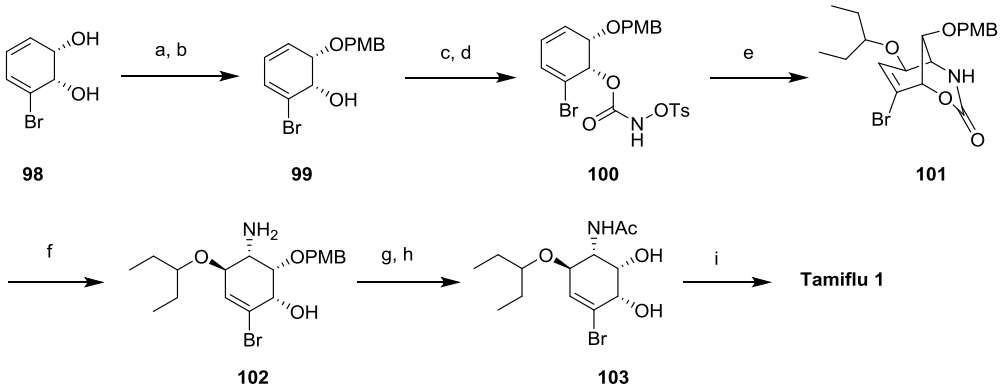
Reagents and conditions: *(a) NaOH, H_2O, rt, 24 h, 83%; (b) $NaBH_4$, THF, 0 ^oC, 2 h, 77%; (c) PhSH, K_2CO_3, MeCN, rt, 3 h; (d) $(Boc)_2O$, H_2O, rt, 24 h, 55% (2 steps); (e) $NaIO_4$, H_2O, 0 ^oC, 3 h; (f) $NaBH_4$, EtOH; (g) MsCl, TEA, DMAP, DCM, 33% (3 steps).*

Banwell's approach (*Tetrahedron Letters* **2008**, *49*, 7018**)**[19a]

Banwell's group has reported the chemoenzymatic formal total synthesis of tamiflu **1** using the diol **98** as starting material, which is summarized in Scheme 15. The diol **98** on *p*-methoxybenzaldehyde dimethoxyacetal treatement followed by DIBAL-H reduction gave the mono-protected diol **99** and regioisomer in the 6:1 ratio.

The hydroxyl derivative **99** on treatment with CDI and $NH_2OH.HCl$ followed by tosylation afforded bromo compound **100**. The tosyl derivative **100** was subjected to the aziridination using the $Cu(MeCN)_4PF_6$[19b] and carbamate was hydrolyzed using LiOH to afford amine **102**. The amine **102** was subjected to acetylation and acidic PMB

deprotection to provide compound **103**. The diol **103** was converted to oseltamivir phosphate **1** *via* appropriate reported reaction sequence.



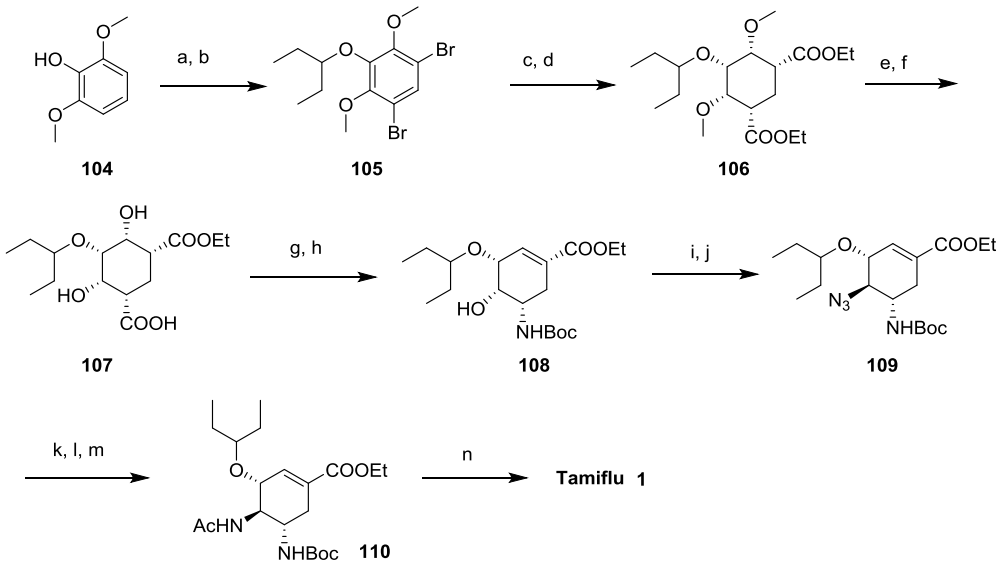
Scheme 15

Reagents and conditions: *(a) 4-Methoxybenzaldehyde dimethyl acetal, (+)-CSA, toluene, 0 ^{o}C, 1.5 h; (b) DIBAL-H, TEA, toluene, -78 ^{o}C to -30 ^{o}C, 5 h, 85% (2 steps); (c) (i) CDI, MeCN, 0 ^{o}C, 1 h; (ii) $NH_2OH.HCl$, imidazole, 0 ^{o}C to 18 ^{o}C, 16 h, 56% (at 88% conversion); (d) pTsCl, TEA, Et_2O, 0 ^{o}C to 18 ^{o}C, 16 h, 79%; (e) $Cu(MeCN)_4PF_6$, K_2CO_3, MeCN, 3-pentanol, 0 ^{o}C to 18 ^{o}C, 16 h, 43%; (f) LiOH, 1, 4-dioxane/water, 100 ^{o}C, 48 h, 85%; (g) AcCl, TEA, 0 ^{o}C to 18 ^{o}C, 1 h, 99%; (h) HCl, MeOH, 35%, 16 h, 90%; (i) ref 19b.*

Zutter's approach (*J. Org. Chem.* **2008**, *73*, 4895**)**[20]

The enzymatic desymmetrization approach has been developed by Zutter and coworkers, as shown in Scheme 16. The synthesis started from the cheap 2, 6-dimethoxy phenol **104**. The phenol **104** was etherified with pentyl mesylate using KO^{t}Bu and the resultant crude ether was subjected to bromination to give highly selective *di*-bromide compound **105**. *Di*- bromide compound **105** was converted into the compound **106** *via* Pd-catalysed ethoxycarbonylation and 5% Ru-Al_2O_3 catalysed aromatic reduction. The compound **106** was subjected to methyl ether deprotection with TMSCl and enzymatic desymmetrization using pig liver esterase (PLE) to afford the mono acid ester **107** in high 96-98% ee with excellent 98% yield. The mono acid **107** was subjected for Curtis rearrangement by

DPPA to give crude amine, which on boc protection and treatment with NaH provided unsaturated ester **108**. The unsaturated ester **108** was reacted with triflic anhydride and pyridine to convert hydroxy to good leaving group which was further reacted with NaN_3 to afford azide **109**. Synthesis of tamiflu **1** was accomplished *via* reduction of azide **109** to amine, amine acylation with acetic anhydride, boc deprotection in HBr condition to provide **110**. The **110** on salt formation with H_3PO_4 provided tamiflu **1**.



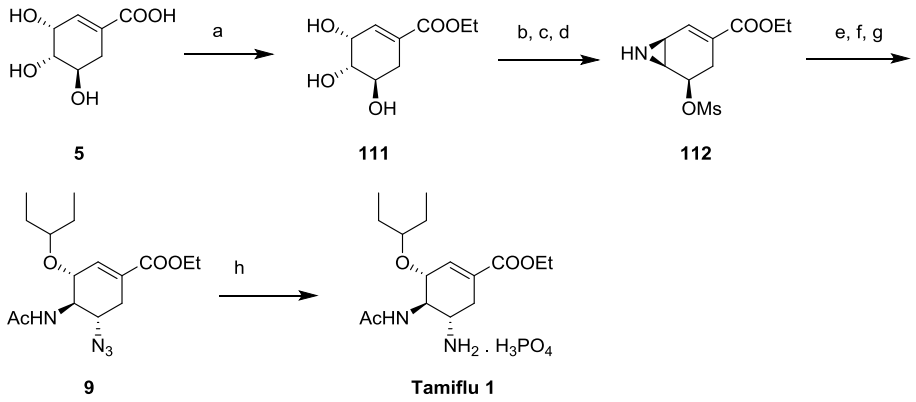
Scheme 16

Reagents and conditions: *(a) Pentyl mesylate, KOtBu, DMSO, 50 ^oC, quant.; (b) NBS, DMF, 0 ^oC to rt, 90%; (c) CO(10 bar), 0.5% $Pd(OAc)_2$, dppp, KOAc, EtOH, 110 ^oC, 20 h, 95%; (d) H_2 (100 bar), 5% Ru-Alox, EtOAc, 60 ^oC, 82%; (e) TMSCl, NaI, MeCN, cat H_2O, 97%; (f) PLE, pH 8 buffer, 98% crude, 96-98% ee; (g) DPPA, TEA, DCM, 40 ^oC, 81%; (h) $(Boc)_2O$, toluene, cat DMAP, rt, then cat NaH, toluene reflux; (i) Tf_2O, py, -10 ^oC, DCM, 85%; (j) NaN_3, rt, acetone-H_2O, 78%; (k) H_2, Ra-Co; (l) Ac_2O, TEA; (m) HBr-AcOH, EtOAc; (n) H_3PO_4, EtOH, 83%.*

Shi's 1st approach (*J. Org. Chem.* **2009**, *74*, 3970**)**[21a]

Shi *et al* have reported tamiflu synthesis from (-)-shikimic acid **5** as shown in the Scheme 17. The (-)-shikimic acid **5** was converted to unsaturated ester **111** in high yield using

known procedure. The unsaturated ester **111** was subjected to mesylation, NaN_3 treatment followed by Staudinger reduction conditions to afford aziridine **112**. The aziridine **112** was acetylated and resultant aziridine was opened with 3-pentanol/$BF_3.Et_2O$ followed by reaction with NaN_3 to furnish azide **9**. The azide **9** was converted to tamiflu **1** using usual reported procedure.



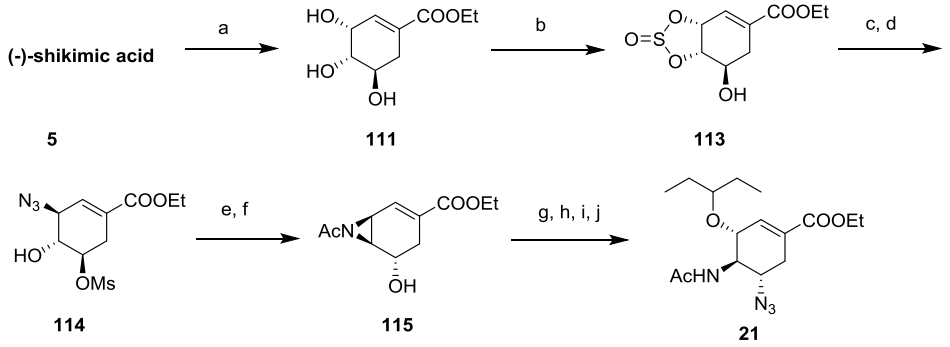
Scheme 17

Reagents and conditions: *(a) Ref 21b, 97%; (b) TEA, MsCl, DMAP, EtOAc, 0 ^oC, 93%; (c) NaN_3, Me_2CO/H_2O (5:1), 0 ^oC, 0.5 h, 98%; (d) PPh_3, THF, rt, 0.5 h; then TEA, H_2O, rt, 24 h, 84%; (e) Ac_2O, TEA, EtOAc, 0 ^oC, 0.5 h, 98%; (f) 3-Pentanol, $BF_3.Et_2O$, -8 ^oC to 0 ^oC, 1 h, 86%; (g) NaN_3, reflux, 8 h, EtOH/H_2O (5:1), 88%; (h) Ref 21c, 91%.*

Shi's II approach (*Tetrahedron Asymmetry* **2012**, *23*, 742**)**[22a]

Shi *et al* have reported the synthesis of oseltamivir phosphate **1** starting from (-)-shikimic acid **5** as shown in Scheme 18. The (-)-shikimic acid **5** was converted to ester **111** using reported procedure,[22b] which further, following reported reaction sequence afforded the compound **113**.[22c] The azide **114** was obtained from alcohol **113** *via* mesylation using mesylchloride/TEA followed by cyclic sulfide opening with NaN_3 selectively from the allylic position to provide azide **114**. The azide **114** was reduced under Staudinger reduction condition using PPh_3/K_2CO_3, followed by aziridine protection with acetic anhydride to afford hydroxy aziridine **115** in 90% yield over two steps. The aziridine **115** was opened with 3-pentanol/$BF_3.Et_2O$ followed by mesylation in MsCl/TEA/DMAP

conditions and further treatment with NaH to give aziridine. The resultant aziridine was subjected to opening with NaN_3/LiCl to get azide **21**. Azide **21** was converted to oseltamivir phosphate **1** in 91% yield according to reported procedure.[22d]



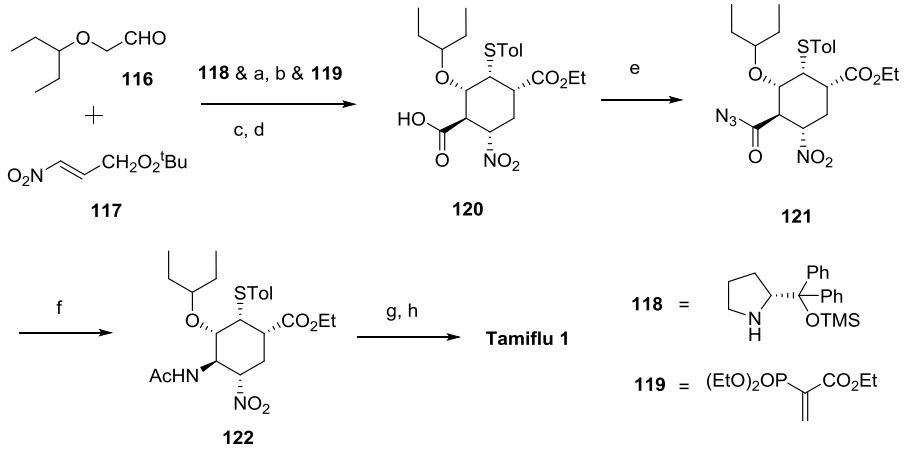
Scheme 18

Reagents and conditions: *(a) Ref 22e; (b) Ref 22f; (c) MsCl, Et_3N, DMAP, 0 ^oC, 1 h, EtOAc; (d) NaN_3, NH_4Cl, rt, 9 h, DMF/H_2O (5:1); (e) Ph_3P, K_2CO_3, rt, 3 h, EtOH, then H_2O, reflux, 3 h, EtOH; (f) Ac_2O, Et_3N, 0 ^oC, 0.5 h, DCM/H_2O (1:1); (g) $BF_3.OEt_2$, -8 ^oC, 1 h, 3-pentanol; (h) MsCl, Et_3N, DMAP, 0 ^oC, 1 h, EtOAc; (i) NaH, rt, 1 h, THF; (j) LiCl, NaN_3, 80 ^oC, 3 h, DMF.*

Hayashi's approach (*Angew. Chem., Int. Ed.* **2009**, *48*, 1304**)**[23a]

Hayashi's group established three "One Pot" operation approach towards tamiflu as outlined in Scheme 19. The aldehyde **116** was subjected to the asymmetric Michael addition using nitroalkene **117** and proline derivative catalyst **118** to afford nitroaldehydes as a mixture. The resultant mixture was subjected to Horner-Wardsworth-Emmons conditions with vinylphosphonate **119** to provide mixture of compounds which were treated with Cs_2CO_3 followed by treatment with the *p*-toluenethiol/Cs_2CO_3 to afford as only one diastereomer which on treatement in acidic condition provided acid **120**. The acid **120** was treated with oxalyl chloride followed by NaN_3 treatment to afford acyl azide **121**. The acyl azide **121** on Curtis rearrangement[23b] in presence of acetic anhydride/acetic acid afforded **122**. The compound **122** on reduction of nitro group,

ammonia bubbling and K_2CO_3/EtOH treatment gave oseltamivir phosphate **1**. Synthesis was completed in 9 reaction steps with excellent 57% overall yield.



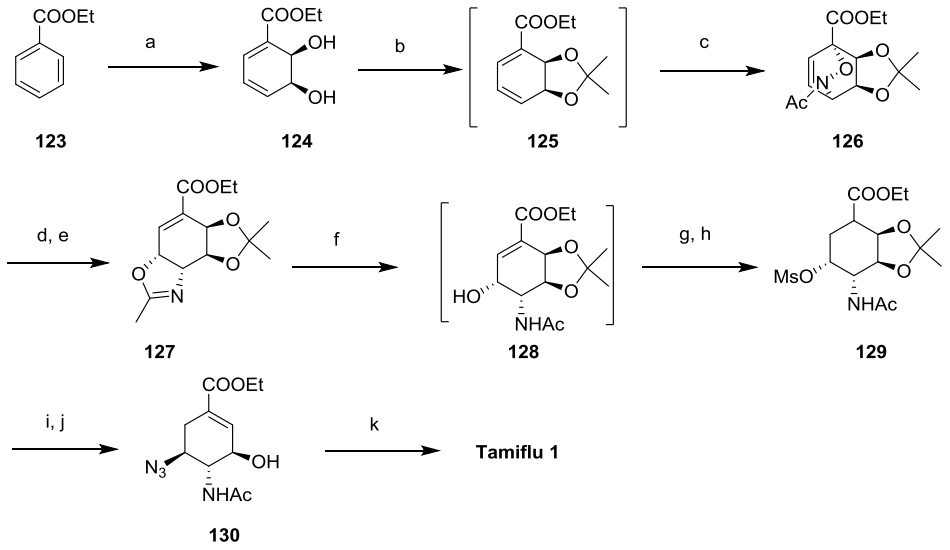
Scheme 19

Reagents and conditions: *(a)* ***118****, $ClCH_2COOH$ (20 mol%), PhMe, rt, 6 h, dr=7.8:1, ee=97%; (b) (i)* ***119****, Cs_2CO_3, PhMe, 0 ^oC, 3 h; (ii) Cs_2CO_3, EtOH, rt, 15 min.; (c) p-MeC_6H_4SH, Cs_2CO_3, EtOH, -15 ^{o} c, 36 h, 74% (4 steps); (d) TFA, DCM, 2h; (e) (i) $(COCl)_2$, DMF (cat.), DCM, 1 h; (ii) NaN_3, H_2O/acetone; (f) Ac_2O, AcOH, rt, 49 h; (g) Zn, TMSCl, EtOH, 70 ^oC, 2 h; (h) (i) NH_3; (ii) K_2CO_3, EtOH, 6 h, 82% (5 steps).*

Hudlicky's approach (*Angew. Chem., Int. Ed.* **2009**, *48*, 4229)[24a]

Hudlicky and coworkers have reported a symmetry based chemoenzymatic synthesis of oseltamivir phosphate **1**, which started from ethyl benzoate **123** as per described in the Scheme 20. Asymmetric oxidation of ester **123** was carried out with strain of *Escherichia coli* JM109 to afford diol **124.**[24b] Diol **124** was protected with DMP, followed by inverse electron-demand Diels-Alder reaction[18c] to afford compound **126**. The *N-O* bond of **126** was cleaved followed by mesylation in basic condition to furnish oxazoline **127**, which was treated with $CaCO_3$ followed by hydrogenation and mesylation to give compound **129**. Compound **129** on NaN_3 treatment gave azide followed by reaction with DBU

provided the advanced intermediate **129**, which on three additional steps was converted into oseltamivir phosphate **1**.



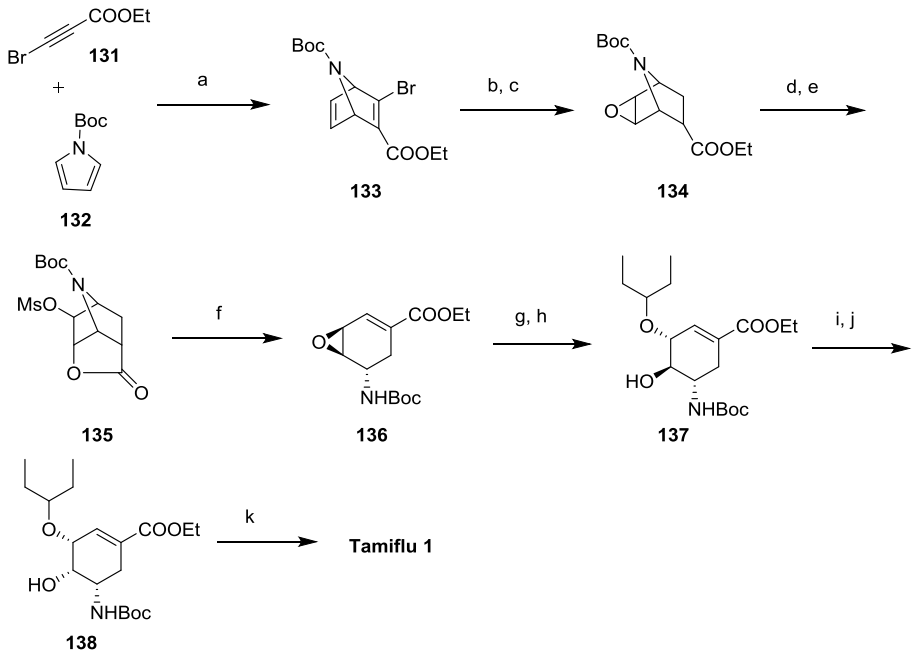
Scheme 20

Reagents and conditions: *(a) E.coli. JM 109 (pDTG601A, ca. 1gm/l); (b) Dimethoxy propane, TsOH, rt; (c) MeCONHOH, $NaIO_4$, MeOH, rt, 70%; (d) $[Mo(CO)_6]$, MeCN/H_2O (15:1), Δ, 75%; (e) MsCl, TEA, DMAP, DCM, rt, 54%; (f) $CaCO_3$, EtOH/H_2O (1:1), reflux, 72%; (g) H_2 (60) psi, Rh/Al_2O_3, 85% aq. EtOH, 95%; (h) Ms_2O, TEA, DCM, rt, 73%; (i) NaN_3, acetone:H_2O, rt, 86%; (j) DBU DCM, rt, 85%; (k) Ref 15a.*

Akio Kamimura's approach (*J. Org. Chem.* **2010**, *75*, 3133**)**[25]

Kamimura *et al* have described the synthesis of oseltamivir phosphate **1**, which started with the Diels-Alder reaction between *N*-boc-pyrrole **132** and bromoacetylene carboxylate **131** to afford the cyclo-adduct **133** as shown in the Scheme 21. The cyclo-adduct **133** was treated with *m*-CPBA followed by reduction in presence of base to furnish epoxy ester **134**. The ester **134** was hydrolyzed with 10% NaOH condition to afford hydroxy lactone, which on mesylation gave lactone **135**. The basic hydrolysis of lactone **135** followed by the esterification with EtI afforded epoxide **136** in 85% yield.

The epoxide **136** was reacted with LDA followed by epoxide opening with 3-pentanol to give hydroxyl compound **137**. The hydroxyl compound **137** was epimerized by oxidation-reduction sequence to furnish the known intermediate **138** for the tamiflu synthesis.



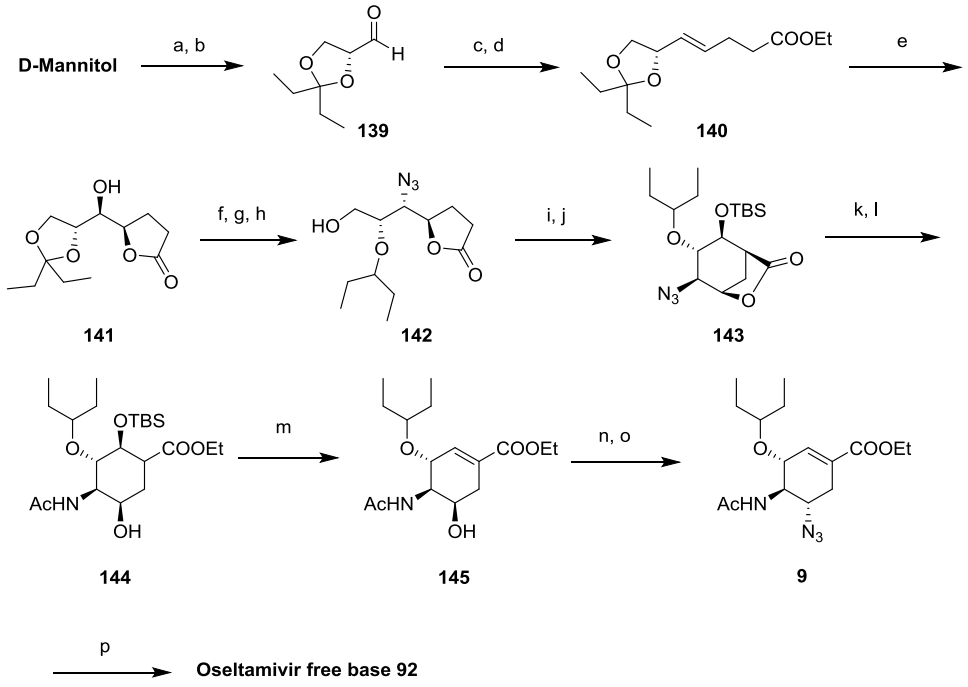
Scheme 21

Reagents and conditions: *(a) 90 ^{o}C, 39 h, 57%; (b) m-CPBA, Et_2O, 0 ^{o}C, 1 h; then 49 h, rt, 46%; (c) H_2, 10% Pd/C, 2-methylpyridine, rt, 50 h, 71%, endo/exo = 4:1; (d) 10% aq. NaOH, 0 ^{o}C, 30 min; then rt, 40 h, 89%; (e) MsCl, TEA, DCM, rt, 24 h, 95%; (f) (i) KOH, DMF, rt, 30 h; (ii) EtI, rt, 24 h, 85%; (g) (i) LDA HMPA, THF; (ii) −50 ^{o}C, 16 h, 62%; (h) 3-Pentanol, $BF_3.OEt_2$, −20 ^{o}C, 20 min, 54%; (i) Dess-Martin periodinane, DCM, rt, 2 h, 87%; (j) $NaBH_4$, MeOH, −50 ^{o}C, 30 min, 91%, dr = 3:1; (k) ref 20.*

Ko's approach (*J. Org. Chem.* **2010**, *75*, 7006–7009**)**[26a]

Ko and coworkers have reported a convenient enantiopure synthesis of tamiflu **1** from the D-mannitol as described in Scheme 22. The pentanide protection and oxidative cleavage provided the glyceraldehyde **139** from D-mannitol, which on Grignard reaction followed

by ortho ester Claisen rearrangement afforded ester **140**.[26b] The ester **140** on Sharpless asymmetric dihydroxylation gave lactone **141**, which on mesylation followed by NaN_3 treatment afforded azide and the pentanide was opened with BH_3.DMS/TMSOTf to afford compound **142**. Lactone **143** was derived from compound **142** via oxidation and TBDMSOTf treatment in Hunig's base to give lactone as single stereoisomer **143**. The lactone **143** was solvolyted followed by azide reduction and insitu amine protection provided amide **144**. The azide **144** was subjected to TBDMS deprotection and elimination to afford **145**, which on mesylation followed by NaN_3 treatment and Staudinger reduction provided oseltamivir free base **92**.



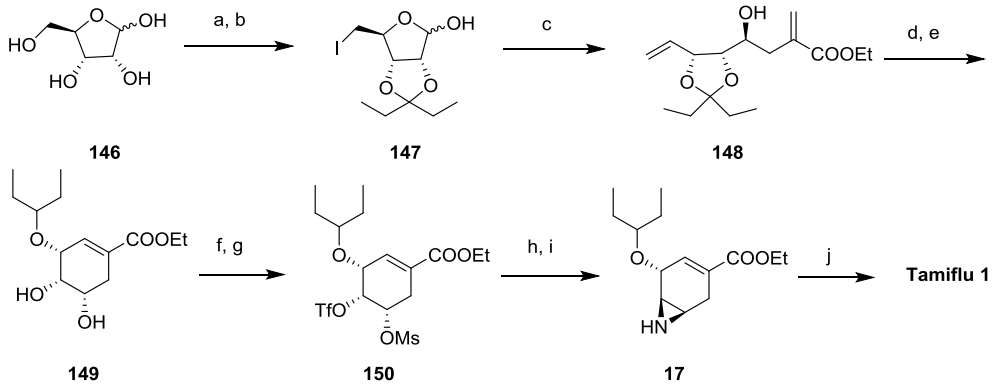
Scheme 22

Reagents and conditions: *(a) 3,3-Dimethoxypentane , CSA, DMF, 40 ^oC, 4 h; (b) KIO_4, $KHCO_3$, H_2O/THF (2.5:1), rt, 4 h; (c) Vinylmagnesium bromide (1 M in THF), 0 ^oC, 5 h, 43% (3 steps); (d) $MeC(OEt)_3$, propionic acid, 132 ^oC, 25 h, 85%; (e) AD-mix-β, t-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0 ^oC, 6 h, 93%; (f) MsCl, TEA, DCM, 0 ^oC, 4 h, 100%; (g) NaN_3, DMF, 120 ^oC, 49 h, 73%; (h) $BH_3.Me_2S$ (2 M in THF), TMSOTf, DCM, -50 ^oC, 30 min; then -20 to -30 ^oC, 22 h, 94%; (i) $(COCl)_2$, DMSO, DCM, TEA, -68 ^oC, 1 h, 92%; (j)*

TBDMSOTf, DIPEA, DCM, 0 ^{o}C, 25 min; then rt, 2 h, 76%; (k) LiBr, DBU, EtOH, 0 ^{o}C, 1 h, 96%; (l) H_2 (balloon), 10% Pd/C, Ac_2O, TEA, EtOAc, rt, 22 h, 96%; (m) DBU, $LiClO_4$, EtOH, reflux, 2.5 h, 62%; (n) MsCl, TEA, DCM, 0 ^{o}C, 1.5 h, 97%; (o) LiN_3, DMF, 90 ^{o}C, 7 h, 78%; (p) Ph_3P, THF/H_2O (5:1), 50 ^{o}C, 19 h, 98%.

Chai's approach (*Org. Lett.* **2010**, *12*, 60)[27a]

Chai and coworkers reported formal approach for tamiflu from the D-ribose **146**, which is outlined in Scheme 23. The pentanide protection of **146** in acidic condition, followed by Apple reaction conditions gave iodide **147**. The iodo compound **147** was subjected under Bernet-Vasella reaction conditions to furnish aldehyde, which on Reformatsky type allylation afforded diene **148**.[27b] The diene **148** was cyclised with Grubbs-Hoveyda catalyst followed by the selective opening of the pentanide was carried out with $AlCl_3$ to provide the desired hydroxy cyclohexene **149** in 63% yield. The less hindered hydroxy group of **149** was mesylated followed by treatment with Tf_2O to give compound **150**. Compound **150** was reacted with NaN_3 and on Staudinger reaction underwent azide reduction and *in situ* cyclisation to furnish aziridine **17**. The aziridine **17** is well known intermediate of the tamiflu **1** synthesis.



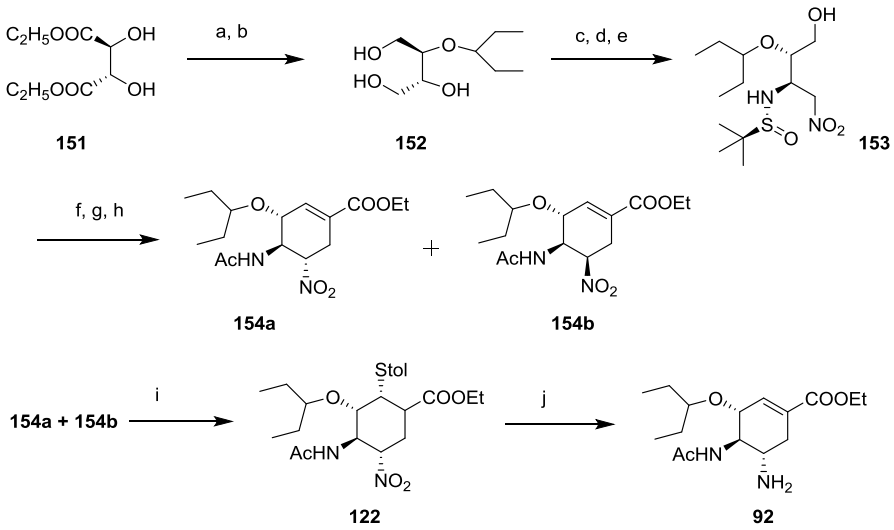
Scheme 23

Reagents and conditions: *(a) 3-Pentanone, HCl (1 M in MeOH), $HC(OMe)_3$, reflux, 6 h, 89%; (b) I_2, Ph_3P, PhMe/MeCN (1:1), reflux, 5 min, 90%; (c) (i) Zn, THF/H_2O (2:1), ethyl 2-(bromomethyl)acrylate, reflux, 3 h; (ii) reflux, 4 h, 78%, dr = 5.2:1; (d) Grubbs-*

Hoveyda catalyst (2 mol%), DCE, reflux, 2 h, 99%; (e) (i) $AlCl_3$,$CHCl_3$, sonication, 0 ^oC; (ii) Et_3SiH, -50 ^oC, 4 h; then 0 ^oC, 16 h, 67%; (f) MsCl, TEA, DCM, -20 ^oC, 40 min; then rt, 1 h, 92%; (g) Tf_2O, py, DCM, -10 ^oC, 30 min; then 0 ^oC, 20 min; (h) NaN_3, acetone/H_2O (9:1), rt, 4 h, 86% (2 steps); (i) Ph_3P, TEA, THF, rt, 17 h, 84%; (j) ref 2.

Lu's approach (*J. Org. Chem.* **2010**, *75*, 3125–3128) [28a]

Lu *et al* reported the synthesis of oseltamivir from the inexpensive and abundant diethyl tartrate as starting material as described in the Scheme 24.



Scheme 24

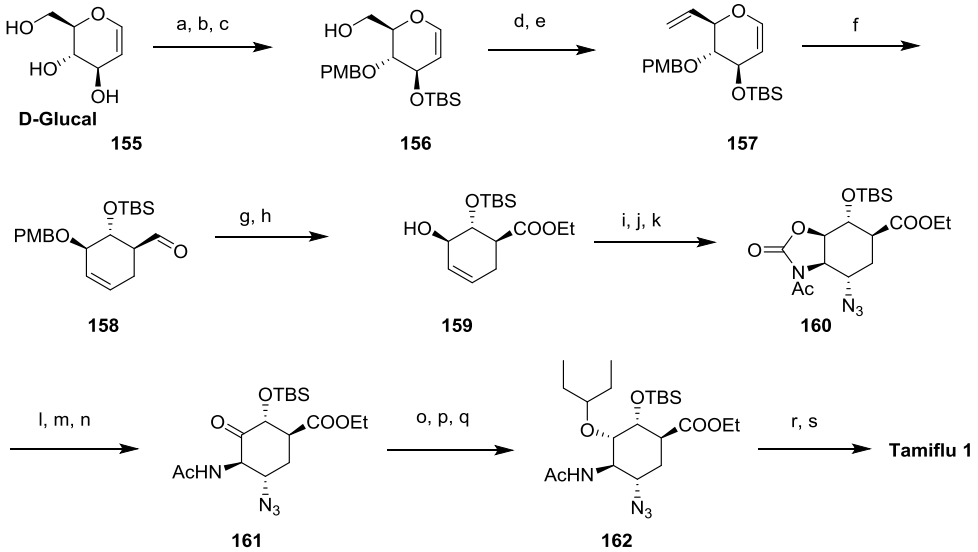
Reagents and conditions: *(a) 3, 3-Dimethoxypentane, p-TsOH, PhMe, reflux, 3 h, 96%; (b) (i) LAH, $AlCl_3$, Et_2O/DCM (1:1), -30 ^oC, 30 min; then 0 ^oC; (ii) rt, 1 h; then, reflux, 2 h, 88%; (c) $NaIO_4$, THF/H_2O (1:1), 95%; (d) $CuSO_4$, DCM, rt, 3 days, 73%; (e) $MeNO_2$, NaOH, 4 Å molecular sieves, rt, 24 h, 86%, dr = 10:1; (f) (i) HCl, MeOH, rt, 2 h; (ii) Ac_2O, MeOH, rt, 30 min, 83%; (g) IBX, EtOAc, reflux, 3 h, 100%; (h) DBU, LiCl, MeCN, -15 ^oC, 14 h; then 0 ^oC, 2 h, 61%, dr = 3:2; (i) p-MeC_6H_4SH, Cs_2CO_3, EtOH, -15 ^oC, 48 h, 95%; (j) (i) Zn (powder), TMSCl, EtOH, 70 ^oC, 2 h; (ii) NH_3 (gas), 0 ^oC, 15 min; (iii) K_2CO_3, rt, 6 h, 86%.*

Accordingly, diol **151** was protected as pentanide, followed by the reduction with

LAH/$AlCl_3$ to give hydroxyl compound **152**. The 1, 2-dinitro groups were installed by using the reaction sequence from diol **152** *via* $NaIO_4$ cleavage, imine formation using sulfinamide followed by the aza-Henry reaction[28b] to furnish nitro compound **153**. Further the key precursor was assembled from the nitro hydroxy compound **153** in next three-step reaction sequence to afford mixture of cyclohexene intermediates **154a** and **154b**. Mixture of **154a** and **154b** was treated with *p*-toluenethiol to afford Michael adduct **122** as single isomer. The reduction of nitro **122**, followed by the treatment with ammonia bubbling and K_2CO_3 treatment afforded intermediate **92**, which is known intermediate for oseltamivir phosphate **1**.

Chen and Liu approach (*Chem. Eur. J.* **2010**, *16*, 4533**)**[29a]

Chen, Liu and coworkers have described the synthesis of tamiflu **1** from the commercially available D-glucal **155** as described in the Scheme 25. The synthesis began with the D-glucal **155**, which was converted to acetal followed by the TBS protection and DIBAL-H reduction which regioselectively afforded into hydroxy compound **156**. The hydroxyl compound **156** was oxidized to corresponding aldehyde followed by Wittig



Scheme 25

Reagents and conditions*: (a) p-Anisaldehyde diethyl acetal, PPTS, DMF, 25 °C, 2 h; (b)*

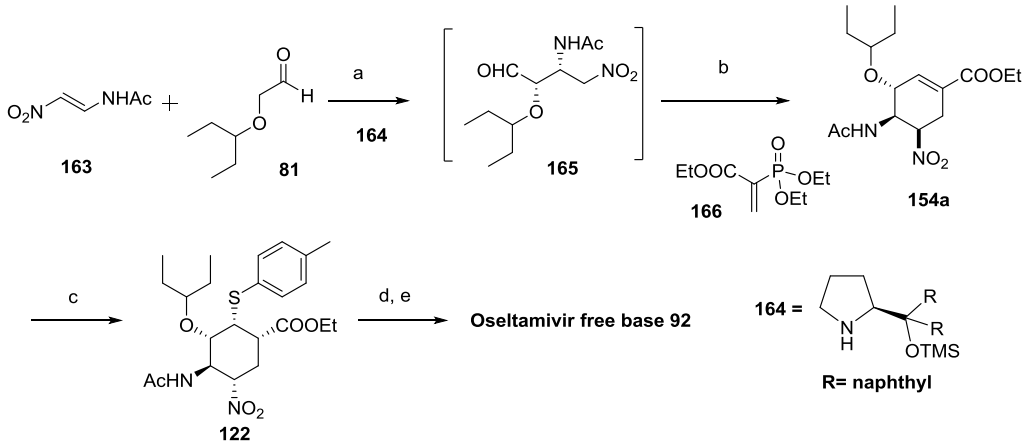
TBSCl, imd, DMAP, DMF, 25 ^{o}C, 3 h; (c) DIBAL-H, DCM, -15 to 0 ^{o}C, 2 h, 65% (3 steps); (d) Dess-Martin periodinane, DCM, 25 ^{o}C; (e) Methyltriphenylphosphonium bromide, n-BuLi, THF, -78 to 25 ^{o}C, 1 h, 67% (2 steps); (f) Diphenyl ether, 210 ^{o}C, 2 h, 88%; (g) (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, t-BuOH/H_2O, 25 ^{o}C, 2 h; (ii) EtI, K_2CO_3, DMF, 25 $^{\circ}$C, 3 h, 87% (2 steps); (h) DDQ, DCM/H_2O, 92%; (i) $Cl_3CCONCO$, K_2CO_3, DCM/MeOH, 87%; (j) (i) CDI, DCM, 25 ^{o}C, 2 h; NH_2OH.HCl, pyridine, 25 ^{o}C, 3 h; (ii)TsCl, TEA, Et_2O, 25 ^{o}C, 12 h, 77% (2 steps); (k) (i) $(CuOTf)_2$·toluene, K_2CO_3, MeCN, 25 ^{o}C, 12 h; (ii) $TMSN_3$, TBAF, THF, 0-25 ^{o}C, 3 h, 82%; (l) (i) AcCl, NaH, THF, 0-25 ^{o}C, 2 h; (ii) DBU, MeCN, 25 ^{o}C, 24 h, 67% (2 steps); (m) Cs_2CO_3 (0.1 equiv), EtOH, 25 ^{o}C, 3 h, 72%; (n) Dess-Martin periodinane, DCM, 25 ^{o}C, 2 h; (o) LiAlH(t-BuO)$_3$, THF, -20 to 25 ^{o}C, 3 h, 70% (2 steps); (p) MsCl, TEA, DCM, 0-25 ^{o}C, 3 h; (q) BF_3.Et_2O, 4 Å MS, 3-pentanol, -20 ^{o}C, 2 h, 52% (2 steps); (r) Ph_3P, THF/H_2O (1:1), reflux, 3 h, 90%; (s) 85% H_3PO_4, EtOH, 55 ^{o}C, 30 min, 85%.

olefination to lead to olefin **157**. The olefin **157** was subjected to Claisen rearrangement[29b] in a sealed tube at 200 ^{o}C to give compound **158**. Aldehyde **158** was converted to alcohol **159** by reaction sequence, Pinnick oxidation of aldehyde **158** to acid followed by esterification with ethyl iodide and DDQ mediated PMB ether cleavage to furnish ester **159**. Both nitrogen functionalities were installed by treating the ester **159** with isocyanate, CDI/NH_2OH followed by TsCl/TEA reaction[29c] to provide aziridine with $(CuOTf)_2$.toluene as catalyst and the second nitrogen was introduced under $TMSN_3$ in TBAF to afford azidoxazolidone **160**. The oxazolidone **160** *N*-was protected with AcCl/NaH followed by Cs_2CO_3 mediated hydrolysis and DMP oxidation of alcohol provided the ketone **161**. The ketone **161** was reduced with L-selectride and subjected to mesylation to obtain aziridine, which was opened using 3-pentanol in BF_3.Et_2O to give compound **162**. The azide **162** was reduced under Staudinger reaction conditions and acidic treatment furnished oseltamivir phosphate **1**.

Ma's approach (*Angew. Chem. Int. Ed.* **2010**, *49*, 4656)[30]

Ma *et al* have published the synthesis of oseltamivir free base **92** using asymmetric

addition of aldehyde **81** to nitrolefin **163** with an organocatalyst. The nitro-olefin **163** on the Michael addition in presence of proline-derived catalyst **164** gave Michael-adduct **165** in 5:1 syn/anti ratio. Aldehyde **165** without purification was treated with vinyl phosphonate **166** to provide cyclohexene **154a**. Further the crude material **154a** was subjected for addition of 4-methylthiophenol to afford compound **122** in 96% ee along



Scheme 26

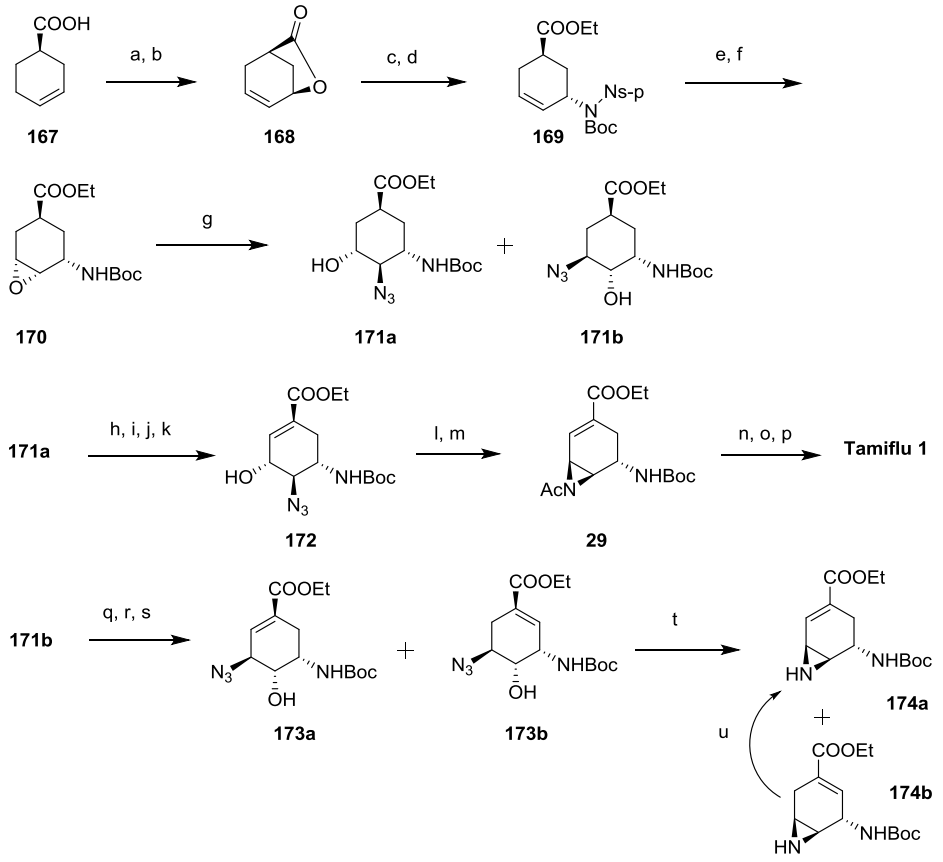
Reagents and conditions: *(a)* ***164*** *(10 mol%), PhCOOH (30 mol%), $CHCl_3$, 4Å MS, -5 ^oC, syn/anti ratio: 5:1; (b) Cs_2CO_3, 0 ^oC, 3 h; (c) p-MeC_6H_4SH, -15 ^oC, 48 h, 54% (3 steps), 96% ee; (d) Zn, TMSCl, EtOH; (e) K_2CO_3, MeOH, 85% (2 steps).*

with its epimer. The nitro compound **122** on reduction followed by 4-methylthiophenol elimination carried out using K_2CO_3/EtOH condition furnished oseltamivir as free base **92** (Scheme 26).

Raghavan's approach (*Tetrahedron* **2011**, *67,* 2044**)**[31a]

Recently Raghavan *et al* from IICT Hyderabad have reported an enantioselective synthesis of oseltamivir as described in the Scheme 27. The synthesis started from the cyclohexene acid **167**,[31b] which on iodolactonization, followed by the elimination with DBU gave iodo-lactone **168**. Lactone **168** was subjected for hydrolysis with K_2CO_3/EtOH, followed by Mitsunobu reaction to afford compound **169**. Epoxide **170**

was derived from the compound **169** by tosyl deprotection and α-carbamate epoxidation to give regiospecific epoxide **170** in good yield. The epoxide **170** was opened with $TMSN_3/Ti(iOPr)_4$ to provide mixture of alcohols **171a** and **171b**. The isomer **171a** was subjected for reaction with TMSCl, diphenyl diselenide and further treatment with H_2O_2 and DBU to provide azide **172**. The azide **172** on Staudinger reduction and acetylation with acetic anhydride afforded aziridine **29**. The aziridine **29** opening was carried out by 3-pentanol/BF_3.Et_2O conditions followed by boc deprotection furnished oseltamivir free base, which was converted to **1** by H_3PO_4 treatment. The undesired hydroxy azide **171b** *via* appropriate reaction sequence led to the desired aziridine **174a**.



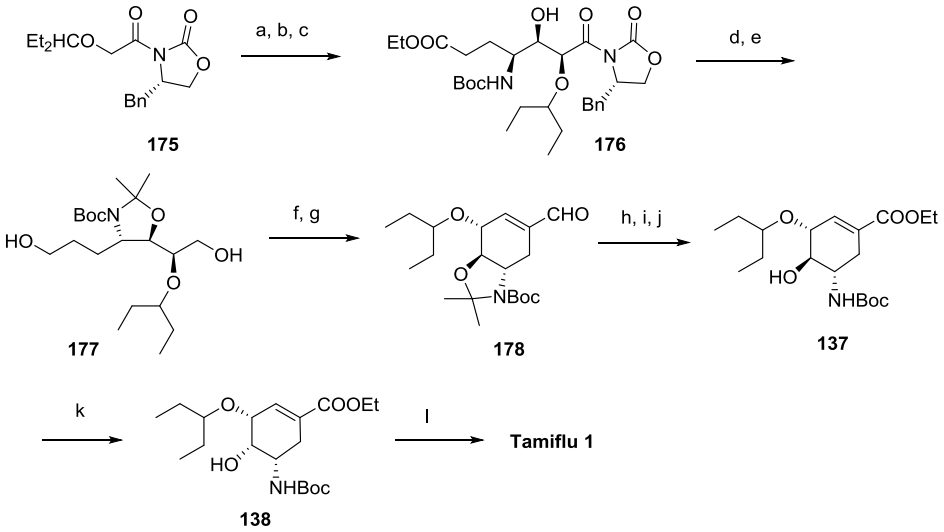
Scheme 27

Reagents and conditions: *(a) I_2, KI, $NaHCO_3$, H_2O, rt, 20 h, 93%; (b) DBU, toluene, reflux, 6 h, 92%; (c) K_2CO_3, EtOH, rt, 5 h, 90%; (d) BocNHNs-p, DEAD, PPh_3, toluene, -*

20 ^{o}C, 6 h, 89%; (e) 2-Mercaptoethanol, DBU, acetone, rt, 3 h, 91%; (f) m-CPBA, DCM, 0 ^{o}C, 6 h, 84%; (g) $TMSN_3$, $Ti(Oi\text{-}Pr)_4$, benzene, 5 to 0 ^{o}C, 2 h, 86%, ***171a/171b*** *3:1; (h) TMSCl, TEA, DCM, 0 ^{o}C, 95%; (i) LDA, PhSeSePh, -78 ^{o}C, 30 min, 74%; (j) 30% H_2O_2, py, DCM, rt, 30 min, 76%, regioisomer ratio 1:1.5; (k) DBU, toluene, 36 h, 65%, regioisomeric ratio: 3:1; (l) PPh_3, toluene, reflux, 3 h, 83%; (m) Ac_2O, DMAP, TEA, DCM, 0 ^{o}C to rt, 30 min, 87%; (n) 3-Pentanol, $BF_3.Et_2O$, -20 ^{o}C, 30 min, 70%; (o) TFA, DCM, rt, 1 h; (p) H_3PO_4 (1M in EtOH), rt to 50 ^{o}C; then 4 ^{o}C, 71%; (q) TMSCl, TEA, DCM, 0 oC, 94%; (r) LDA, PhSeBr, THF, -78 ^{o}C, 58%; (s) H_2O_2, py, DCM, rt, 30 min, 68%, regioisomeric ratio: 1:3; (t) PPh_3, PhMe, reflux, 3 h, 71%; (u) DBU, PhMe, 24 h, 58%,* ***174a*** *:* ***174b*** *ratio: 2:3.*

Saicic's approach (*Org. Biomol. Chem.*, **2011**, *9*, 6927)[32a]

Saicic and coworkers have reported the synthetic approach for oseltamivir phosphate **1** as delineated in Scheme 28.[25] The key transformations utilised in synthesis are two aldol reaction and Evans oxazolidinone to fix structural prerequisites. The first aldol was carried out between compound **175** and aldehyde using boron enolates to furnish single isomer **176**. The compound **176** on aminal protection followed by the reduction with



Scheme 28

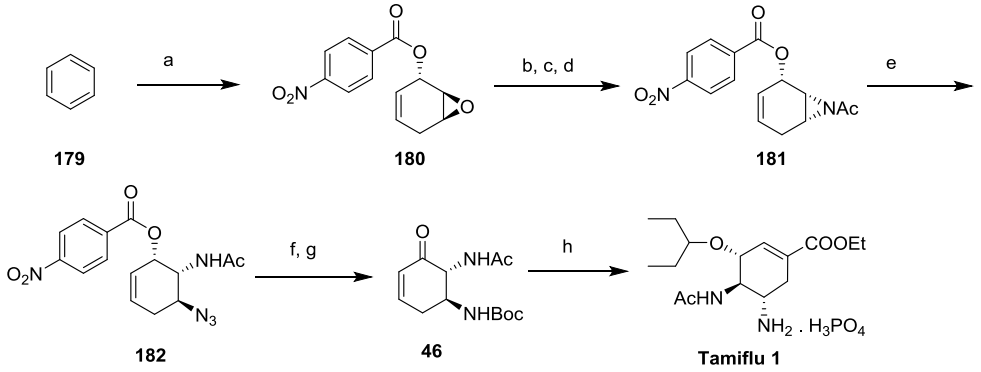
Reagents and conditions: *(a) n-Bu_2BOTf, TEA, DCM; (b) -78 to -20 ^{o}C; (c) H_2O_2,*

*MeOH; (d) 2,2-Dimethoxypropane, DCM; (e) $NaBH_4$, THF/H_2O, 65 ^oC, 4 h; (f) DMP, DCM, rt, 30 min; (g) Bn_2NH.TFA, toluene, rt , 3 h; (h) Oxone, DMF, rt, 3 h; (i) K_2CO_3, EtOH, H_2O; (j) EtI, DMSO, rt, 40 h; (k) Ref **25**, 54% over 3 steps; (l) Ref **32b**.*

$NaBH_4$ afforded diol **177**. Diol **177** was oxidized to dialdehyde and on intramolecular aldol cyclisation with dibenzylamine provided enal **178**. The enal **178** when treated with oxone, resulted in acid formation as well as deprotection of aminal. The acid was esterified under basic conditions to furnish intermediate **137**. Epimerization of **137** was carried out by using reported reaction sequence to afford compound **138**, which has been earlier utilized to obtain oseltamivir phosphate **1**.

Gunasekera's approach (*Synlett* **2012**, *23*, 573-576**)** [33a]

Gunasekera and coworkers have reported the formal synthesis of tamiflu **1** from the benzene **179** as starting material, which is outlined in Scheme 29. Benzene **179** was converted to optically pure epoxide **180** using reported three steps procedure in 21%



Scheme 29

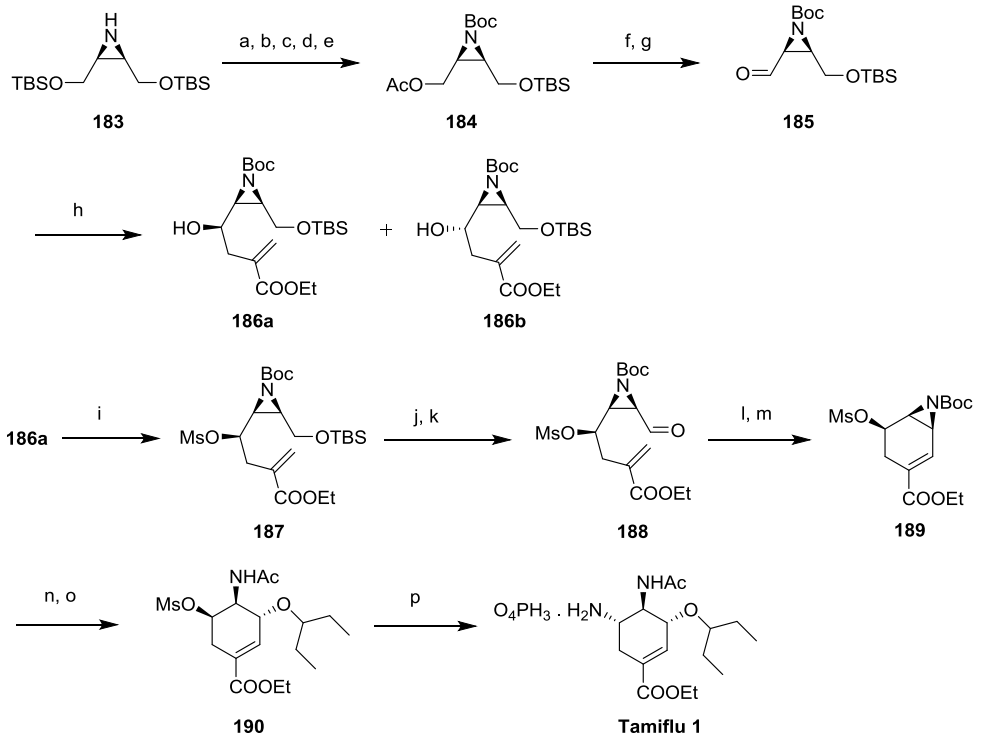
Reagents and conditions: *(a) (i) ref 33c; (ii) ref 33d; (b) NaN_3, $CeCl_3$, MeCN, 70 ^oC, 5 h, 74%; (c) PPh_3, MeCN, 70 ^oC, 3 h; (d) Ac_2O, TEA, py, 6 h, 76%; (e) $TMGN_3$, MeCN, 70 ^oC, 7 h, 83%; (f) (i) PPh_3, MeCN, 60 ^oC, 2 h; (ii) Boc_2O, TEA, DCM,, 0 ^oC, 3 h, 91%; (g) (i) NaOMe, MeOH, 26 ^oC, 1 h; (ii) DMP, DCM, 5 ^oC, 4 h, 86%; (h) ref 11.*

yield, which was subjected to epoxide opening with NaN_3 and further aziridine **181** was

obtained by using Ittah procedure.[33b] The aziridine **181** opening was done using tetramethylguanidinium azide to furnish azide **182** in excellent yield, which was reduced to amine and resultant amine on protection with boc anhydride followed by basic hydrolysis and DMP oxidation afforded Shibasaki's intermediate **46**. The Shibasaki's intermediate **46** could be easily converted into tamiflu **1** using reported procedure.

Kang's approach (*J. Org. Chem.*, **2012**, *77*, 8792**)**[34a]

Recently Kang *et al* have synthesized the oseltamivir phosphate **1** starting from the meso *cis*-aziridine **183** which is described in Scheme 30. The *cis*-aziridine **183** was prepared from the *cis*-butene diol using known reported reaction sequences.[34b] The aziridine was protected with boc anhydride followed by TBS deprotection using TBAF to afford hydroxy aziridine. The hydroxy aziridine was desymmertized using amino lipase and TBS protection furnished aziridine **184**. The acetate **184** was hydrolyzed using K_2CO_3/MeOH followed by oxidation with DMP to afford aldehyde **185**. The aldehyde



Scheme 30

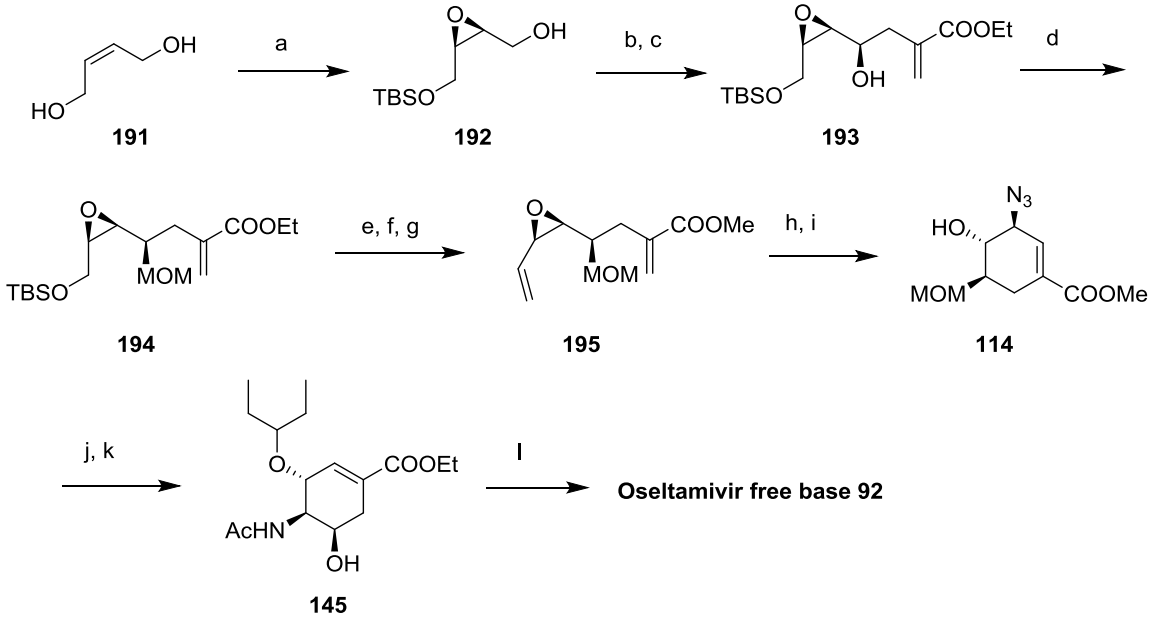
Reagents and conditions: *(a) Boc_2O, TEA, DCM, 88%. (b) TBAF, THF, 76%; (c) Amino lipase PS, vinyl acetate, n-hexane/THF, 68%; (d) BzCl, TEA, DMAP, 75%; (e) TBSCl, imd, DCM, 94%; (f) K_2CO_3, MeOH, 87%; (g) DMP, DCM, 87%; (h) Ethyl 2-(bromomethyl)acrylate, Zn, THF: aq. NH_4Cl 1:1* ***186a*** *(71%) +* ***186b*** *(25%); (i) MsCl, DCM, DMAP, 84%; (j) TBAF, THF, 72%; (k) DMP, DCM, 91%; (l) KHMDS, PPh_3MeBr, 63%; (m) Grubbs' 2nd gen. cat., DCM, 68%; (n) 3-Pentanol, $BF_3.Et_2O$, 84%; (o) (i) TFA ; (ii) Ac_2O, TEA, DCM, 93% (2 steps); (p) (i) NaN_3; (ii) H_2, Lindlar; (iii) H_3PO_4, 80% (3 steps).*

185 was treated with Zn and ethyl 2-(bromomethyl)acrylate to gave mixture of the alcohol **186a**:**186b** in the ratio 3:1. The major isomer **186a** was treated with MsCl/DMAP conditions to furnish **187**, which on TBS deprotection followed by oxidation led to aldehyde **188**. Aldehyde **188** was converted to cyclohexene **189** using Wittig olefination followed by ring closing metathesis (RCM) using Grubbs' second generation catalyst. The aziridine **189** was opened with 3-pentanol/$BF_3.Et_2O$ followed by *N*-Boc deprotection, to obtain amine and further acetylated with acetic anhydride to afford mesylate **190** in good yield. Final compound **1** was derived from the mesylate **190** by displacement with NaN_3 and further reduction of azide followed by H_3PO_4 treatment to give oseltamivir phosphate **1** 80% (3 steps).

Sudalai's approach (*Org. Biomol. Chem.,* **2012**, *10*, 3988**)**[35a]

Sudalai *et al* from NCL have described synthesis of oseltamivir free base **92** from the *cis*-butadiene **191** as starting material, which is outlined in the Scheme 31. The *cis*-butene diol **191** was subjected for the mono TBS ether formation followed by the Sharpless asymmetric epoxidation using (-)-DET to give epoxide **192** in 96% ee.[35b] Oxidation of alcohol **192** to aldehyde, followed by Barbier allylation afforded alcohol **193**. The resultant major alcohol **193** was protected with MOMCl to provide unsaturated ester **194**.[35c] Diene **195** was derived from unsaturated ester **194** *via* deprotection of TBS, primary hydroxy group oxidation of the resultant alcohol to aldehyde with IBX and the crude aldehyde converted to diene **195** using the Bestman-Ohira reagent followed by

selective reduction of alkyne with Pd/quinoline/pyridine/1-octene to obtain diene **195**. The cyclohexene core **114** was constructed using RCM in presence of Grubbs' 2nd generation catalyst and subsequent epoxide opening to give azide **114**. Azide **114** was subjected for the Staudinger reduction and acetylation of aziridine followed by aziridine ring opening with 3-pentanol/$BF_3.Et_2O$ in acidic condition to give cyclohexene ester **145**. Finally cyclohexene ester **145** was converted to oseltamivir free base **92** following the reported reaction sequences.



Scheme 31

Reagents and conditions: *(a) (i) TBSCl, imid, DCM, 0 ^oC, 73%; (ii) (+)-DET, Ti($^iPrO)_4$, TBHP, 4 Å MS, 96% ee; (b) TEMPO, $PhI(OAc)_2$, 75%; (c) Ethyl 2-(bromomethyl)acrylate, Zn, aq. Sat. NH_4Cl, THF, 10 h, dr = 4:1, 64%; (d) MOMCl, DIPEA, 90%; (e) TBAF, THF, 0 ^oC, 2 h, 88%; (f) (i) IBX, DMSO, 25 ^oC, 1 h; (ii) K_2CO_3, MeOH, Bestman-Ohira reagent, 82%; (g) H_2, py/1-octene/EtOAc, Lindlar's catalyst, 95%; (h) Grubbs' 2nd gene. catalyst, DCM, 90%; (i) NaN_3, NH_4Cl, DMF/EtOH/H_2O, 83%; (j) (i) PPh_3, PhMe, reflux, 3 h; (ii) Ac_2O, DMAP, TEA, DCM, 81% (2 steps); (k) (i) 3-Pentanol, $BF_3.OEt_2$; (ii) 2 N HCl, EtOH, 64%; (l) Ref 35c.*

1.1.4 References

1) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H. T.; Zhang, L. J.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc*. **1997**, *119*, 681; (b) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H. W.; Zhang, L. J.; Chen, X. W.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem*. **1998**, *41*, 2451; (c) McGowan, D. A.; Berchtold, G. A. *J. Org. Chem.* **1981**, *46*, 2381.

2) (a) Karpf, M.; Trussardi, R. *J. Org. Chem*. **2001**, *66*, 2044; (b) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

3) Kamps, Hoffmann and Preiser, *Influenza report* **2006**.

4) (a) Laver, W. G.; Bischofberger, N.; Webster, R. G. *Sci. Am.* **1999**, *280*, 78; (b) Laver, W. G.; Bischofberger, N.; Webster, R. G. *Perspect. Biol. Med.* **2000**, *43*, 173; (c) Farina, V.; Brown, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 7330; (d) Taubenberger, J. K.; Reid, A. H.; Fanning, T. G. *Virology* **2000**, *274*, 241.

5) (a) Davies, B. E. *J. Antimicrob. Chemother.* **2010**, *65*, 5; (b) Moscona, A. *The New Engl. J. Med.* **2005**, *353*, 1363.

6) Palese, P.; Tobita, K.; Ueda, M.; Compans, R. W. *Virology* **1974**, *61*, 397.

7) (a) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545; (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575; (c) Molin, H.; Pring, B. G. *Tetrahedron Letters* **1985**, *26*, 677; (d) Wan, X.; Doridot, G.; Joullie, M. M. *Org. Lett.* **2007**, *9*, 977.

8) (a) Yeung, Y. Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310; (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

9) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2006****, 128, 6312.*

10) (a) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2; (b) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070.

11) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Letters* **2007**, *48*, 1403.

12) (a) Alagiri, K.; Furutachi, M.; Yamatsugu, K.; Kumagai, N.; Watanabe, T.; Shibasaki, M. *J. Org. Chem.* **2013**, *78*, 4019; (b) Trost, B. M.; Braslau, R. *Tetrahedron Letters* **1989**, *30*, 4657; (c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406; Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745.

13) (a) Cong, X.; Yao, Z. J. *J. Org. Chem.* **2006**, *71*, 5365; (b) Mckillop, A.; Taylor, R. J. K.; Waston, R. J.; Lewis, N. *Synthesis* **1994**, *31;* (c) Dondoni, A.; Perrone, P. *Synthesis **1997**, 527;* (d) Cong, X.; Liao, Q. J.; Yao, Z. J. *J. Org. Chem.* **2004**, *69*, 5314; (e) Mengel, A.; Reiser, O. *Chem. Re*v. **1999**, *99*, 1191.

14) (a) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243; Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta.* **2006**, *39*, 79; (c) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.

15) (a) Shie, J. J.; Fang, J. M.; Wang, S. Y.; Tsai, K. C.; Cheng, Y. S. E.; Yang, A. S.; Hsiao, S. C.; Su, C. Y.; Wong, C. H. *J. Am. Chem. Soc. **2007**, 129, 11892*; (b) Suhara, Y.; Nihei, K. I.; Kurihara, M.; Kittaka, A.; Yamaguchi, K.; Fujishima, T.; Konno, K.; Miyata, N.; Takayama, H. *J. Org. Chem. **2001**, 66, 8760.* (c) Stigers, K. D.; Mar-Tang, R.; Bartlett, P. A. *J. Org. Chem.* **1999**, *64*, 8409.

16) (a) Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183; (b) Pearson, A. *J. In Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, **1995**, *12*, 637; Pearson, A. J. *Iron Carbonyl Compounds in Organic Synthesis*; Academia Press: London, **1994**.

17) Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3759.

18) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*,
815.

19) (a) Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron Letters* **2008**, *49*, 7018; (b) Shie, J. J.; Fang, J. M, Wong, C. H. *Angew. Chem, Int. Ed.* **2008**, *47*, 5788.

20) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895.

21) (a) Nie, L. D.; Shi, X. X.; Ko, K. H.; Lu, W. D. *J. Org. Chem.* **2009**, *74*, 3970; (b) Federspiel, M.; Fisher, R.; Henning, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266; (c) Nie, L. D.; Shi, X. X. *Tetrahedron: Asymmetry* **2009**, *20*, 124.

22) (a) Nie, L. D.; Ding, W.; Shi, X. X.; Quan, N.; Lu, X. *Tetrahedron: Asymmetry* **2012**, 23, 742; (b) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266; (c) Nie, L. D.; Shi, X. -X.; Quan, N.; Wang, F. F.; Lu, X. *Tetrahedron Asymmetry* **2011**, *22*, 1692; (d) Nie, L. D.; Shi, X. X. *Tetrahedron: Asymmetry* **2009**, *20*, 124; (e) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266; (f) Nie, L. D.; Shi, X. X.; Quan, N.; Wang, F. F.; Lu, X. Tetrahedron: Asymmetry **2011**, *22*, 1692.

23) (a) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304; (b) Naegeli, C.; Tyabji, A. *Helv. Chim. Acta* **1934**, *17*, 931; Barnum, E. R.; Hamilton, C. S. *J. Am. Chem. Soc.* **1942**, *64*, 540; (c) Press, J. B.; Hofmann, C. M.; Safir, S. R. *J. Org. Chem.* **1979**, *44*, 3292.

24) (a) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229; Hudlicky, T. *Pure Appl. Chem.* **2010**, *82*, 1785; (b) Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940; (c) Fabris, F.; Collins, J.; Sullivan, B.; Leisch, H.; Hudlicky, T. *Org. Biomol. Chem.* **2009**, *7*, 2619.

25) Kamimura, A.; Nakano, T. *J. Org. Chem.* **2010**, *75*, 3133.

26) (a) Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006; (b) Kametani, T.; Suzuki, T.; Sato, E.; Nishimura, M.; Unno, K. *J. Chem. Soc. Chem. Commun.* **1982**, 123; Merrer, Y. L.; Gravier-Pelletier, C.; Micas-Languin, D.; Mestre, F.; Dureault, A.; Depezay, J. -C. *J. Org. Chem.* **1989**, *54*, 2409.

27) (a) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60; (b) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.

28) (a) Weng, J.; Li, Y. B.; Wang, R. B.; Li, F. Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125. (b) Garcia Ruano, J. L.; Topp, M.; Lopez-Cantarero, J.; Aleman, J.; Remuinan, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407.

29) (a) Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Thanh, A.; Chen, P.; Liu, X. W. *Chem. Eur. J. A* **2010**, *16*, 4533; (b) Buchi, G.; Powell, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 4559; (c) Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587.

30) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4656.

31) (a) Raghavan, S.; Babu, V. S. *Tetrahedron* **2011**, *67*, 2044; (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem. In. Ed.* **1985**, *97*, 116; (c) Poll, T.; Sebezak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Letters* **1985**, *26*, 3095; (d) Corey, E. J.; Huang, H. C. *Tetrahedron Letters* **1989**, *30*, 5235.

32) (a) Trajkovic, M.; Ferjancic, Z.; Saicic, R. N. *Org. Biomol. Chem.* **2011**, *9*, 6927; (b) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895.

33) (a) Dinara S. Gunasekera *Synlett* **2012**, *23*, 573; (b) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271; (c) (i) Brandsma, L.; Vansoolingen, J.; Andringa, H. *Synth. Commun.* **1990**, *20*, 2165. (ii) Ruggles, E.; Deker, P.; Hondal, R. *Tetrahedron* **2009**, *65*, 1257; (d) Tan, Q. T.; Hayashi, M. *Org. Lett.* **2009**, *11*, 3314.

34) (a) Oh, H. S.; Kang. H. Y. *J. Org. Chem.* **2012**, *77*, 8792; (b) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Taga, T.; Miwa, Y. *Tetrahedron Letters* **1990**, *31*, 6663.

35) (a) Rawat, V.; Dey, S.; Sudalai, A. *Org. Biomol. Chem.* **2012**, *10*, 3988; (b) Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964; (c) Lu, X.; Wang, F. F.; Quan, N; Shi, X. X.; Nie, L. D. *Tetrahedron: Asymmetry* **2011**, *67*, 1692.

Section 2

Attempted synthesis towards Tamiflu

1.2.1 Present work

1.2.1.1 Objective

The thorough literature survey revealed that oseltamivir phosphate (Tamiflu®) has attracted attention of synthetic community due to its oral bioavailability, good toleration and active against both H5N1 as well as H1N1 viral strains. It has also revealed that the current manufacturing process for tamiflu used (-)-shikimic acid as a chiral starting material, which available as limited natural source, its lack of supply in the enantiopure form and synthesis is uneconomical. To the best of our knowledge the synthetic methods towards tamiflu and its analogue pass through the similar intermediate and common strating materials. As a substitute of (-)-shikimic acid chemists have reported tamiflu synthesis using L-serine, D-xylose, D-ribose, D-mannitol, L-methionine and D-tartarate as chiral starting materials.[1] Few reported synthesis has based on chiral induction methodologies from the achiral starting materials. The reported approaches are associated with usage of potentially hazardous chemicals such as sodium azide and include aziridine ring complexity. In this context, there is need to develop a synthetic strategy for Tamiflu, which starts from cheap and commercially available chemicals, free from use of hazards and explosive chemicals like sodium azide and it should avoid the aziridine ring complexity.

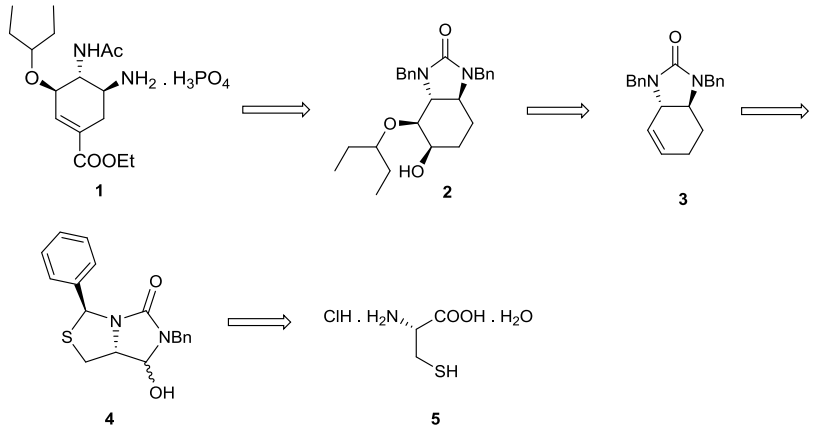
Our group over several years is engaged in the synthesis of biologically active compounds and developed practical, efficient and economically viable protocol for the synthesis of natural products such as D-(+)-biotin, camptothesin, venlafaxine *etc*. In continuation of this synthesis of oseltamivir phosphate was undertaken.

In the present section, chiral pool strategy for tamiflu synthesis is described. The novel route involved common intermediate alcohol **4**, which already has explored for synthesis of D-(+)-biotin using stereospecific amidoalkylation protocol.

1.2.1.2 Retrosynthetic analysis

Taking account of own developed stereospecific amidoalkylation methodology which provides the vicinal diamine exclusively in *trans* fashion that as per the structural requirement of neuraminidase inhibitory drug **1**.

According to our retrosynthetic plan tamiflu **1** could be obtained from alcohol **2** which could be derived from the crucial intermediate **3**. The intermediate **3** can be derived from compound **4** by proper chemical transformations. The compound **4** can be easily prepared from the L-cysteine hydrochloride salt **5** using reported procedure (Scheme 1).



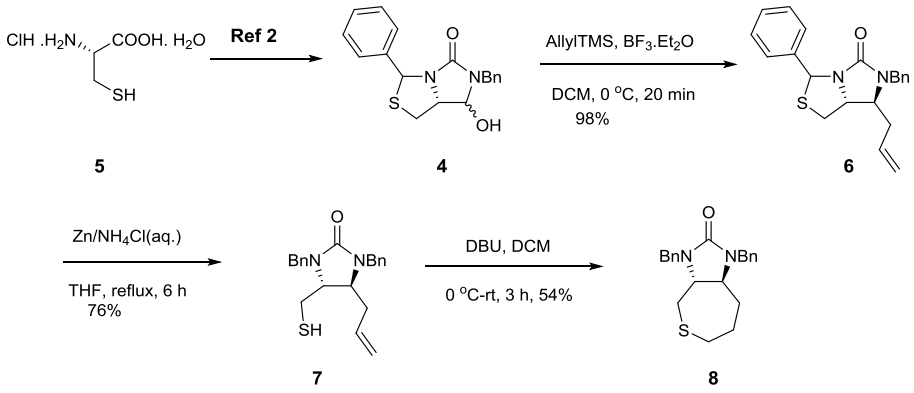
Scheme 1 Reterosynthetic analysis of tamiflu **1**

1.2.1.3 Results and discussion

The hydroxy **4** was easily prepared from the L-cysteine hydrochloride salt **5** using reported procedure.[2] The allyl compound **6** was prepared by using our own developed stereospecific amidoalkylation from alcohol **4** intermediate using allyltrimethylsilane and $BF_3.Et_2O$ at 0 ^oC in excellent yield. The allylic compound **6** was subjected to C-S bond cleavage using zinc dust and ammonium chloride saturated aq. solution at refluxing in THF for 6-7 h to afford thiol **7**. The crude thiol **7** was with DBU in DCM at 0 ^oC to room temperature resulted into the cyclic sulfide **8** in low yield 54%. The yield of cyclic sulfide **8** was improved by using reported method on thiol **7**, which was stirred in water to provide cyclic sulfide **8** in 81% yield.[3]

The disappearances of band in IR 1640 cm^{-1} spectrum of olefin clearly supported to formation of sulfide **8**. The ^1H NMR spectrum showed peaks at 2.97 (dd, J = 12, 4 Hz, 1H), 2.60-2.53 (m, 1H), 2.58-2.54 (m, 1H) and 2.26 (dd, J = 12, 8 Hz, 1H) were assigned protons of CH_2-S-CH_2 linkage and peaks at 2.12-2.15 (m, 1H), 1.96-1.93 (m, 1H), 1.78 – 1.71 (m, 1H) and 1.43-1.36 (m, 1H) ppm were revealed to four protons. The ^{13}C NMR spectrum showed peaks at 46.6, 46.1, 32.1, 29.9, 28.9 and 28.3 ppm were revealed for six

methylene carbons. The HRMS was observed at 375.1497 confirmed the molecular formula $C_{21}H_{24}N_2OS$ of sulfide **8** (Scheme 2).

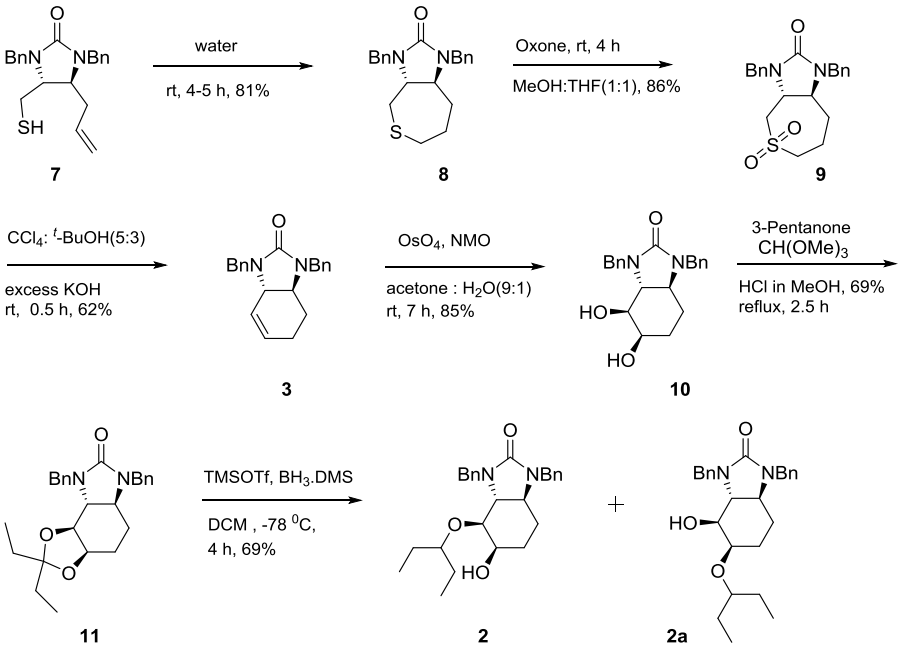


Scheme 2 Synthesis of sulfide **8**

The cyclic sulfide **8** was oxidized to sulfone **9** using oxone in MeOH:THF in 84% yield as white solid.[4] IR spectrum of sulfone **9** showed the peaks at 1704 cm^{-1} indicating the urea carbonyl. The ^1H NMR spectrum of **9** showed peaks at δ 4.76 (d, *J*=16Hz, 1H), 4.67 (d, *J* = 16Hz, 1H), 4.22 (d, *J*= 12Hz, 1H) and 4.15 (d, *J*=12 Hz, 1H) ppm corresponding to four protons of benzylic –CH2 groups. In ^{13}C NMR spectrum of **9** peak at δ 160.2 ppm indicated urea carbonyl and its DEPT spectrum showed peaks at δ 58.4, 53.4, 46.2, 46.0, 29.6 and 18.7 ppm corresponded for six $–CH_2$ carbons. The peak was observed at 407.1398 in HRMS spectrum confirmed molecular formula $C_{21}H_{24}N_2O_3S$ of sulfone **9**. The melting point of the sulfone **9** was recorded at 155-157 ^oC.

Next plan was to obtain intermediate **3**, accordingly sulfone **9** was subjected to Ramberg-Backlund reaction using KOH flakes in CCl_4: *t*BuOH to furnish olefin **3** as a white solid in 62% yield.[5] The appearance of band in IR at 1629 cm^{-1} strongly supported the formation of cyclohexene **3**. The characteristic peaks at δ 6.08 & 6.75 ppm in ^1H-NMR spectrum of **3** corresponded to double bond protons. The ^{13}C NMR spectrum showed peaks at δ 127.3 and 124.0 ppm which were assigned for olefin carbons. In ^{13}C DEPT NMR spectrum of **3** peaks observed at δ 47.4 and 47.2 ppm corresponding for methylene carbons of benzyl groups and peaks at δ 25.1 and 24.5 ppm assigned for two $–CH_2$ carbons of cyclohexene. The HRMS spectrum showed peak at 341.1619 which confirmed

molecular formula $C_{21}H_{22}N_2O$ of olefin **3**. The melting point of olefine **3** was recorded at 75-77 ^oC (Scheme 3).



Scheme 3 Synthesis of regioisomer **2** & **2a**

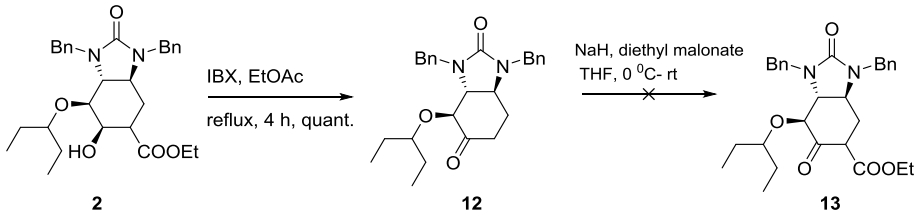
The olefin **3** was subjected to dihydroxylation using OsO_4 to give diol **10** in 85% yield.[6] The disapperance of peak at 1629 cm^{-1} in IR spectrum strongly supported to diol formation. The disapperance of peaks at δ 6.08 & 6.75 ppm in ^1H NMR spectrum was indicated dihydroxylation of olefin **3** to provide diol **10**. The ^{13}C NMR specturm showed peaks at δ 73.7 and 70.1 ppm for two–CHOH carbons and its ^{13}C DEPT spectrum showed peaks at δ 28.3 and 25.5 ppm corresponding to cyclohexane $–CH_2$ carbons. The peak at 375.1676 in HRMS confirmed molecular formula $C_{21}H_{24}N_2O_3$ of diol **10**.

The diol **10** was subjected to pentanide protection using 3-pentanol/HCl in MeOH (1M solution) to afford pentanide **11**.[7] The disaaperance of band at 3369 cm^{-1} in IR spectrum indicating the diol protection. The peaks at δ 1.00 - 0.50 (m, 6H) ppm in ^1H NMR spectrum corresponded to methyl protons which strongly supported formation of pentanide **11**. The ^{13}C NMR spectrum of **11** showed the peak at δ 163.6 ppm for urea carbonyl carbon and peak at δ 113.1 ppm one quaternary carbon. The ^{13}C DEPT NMR spectrum peaks observed at δ 26.9, 26.3, 25.4 and 22.9 ppm corresponding to four

methylene carbons. The peak in HRMS at 443.2303 which confirmed molecular formula $C_{26}H_{32}N_2O_3$ of pentanide **11**.

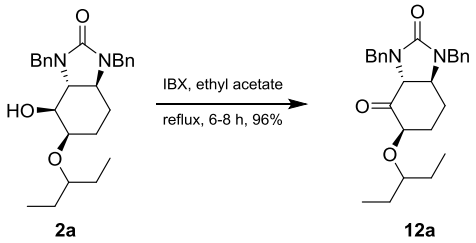
The pentanide **11** was subjected to BH_3.DMS and TMSOTf treatment at -78 ^oC to furnish alcohols **2** and **2a** in 1:1 ratio with 69% yield.[8] The presence of band in IR at 3385 cm^{-1} indicated presence of hydroxy functionality. The ^1H NMR spectrum showed peaks at 0.94 - 0.75 (m, 6H) ppm for six protons of methyl group and peaks at δ 1.84 - 1.35 (m, 6H) ppm strongly supported presence of isopentyl group. The ^{13}C NMR spectrum at 163.3 ppm for urea carbonyl carbon while its DEPT spectrum showed the peak at δ 9.7 and 9.5 for methyl group and peaks at δ 80.6, 75.8, 65.4, 62.5 and 53.4 ppm corresponding to five –CH carbons which confirmed formation of **2**. In HRMS spectrum peak observed at 423.2639 confirmed molecular formula $C_{26}H_{34}N_2O_3$ of pentanide.

The desired alcohol **2** was subjected to oxidation using IBX in ethyl acetate at reflux condition to give keton **12** in quantitative yield. The presence of strong band at 1713 cm^{-1} and disappearance of band at 3385 cm^{-1} in IR spectrum strongly supported for oxidation of alcohol **2**. The ^1H NMR spectrum was showed the peak at 1.47 - 1.39 (m, 4 H) ppm for and peaks at 0.95 (t, J = 7.6 Hz, 3H) and 0.85 - 0.80 (m, 3H) ppm were revealed protons of iso-pentyl group. The peaks at 201.1 and 162.2 ppm in ^{13}C NMR indicating presence of ketone and urea functionality and its DEPT spectrum showed peaks at 82.5, 79.3, 64.1 and 60.5 ppm corresponding to four –CH carbons. The HRMS showed peak at 443.2302 which confirmed the molecular formula $C_{26}H_{32}N_2O_3$ for the ketone **12**.



Scheme 4 Attempt towards synthesis of ketone ester **13**

The ketone **12** was subjected to different reaction conditions like sodium hydride/DBU/^{t}BuOK in THF and diethyl carbonate/dimethyl carbonate and also by stepwise manner using Vilsmeyer-Hack formylation but failed to achieve the target compound **13** (Scheme 4).



Scheme 5 Synthesis of Ketone **12a**

The Ketone **12a** was obtained by oxidation of alcohol **2a** using IBX refluxing in ethyl acetate (Scheme 5). The stereochemistry of ketone **12a** was fully assigned by using 2D-NMR experiments like COSY, NOESY, HSQCGP and HMBC. Partial COSY indicating correlation of the ring protons, which suggested confirmation of compound **12a**.

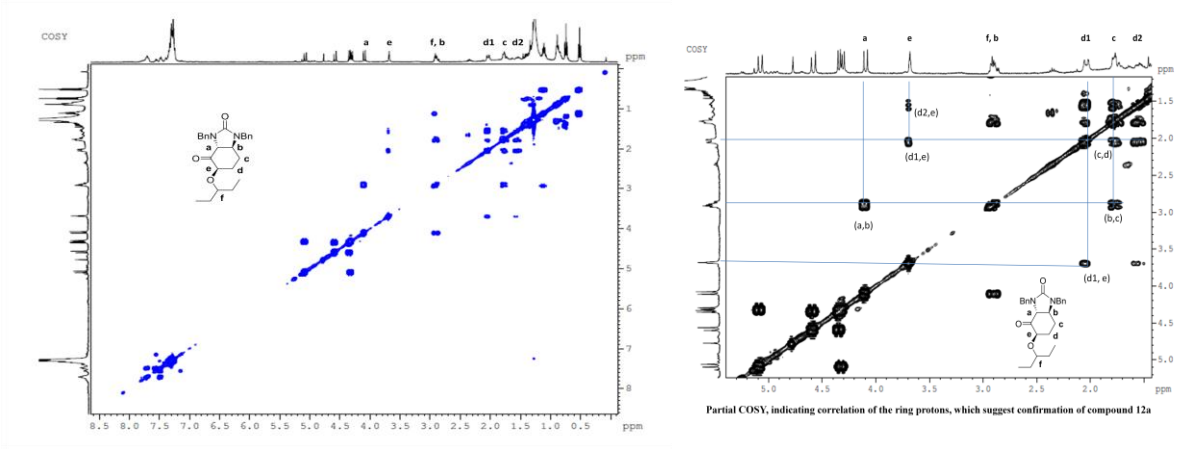


Fig 1a Full COSY and Partial COSY of **12a**

The absence of NOESY cross peak between a and e proton of **12a** shows *trans* correlation.

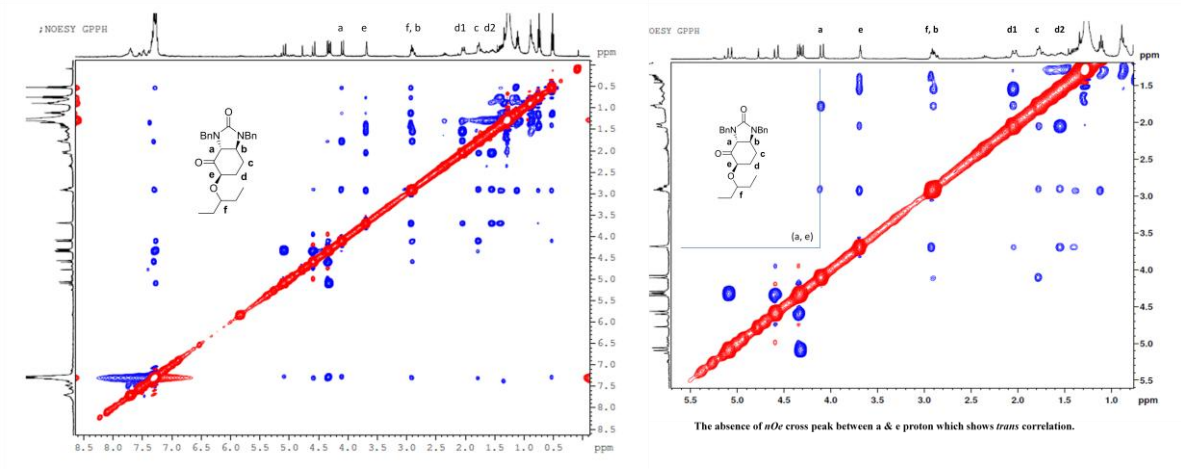


Fig 1b Full NOESY and Partial NOESY of **12a**

Partial HSQCGP of CHs which are attached to nitrogen (N) and oxygen (O) nuclei of **12a**.

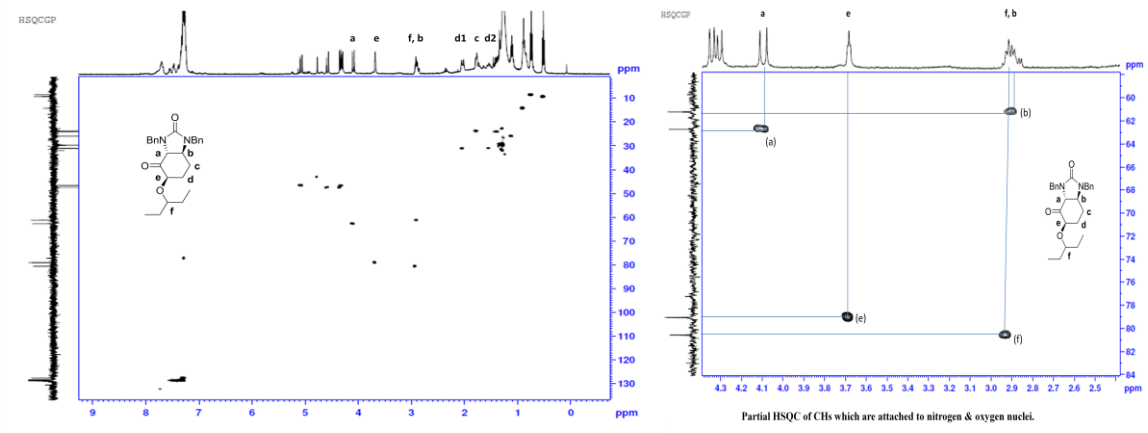


Fig 1c Full HSQCGP and Partial HSQCQP of **12a**

Partial HMBC of **12a** showing weak two bond heteronuclear correlation of a and e proton with carbonyl carbon.

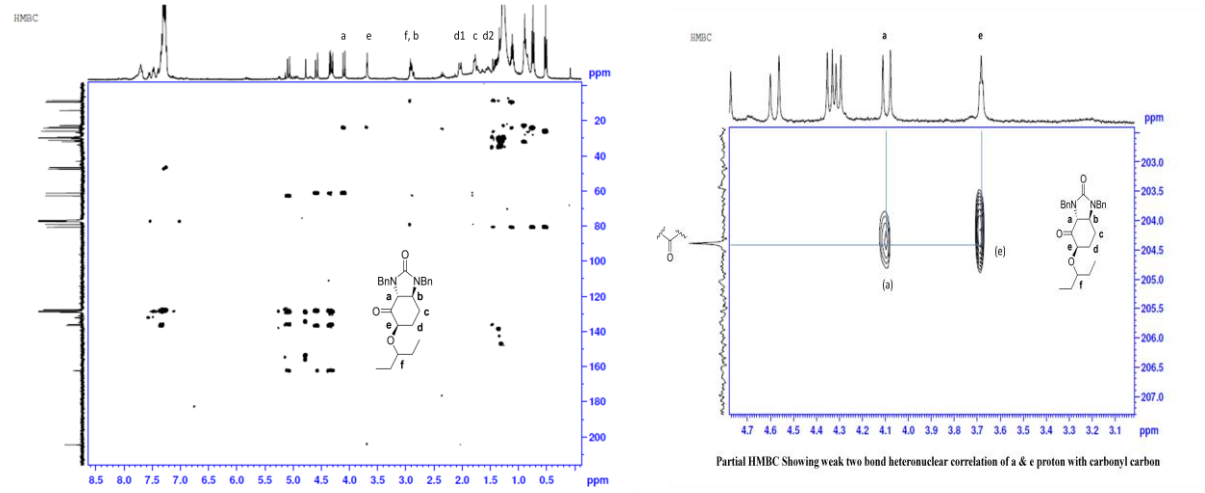


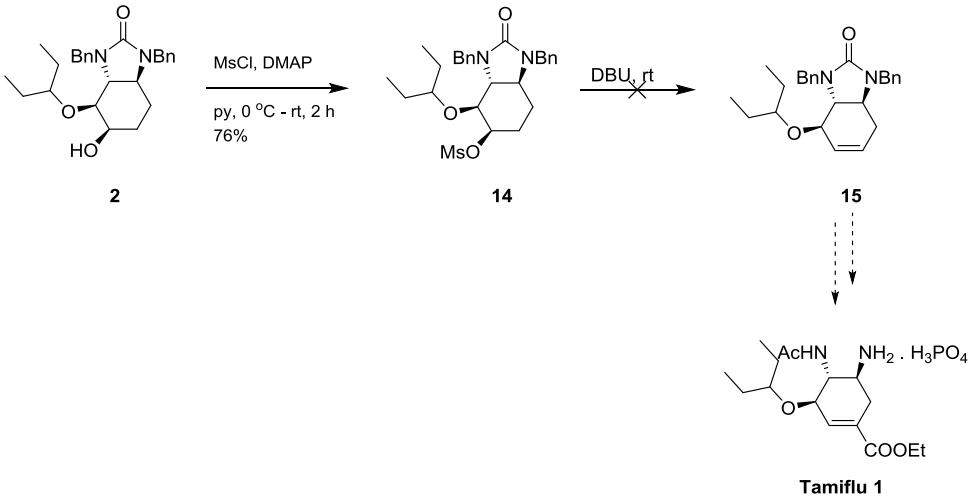
Fig 1d Full HMBC and Partial HMBC of **12a**

The 2D-NMR experimental study strongly supported the structure of compound **12a** which inturn confirmed the stereochemistry for regeoisomer **2** and **2a**.

By another alternative strategy for the synthesis of Tamiflu, hydroxy **2** was subjected to mesylation using MsCl and cat. DMAP in pyridine as solvent to afford mesyl compound **14** in 76%. The band at 1701 cm^{-1} in IR spectrum corresponded to urea carbonyl. The 1H spectrum of mesyl **14** showed the peaks at δ 2.95 (s, 3H) ppm assigned for methyl group

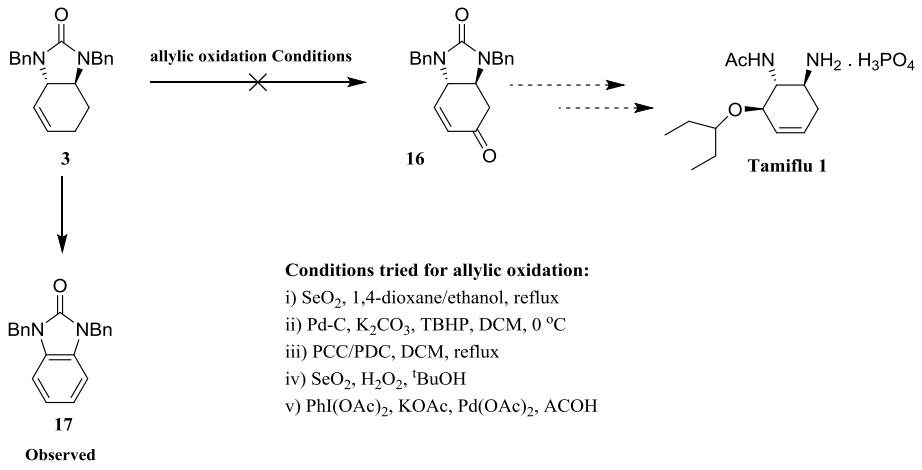
of mesyl functionality. In ^{13}C spectrum peak at 162.9 ppm for urea carbonyl carbon and its DEPT spectrum showed peak at 39.4 ppm for methyl carbon of mesyl group which strongly supported formation of mesylate **14**. In HRMS spectrum peak at 523.2236 which confirmed the molecular formula $C_{27}H_{36}N_2O_5S$ of the mesyl **14** (Scheme 6).

The mesyl **14** was treated with DBU as base for elimination in DCM but failed to obtain compound **15**.



Scheme 6 Mesylation based attempt for tamiflu **1**

An alternative strategy was planned for tamiflu from olefin **3**. Accordingly, olefin **3** was



Scheme 7 Allylic oxidation based attempt for tamiflu **1**

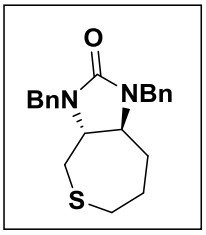
subjected under different allylic oxidation under different conditions like SeO_2, Pd-C/TBHP, PCC, PDC, SeO_2/H_2O_2 and $PhI(OAc)_2/Pd(OAc)_2$ (Scheme 7).[9] All attempts for allylic oxidation provided urea **17** instead of desired enone **16**. The band at 1704 cm-1 indicating presence of urea functionality. The peaks at δ 6.9 and 6.8 ppm in 1H NMR spectrum for four protons which indicated aromatization of **3**. The ^{13}C NMR spectrum showed peak at δ 154.5 ppm for carbonyl carbon of urea functionality. In DEPT spectrum of **17** peak at δ 45.0 ppm corresponding to methylene carbon of benzyl group. The HRMS peak at 341.1619 was confirmed molecular formula $C_{21}H_{18}N_2O$ of **17**.

1.2.2 Conclusion

In conclusion, we have synthesized olefin **3** as key intermediate using Ramberg-Backlund reaction and stereospecific amidoalkylation protocol. Also we have prepared alcohol **2** and ketone **12** which would be explored to tamiflu *via* appropriate functional transformations. The olefin **3** under allylic oxidation conditions provided urea **17**.

1.2.3 Experimental

(3a*R*, 8a*S*)-1, 3-Dibenzylhexahydro-1H-thiepino-[3, 4-*d*]-imidazol-2(3*H*)-one (8)



To the compoud allyl **6** (20 gm, 57.14 mmol) strirred in THF (200 mL) was added zinc dust (111 gm, 1.74 mol) and saturated aq solution of ammonium chloride (200 mL). The reaction mixture was refluxed for 6 h and progress of reaction was monitored by TLC. The reaction mixture was filtered through celite and washed with ethyl acetate (2 X 100 mL). The filtrate was washed with 10% HCl (100 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish thiol **7**.

The crude thiol **7** (20.00 gm, 56.74 mmol) was stirred at room temperature in water (100 mL) for 4-5 h. The progress of reaction was monitored by TLC, compound was extracted with ethyl acetate (3 X 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue. The residue was purified by column chromatography over flash silica gel with 10% ethyl acetate in pet ether as the eluent to afford cyclic sulphide **8** (16.20 gm, 81%) as a colourless liquid.

***R*$_f$:** 0.6 (Pet. ether: ethyl acetate, 70:30)

MF: $C_{21}H_{24}N_2OS$, **MW:** 352.50

$[\alpha]_D^{25}$: +37.6 (*c* 2.5, $CHCl_3$)

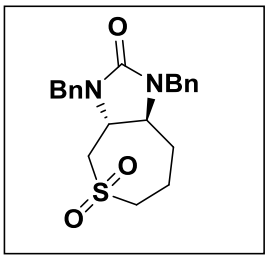
IR ($CHCl_3$, cm^{-1}): νmax 3030, 1709, 1604, 1447, 1029

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.35 -7.25 (m, 10H), 4.76 (d, *J* = 16 Hz, 1H), 4.67 (d, *J* = 16 Hz, 1H), 4.22 (d, *J* = 16 Hz, 1H), 4.18 (d, *J* = 16 Hz, 1H), 3.27-3.22 (m, 2H), 2.97 (dd, *J* = 12.7, 3.6 Hz, 1H), 2.57 (ddd, *J* = 15.3, 8.2, 3.0 Hz, 1H), 2.58-2.54 (m, 1H), 2.26 (dd, *J* = 12.6, 10.0 Hz, 1H), 2.12-2.15 (m, 1H), 1.96-1.93 (m, , 1H), 1.78 – 1.71 (m, 1H), 1.43-1.36 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 160.8, 137.0, 128.67, 128.63, 128.1, 128.0. 127.5, 127.2, 62.4, 58.8, 46.4, 45.9, 31.9, 29.8, 28.8, 28.1.

HRMS: Observed- 375.1497, calculated-375.1502.

(3a*R*, 8a*S*)-1, 3-Dibenzylhexahydro-1H-thiepino[3,4-*d*]imidazol-2(3*H*)-one 5, 5 dioxide (9)



To a solution of sulfide **8** (10.00 gm, 28.37 mmol) in THF: MeOH(1:1) was added oxone (52 gm , 81.11 mmol) in water (100 mL). After stirring at room temperature for 4- h, the reaction mixture was filtered through celite and celite was washed thoroughly with methanol (3 X 60 mL). Filtrate was concentrated under reduced pressure and water (100 mL) was added to the residue. Compound was extracted with ethyl acetate (3 X 100 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude residue. The residue was purified by column chromatography over silica gel with 30% ethyl acetate in pet. ether as an eluent to afford compound **9** (9.16 gm, 84%) as a white solid.

***R_f*:** 0.3 (Pet. ether-ethyl acetate, 50:50)

MF: $C_{21}H_{24}N_2O_3S$, **MW:** 384.49

$[\alpha]_D^{25}$: +49.09 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 2924, 1704, 1602, 1450, 1170.

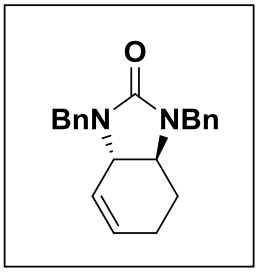
MP : 155-157 ^{0}C.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.42 - 7.22 (m, 10 H), 4.76 (d, *J*=16 Hz, 1H), 4.67 (d, *J* = 16 Hz, 1H), 4.22 (d, *J*=12 Hz, 1H), 4.15 (d, *J*=12 Hz, 1H), 3.60 - 3.22 (m, 3 H), 3.08 - 2.83 (m, 3H), 2.33 - 1.87 (m, 3 H), 1.50 - 1.33 (m, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 160.2, 136.3, 135.9, 136.1, 128.9, 128.8, 128.1, 127.9, 127.8, 127.7, 77.1, 58.7, 58.4, 54.5, 53.4, 46.6, 46.0, 29.6, 18.7.

HRMS : observed- 407.1398, calculated- 407.1400.

(3a*S*, 7a*S*)-1, 3-Dibenzyl-3, 3a, 7, 7a-tetrahydro-1H-benzo[*d*]imidazol-2(6*H*)-one (3)



To a solution of sulfone **9** (3.00 gm, 7.80 mmol) in CCl_4:*t*-BuOH(40 mL, 5:3) was added potassium hydroxide flakes (660 mg, 11.71 mmol) and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure and saturated solution of ammonium chloride was added to the residue. Compound was extracted with ethyl acetate (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain residue, which was purified by column chromatography over silica gel with 5% ethyl acetate in pet ether as an eluent to give compound **3** (1.54 gm, 62%) as a white solid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 80:20).

MF: $C_{21}H_{22}N_2O$, **MW:** 318.42.

$[\alpha]_D^{25}$: +30.0 (*c* 0.4, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 2925, 1704, 1629, 1495, 1238.

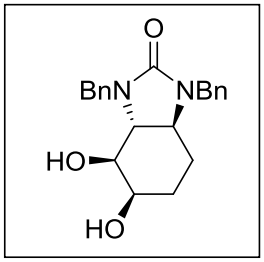
MP: 75-77 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 7.39 - 7.23 (m, 33 H), 5.74 (dd, *J* = 1.7, 9.9 Hz, 2 H), 5.49 - 5.41 (m, 2 H), 4.57 (d, *J* = 15 Hz, 1 H), 4.50 (d, *J* = 15 Hz, 1 H), 4.43 (d, *J* = 15 Hz, 1 H), 4.39 (d, *J* = 15 Hz, 1 H), 3.43 - 3.37 (m, 1 H), 3.01 - 2.93 (m, 1 H), 2.26 - 2.04 (m, 2H), 1.94 - 1.85 (m, 1 H), 1.52 - 1.41 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 164.0, 137.6, 137.2, 128.6, 128.5, 128.3, 127.6, 127.5, 127.4, 127.3, 124.0, 59.0, 58.7, 47.4, 47.2, 25.2, 24.56.

HRMS : Observed- 341.1619, calculated- 341.1624.

(3a*R*, 4*S*, 5*R*, 7a*S*)-1, 3-Dibenzyl-4,5-dihydroxyoctahydro-2H-benzo[d]imidazol-2-one (10)



To a solution of olefin **3** (500 mg, 1.57 mmol) in acetonitrile: H_2O (9:1, 5 mL) was added cat. OsO_4 (5 drops) and NMO (368 mg, 3.14 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 7 h and quenched with saturated aq. solution of sodium sulfite (5 mL). The solvent was evaporated under reduced pressure and to the crude residue thus obtained was added water (5 mL). The compound was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel with 20% ethyl acetate in pet ether as an eluent to afford compound **10** (467 mg, 85%) as a colourless syrup.

R_f: 0.2 (Pet.ether: ethyl acetate, 40:60).

MF: $C_{21}H_{24}N_2O_3$, **MW:** 352.43.

$[\alpha]_D^{25}$: +101.6 (*c* 1.8, $CHCl_3$).

Yield: 85%.

IR ($CHCl_3$, cm^{-1}): νmax 3369, 2925, 1702, 1603, 1495, 1038.

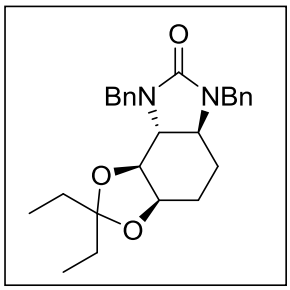
^{1}H NMR (200MHz, $CDCl_3$ + CCl_4) δ = 7.51 - 7.07 (m, 10 H), 5.24 - 3.74 (m, 6 H), 3.63 - 3.11 (m, 2 H), 2.82 - 2.09 (m, 4 H), 1.97 - 1.54 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 155.9, 137.6, 135.6, 128.6, 128.5, 127.9, 127.8, 127.4, 73.6, 70.1, 63.9, 53.4, 47.5, 47.2, 28.3, 25.5.

HRMS : Observed- 375.1676, calculated- 375.1679.

(3a*R*, 5a*S*, 8a*R*, 8b*S*)-6, 8-dibenzyl-2,2-diethyloctahydro-7H [1, 3] dioxolo [4',5':3,4] benzo-[1, 2-d]imidazol-7-one (11)

To a solution of diol **10** (400 mg, 1.36 mmol) in 3-pentanol (0.5 mL) was added trimethyl orthoformate (0.5 mL) and HCl (1M solution in MeOH, 0.5 mL) at 0 ^oC. The reaction mixture was refluxed for 2.5 h and the progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure obtained crude residue, water (5 mL)



was added. The compound was extracted with ethyl acetate (3 X 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish crude residue, which was purified by flash column chromatography over silica gel with 10% ethyl acetate in pet. ether as an eluent to give compound **11** (329 mg, 69%) as a colourless syrup.

***R_f*:** 0.7 (Pet.ether: ethyl acetate, 80:20).

MF: $C_{26}H_{32}N_2O_3$, **MW:** 420.55.

$[\alpha]_D^{25}$: +101.6 (*c* 1.8, $CHCl_3$).

Yield: 69%.

IR ($CHCl_3$, cm^{-1}): νmax 2925, 1704, 1604, 1495, 1443, 700.

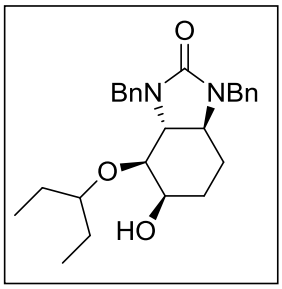
^{1}H NMR (200MHz, $CDCl_3$ + CCl_4): δ 7.65 - 7.07 (m, 10 H), 5.25 - 3.85 (m, 6 H), 3.51 - 3.00 (m, 1 H), 2.88 - 2.46 (m, 1 H), 2.13 - 1.22 (m, 8 H), 1.00 - 0.50 (m, 6 H).

^{13}C NMR (100MHz, $CDCl_3$ + CCl_4): δ 163.6, 138.3, 137.3, 128.6, 128.54, 128.50, 128.2, 127.3, 126.9, 113.1, 80.3, 73.87, 60.6, 58.6, 47.5, 47.3, 26.9, 26.3, 25.4, 22.9, 9.7, 9.2.

HRMS : Observed- 423.2639, calculated- 423.2642.

(3a*R*, 4*S*, 5*R*, 7a*S*)-1, 3-Dibenzyl-5-hydroxy-4-(pentan-3-yloxy)octahydro-2H-benzo[d]imid azol-2-one (2)

To a solution of pentanoid 11 (300 mg, 0.714 mmol) in dry DCM (5 mL) was added TMSOTf (0.27 mL, 1.42 mmol) and BH_3.DMS (0.14 mL, 1.42 mmol) at -78 ^oC. The reaction mixture was stirred at same temperature for 4 h and quenched with saturated aq. solution of $NaHCO_3$ (3 mL). Water was added to the reaction mixture and compound was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue



which was purified by flash column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compounds **2** and **2a** (130 and 130 mg respectively, 86%) as a colourless syrup.

***R**f*: 0.4 (Pet. ether: ethyl acetate, 75:35).

MF: $C_{26}H_{34}N_2O_3$, **MW:** 422.57.

$[\alpha]_D^{25}$: -2.60 (*c* 2.3, $CHCl_3$).

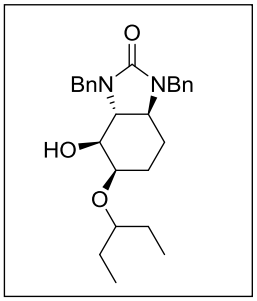
IR ($CHCl_3$, cm^{-1}): νmax 3385, 2925, 1705, 1604, 1445, 1231, 701.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.47 - 7.17 (m, 10H), 4.88 - 4.24 (m, 4H), 4.09 (bs, 1H), 3.40 (bs, 1H), 3.28 - 3.08 (m, 2H), 2.67 (d, *J* = 8.3 Hz, 1H), 1.84 - 1.35 (m, 6H), 0.94 - 0.75 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 163.3, 137.7, 137.1, 128.6, 128.47, 128.45, 128.1, 127.4, 127.2, 80.6, 75.8, 65.4, 62.5, 53.4, 47.6, 46.6, 26.5, 26.3, 25.8, 25.7, 9.7, 9.6.

HRMS : Observed- 445.2456, calculated- 445.2462.

(3a*R*, 4*S*, 5*R*, 7a*S*)-1, 3-Dibenzyl-4-hydroxy-5-(pentan-3-yloxy)octahydro-2H-benzo [d]imidazol-2-one (2a)



***R**f*: 0.5 (Pet.ether: ethyl acetate, 75:35).

MF: $C_{26}H_{34}N_2O_3$, **MW:** 422.57.

$[\alpha]_D^{25}$: -50.66 (*c* 1.5, $CHCl_3$).

Yield: 86%.

IR ($CHCl_3$, cm^{-1}): νmax 3444, 3018, 1965, 1322, 1047, 755.

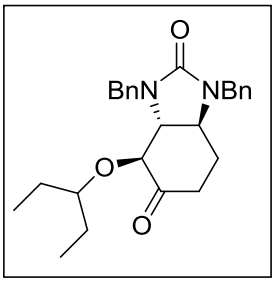
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.20 (m, 10H), 4.77 (d, *J* = 14.6 Hz, 1H), 4.56 - 4.46 (m, 2H), 4.32 (d, *J* = 15.0 Hz, 1H), 3.61 (d, *J* = 2.4 Hz, 1H), 3.55 (d, *J* = 7.6 Hz, 1H), 3.17 - 3.06 (m, 2H), 2.59 (dt, *J* = 2.9, 11.7 Hz, 1H), 2.36 (bs, 1H), 1.93 (dd, *J* =

2.4, 14.6 Hz, 1H), 1.60 (d, *J* = 9.2 Hz, 1H), 1.53 - 1.30 (m, 6H), 1.24 - 1.14 (m, 1H), 0.79 (q, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 163.6, 138.3, 137.3, 128.54, 128.50, 128.2, 127.3, 126.9, 80.3, 75.1, 73.8, 60.6, 58.6, 47.5, 47.3, 26.9, 26.3, 25.4, 22.9, 9.7, 9.2.

HRMS : Observed- 445.2456, calculated- 445.2462.

(3a*S*, 7*S*, 7a*R*)-1, 3-Dibenzyl-7-(pentan-3-yloxy)hexahydro-1H-benzo[d]imidazole-2, 6-dio ne (12)



To a solution of alcohol **2** (100 mg, 0.236 mmol) in ethyl acetate (3 mL) was added IBX (200 mg, 0. 711 mmol) at room temperature. The reaction mixture was refluxed for 4 h and progress of reaction was monitored by TLC. The reaction mixture was filtered through Whatmann filter paper and thoroughly washed with ethylacetate (3 X 5 mL). The combined organic layer was concentrated under reduced pressure to furnish crude residue. The residue was purified by column chromatography over flash silica gel with 20% ethyl acetate in pet ether as an eluent to afford ketone **12** (78 mg, 79%) as a colourless syrup.

***R_f*:** 0.5 (Pet. ether: ethyl acetate, 75:25).

MF: $C_{26}H_{32}N_2O_3$, **MW:** 420.55.

$[\alpha]_D^{25}$: -25.6 (*c* 1.8, $CHCl_3$).

Yield: 100%.

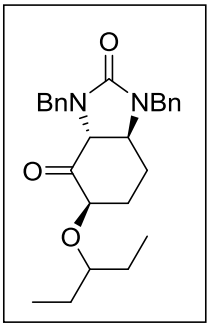
IR ($CHCl_3$, cm^{-1}): νmax 2929, 1713, 1604, 1445, 1216, 1015.

^{1}H NMR (400MHz, $CDCl_3$ + CCl_4): δ 7.35 - 7.21 (m, 10H), 5.14 - 5.04 (m, 2 H), 4.54 (d, *J* = 15.1 Hz, 1 H), 4.31 (dd, *J* = 6.9, 14.7 Hz, 3 H), 3.85 - 3.76 (m, 1 H), 3.28 - 3.12 (m, 2 H), 3.03 - 2.91 (m, 1 H), 2.39 - 2.29 (m, 2 H), 2.25 - 2.14 (m, 2 H), 1.94 (dd, *J* = 3.2, 11.4 Hz, 3 H), 1.57 - 1.49 (m, 4 H), 1.47 - 1.39 (m, 4 H), 0.95 (t, *J* = 7.6 Hz, 4 H), 0.85 - 0.80 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 201.1, 162.2, 136.5, 135.9, 129.1, 128.8, 128.76, 128.72, 128.3, 127.8, 127.7, 127.6, 82.5, 79.3, 64.1, 60.5, 47.8, 46.6, 32.1, 26.6, 26.0, 25.4, 9.6, 9.4.

HRMS : Observed- 443.2302, calculated- 443.2305.

(3aR,5R,7aS)-1,3-Dibenzyl-5-(pentan-3-yloxy)hexahydro-1H-benzo[d]imidazole-2,4-dione 12a



R_f: 0.6 (Pet.ether: ethyl acetate, 75:35).

MF: $C_{26}H_{32}N_2O_3$, **MW:** 420.55.

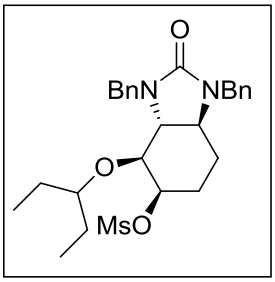
Yield: 96%.

IR ($CHCl_3$, cm^{-1}): νmax 2929, 1713, 1604, 1445, 1216, 1015.

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 204.1, 162.1, 136.6, 136.1, 129.0, 128.8, 127.8, 128.3, 127.8, 127.6, 80.4, 79.0, 62.6, 61.2, 47.5, 46.6, 31.0, 25.9, 24.0, 23.8, 9.3, 8.5.

^{1}H NMR (200MHz, $CDCl_3$+CCl_4): d 7.37-7.16 (m, 10 H), 5.07 (d, *J* = 14.7 Hz, 1H), 4.67 - 4.48 (m, 1H), 4.28 (dd, *J* = 1.8, 15.0 Hz, 2H), 4.04 (d, *J* = 13.1 Hz, 1H), 3.64 (t, *J* = 2.8 Hz, 1H), 3.00 - 2.73 (m, 2 H), 2.12 - 1.95 (m, 1H), 1.85 - 1.68 (m, 2H), 1.66 - 1.47 (m, 1H), 1.47 - 1.31 (m, 2H), 1.20 - 0.97 (m, 2H), 0.73 (t, *J* = 7.5 Hz, 3H), 0.48 (t, *J* = 7.4 Hz, 3H)

(3a*R*, 4*S*, 5*R*, 7a*S*)-1, 3-Dibenzyl-2-oxo-4-(pentan-3-yloxy)octahydro-1H-benzo [d]imidazol-5-yl methanesulfonate (14)



To a stirred solution of alcohol **2** (100 mg, 0.236 mmol) in dry pyridine (1 mL) at 0 ^{o}C was added mesyl chloride (0.03 mL, 0.355 mmol) dropwise followed by cat. DMAP. Reaction mixture was stirred for 2 h at room temperature and monitored with TLC. The reaction mixture was quenched with 10% dil. HCl (2 mL) and compound was extracted with DCM (3 X 5

mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over flash silica gel with 15% ethyl acetate in pet ether as an eluent to afford mesylate **14** (108 mg, 76%) as a colourless syrup.

***R_f*:** 0.5 (Pet.ether: ethyl acetate, 70:30).

MF: $C_{27}H_{36}N_2O_5S$, **MW:** 500.65.

$[\alpha]_D^{25}$: -30.0 (*c* 0.4, $CHCl_3$).

Yield: 76%.

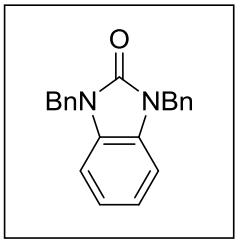
IR ($CHCl_3$, cm^{-1}): νmax 3019, 2931, 1701, 1585, 1444, 1215, 758, 688.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.33 - 7.11 (m, 10H), 5.15 - 3.95 (m, 6H), 3.37 - 2.97 (m, 4H), 2.92 - 2.75 (m, 1H), 2.69 - 2.40 (m, 1H), 1.82 - 1.26 (m, 8H), 0.85 - 0.67 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 162.9, 137.4, 136.0, 129.1, 128.8, 128.5, 128.1, 127.7, 127.5, 81.1, 74.4, 59.7, 53.8, 47.6, 45.7, 39.5, 32.0, 26.2, 26.0, 25.6, 9.7, 9.3.

HRMS : Observed- 523.2236, calculated- 523.2237.

1, 3-Dibenzyl-1, 3-dihydro-2H-benzo[d]imidazol-2-one (16)



To a solution of olefin **3** (50 mg, 0.257 mmol) in 1, 4-dioxane (2 mL) was added SeO_2 (44 mg, 0.39 mmol) at room temperature. The reaction mixture was refluxed for 8 h and progress of reaction was monitored by TLC. The reaction mixture was quenched with saturated aq. solution of $NaHCO_3$ and compound was extracted with ethylacetate (3 X 5 mL). The combined organic layer was concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel with 10% ethyl acetate in pet. ether as an eluent to afford compound **16** (34 mg, 70%) as a white solid.

R_f: 0.8 (pet. ether: ethyl acetate, 80:20).

MF: $C_{21}H_{18}N_2O$, **MW:** 314.39.

Yield: 76%.

MP: 98-100 ^oC.

IR ($CHCl_3$, cm^{-1}): vmax 2925, 1704, 1620, 1609, 1495, 1358, 1080.

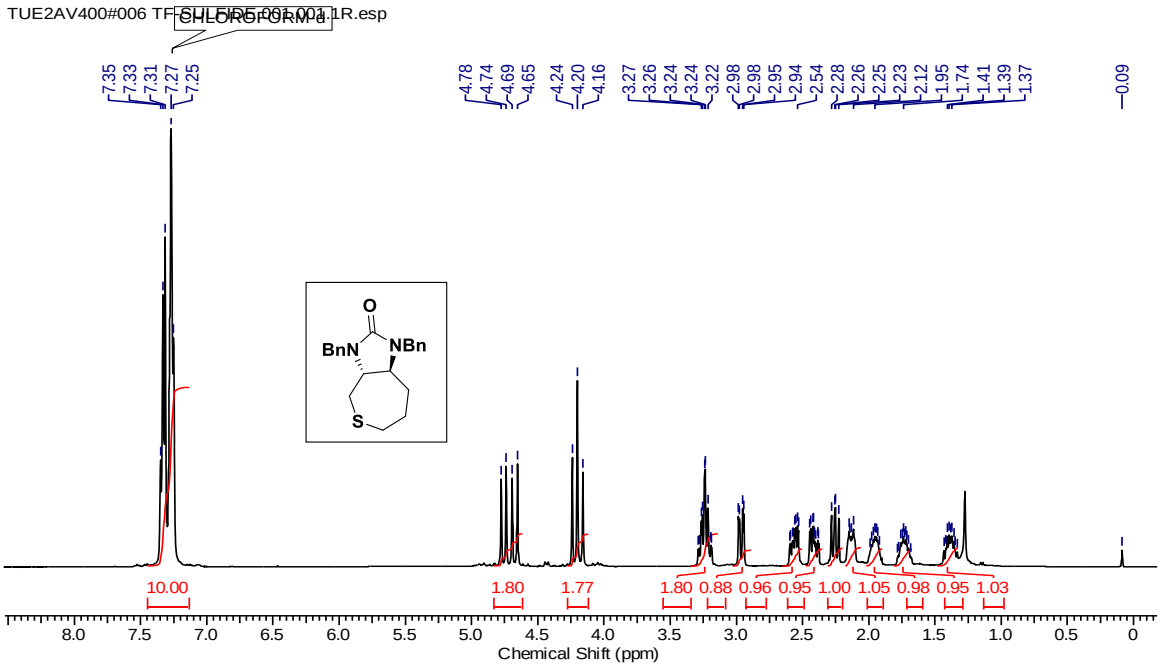
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.37 - 7.25 (m, 10 H), 6.96 (dd, *J* = 5, 5 Hz, 2 H), 6.86 (dd, *J* = 5, 5 Hz, 2 H), 5.13 (s, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 154.5, 136.3, 129.3, 128.8, 127.7, 127.5, 121.4, 108.3, 45.0.

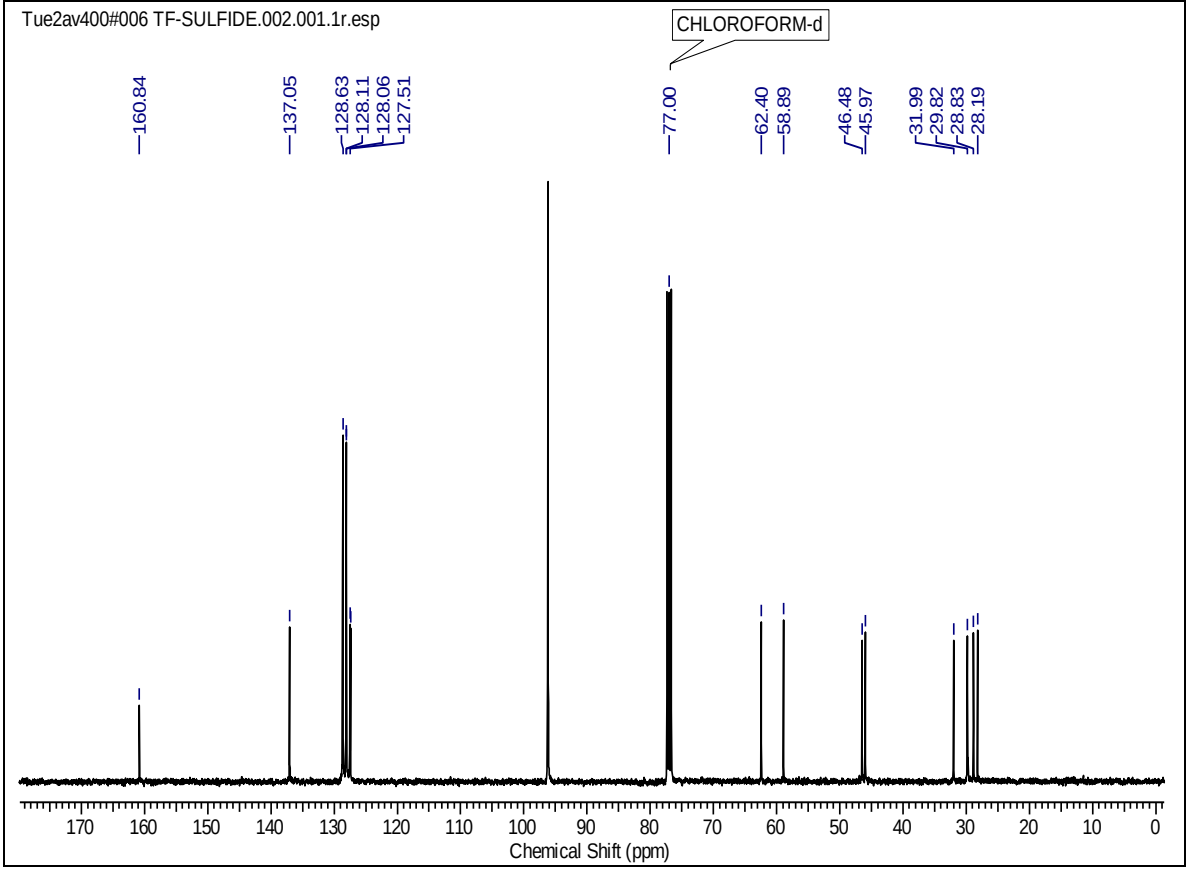
HRMS : Observed- 315.1487, calculated- 315.1492.

1.2.4 Spectral data

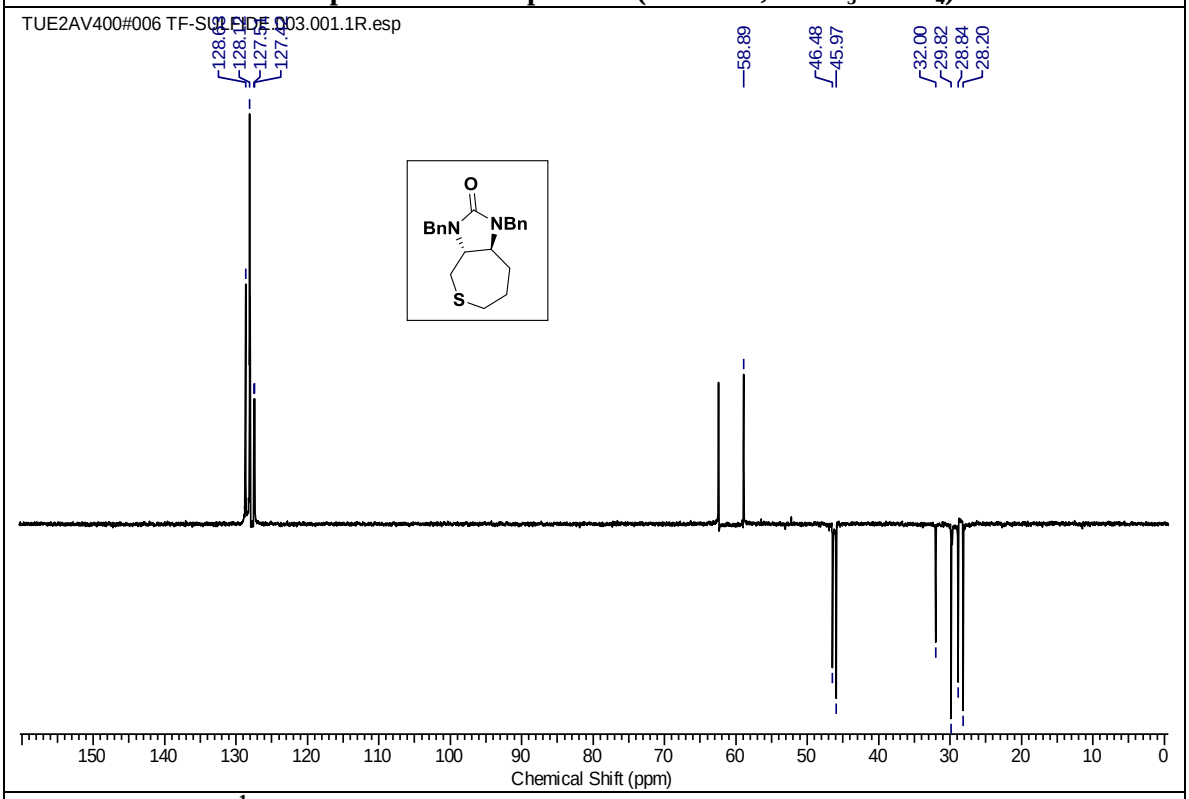
^{1}H NMR spectrum of compound 8 (400 MHz, $CDCl_3$ + CCl_4)



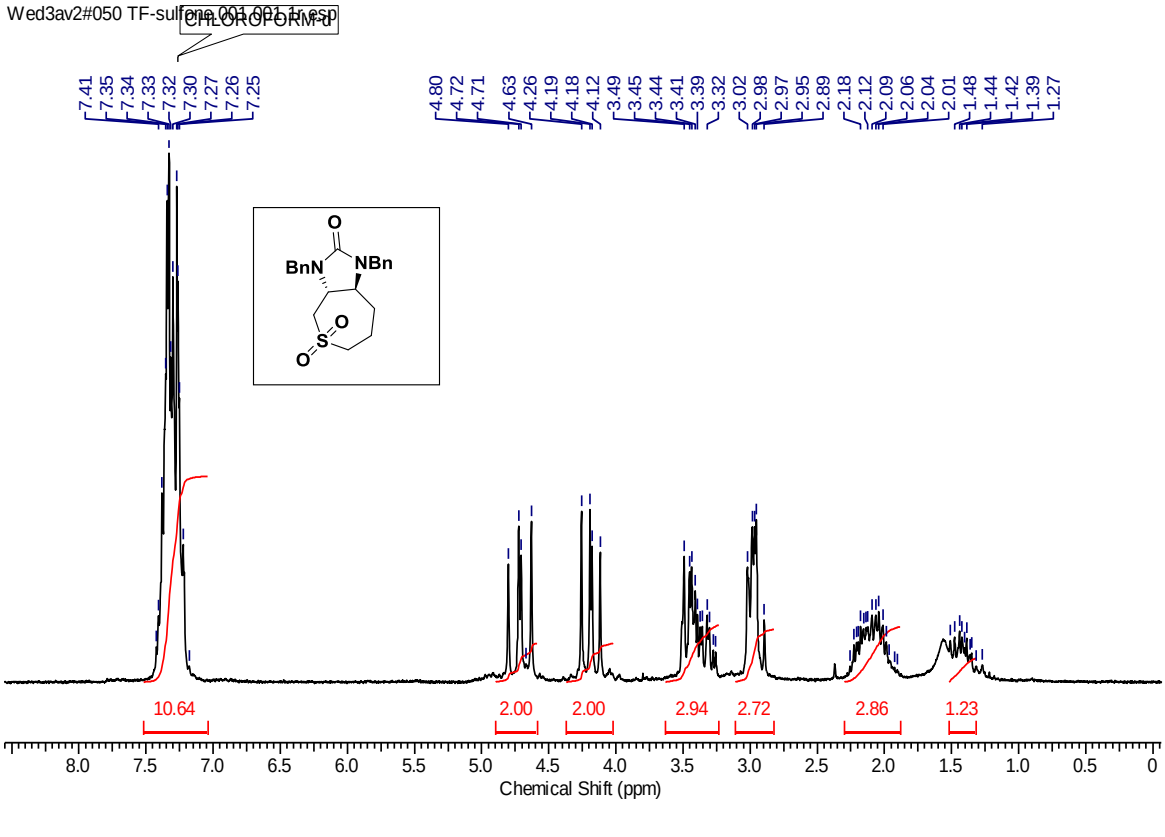
^{13}C NMR spectrum of compound 8 (100 MHz, $CDCl_3$ + CCl_4)



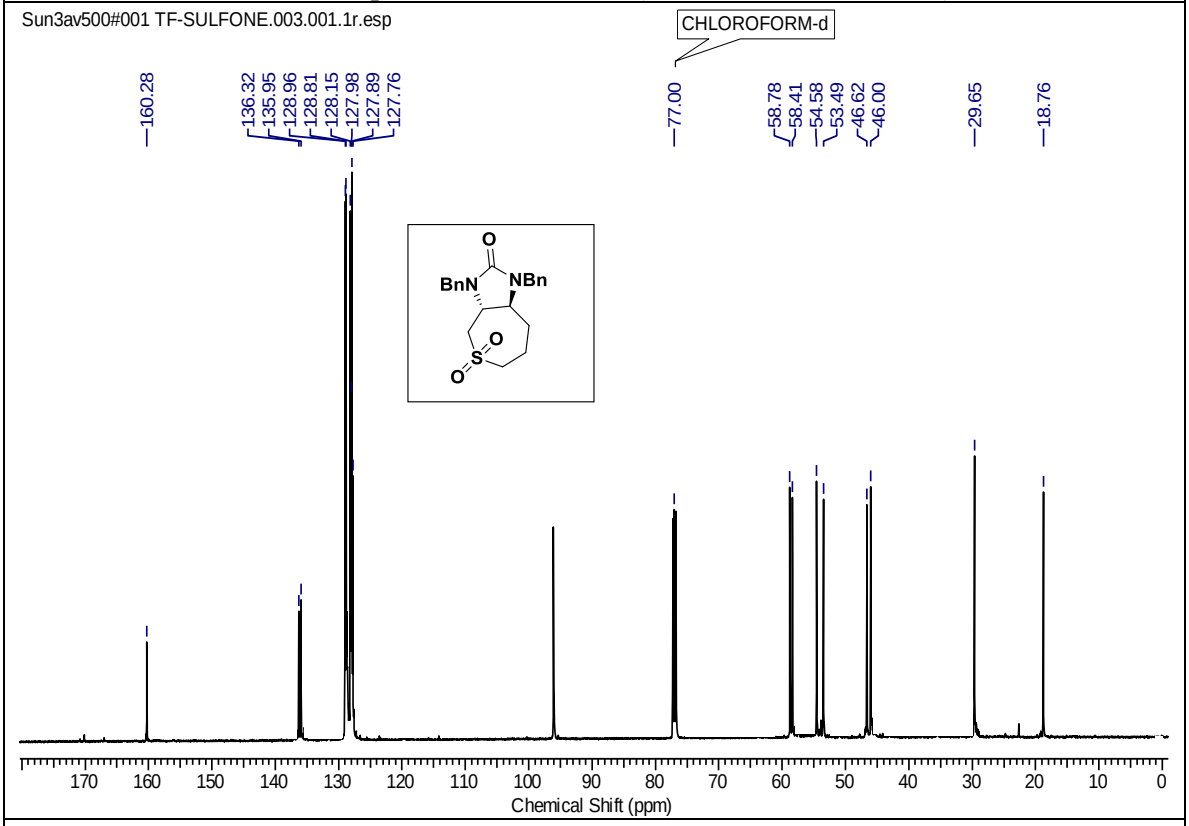
DEPT spectrum of compound 8 (100 MHz, $CDCl_3$ + CCl_4)



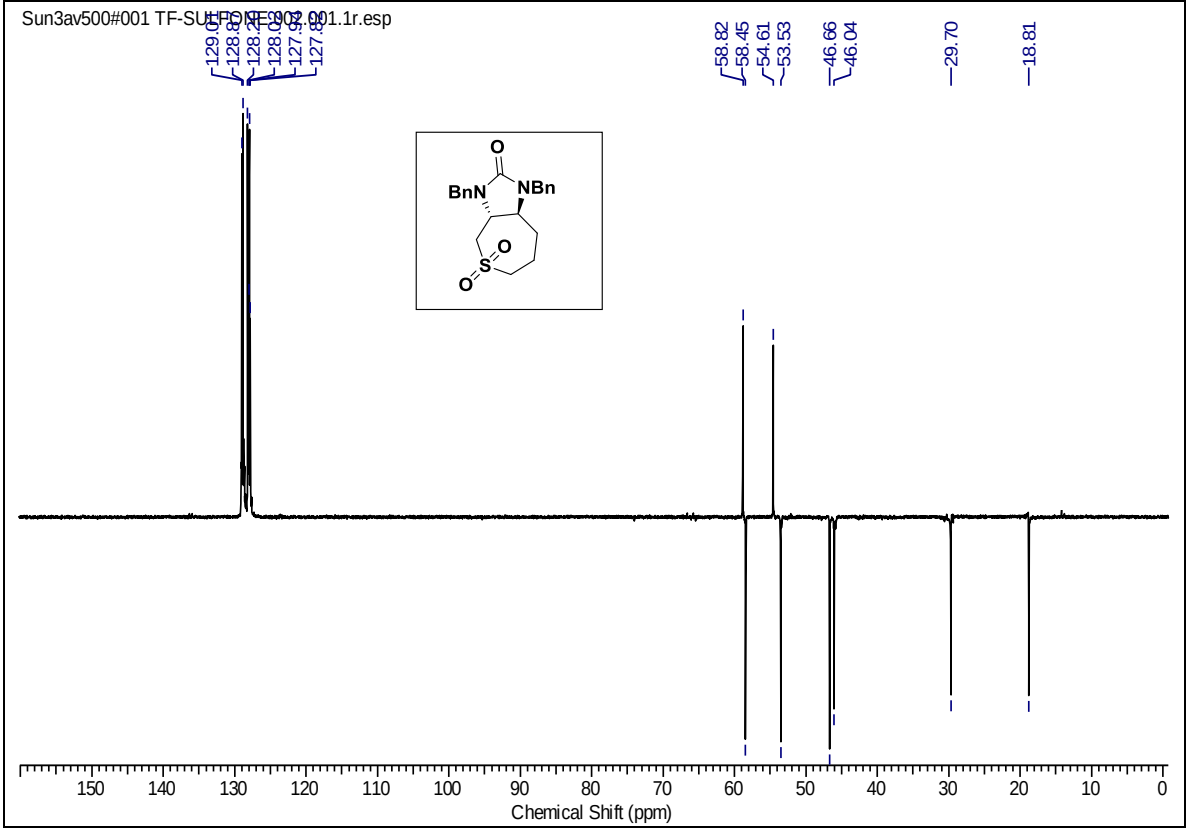
^{1}H NMR spectrum of sulfone 9 (200 MHz, $CDCl_3$ + CCl_4)



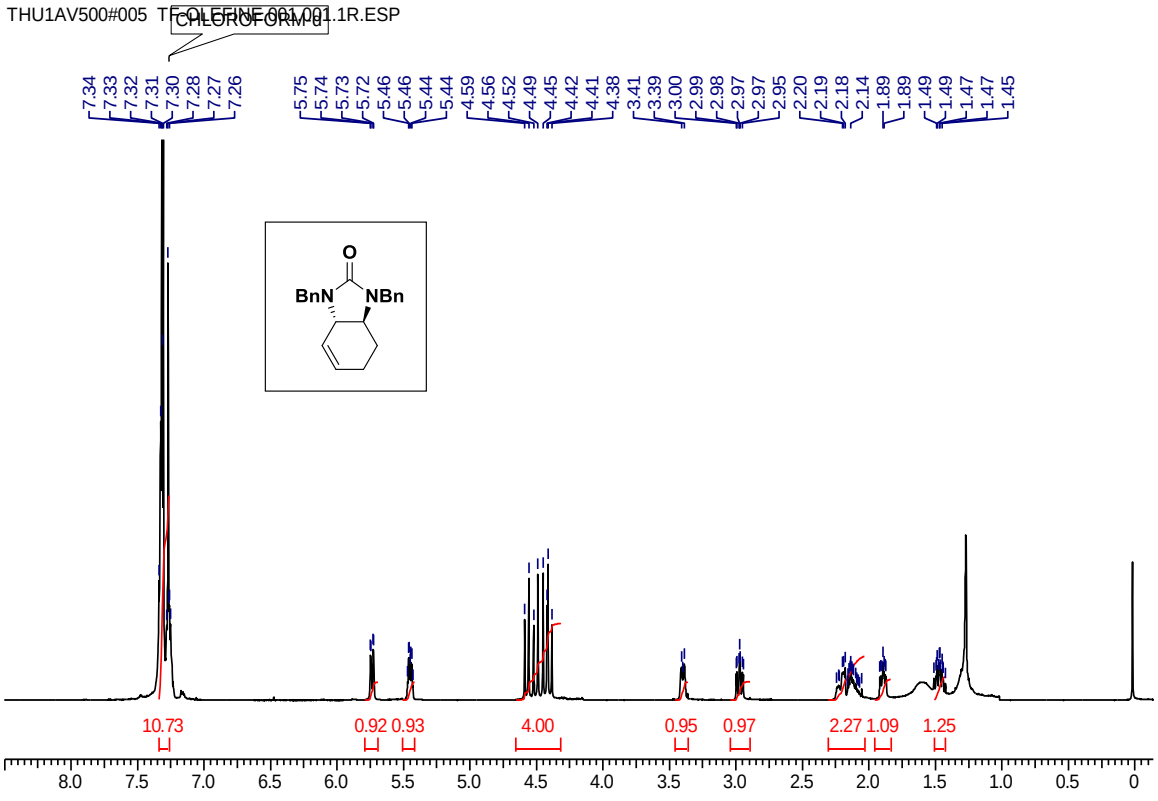
^{13}C NMR spectrum of sulfone 9 (125 MHz, $CDCl_3$ + CCl_4)



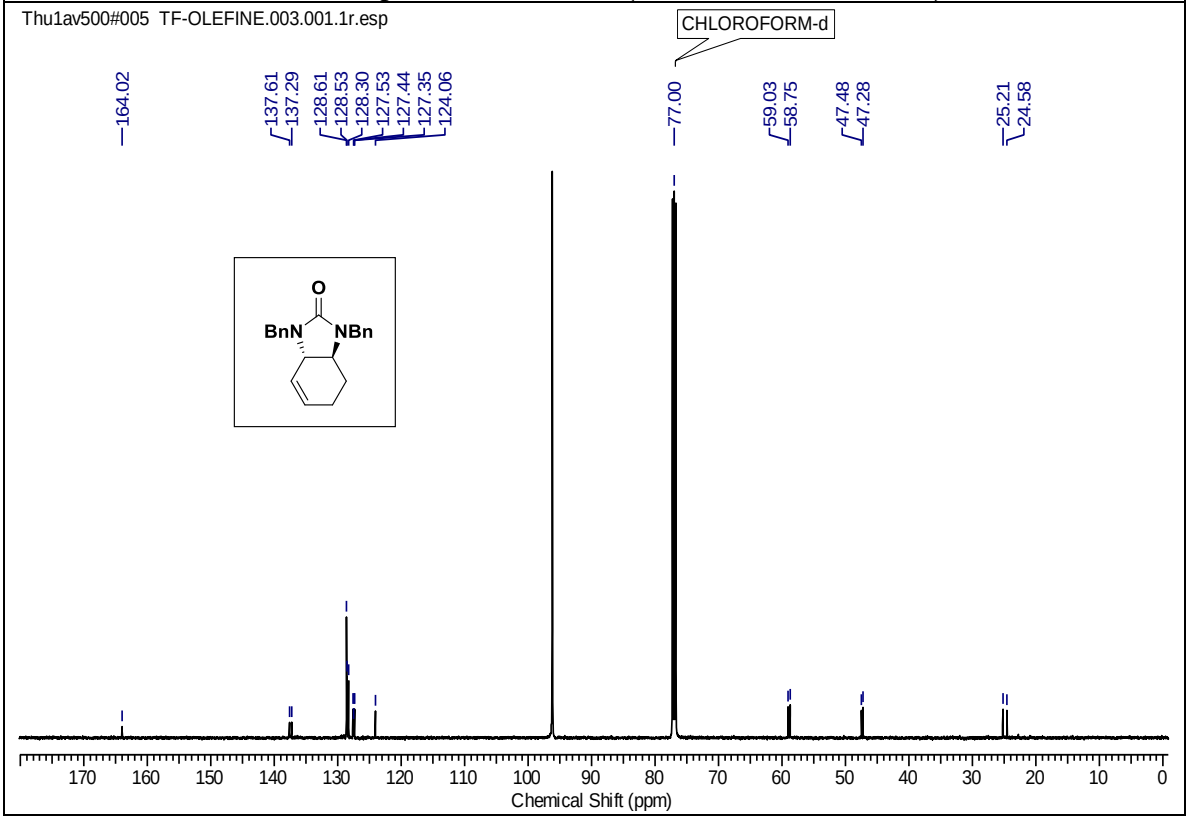
DEPT spectrum of sulfone 9 (125 MHz, $CDCl_3$ + CCl_4)



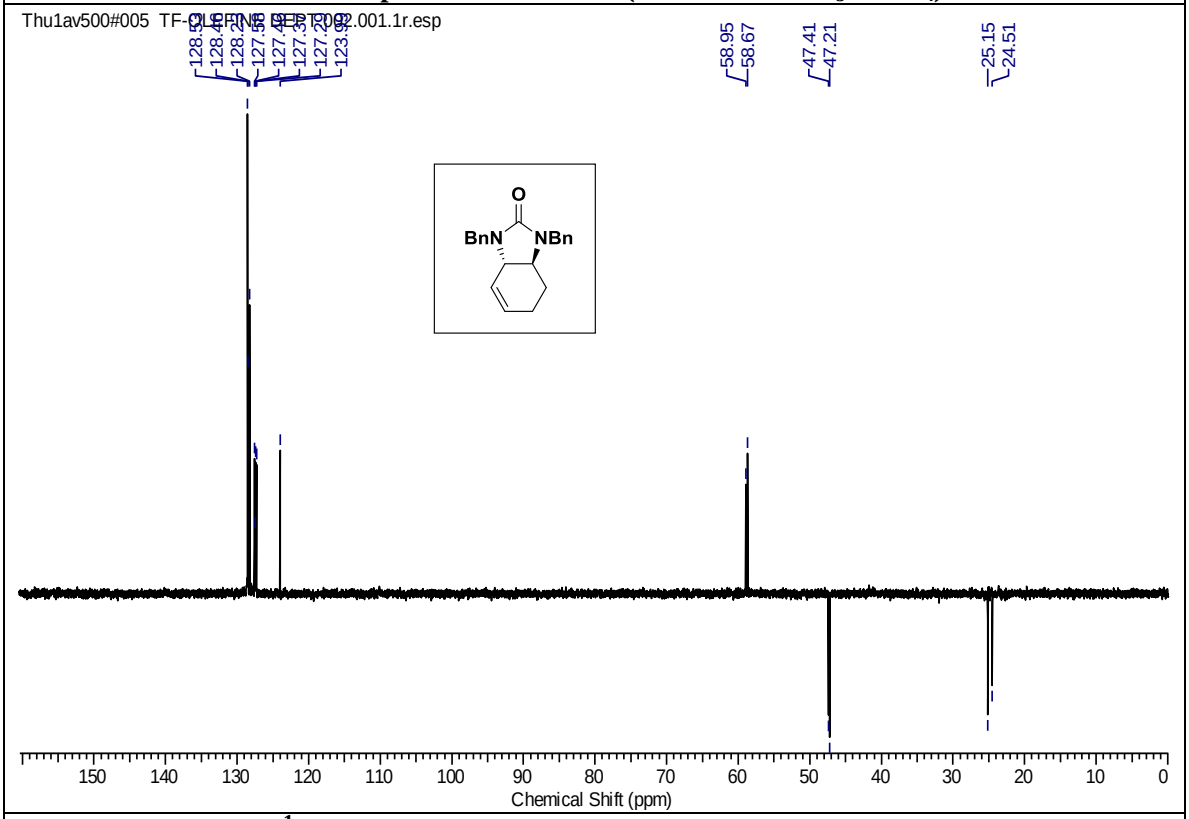
^{1}H NMR spectrum of olefin 3 (500 MHz, $CDCl_3$ + CCl_4)



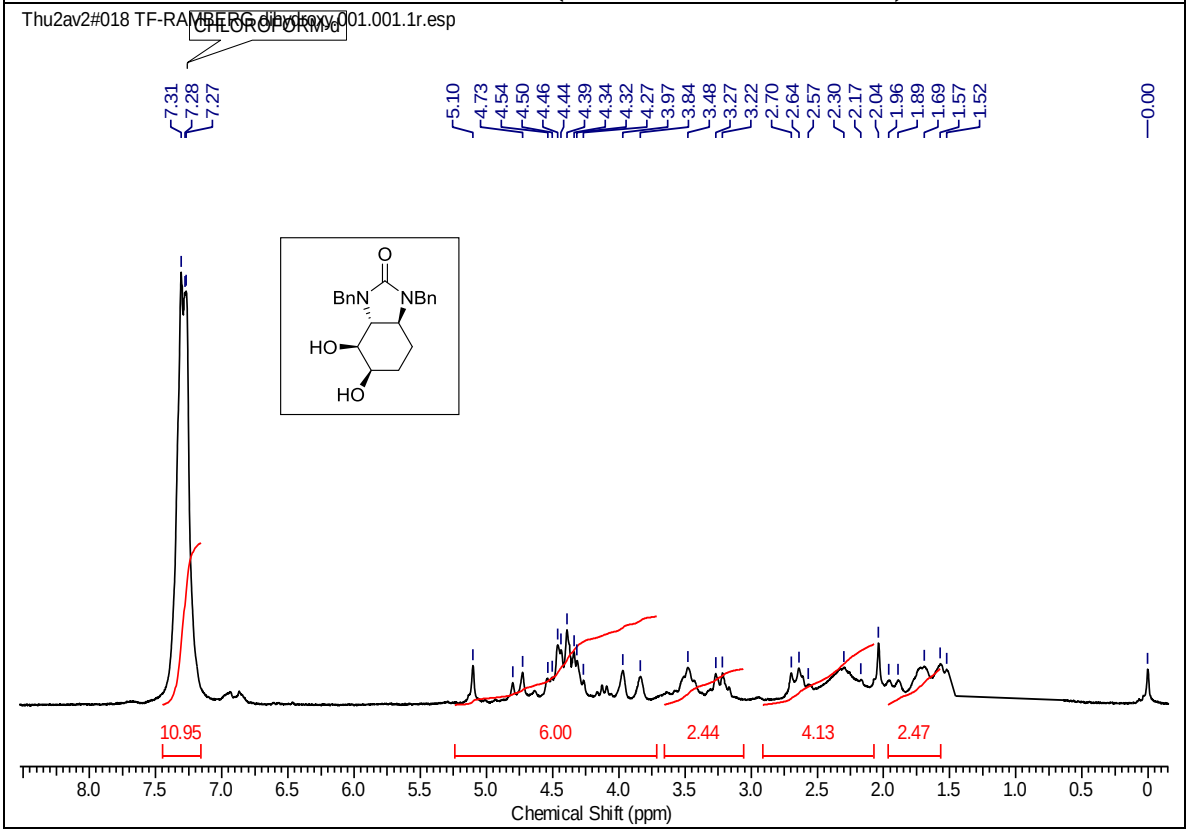
^{13}C NMR spectrum of olefin 3 (125 MHz, $CDCl_3$ + CCl_4)



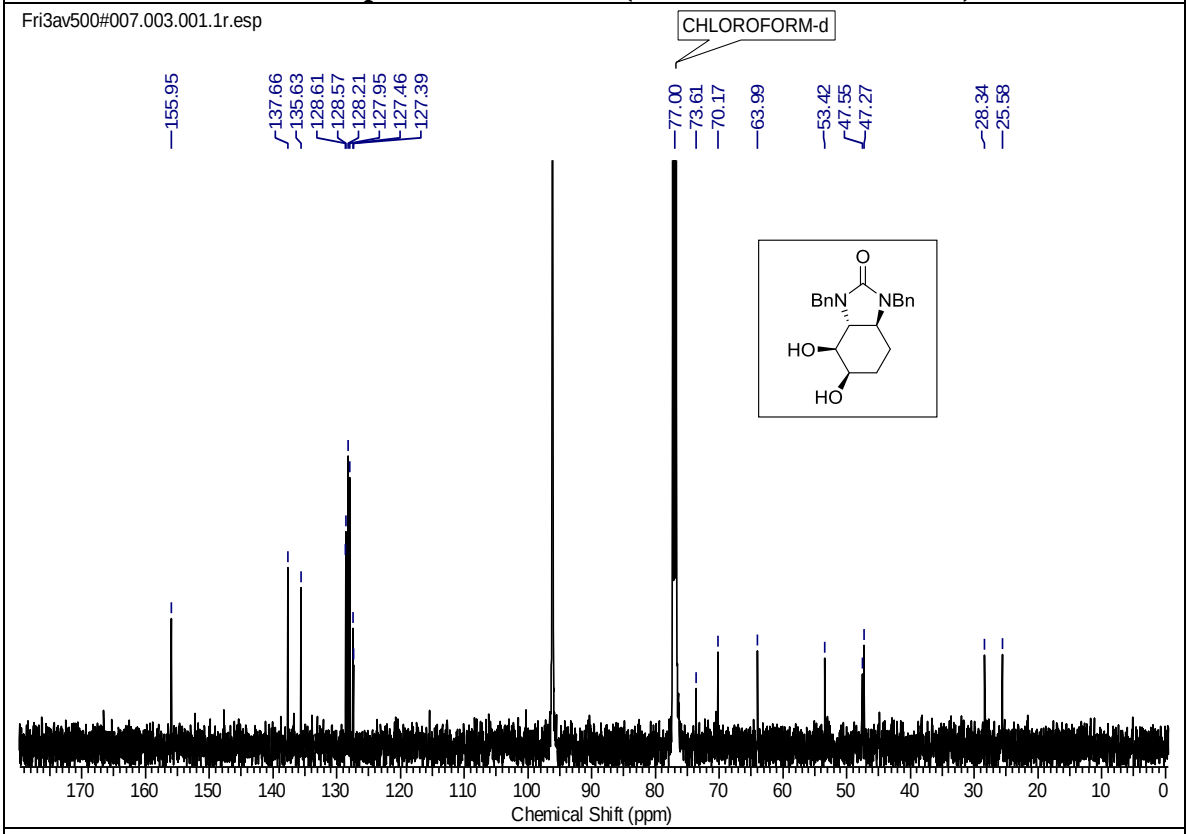
^{13}C NMR spectrum of olefin 3 (125 MHz, $CDCl_3$ + CCl_4)



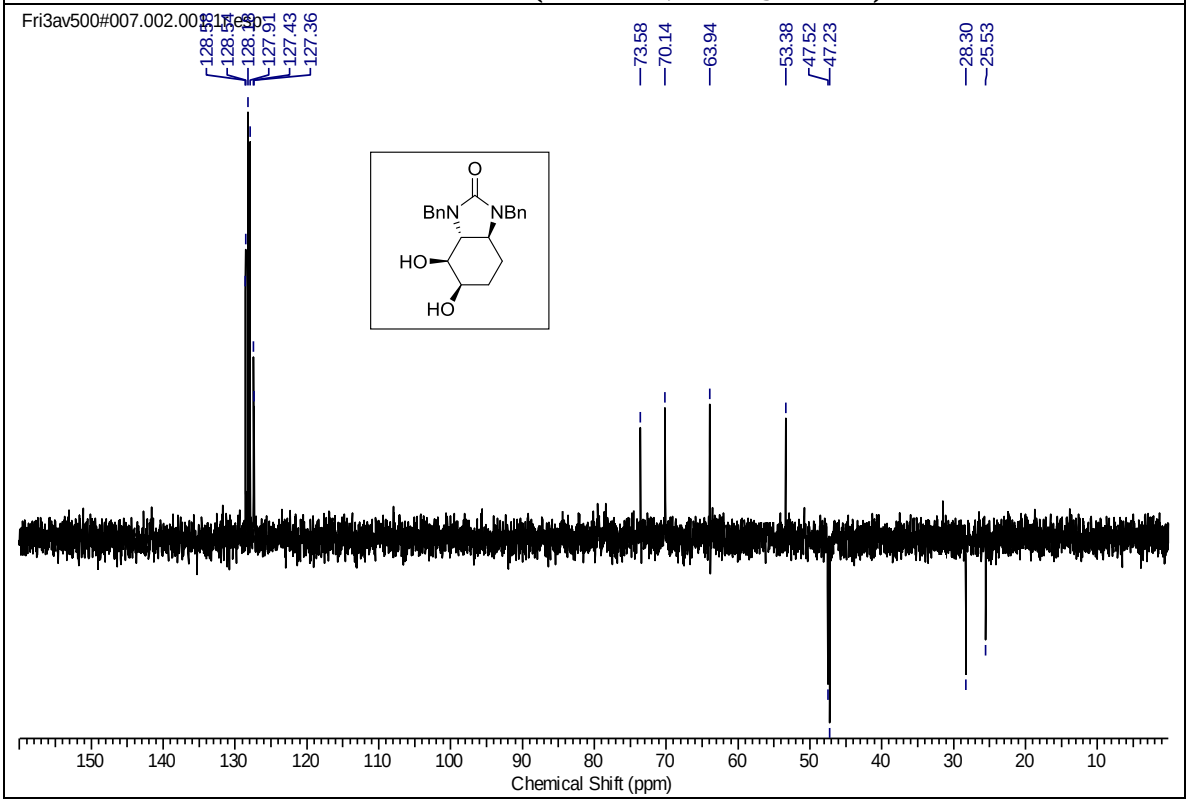
^{1}H NMR of diol 10 (200 MHz, $CDCl_3$ + CCl_4)



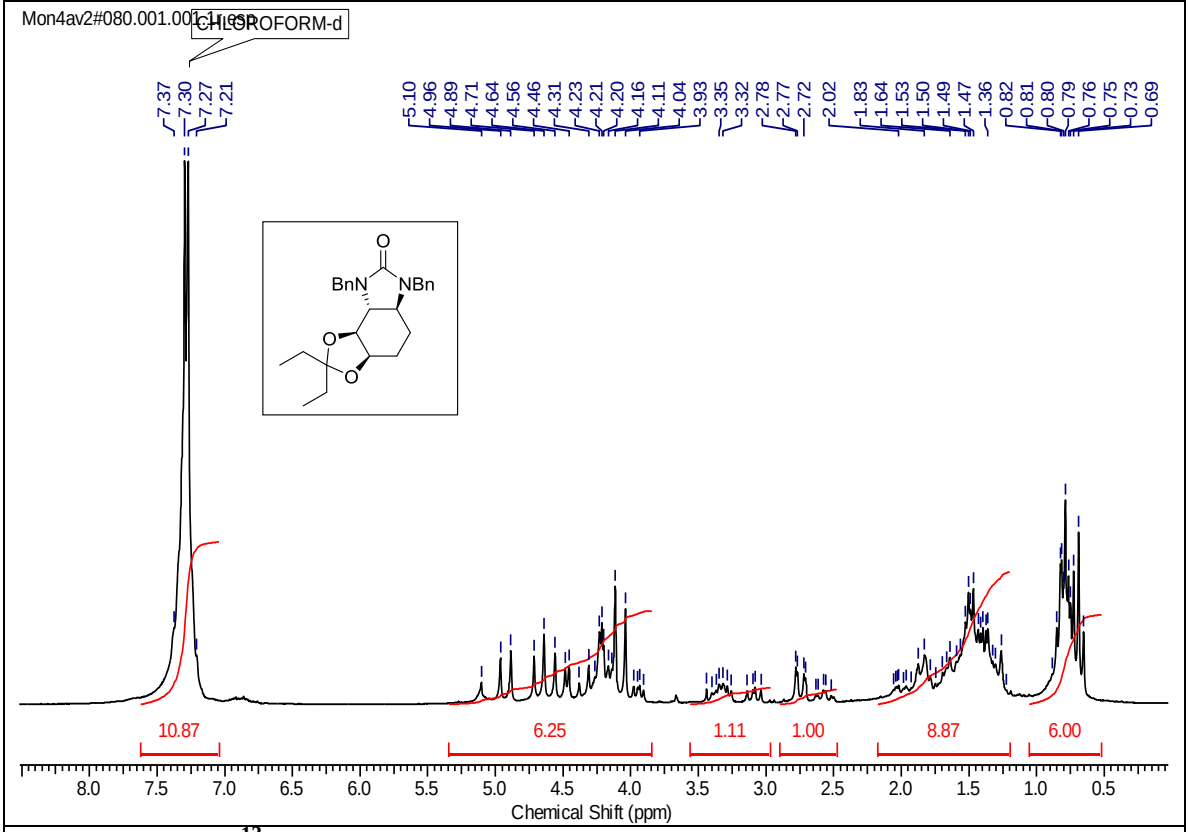
^{13}C NMR spectrum of diol 10 (125 MHz, $CDCl_3$ + CCl_4)



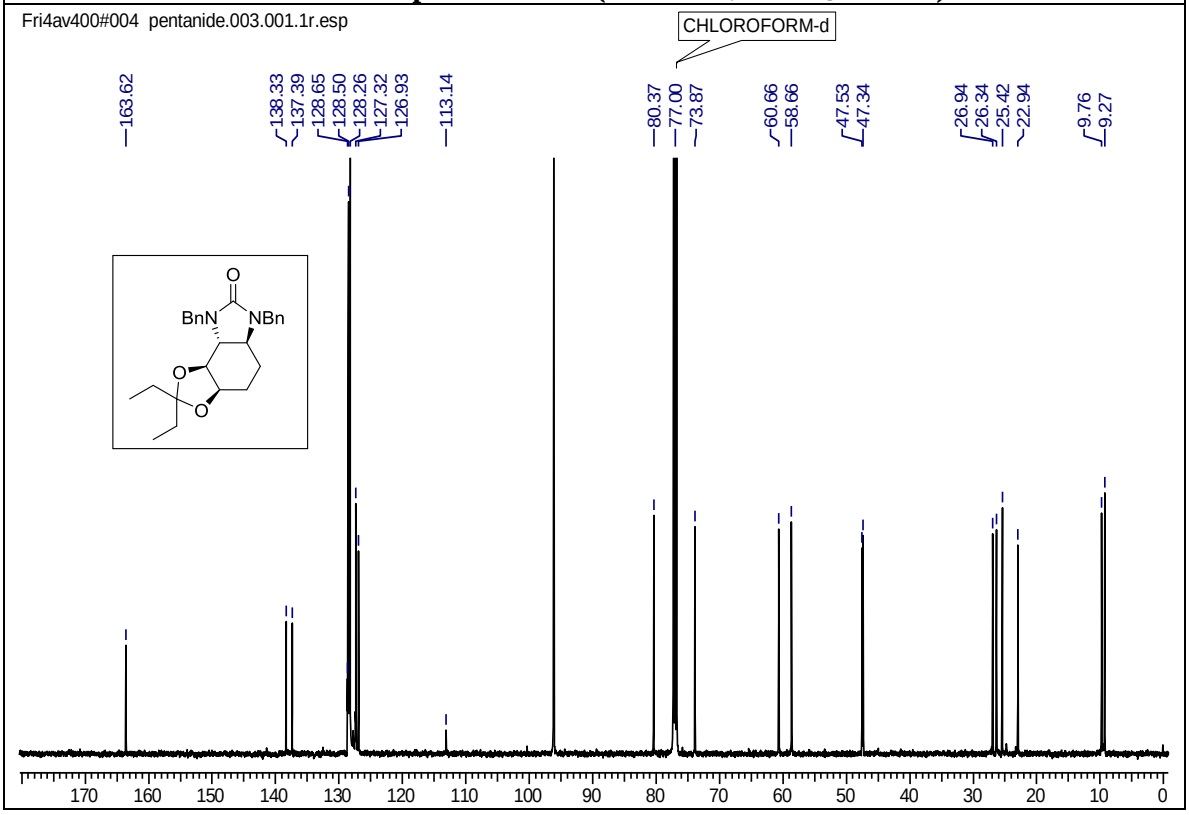
DEPT of diol 10 (125 MHz, $CDCl_3$ + CCl_4)



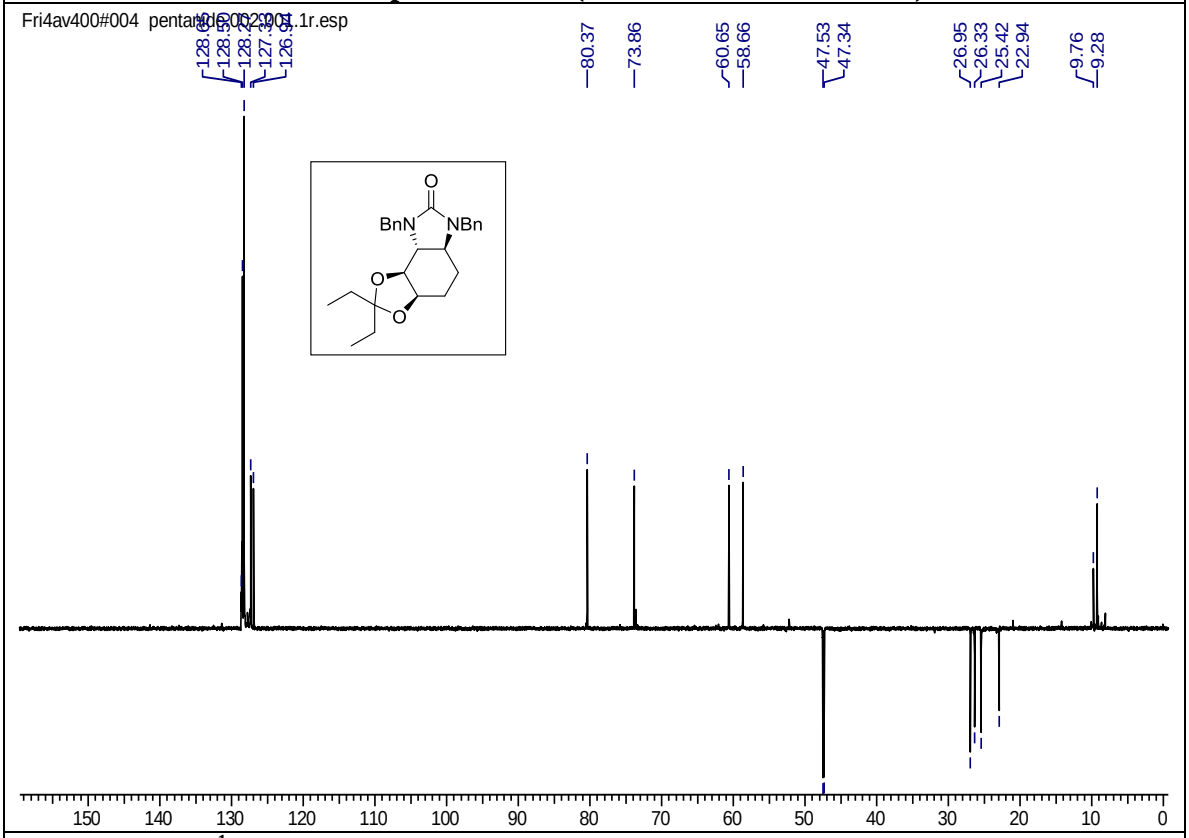
^{1}H NMR of pentanide 11 (200 MHz, $CDCl_3$ + CCl_4)



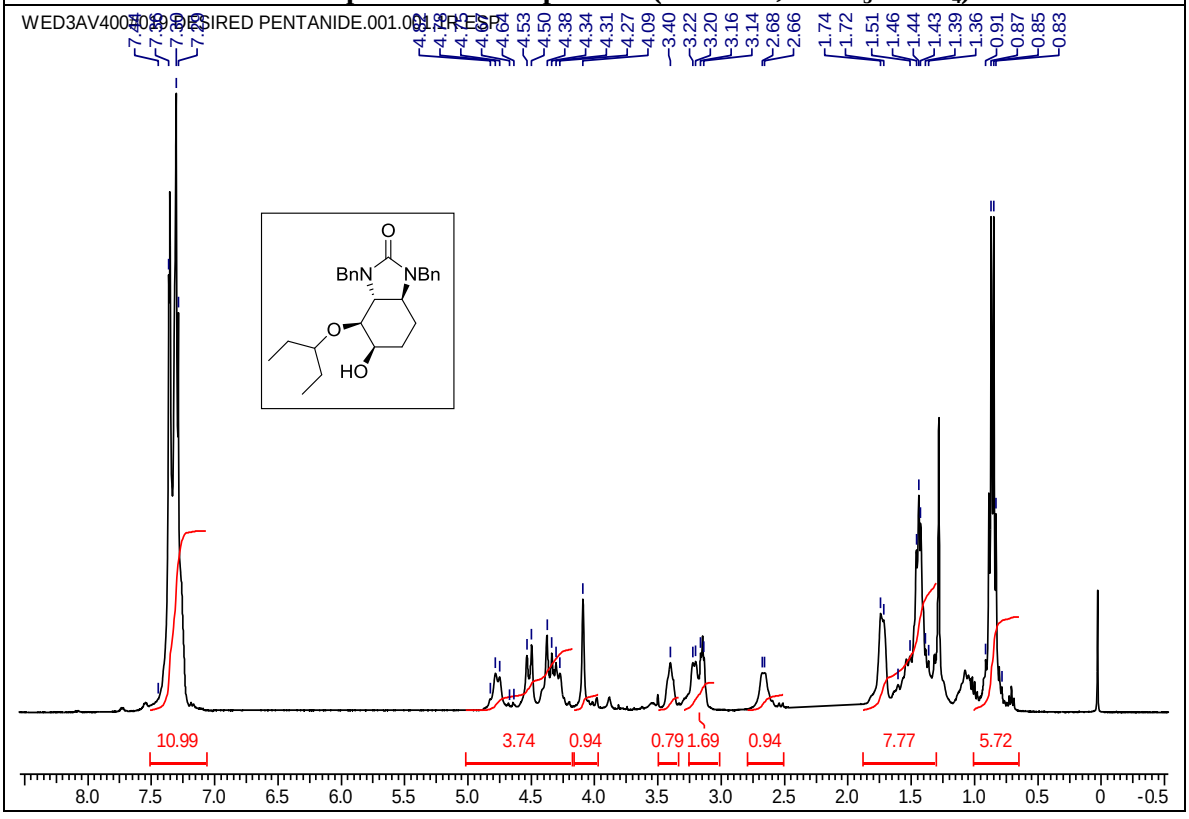
^{13}C NMR of pentanide 11 (100 MHz, $CDCl_3$ + CCl_4)



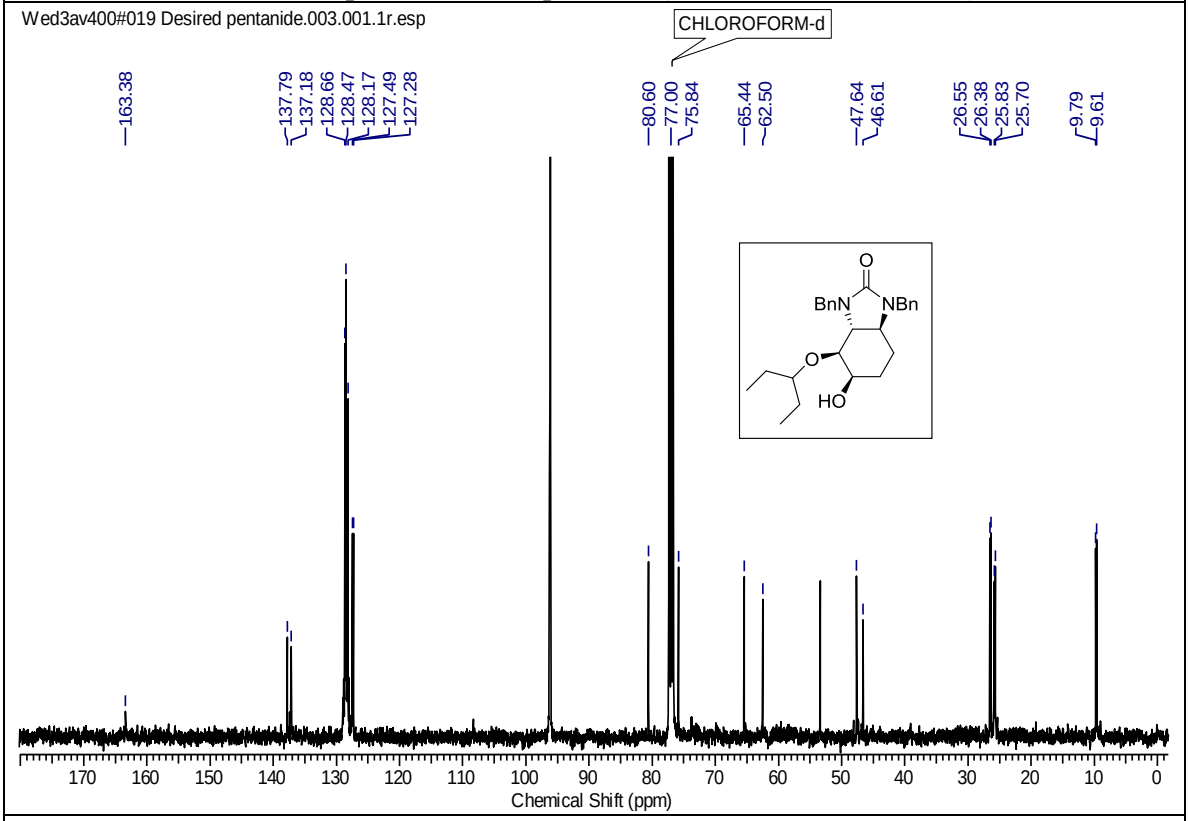
DEPT of pentanide 11 (100 MHz, $CDCl_3$ + CCl_4)



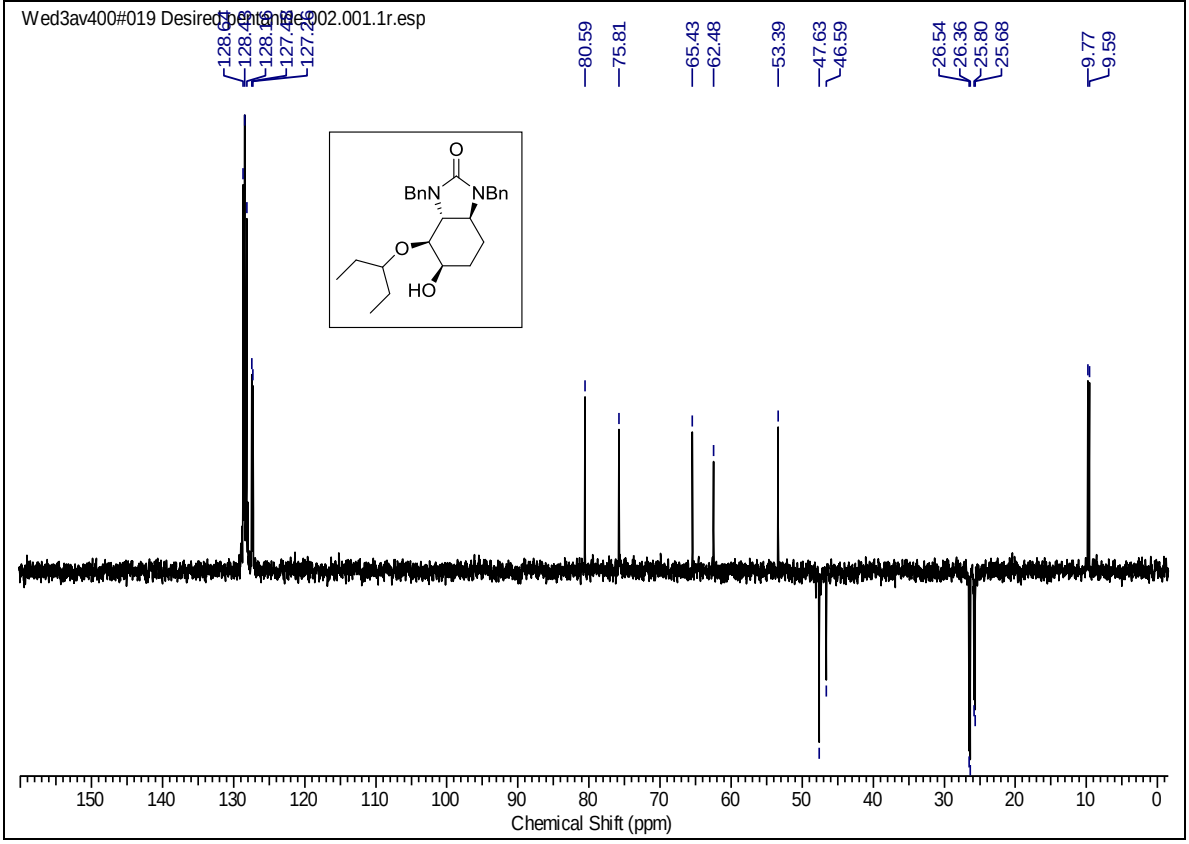
^{1}H NMR spectrum of compound 2 (400 MHz, $CDCl_3$ + CCl_4)



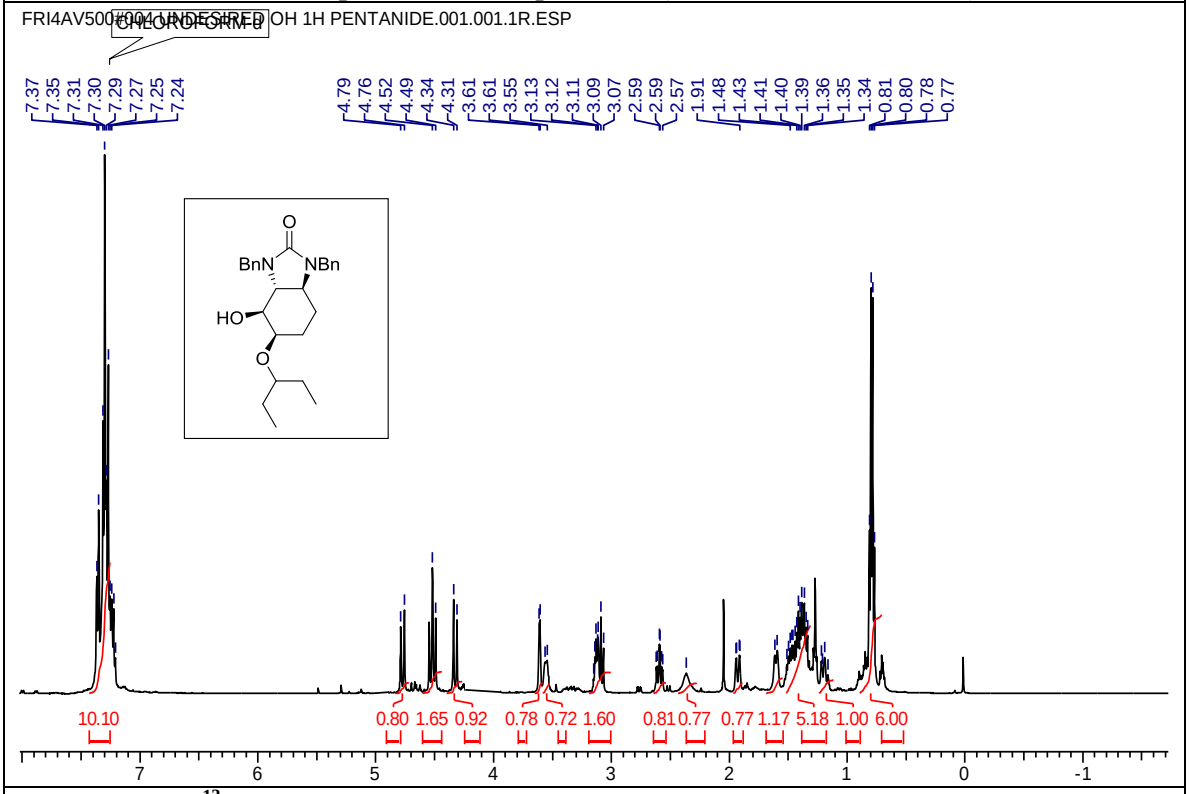
^{13}C NMR spectrum of compound 2 (100 MHz, $CDCl_3$ + CCl_4)



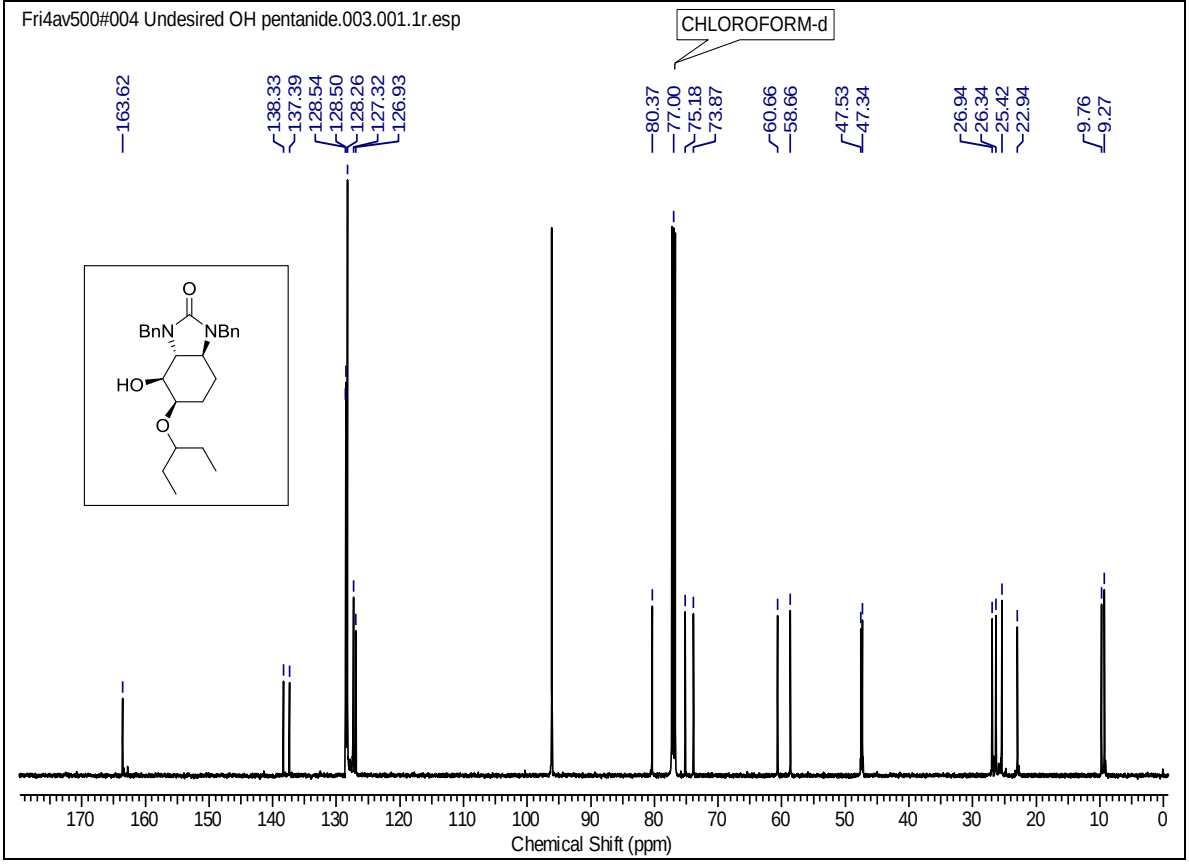
DEPT spectrum of compound 2 (100 MHz, $CDCl_3$ + CCl_4)



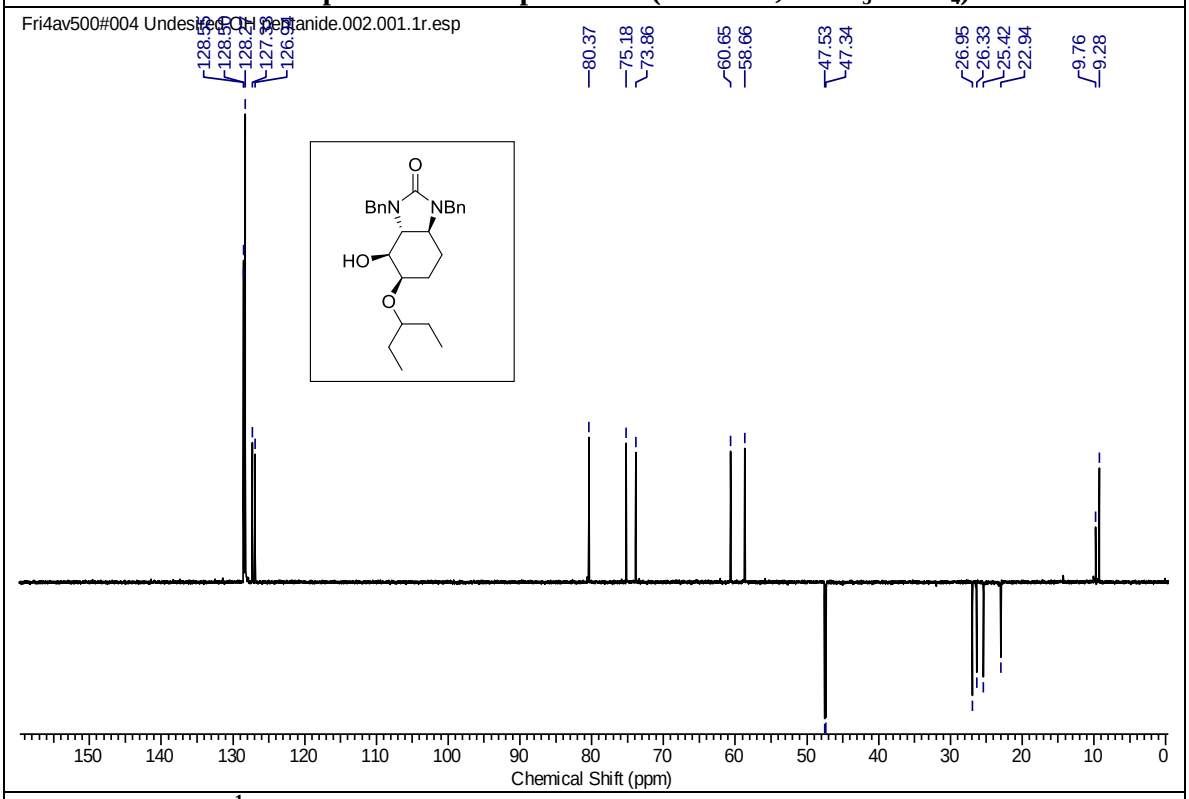
^{1}H NMR spectrum of compound 2a (500 MHz, $CDCl_3$ + CCl_4)



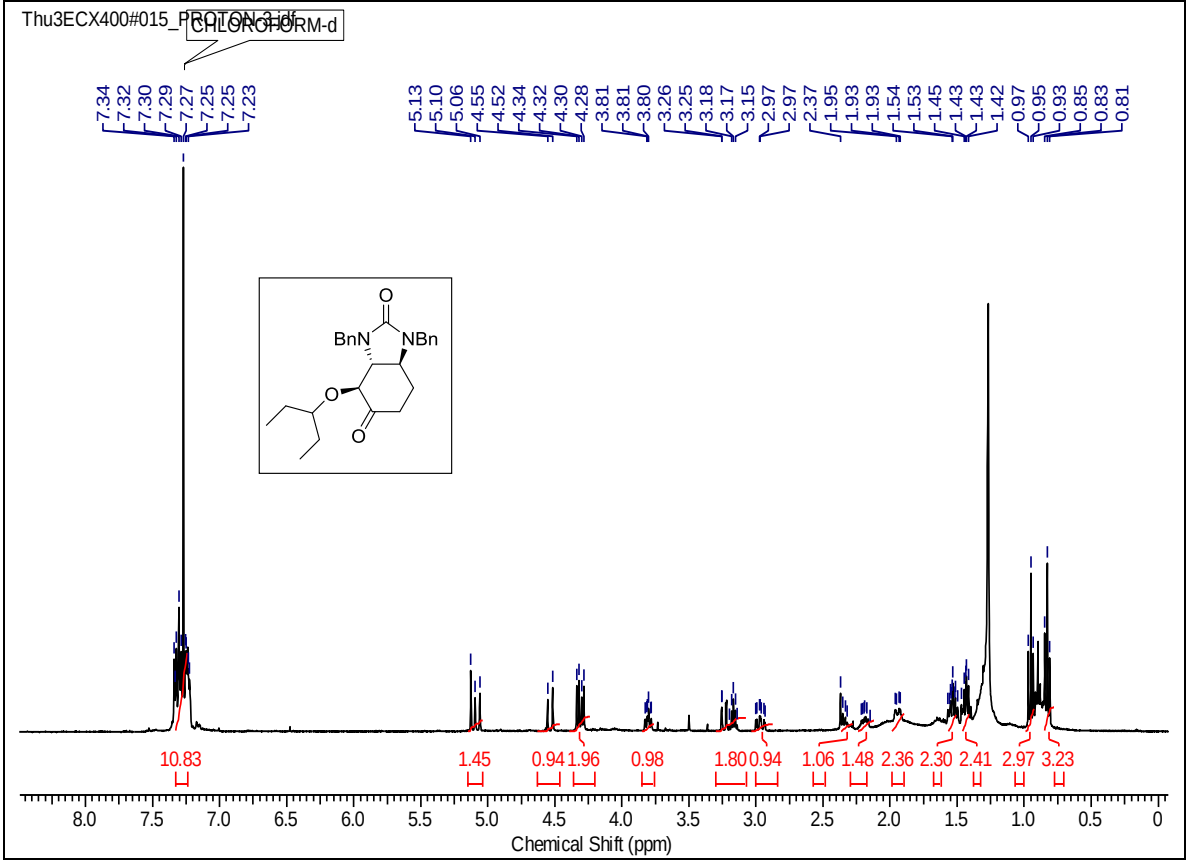
^{13}C NMR spectrum of compound 2a (125 MHz, $CDCl_3$ + CCl_4)



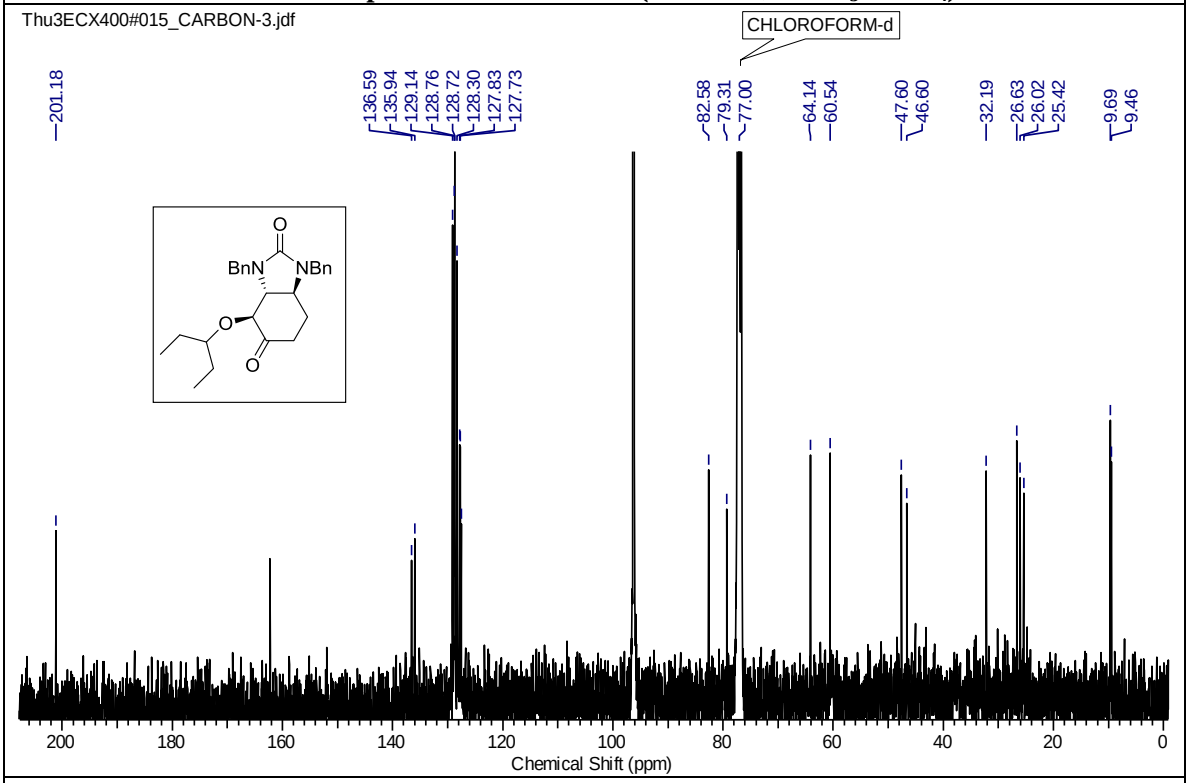
DEPT spectrum of compound 2a (125 MHz, $CDCl_3$ + CCl_4)



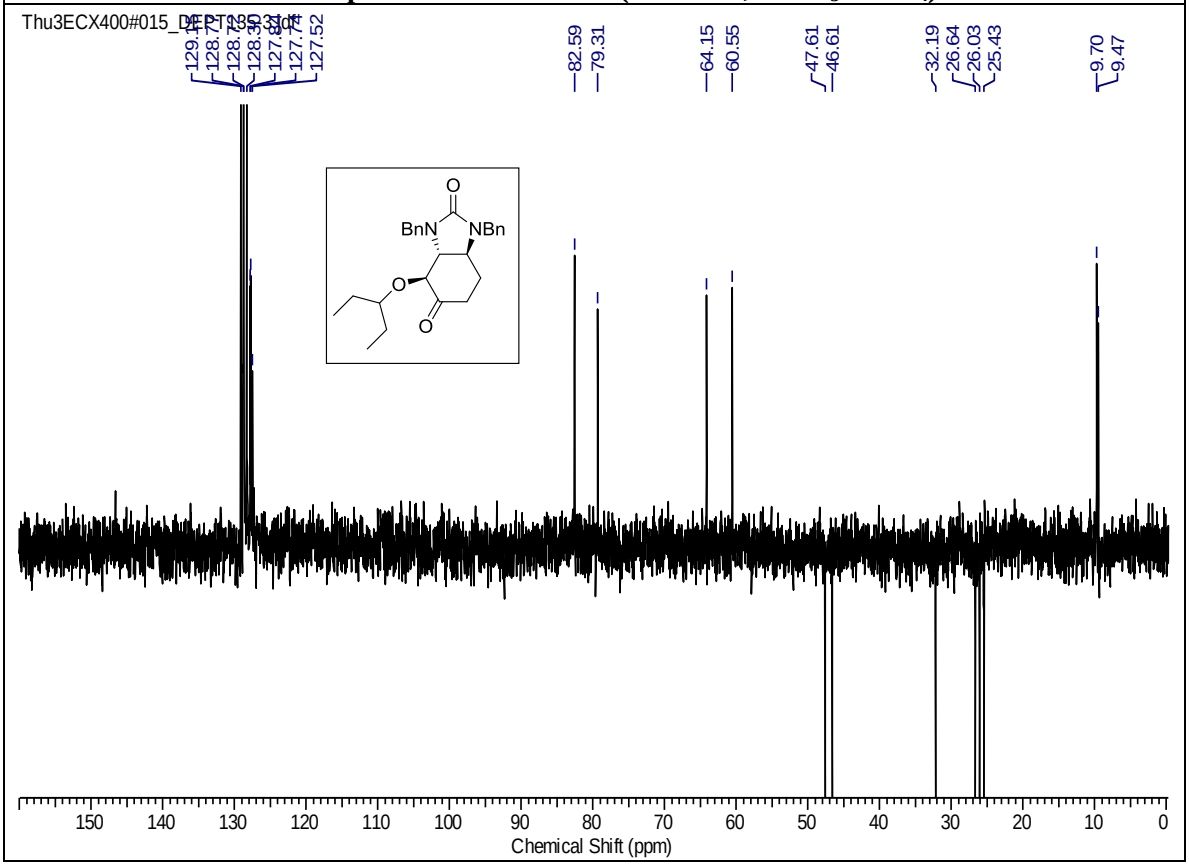
^{1}H NMR spectrum of ketone 12 (400 MHz, $CDCl_3$ + CCl_4)



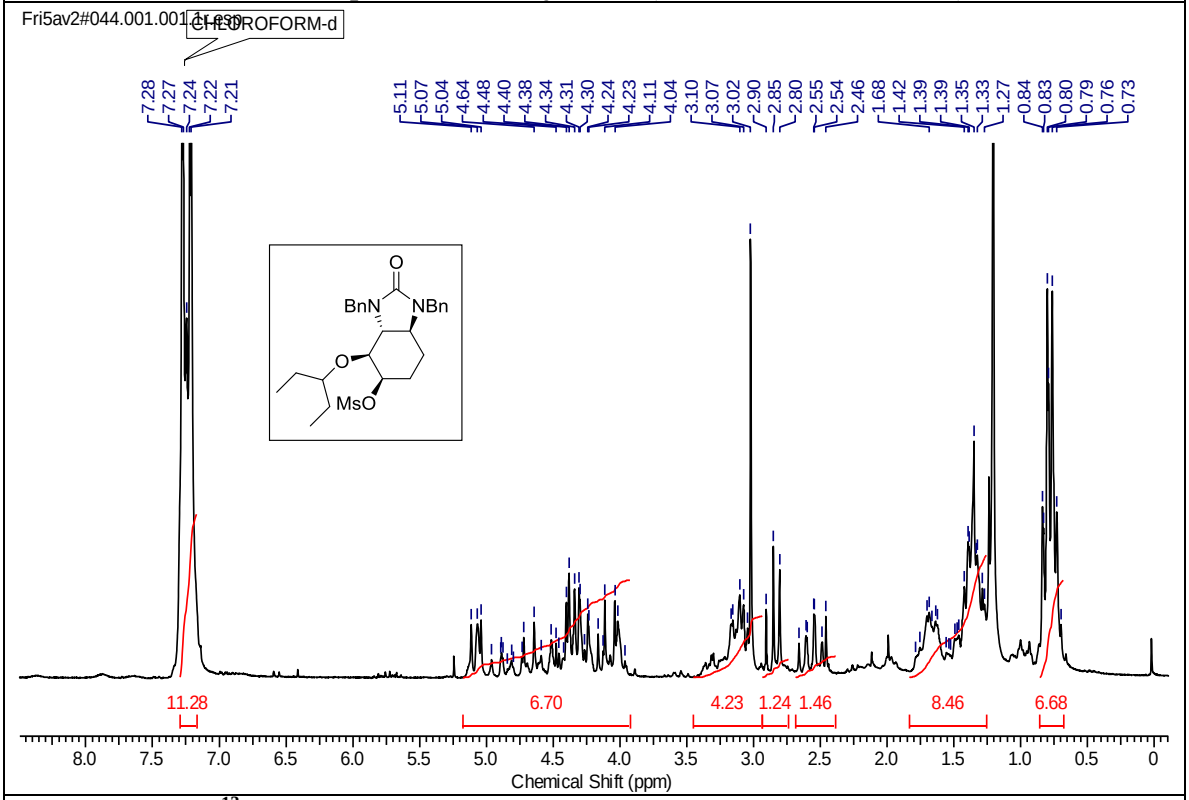
^{13}C NMR spectrum of ketone 12 (100 MHz, $CDCl_3$ + CCl_4)



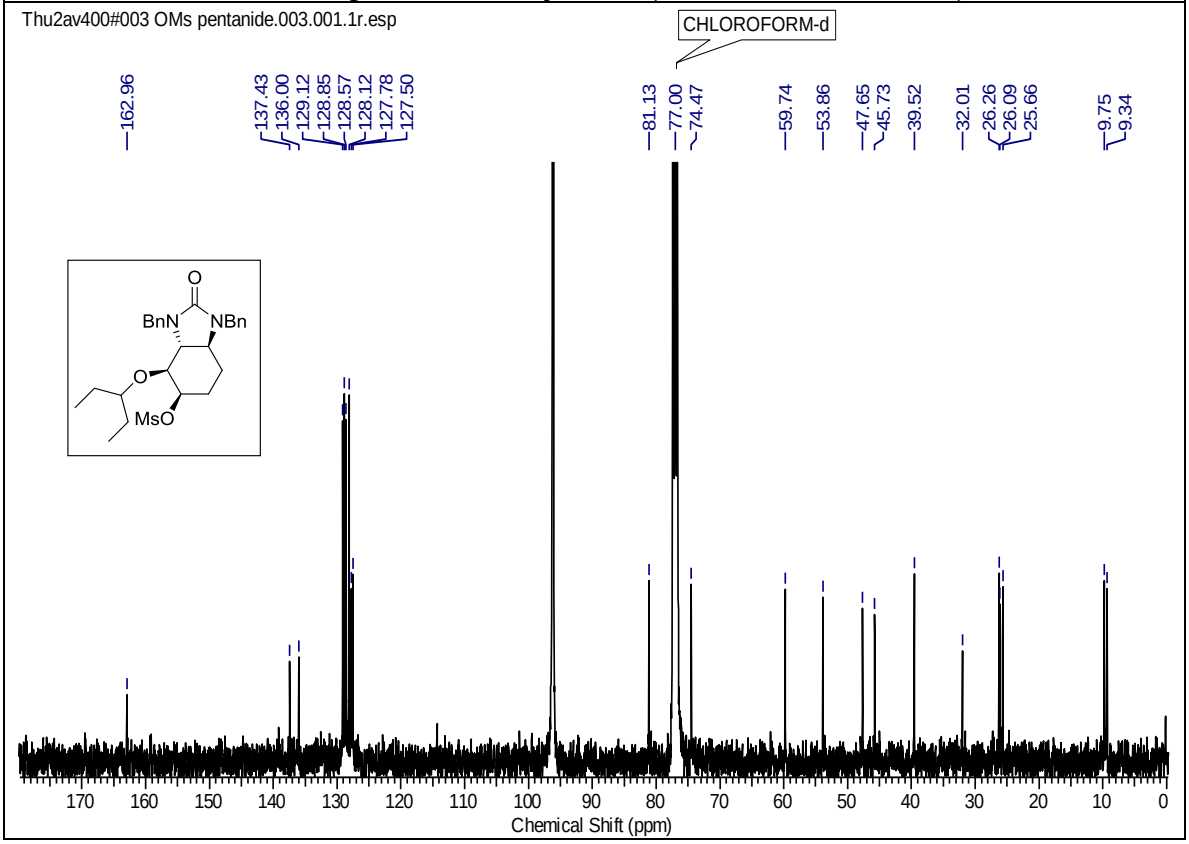
DEPT spectrum of ketone 12 (100 MHz, $CDCl_3$ + CCl_4)



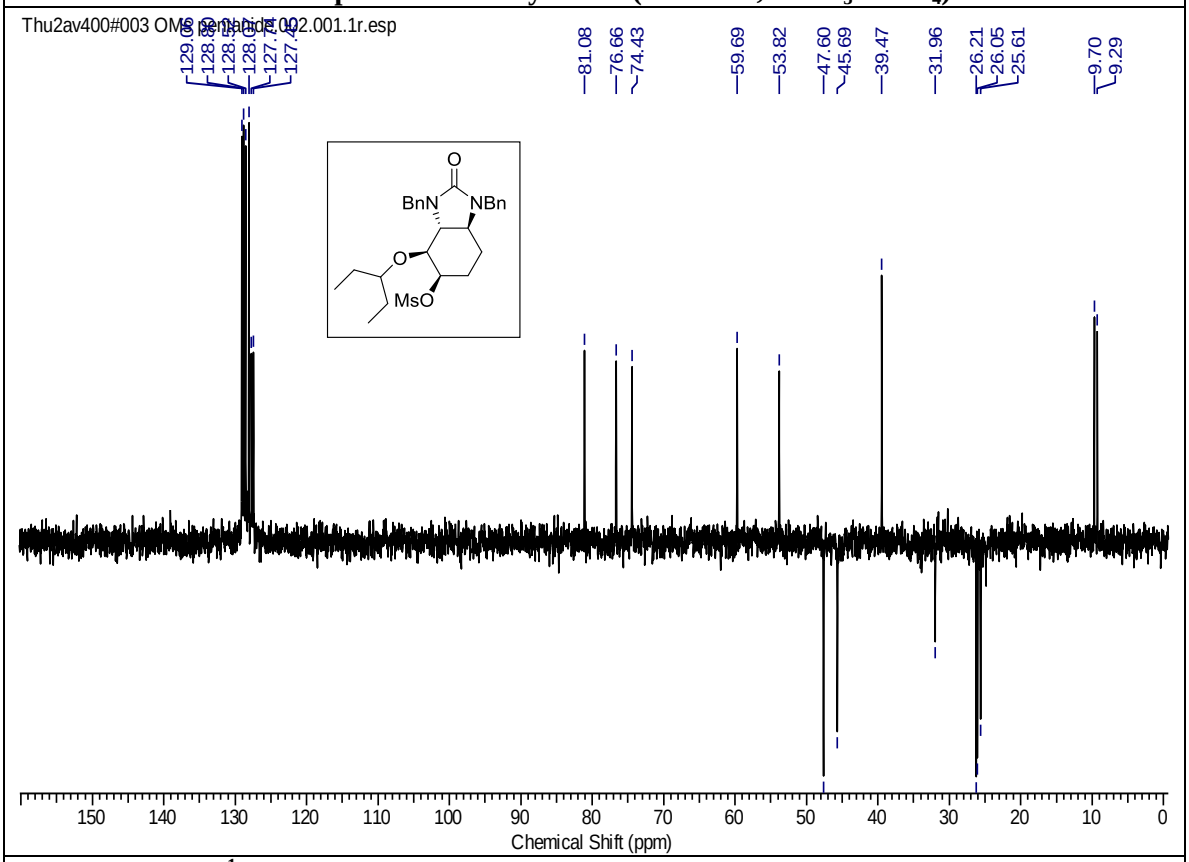
^{1}H NMR spectrum of mesylate 14 (200 MHz, $CDCl_3$ + CCl_4)



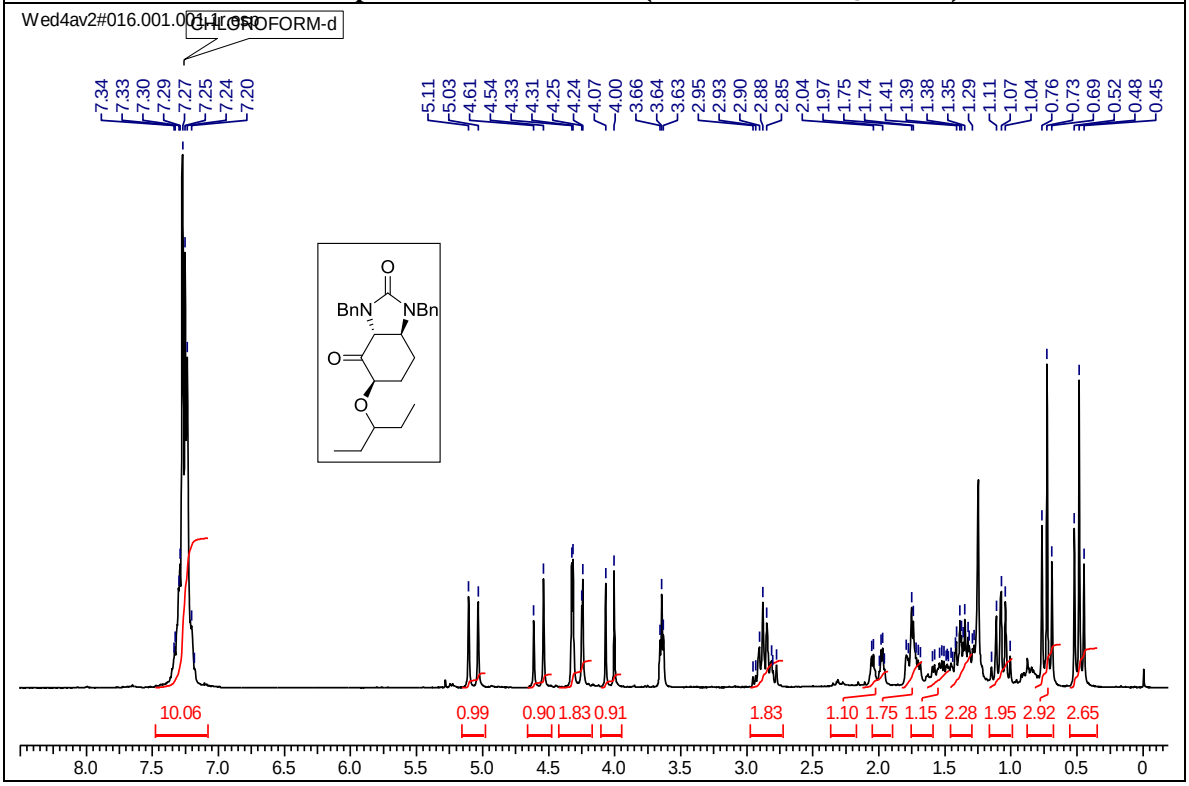
^{13}CNMR spectrum of mesylate 14 (100 MHz, $CDCl_3$ + CCl_4)



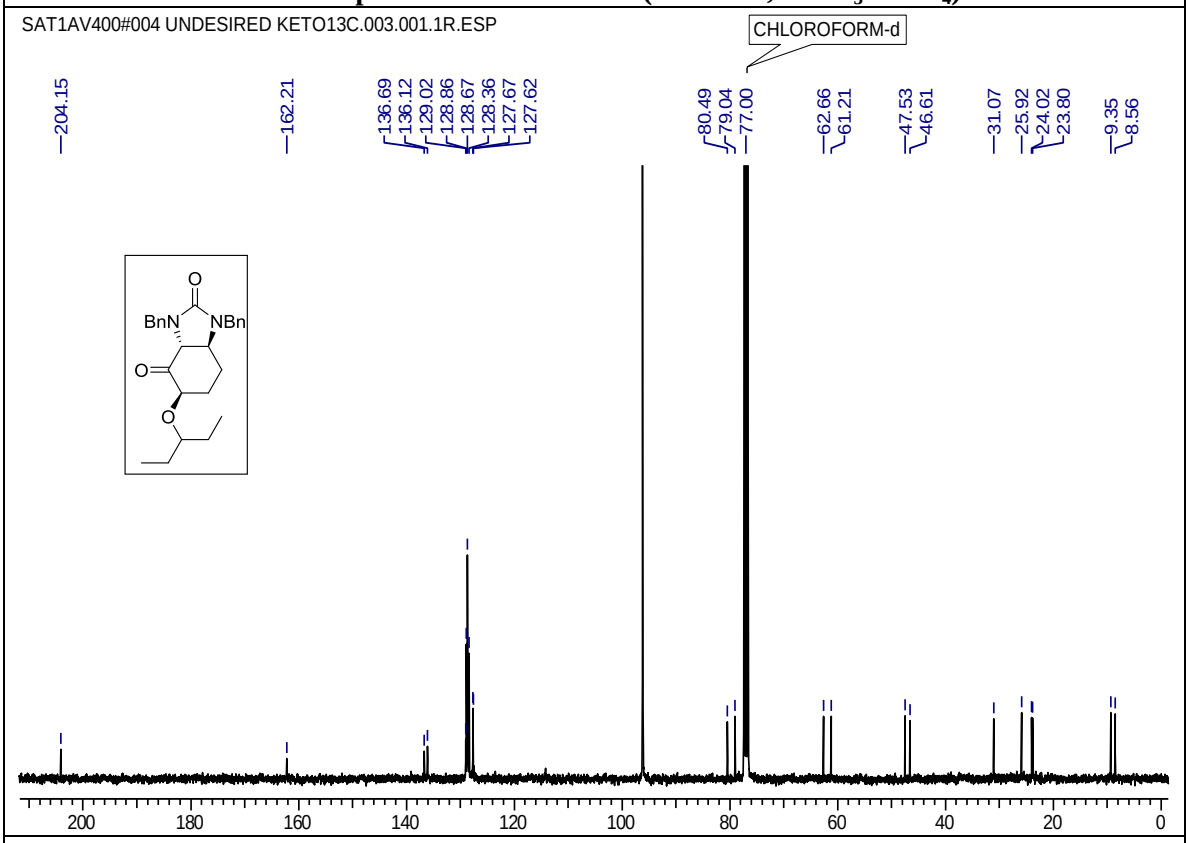
DEPT spectrum of mesylate 14 (100 MHz, $CDCl_3$ + CCl_4)



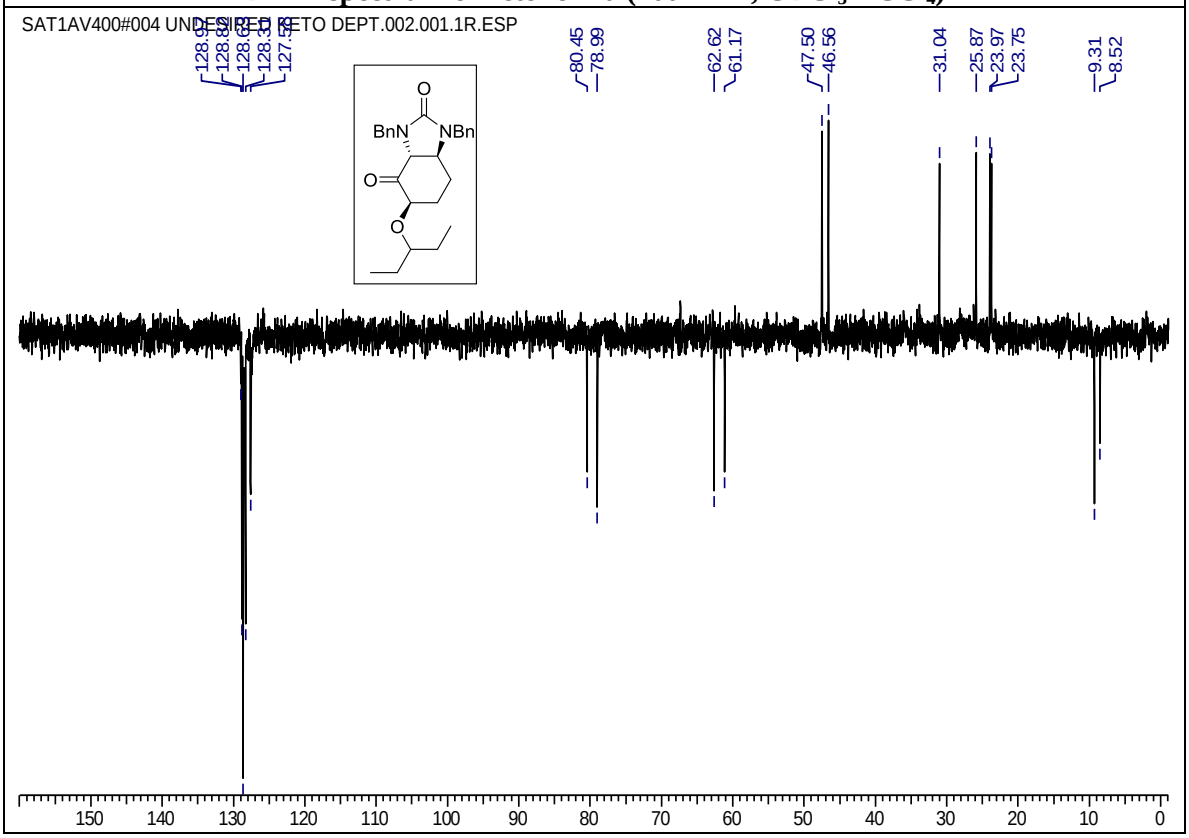
^{1}H NMR spectrum of ketone 12a (200 MHz, $CDCl_3$ + CCl_4)



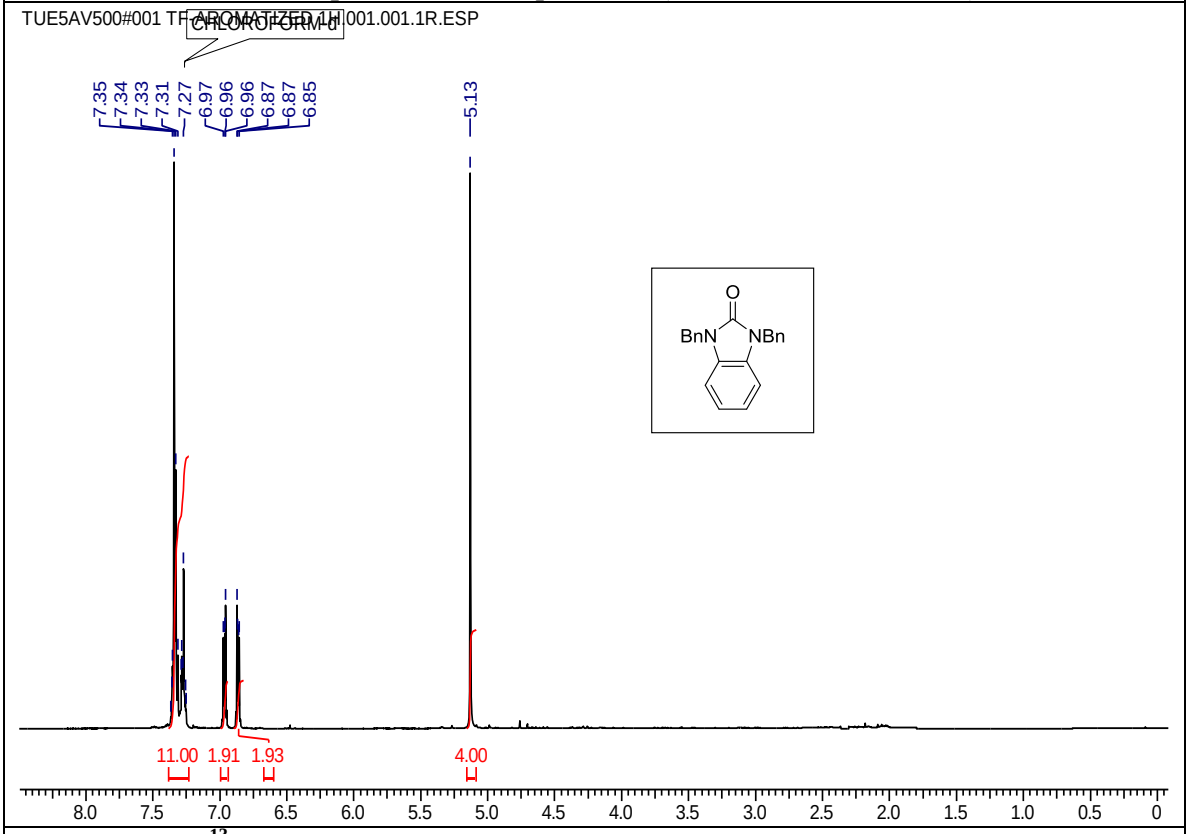
^{13}CNMR spectrum of ketone 12a (100 MHz, $CDCl_3$ + CCl_4)



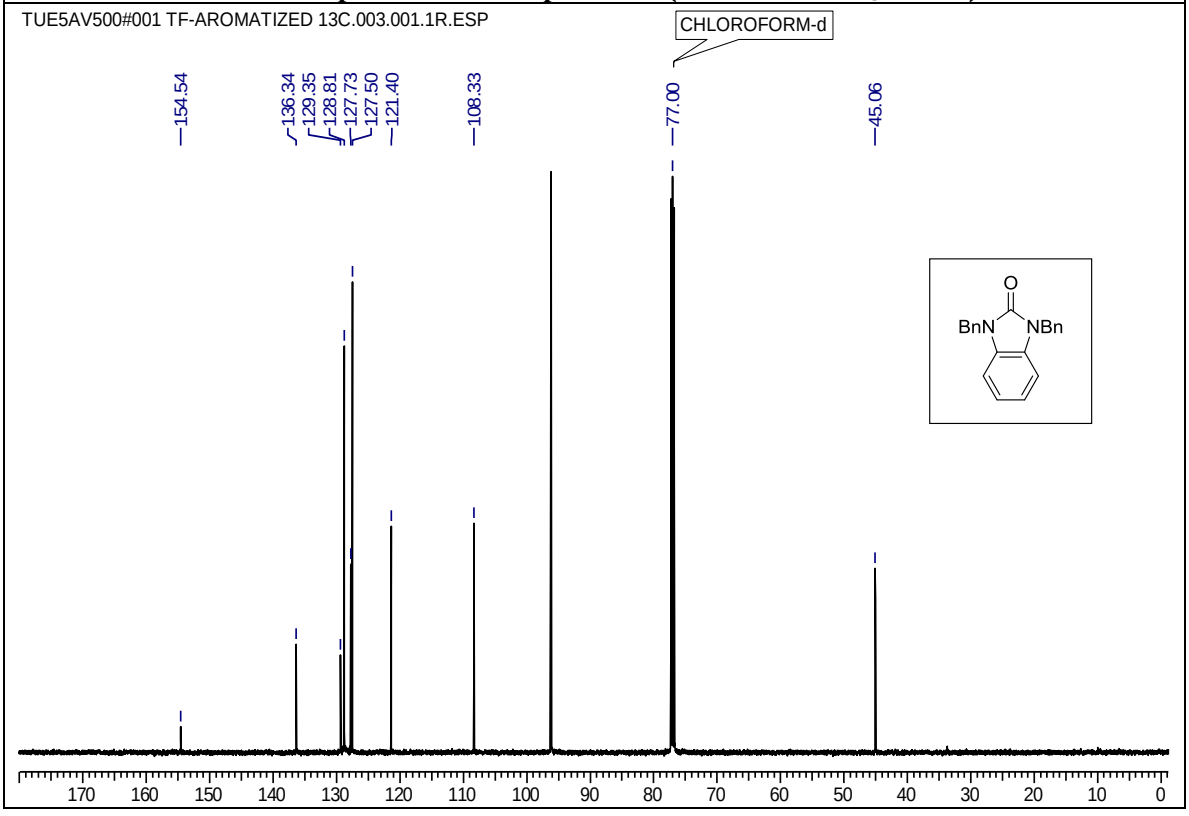
DEPT spectrum of ketone 12a (100 MHz, $CDCl_3$ + CCl_4)



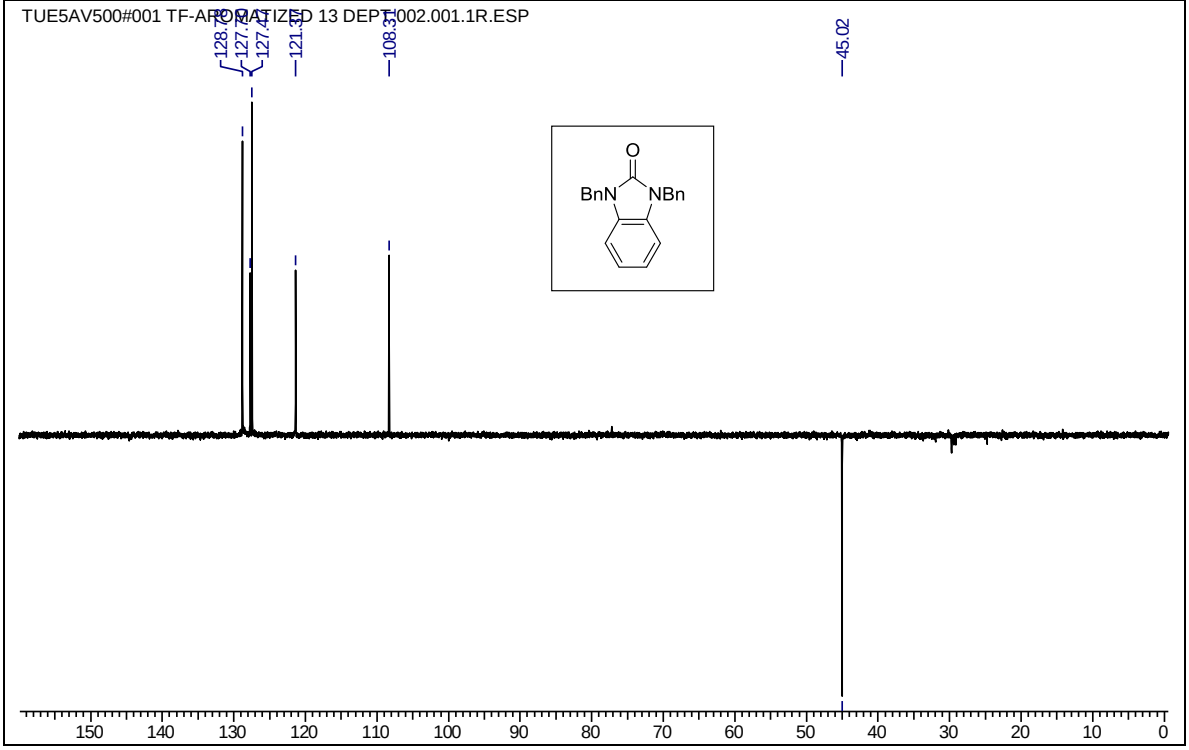
^{1}HNMR spectrum of Compound 16 (500 MHz, $CDCl_3$ + CCl_4)



^{13}CNMR spectrum of Compound 16 (125MHz, $CDCl_3$ + CCl_4)



DEPT spectrum of Compound 16 (125MHz, $CDCl_3$ + CCl_4)



1.2.5 References

1) (a) Cong, X.; Yao, Z. J. *J. Org. Chem.* **2006**, *71*, 5365; (b) Shie, J. J.; Fang, J. M.; Wang, S. Y.; Tsai, K. C.; Cheng, Y. S. E.; Yang, A. S.; Hsiao, S. C.; Su, C. Y.; Wong, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 11892; (c) Osato H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60; (d) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783; (e) Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006; (f) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787; (g) Weng, J.; Li, Y. B.; Wang, R. B.; Li, F. Q.; Liu, C.; Chan, A. s. c.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125.
2) Chavan, S. P.; Chittiboyina, A. G.; Ravindranathan, T.; Kamat, S. K.; Kalkote, U. R. *J. Org. Chem.* **2005**, *70*, 1901.
3) Ranu, B. C.; Manda, T. *Synlett* **2007**, *6*, 925.
4) Aranapakam.V.; Grosu, G. T.; Davis, J. M.; Hu, B.; Ellingboe, J.; Baker, J. L.; Skotnicki, J. S.; Zask, A.; Dijosepf, J. F.; Sung, A.; Sharr, M. A.; Killer, L. M.; Walter, T.; Jin, G.; Cowling , R. *J. Med. Chem.* **2003**, *46*, 2361.
5) Ludwig, R.; Birger, B. *Archives of Chemistry, Mineralogy and Geology* **1940**, 27, 1.
6) Bartels, B.; Hunter, R. *J. Org. Chem.* **1993**, *58*, 6756.
7) Zhu, X.; Jin, Y.; Wickham, J. *J. Org. Chem*. **2007**, *72*, 2670.
8) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60.
9) (a) Mann, K. R.; Lewis, N. S.; Miskowski, V. M.; Erwin, D. K.; Hammond, G. S.; Gray, H. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526; (b) Pilarski, L. T.; Selander, N.; Bose, D.; Szabo, K. J. *Org. Lett.* **2009**, *11*, 5518; (c) Muzart, J. *Chem. Rev.* **1992**, *92*, 113.

Section 3

Formal synthesis of Tamiflu employing stereospecific amidoalkylation and Ramberg-Backlund reaction

1.3.1 Present work

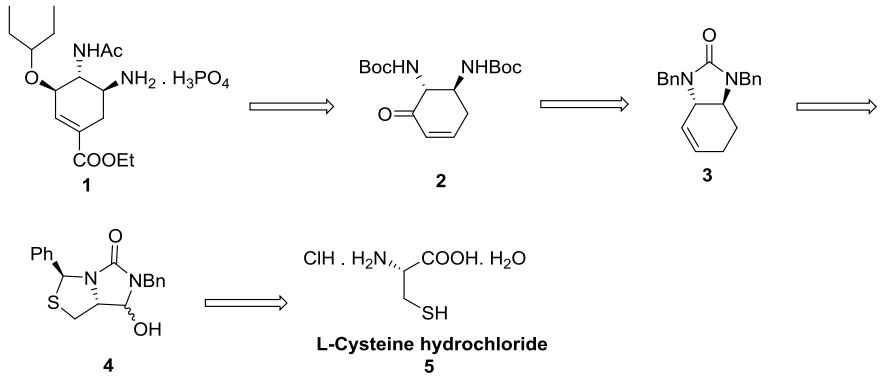
1.3.1.1 Objective

The stereospecific amidoalkylation protocol has been developed in our lab which was previously explored for the synthesis of D-(+)-biotin.[1] This novel protocol has potential application to provide the vicinal diamine in *trans* fashion on urea hydrolysis. In Chapter 1 Section 2 we have described an attempt towards the synthesis of oseltamivir phosphate (Tamiflu) using stereospecific amidoalkylation protocol and Ramberg-Backlund reaction but it led to failure.

In the present section the formal synthesis of oseltamivir phosphate (Tamiflu) starting from L-cysteine hydrochloride salt as chiral starting material was undertaken. Efforts were mainly focused to develop new synthetic strategy which should be azide and aziridine intermediate free using simple protocol for tamiflu.

1.3.1.2 Retrosynthetic analysis

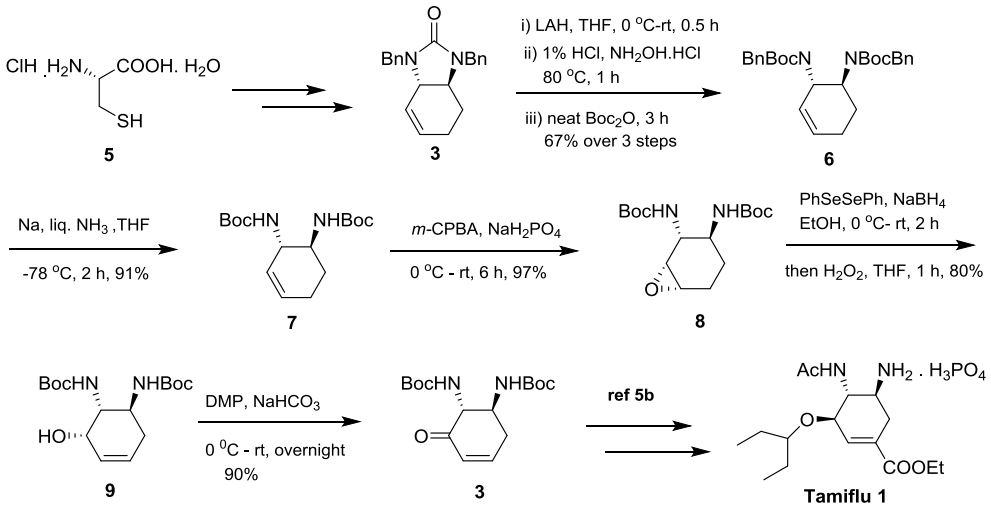
We envisioned the enone **2**, which is the known intermediate for tamiflu by Shibasaki, as our goal. The enone **2** could be obtained from cyclohexene compound **3** by urea hydrolysis, Birch reduction, epoxidation, epoxide opening and oxidation as key transformations. The compound **3** can be easily derived from alcohol **4** which could be easily accessed from L-cysteine hydrochloride **5** (scheme 1).



Scheme 1 Retrosynthetic analysis for tamiflu **1**

1.3.1.3 Results and discussion

The synthesis of tamiflu was started from the L-cysteine hydrochloride **5**. The conversion of **5** to olefin **3** is discussed in chapter 1, section 2. The major task was to hydrolyze cyclic urea to diamine. Accordingly, the olefin **3** was subjected to reduction with $LiAlH_4$ in THF to furnish imidazolidine, which without purification was subjected to hydrolysis in 1% HCl to afford corresponding vicinal diamine.[2] The crude vicinal diamine was masked as its carbamate derivative using neat Boc anhydride to give diboc derivative **6** in 67% yield (over 3 steps). Its IR spectrum showed the intense bands at 1695 and 1603 cm^{-1} corresponding to carbamate and olefin functional groups respectively. The ^1H NMR spectrum showed the peak at δ 5.93-5.31 ppm related to olefinic two protons and the peak at δ 1.59-1.22 ppm for 18 protons supporting the formation of diboc compound **6**. The HRMS peak observed at 515.2880 confirmed the molecular formula $C_{30}H_{40}N_2O_4$ of the dicarbamate **6**.



Scheme 2 Synthesis of Shibasaki's intermediate **1**

Further the dicarbamate **6** was subjected to chemeoselective debenzylation under Birch condition Na/liq. NH_3 in dry THF at -78 °C to afford compound **7** in 91% (Scheme 2).[3] The intense peaks at 3360, 1675 and 1600 cm^{-1} in IR spectrum of **7** were assigned to –NH of carbamate, carbonyl carbon of carbamate and olefin functionality respectively. The ^1H NMR spectrum showed the peaks at δ 5.04 (bd, J = 5 Hz, 1 H) and 4.74 (bd, J = 10 Hz, 1 H) ppm supporting the presence of the –NHCO- protons while the peaks at δ 5.81 - 5.70

(m, 1H) and 5.48 (bd, *J* = 10 Hz, 1H) revealed the olefinic protons. The ^{13}C NMR spectrum showed the peaks at δ 156.5 and 156.0 for the carbons of diboc functionality while ^{13}C DEPT NMR spectrum showed the peaks at δ 28.6 and 24.8 for two methylene carbons. The peak in HRMS spectrum was observed at 335.1942 which confirmed molecular formula $C_{16}H_{28}N_2O_4$ of compound **7**.

Further the diboc **7** was subjected to the epoxidation using *m*-CPBA and Na_2HPO_4 as buffering agent in DCM to furnish the regiospecific epoxide **8** as single product in excellent 97% yield.[4] The disapperance of peak at 1600 cm^{-1} in IR spectrum of **8** supported the epoxidation of olefin **7**. The ^1H NMR spectrum of **8** showed the peaks at δ 3.27 (1H) and 3.24 (1H) for two protons and the the disapperance of the peaks at δ 129.7 and 127.9 for two olefinic –CH carbons in ^{13}C NMR spectrum strongly supporting the formation of the epoxide **8**. The HRMS spectrum showed peak at 351.1890 which confirmed the molecular formula $C_{16}H_{28}N_2O_5$ of epoxide **8**. The Relative stereochemistry of epoxide **8** was fully established by NOSEY mult and finally unequivocally confirmed by a single crystal X-ray analysis (Fig 1).

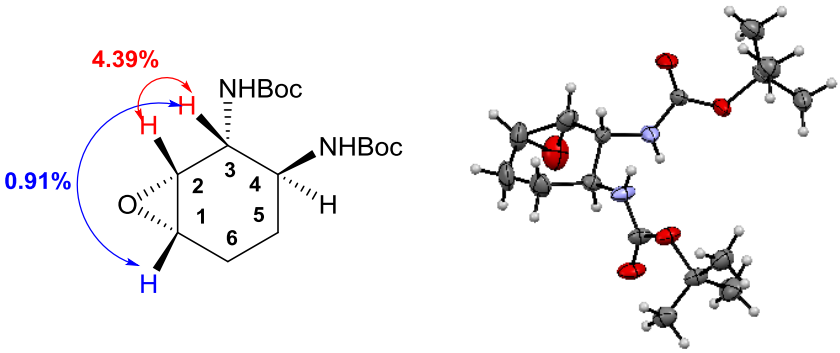


Figure 1 NOESY and X-ray single crystal analysis of epoxie **10** (ORTEP diagram; ellipsoids are drawn at 30% probabilities)

The epoxide **8** was treated under Sharpless-Reich, one-pot two-step protocol leading to allylic alcohol **9**.[5] Accordingly, to epoxide **8** in EtOH at 0 ^oC was added PhSeSePh and $NaBH_4$ and the reaction mixture was stirred for 2 h. Then THF was added followed by 30% H_2O_2 added slowly at 0 ^oC. The resultant reaction mass was stirred at room temperature for 1 h to give allylic alcohol **9** in 80% over two steps. The IR spectrum of

allylic alcohol **9** showed the peaks at 3430 and 1645 cm^{-1} corresponding to hydroxy group and double bond respectively. The peaks at δ 5.67 (bd, *J* = 5 Hz, 1 H) and 5.54 (bd, *J* = 5 Hz, 1H) in ^{1}H NMR spectrum were related to the olefinic protons. The ^{13}C NMR spectrum showed the peaks at δ 129.8 and 124.7 ppm for the two olefinic –CH carbons which strongly supported the formation of allylic alcohol **9**. The HRMS peak was observed at 351.1891 which confirmed the molecular formula $C_{16}H_{28}N_2O_5$ of allylic alcohol **9**.

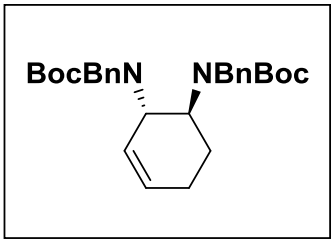
Final task was to obtain enone **2**, accordingly the allylic alcohol **9** was subjected to oxidation using DMP and $NaHCO_3$ in DCM to furnish the unsaturated ketone **2** in 90%. The IR spectrum of enone **2** showed the peak at 1695 cm^{-1} corresponding to unsaturated ketone functionality, which clearly indicated the oxidation of allylic alcohol **9**. The ^{1}H NMR spectrum showed the peaks at δ 5.67 (bd, *J* = 1.5 Hz, 1 H) and 5.54 (bd, *J* = 7.0 Hz, 1H) ppm for the two protons of double bond. The ^{13}C NMR spectrum showed the peak at δ 194.3 for carbonyl carbon of unsaturated ketone and peaks at δ 157.7 and 155.7 ppm for two carbamate groups. The ^{13}C DEPT NMR spectrum showed the peak at δ 34.6 ppm for one methylene carbon. The spectral data for **2** is in full agreement with reported by Shibasaki.[6]

1.3.2 Conclusion

In conclusion, the formal synthesis of tamiflu has been achieved from inexpensive and abundant L-cysteine as the natural renewable resource. The notable features of the synthesis involve utilisation of efficient stereospecific amidoalkylation protocol *a*nd Ramberg-Backlund reaction to access required *trans* diamine and cyclohexene core skeleton of neuraminidase inhibitor drug 1 respectively. We successfully demonstrated azide and aziridine intermediate free synthetic route and utilised the mild reactions conditions throughout the synthesis. Our novel methodology could be helpful for preparation of 1, 2-diamine functional ligands and other related bioactive compounds.

1.3.3 Experimental

Di-tert-butyl (1*S*, 2*S*)-cyclohex-3ene-1, 2-diylbis (benzylcarbamate) (6):



To a cooled solution of olefin **3** (1.2 gm, 3.77 mmol) in dry THF at 0 ^{o}C was added lithium aluminium hydride portionwise (715 mg, 18.84 mmol). The reaction mixture was stirred at room temperature for 30 min and was quenched by addition of 15% NaOH solution and ice pieces. Then anhydrous Na_2SO_4 was added to the reaction and stirred for 10 min. The resultant solution was filtered and the residue was washed with the ethyl acetate (2 X 15 mL). The filterate was concentrated under reduced pressure. Crude compound was directly subjected for further reaction without purification.

The crude compound (1.15 gm) was subjeted to hydrolysis by treatment with aq 1% HCl (10 mL) and $NH_2OH.HCl$ (3.5 gm, excess) and heating at 80 ^{o}C for 1h. The reaction mixture was neutralised with solid $NaHCO_3$ and compound was extracted with DCM (3 X 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude diamine.

The crude diamine (1.1 gm) without purification was chemically masked with neat $(Boc)_2O$ (1.93 mL, 11.30 mmol) and cat. DMAP (100 mg). The reaction mixture was stirred at room temperature for 3 h, water was added and the compound was extracted with DCM (3 X 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 5% ethyl acetate in pet ether as an eluent to afford compound **6** (1.54 gm, 67% over three steps) as a colourless syrup.

***R_f*:** 0.7 (Pet ether: ethyl acetate, 80:20).

MF: $C_{30}H_{40}N_2O_4$, **MW:** 492.66.

Yield: 67% (over three steps).

$[\alpha]_D^{25}$: +6.0 (*c* 2.0, $CHCl_3$).

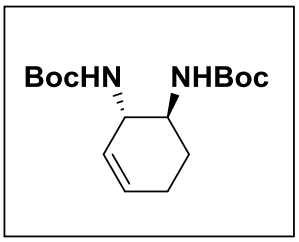
IR ($CHCl_3$, cm^{-1})**:** ν_{max} 2924, 1695, 1603, 1365, 1165.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.48 - 7.04 (m, 10H), 5.93 - 5.31 (m, 2H), 5.26 - 3.27 (m, 6H), 2.40 - 1.74 (m, 4H), 1.59 - 1.22 (m, 18H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.2, 155.7, 140.6, 129.5, 128.8, 128.2, 128.0, 127.8, 127.3, 126.5, 126.4, 126.2, 79.6, 79.5, 58.6, 58.0, 54.4, 53.2, 28.4, 28.3, 27.4, 25.7.

HRMS : observed- 515.2880, calculated- 515.2880.

Di-tert-butyl ((1*S*, 2*S*)-cyclohex-3-ene-1, 2-diyl)dicarbamate (7)



To a solution of diboc compound **6** (300.00 mg, 0.58 mmol) in THF (5 mL) and ammonia (10 mL) at -78 ^oC was added sodium metal (428 mg, 18.75 mmol) portionwise and stirred at same temperature for 2 h. The reaction mixture was quenched with solid ammonium chloride and the reaction mass was brought to room temperature. Water (10 mL) was added to the residue and compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet ether as an eluent to afford compound **7** (173 mg, 91%) as a white solid.

***R_f*:** 0.4 (Pet ether: ethyl acetate, 70:30).

MF: $C_{16}H_{28}N_2O_4$, **MW:** 312.41.

Yield: 91%.

$[\alpha]_D^{25}$: +12.5 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1})**:** ν_{max} 3360, 2923, 1675, 1600, 1463, 1166.

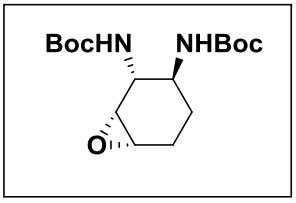
MP : 135-137 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.81 - 5.70 (m, 1H), 5.48 (bd, *J* = 10 Hz, 1H), 5.04 (bd, *J* = 10 Hz, 1H), 4.74 (bd, *J* = 10 Hz, 1H), 4.15 - 4.03 (m, 1H), 3.48 (bd, *J* = 10 Hz, 1H), 2.34 - 1.93 (m, 4H), 1.44 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.5, 156.0, 129.5, 127.6, 79.5, 79.0, 53.2, 52.5, 28.6, 28.4, 24.8.

HRMS : Observed- 335.1942, calculated- 335.1940.

Di-tert-butyl ((1*R*, 2*R*, 3*S*, 6*S*)-7-oxabicyclo-[4.1.0]-heptane-2, 3-diyl)dicarbamate (8):



To a cooled (0 ^{o}C) and stirred solution of diboc olefin **7** (90 mg, 0.29 mmol) in DCM (2 mL) was added NaH_2PO_4 (315 mg, 2.01 mmol) followed by *m*-CPBA (355 mg, 2.01 mmol). Reaction mixture was stirred at 0 ^{o}C for 30 min and then allowed to stir at room temperature for 6 h. After completion of the reaction, saturated aq. solution of $Na_2S_2O_3$ (3 mL) was added and the reaction mixture was further stirred for 30 min. Water (3 mL) was added to the reaction mixture and it was extracted with ethyl acetate (3 X 5 mL). The combined organic layer was washed with saturated aq. solution of $NaHCO_3$ (3 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford compound **8** (92 mg, 97%) as a white solid.

***R_f*:** 0.4 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{16}H_{28}N_2O_5$, **MW:** 328.41.

Yield: 97% (over two steps).

$[\alpha]_D^{25}$: +27.27 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1})**:** ν_{max} 3359, 1681, 1519, 1168.

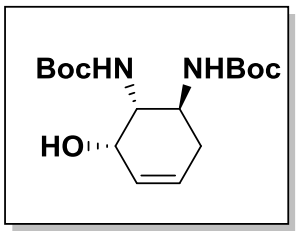
MP: 135-137 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.11 (bd, *J* = 10 Hz, 1H), 4.87 (bs, 1H), 3.87 - 3.75 (m, 1H), 3.52 (bd, *J* = 10 Hz, 1H), 3.27 (bs, 1H), 3.24 (bs, 1H), 2.11 - 1.88 (m, 3H), 1.81 (d, *J* = 10 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.5, 155.9, 79.7, 79.2, 56.1, 53.9, 53.4, 49.7, 28.6, 28.47, 28.44, 22.7.

HRMS : Observed- 351.1890, calculated- 351.1890.

Di-tert-butyl (1*R*, 2*R*, 3*S*, 6*S*)-7- oxabicyclo-[4.1.0]-heptane-2, 3-diyldicarbamate (9)



To a stirred solution of epoxide **8** (60 mg, 0.18 mmol) in methanol (1 mL) was added diphenyl diselenide (4 mg, 0.01 mmol) followed by sodium borohydride (8 mg, 0.21 mmol) and reaction mixture was stirred at rt for 2 h. After disappearance of starting material which was monitored by TLC, THF (1 mL) was added followed by H_2O_2 (0.38 mL, 30%, 3.65 mmol) and it was further stirred for 1 h. The reaction mixture was concentrated; water was added and extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford allylic alcohol **9** (50 mg, 80%) as white solid.

***R_f*:** 0.3 (Pet ether: ethyl acetate, 70:30).

MF: $C_{16}H_{28}N_2O_5$, **MW:** 328.41.

Yield: 80%.

$[\alpha]_D^{25}$: -41.25 (*c* 3.2, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 3430, 1679, 1645, 1528, 1366, 1163.

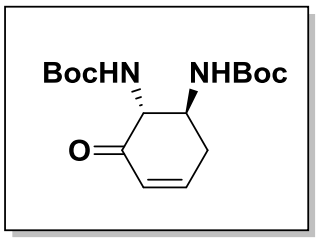
MP: 121-123 ^{o}C.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 5.67 (bd, *J* = 1.5 Hz, 1H), 5.54 (bd, *J* = 5 Hz, 1H), 4.19 - 4.14 (m, 1H), 3.81 - 3.70 (m, 1H), 3.51 - 3.43 (m, 1H), 2.46 (dd, *J* = 5, 15Hz, 1H), 2.10 - 1.96 (m, 2H), 1.46 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 158.1, 156.7, 129.8, 124.7, 79.9, 73.5, 60.4, 48.8, 32.3, 28.3.

HRMS : Observed- 351.1891, calculated- 351.1890.

Di-tert-butyl (1*R*, 2*R*, 3*S*, 6*S*)-7- oxabicyclo-[4.1.0]heptane-2, 3-diyldicarbamate (2)



To the solution of allylic alcohol **9** (25 mg, 0.07 mmol) in DCM (1 mL) was added $NaHCO_3$ (50 mg, 0.76 mmol) and Dess-Martin periodinate (85 mg, 0.22 mmol) at 0 ^oC. The reaction mixture was stirred for overnight at rt. After completion of reaction, water (3 mL) was added to the reaction mass and compound was extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compound **2** (22 mg, 90%) as semisolid mass.

***R_f*:** 0.4 (Pet. ether: ethyl acetate, 70:30).

MF: $C_{16}H_{26}N_2O_5$, **MW:** 326.39.

Yield: 90%.

$[\alpha]_D^{25}$: -114.9 (*c* 0.5, $CHCl_3$), lit. -116.3 (*c* 0.945, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3411, 2926, 1695, 1514, 1173.

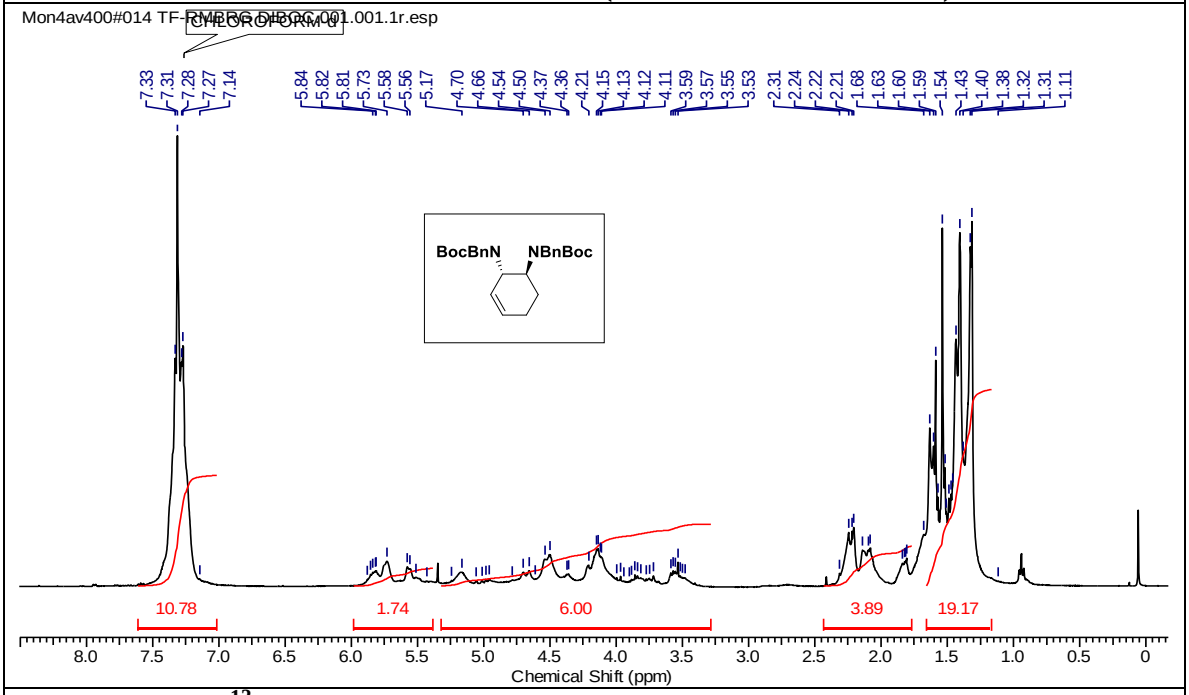
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.00 - 6.92 (m, 1H), 6.14 (dd, *J* = 10.1 Hz, 3.1 Hz, 1H), 5.98 (d, *J* = 7.3 Hz, 1H), 5.52 (d, *J* = 6.1 Hz, 1 H), 4.30 (dd, *J* = 13.1, 6.4 Hz, 2H), 3.97 - 3.81 (m, 1H), 3.00-2.94 (m, 1H), 2.50 - 2.24 (m, 2H), 1.48 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 194.3, 157.7, 155.7, 148.4, 128.5, 80.4, 79.3, 60.5, 54.4, 34.6, 28.4, 28.3.

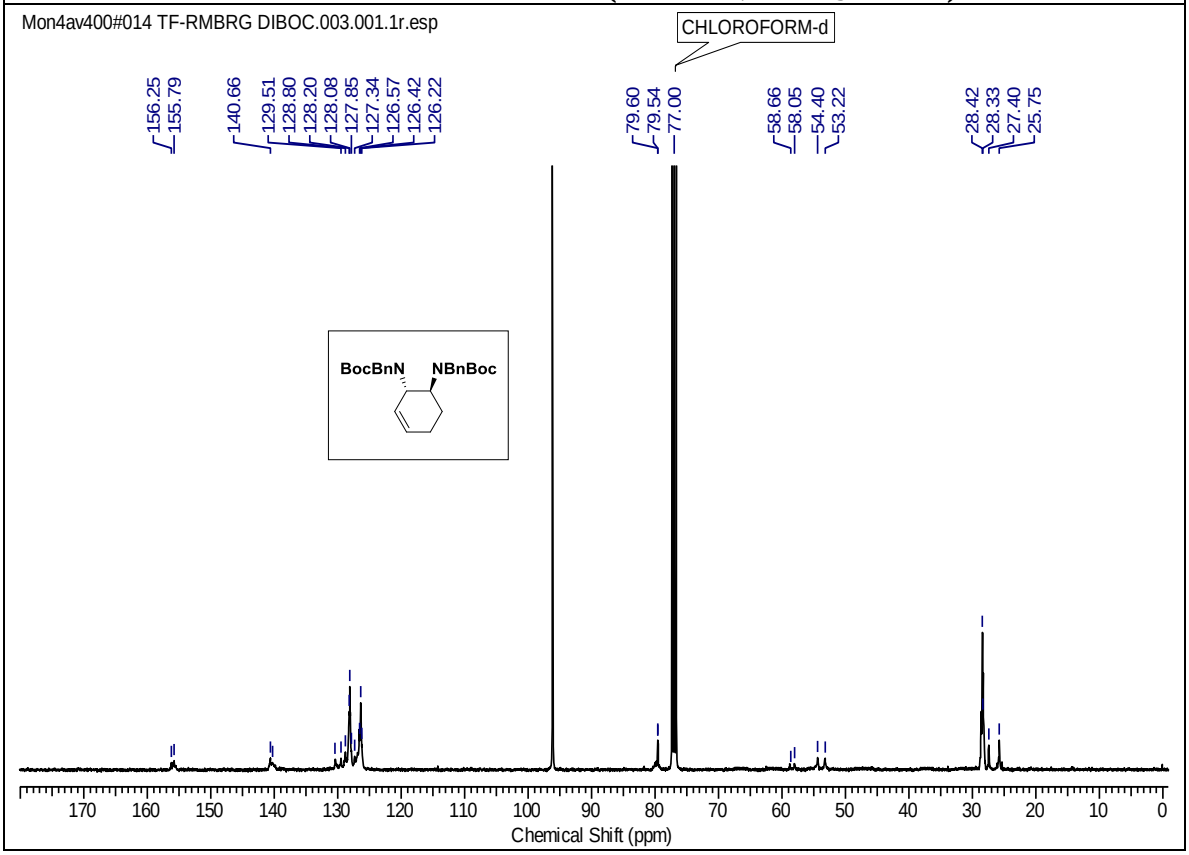
HRMS : Observed- 349.0231, calculated- 349.0236.

1.3.4 Spectral data

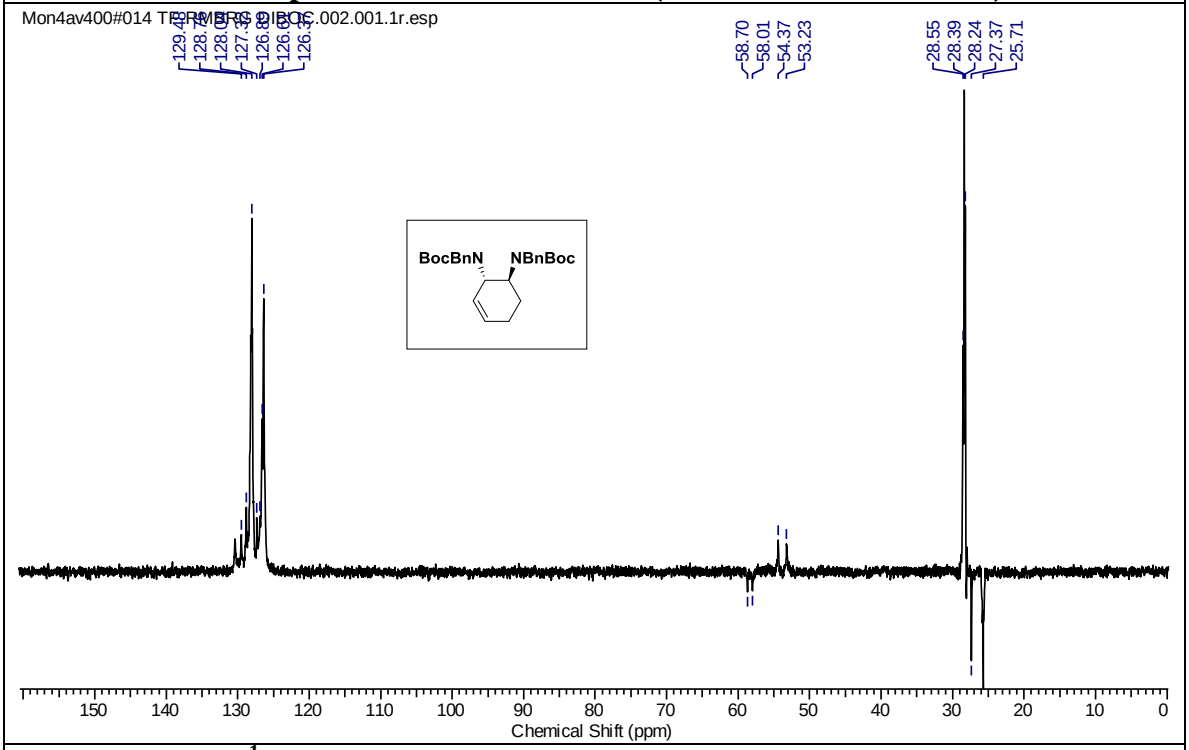
^{1}H NMR of dicarbamate 6 (400 MHz, $CDCl_3$ + CCl_4)



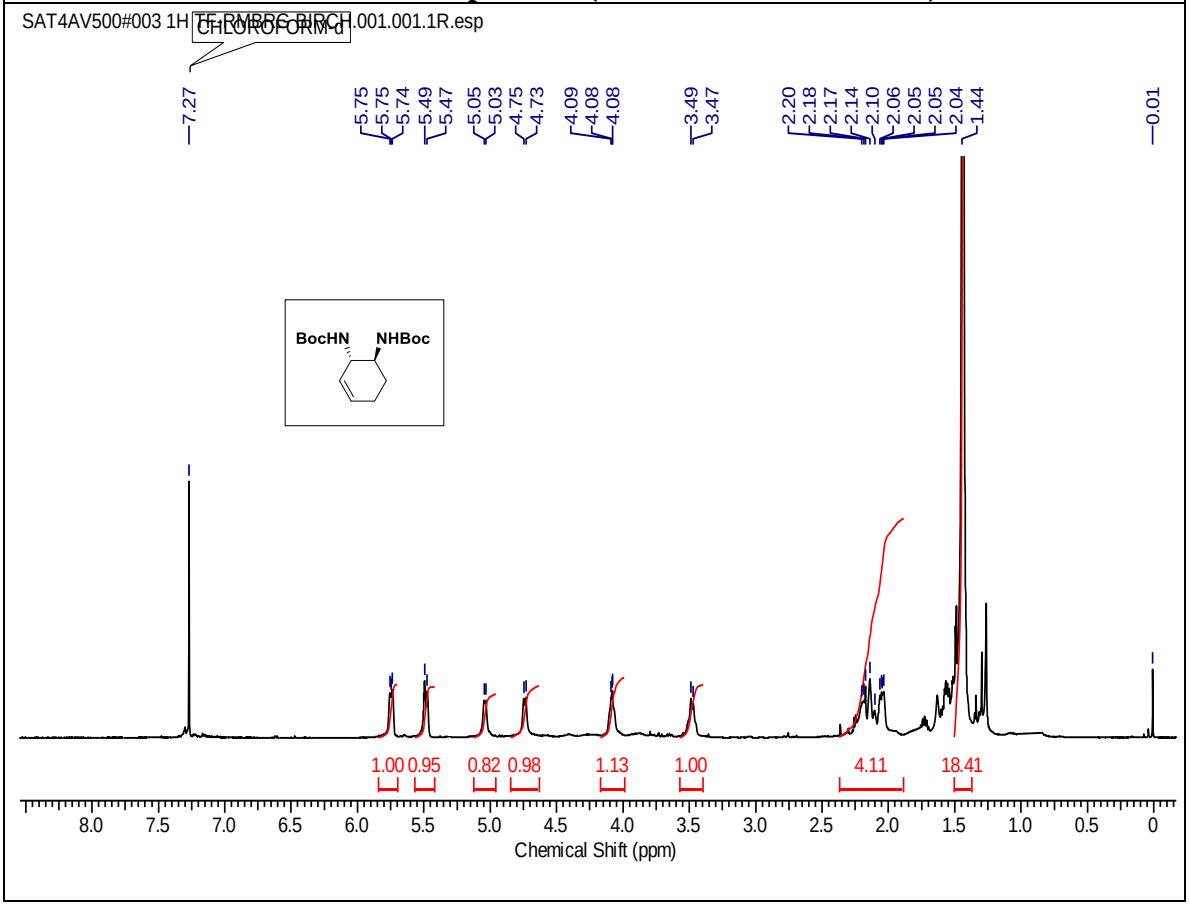
^{13}C NMR of dicarbamate 6 (100 MHz, $CDCl_3$ + CCl_4)



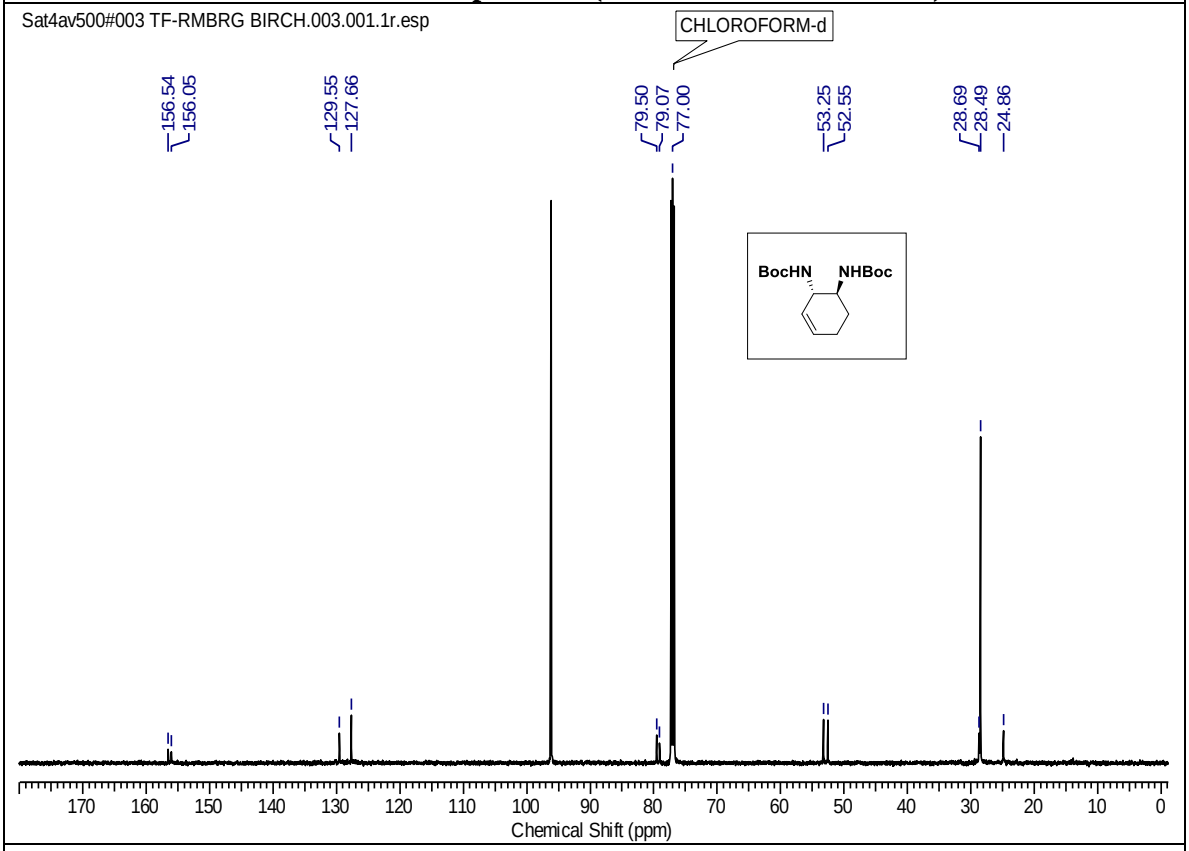
DEPT spectrum of dicarbamate 6 (100 MHz, $CDCl_3$ + CCl_4)



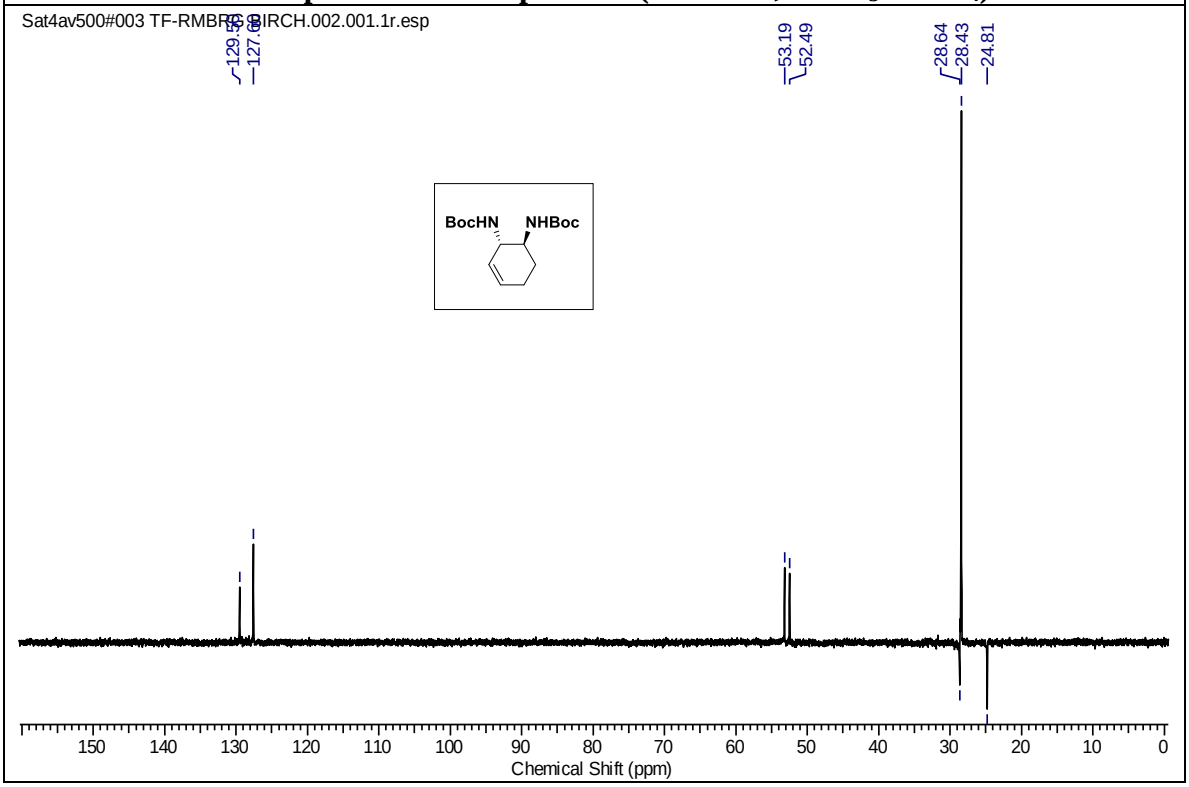
^{1}H NMR of compound 7 (500 MHz, $CDCl_3$ + CCl_4)



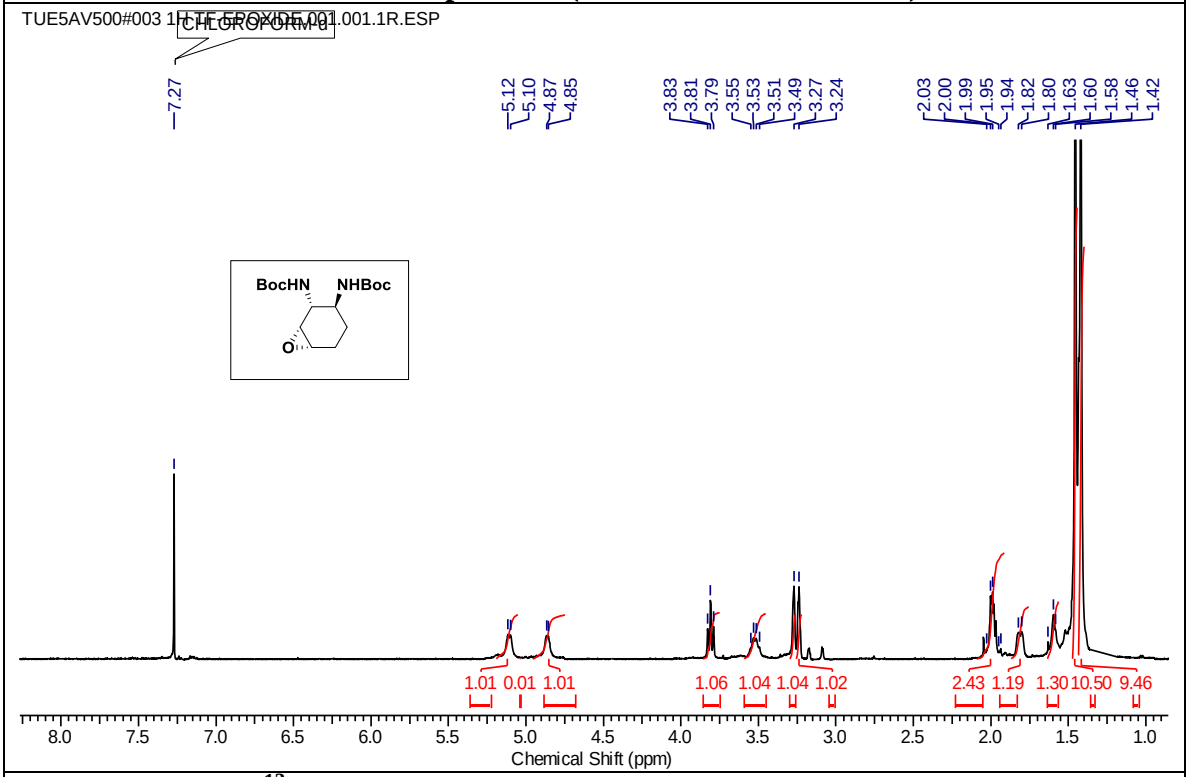
^{13}C NMR of compound 7 (125 MHz, $CDCl_3$ + CCl_4)



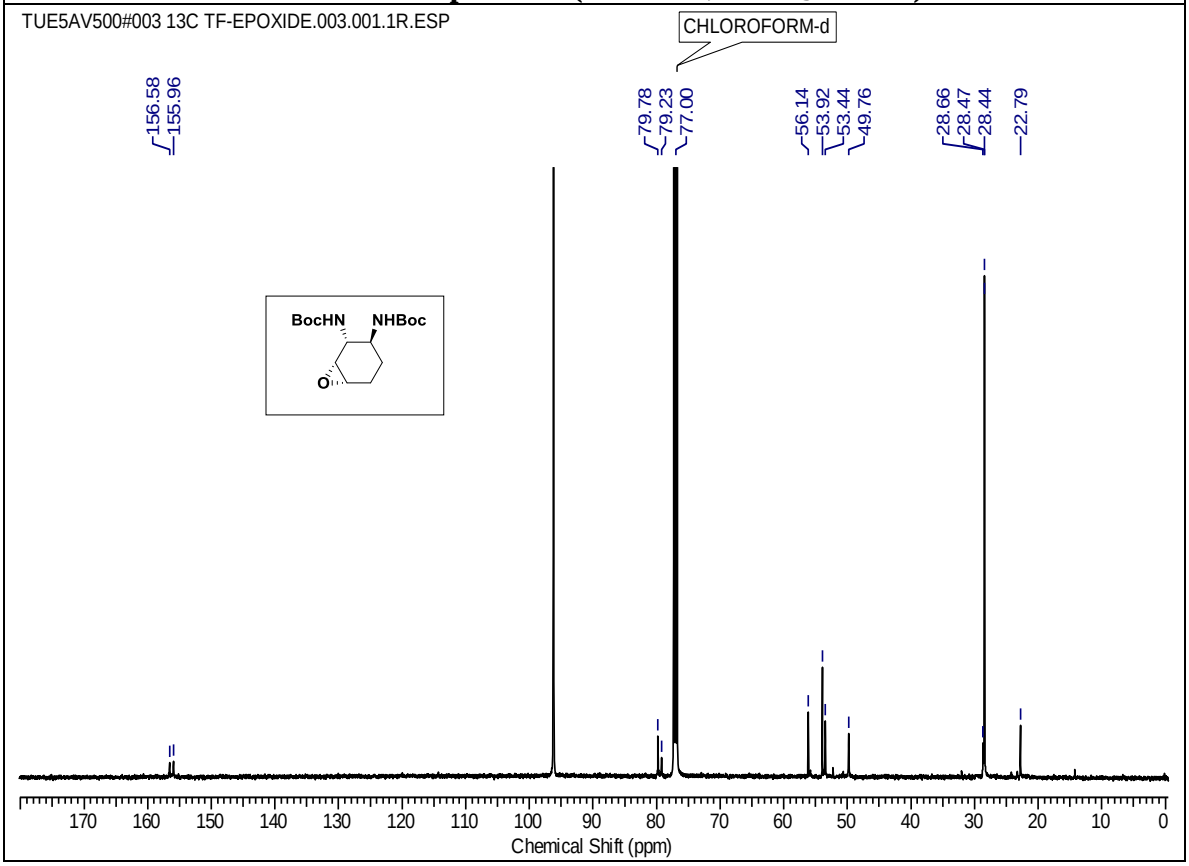
DEPT spectrum of compound 7 (125 MHz, $CDCl_3$ + CCl_4)



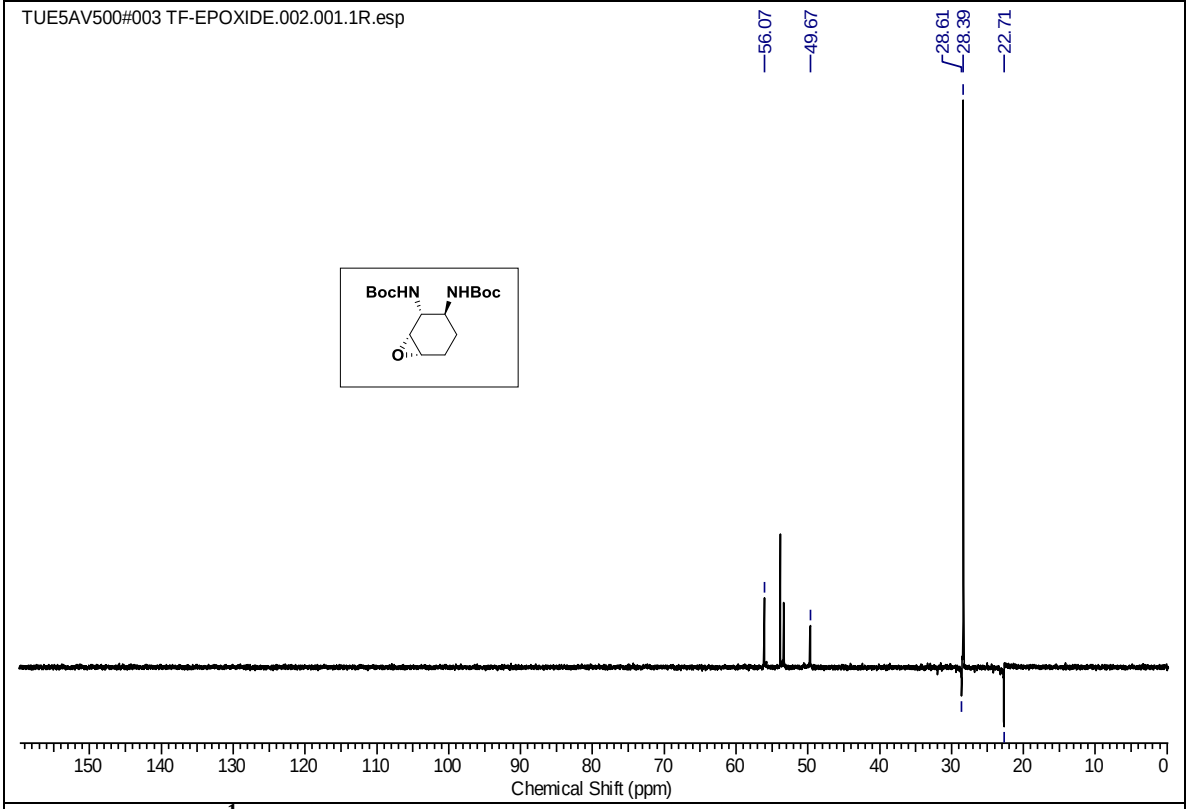
^{1}H NMR of epoxide 8 (500 MHz, $CDCl_3$ + CCl_4)



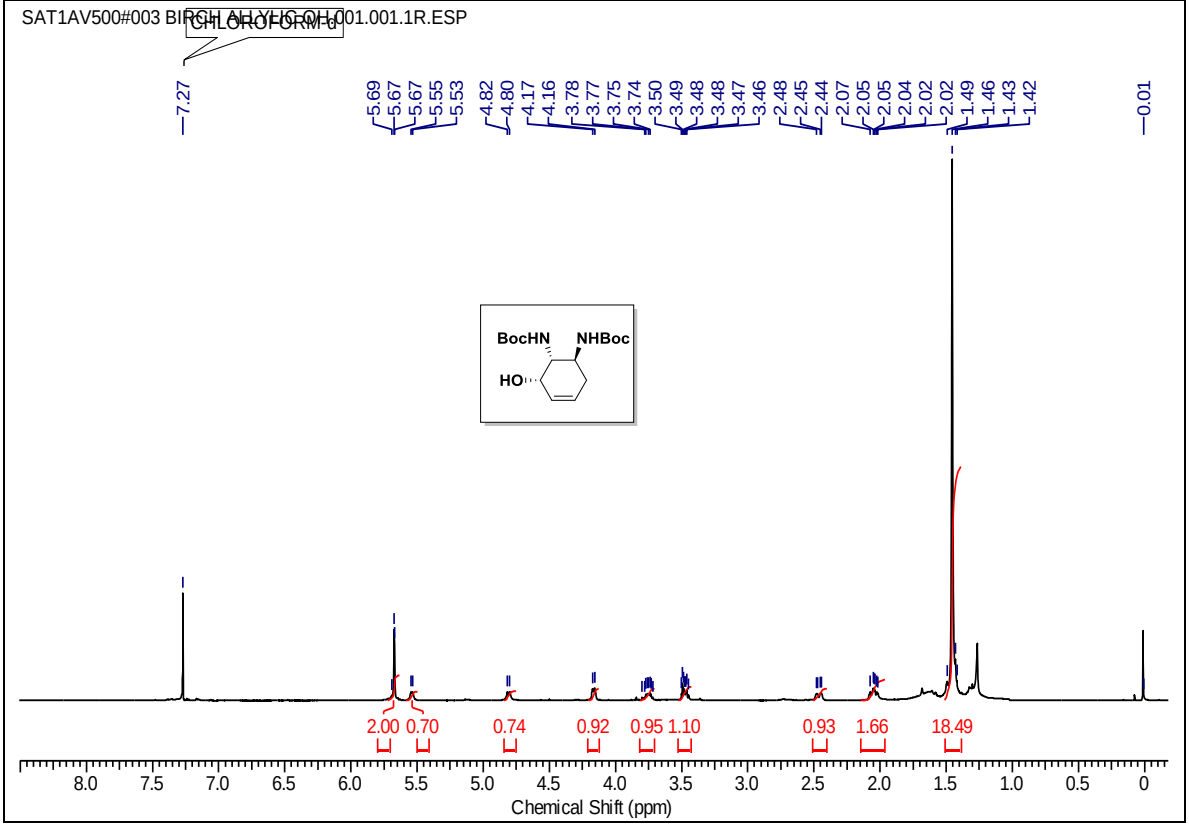
^{13}C NMR of epoxide 8 (125 MHz, $CDCl_3$ + CCl_4)



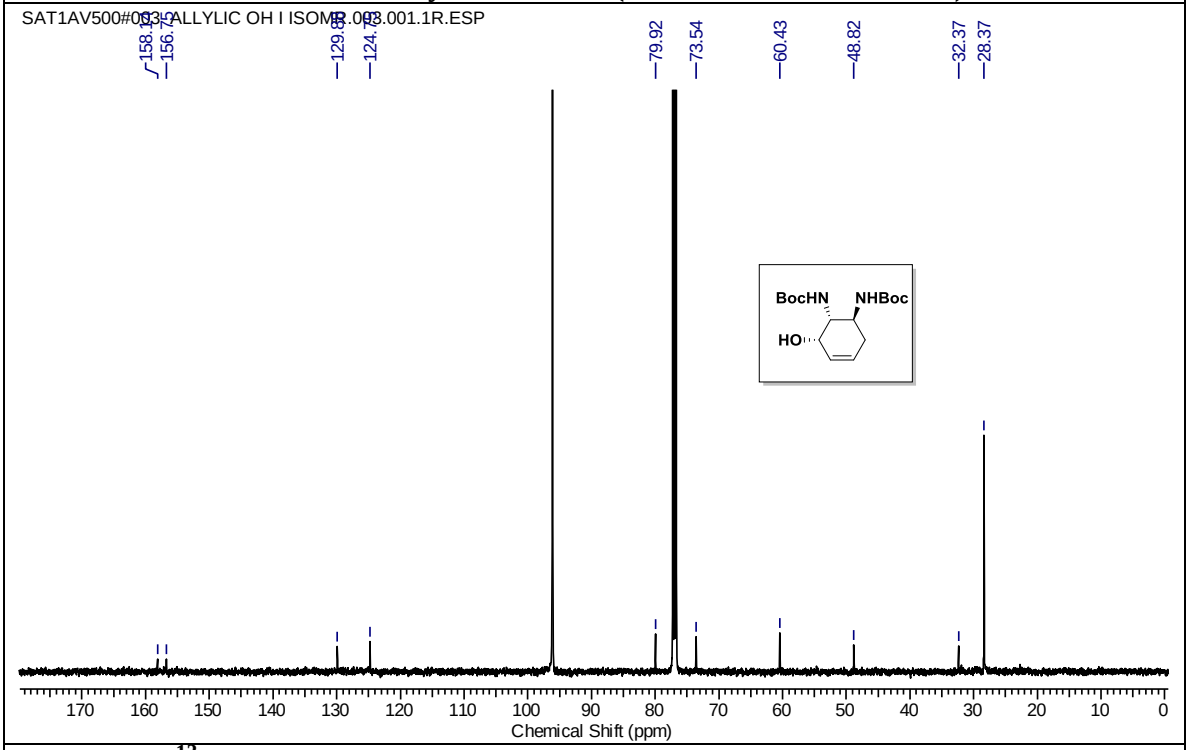
DEPT spectrum of epoxide 8 (125 MHz, $CDCl_3$ + CCl_4)



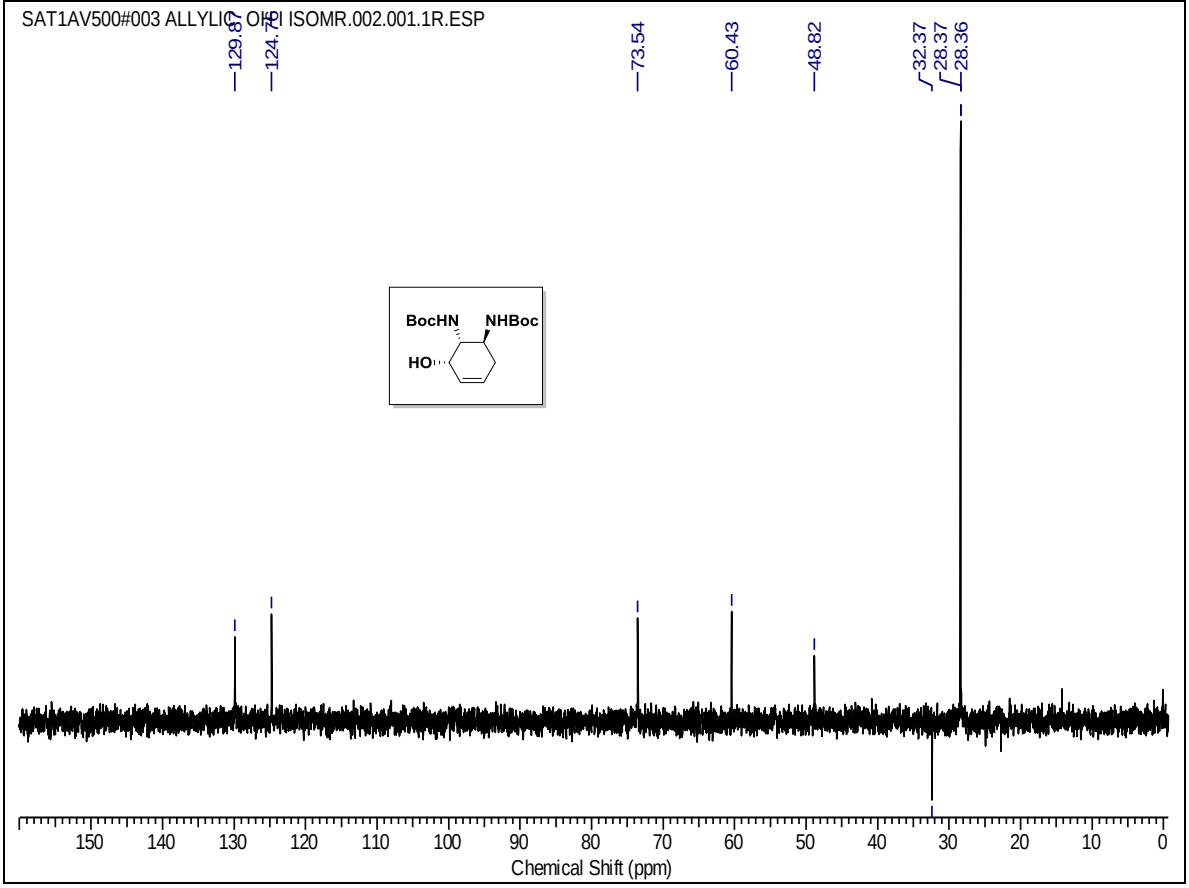
^{1}H NMR of allylic alcohol 9 (500 MHz, $CDCl_3$ + CCl_4)



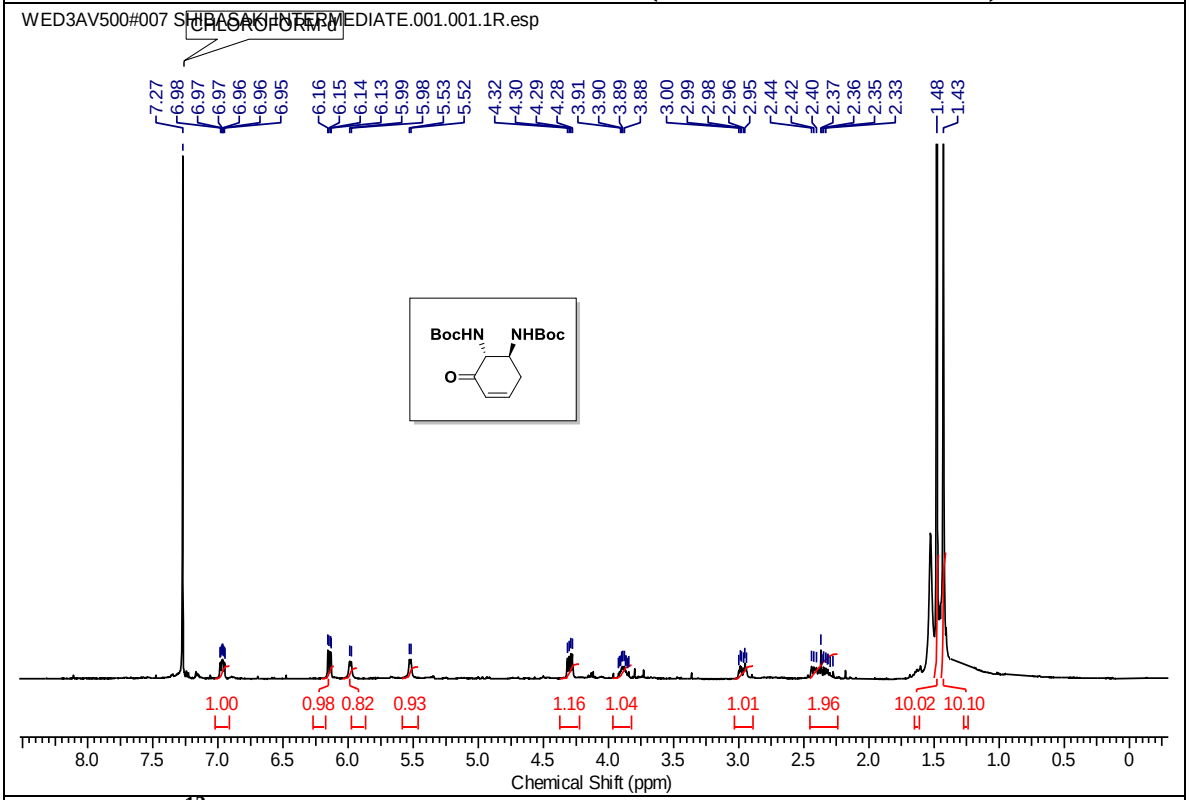
^{13}C NMR of allylic alcohol 9 (125 MHz, $CDCl_3$ + CCl_4)



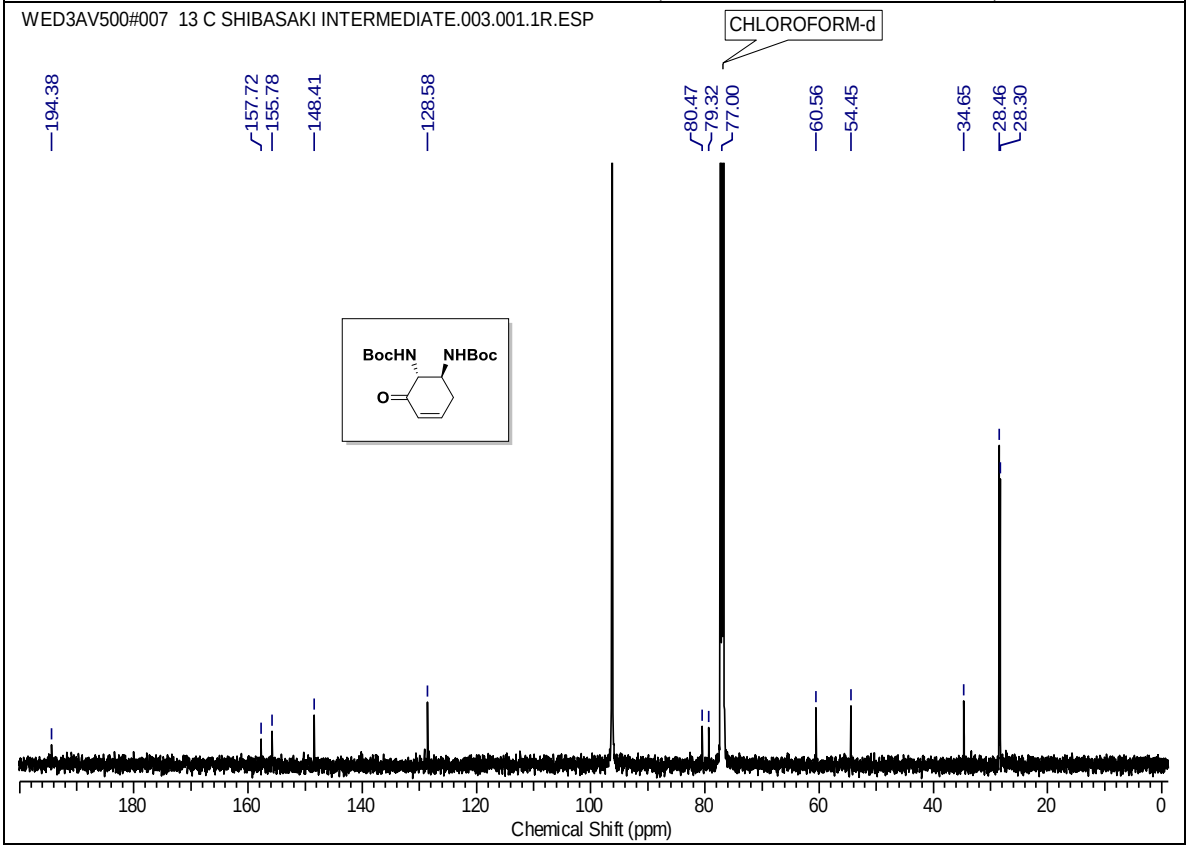
^{13}C DEPT NMR of allylic alcohol 9 (125 MHz, $CDCl_3$ + CCl_4)



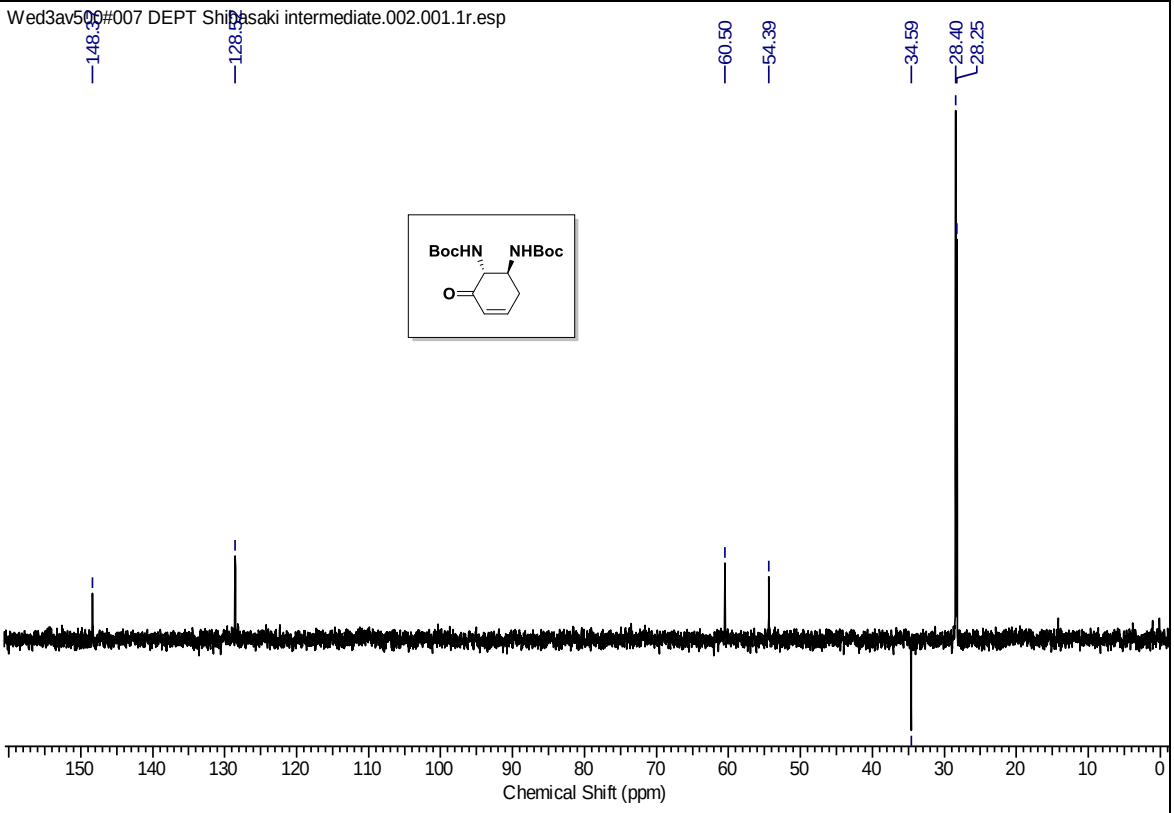
^{1}H NMR of unsaturated ketone 2 (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of unsaturated ketone 2 (125 MHz, $CDCl_3$ + CCl_4)



^{13}C DEPT NMR of unsaturated ketone 2 (125 MHz, $CDCl_3$ + CCl_4)



1.3.5 References

1) Chavan, S. P.; Chittiboyina, A. G.; Ravindranathan, T.; Kamat, S. K.; Kalkote, U. R. *J. Org. Chem.* **2005**, *70*, 1901.
2) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc*. **2003**, *125*, 11837.
3) Birch, A. J. *J. Am. Chem. Soc*. **1944**, *117*, 430.
4) Raghavan S.; Babu, V. S. *Tetrahedron* **2011**, 67, 2044.
5) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *9*, 2697; (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Ckem.* **1978**, *43*, 1697.
6) Fukuta, Y.; Mita, T., Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

Section 4

Formal synthesis of Tamiflu employing stereospecific amidoalkylation protocol and ring closing metathesis (RCM)

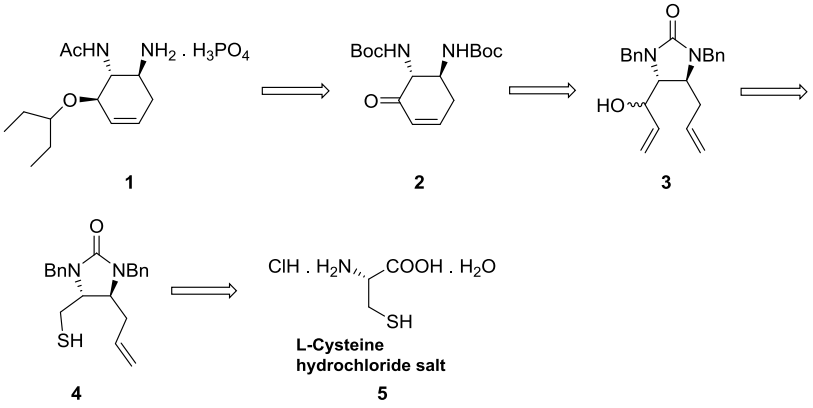
1.4.1 Present work

1.4.1.1 Objective

We have accomplished a formal synthesis of tamiflu using stereospecific amidoalkylation protocol and Ramberg-Backlund reaction, which has been discussed in Chapter 1 Section 3. In continuation of this, formal synthesis of oseltamivir phosphate (tamiflu) was undertaken starting from the L-cysteine hydrochloride, which involved ring closing metathesis and urea hydrolysis as key essentials.

1.4.1.2 Retrosynthetic analysis

Our strategy involved transformation of intermediate thiol **4** to unsaturated ketone **3** (Scheme 1). Thiol **4** was obtained from the L-cysteine hydrochloride **5** using reported procedure. Thiol **4** could provide allylic alcohol **3** using appropriate functional group transformations, which would give unsaturated ketone **2** *via* ring closing metathesis (RCM), urea hydrolysis and DMP oxidation as key chemical reactions. The unsaturated ketone **2** is a key intermediate reported for tamiflu by Shibasaki.[1]



Scheme 1 Retrosynthetic analysis for tamiflu **1**

1.4.1.3 Results and discussion

The thiol **4** was prepared from the L-cysteine hydrochloride **5** using reported method in excellent yield, which is described in Chapter 1 Section 2. Thiol **4** was subjected to coupling using $Cu(OAc)_2$, phenyl boronic acid and pyridine in DMF at 80 ^oC to afford phenyl sulfide **6** in 79% yield.[2]

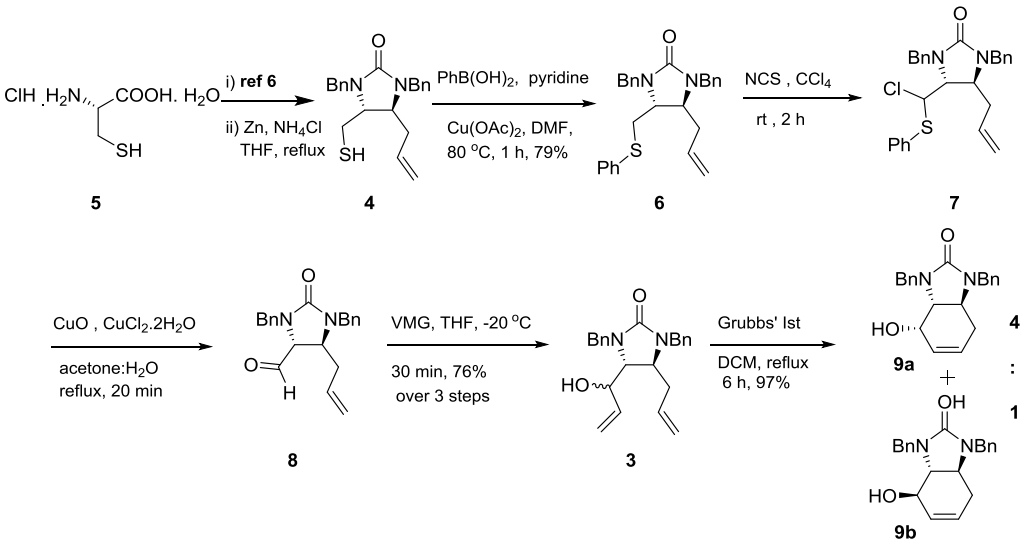
The IR spectrum of phenyl sulfide **6** showed the presence of bands at 1694 and 1604 cm^{-1} indicating the presence of urea carbonyl and olefin functionalities respectively. Multiplet at δ 7.33-7.05 for 15 protons in its ^{1}H-NMR spectrum clearly confirmed formation of the sulfide **6**. The ^{13}C NMR spectrum showed peak at δ 159.3 for the urea carbonyl carbon and ^{13}C DEPT NMR spectrum showed the peak at δ 36.3 assigned for the methylene carbon of $–CH_2SPh$ group. The HRMS value observed at 451.1812 confirmed molecular formula $C_{27}H_{28}N_2OS$ of the coupled product **6**.

The next plan was to convert phenyl sulfide **6** into hydroxyl compound **3**. Accordingly, sulfide **6** was treated with *N*-chlorosuccinimide in CCl_4 to furnish chloro compound **7**. The crude chloro compound **7** was subjected to hydrolysis using copper oxide and cupric chloride (II) to give aldehyde **8**.[3] Crude aldehyde **8** on reaction with vinyl magnesium bromide in THF afforded diastereomeric mixture of compound **3** in 76% yield (3 steps).[4] The IR spectrum of diallyl compound **3** showed bands at 3355, 1672 and 1604 cm^{-1} assigned to the hydroxy, urea carbonyl and olefin functionality respectively. The ^{1}H NMR spectrum showed multiplets for two olefinic protons at δ 5.67-5.53 and 5.45-5.30 which strongly supported the formation of the diallyl compound **3**. The ^{13}C DEPT NMR spectrum showed the peaks at δ 117.3 and 117.1 ppm for the methylene carbons of the olefinic group which supported to the vinyl magnesium bromide addition. In the HRMS spectrum a peak at 385.1880 was observed which confirmed molecular formula $C_{23}H_{26}N_2O_2$ of diallyl compound **3**.

The diastereomeric mixture **3** was subjected to RCM using Grubbs' 1st generation catalyst to afford easily separable distereomeric mixture **9a:9b** in 4:1 ratio respectively with 97% yield (Scheme 2). [5]

The IR spectrum of **9a** showed the peaks at 3391 and 1667 cm^{-1} for the hydroxy and urea carbonyl functional group respectively. The ^{1}H NMR spectrum of the diastereomer **9a** showed the peaks at 5.63-5.60 and 5.46 for two protons of double bond. The ^{13}C NMR spectrum showed the disappearance of peaks at δ 117.3 and 117.1 for two methylene carbon of olefin and appearance of the peaks at δ 127.4 and 126.0 for two carbons of –CH group of olefin which strongly supported to cyclisation of the allylic alcohol **3**. The

HRMS spectrum showed the peak at 357.1569 which confirmed molecular formula $C_{21}H_{22}N_2O$ of hydroxy compound **9a**.



Scheme 2 Synthesis of **9a** and **9b**

The ^{1}H NMR spectrum of minor compound **9b** showed the peak at δ 5.71 for two olefinic protons indicating the characteristic difference from major diatereomer **9a**. The ^{13}C NMR spectrum showed the peaks δ 63.4, 62.6 and 50.8 ppm for three –CH carbons and δ 48.3, 47.9, 31.2 ppm indicating presence of three methylene groups which strongly supported the structure of **9b**. The HRMS spectrum showed the peak at 357.1569 which confirmed molecular formula $C_{21}H_{22}N_2O$ of hydroxy compound **9b**. The relative stereochemistry of **9b** was fully characterized by single crystal X-ray analysis (Fig 1).

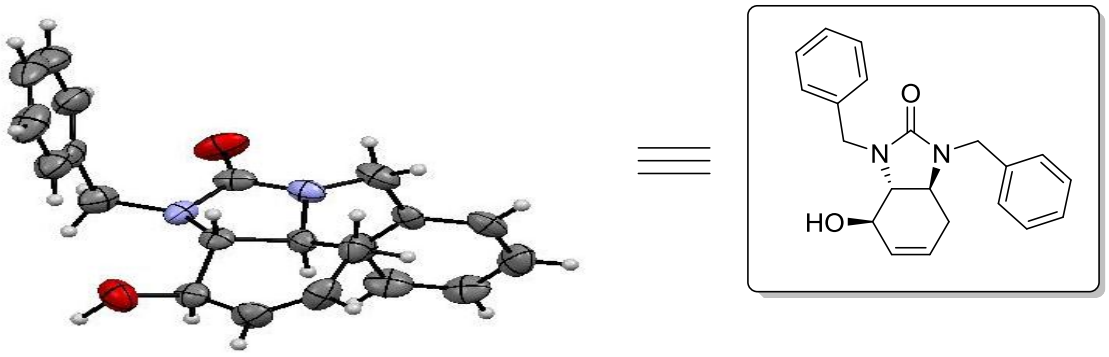


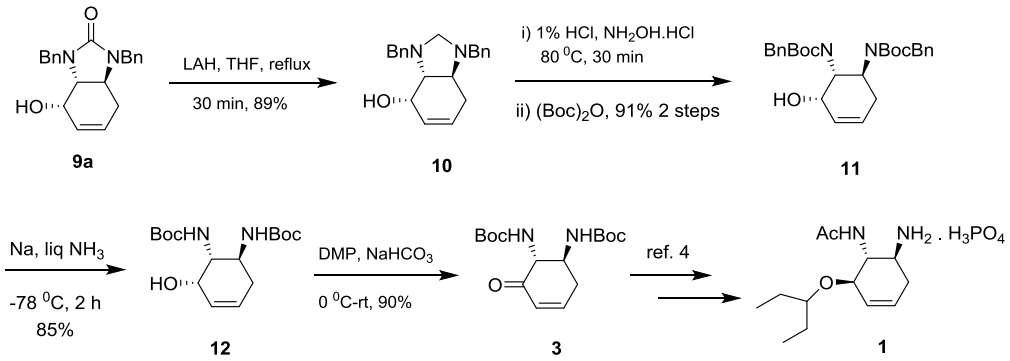
Fig 1 ORTEP diagram of alcohol **9b**

After successfully synthesis of cyclohexene, which is the core skeleton of tamiflu, the next task was to obtain intermediate **2**. Accordingly, major diastereomer **9a** was subjected to reduction using lithium aluminium hydride in THF to afford compound **10** in 89% yieid. The disappearance of the band at 1667 cm^{-1} in IR spectrum strongly supports to reduction of the urea **9a** and appearance of bands at 3429 and 1643 cm^{-1} indicated the presence of hydroxy and double bond functionality. The ^{1}H NMR spectrum showed the peaks at δ 4.52 and 3.44 ppm for two protons of $–NCH_2N-$ linkage and peak at δ 4.73 ppm as broad singlet for one proton of –CHOH group and multiplet at δ 5.69 - 5.60 for two olefinic protons, which supported to formation of the compound **10**. The ^{13}C DEPT NMR spectrum showed the peak at δ 77.2 for methylene carbon of $–NCH_2N-$ linkage. The HRMS spectrum showed the peak at 321.1962 confirming molecular formula $C_{21}H_{24}N_2O$ of the diamine **10**.

Further, diamine **10** was hydrolyzed with 1% HCl and $NH_2OH.HCl$ to furnish diamine.[6] Resultant diamine was masked as urethane on treatment with neat boc anhydride to give diboc derivative **11** in 91% yield (2 steps). The IR spectrum of **11** showed bands at 3435, 1692 and 1605 cm^{-1} for hydroxy, carbamate and olefin functionality respectively. Peaks in ^{1}H NMR spectrum at δ 5.57 - 5.42 as multiplet for two protons of double bond and peak at 1.64 - 1.24 for 18 protons confirmed diboc protection. The ^{13}C NMR spectrum showed the peaks at δ 156.8 and 155.8 for two carbonyl carbons of diboc derivative **11**. The ^{13}C DEPT NMR spectrum showed peaks at δ 47.1, 30.5 and 46.8 for three methylene carbons of the compound **11**. The peak observed in the HRMS spectrum at 531.2827 confirmed molecular formula $C_{30}H_{40}N_2O_5$ of the diboc derivative **11**.

In the next step, diboc derivative **11** was subjected to chemoselective debenzylation in presence of double bond under Birch reduction condition to afford allylic alcohol **12** in 85% yield (Scheme 3). The characterization data of allylic alcohol **12** is described in Chapter 1 Section 3.

The minor isomer **9b** was subjected under similar reduction condition using lithium aluminium hydride in dry THF to furnish compound **13**. The disappearance of band at 1667 cm^{-1} in IR spectrum indicated the reduction of urea **9b** and presence of bands at3429 and 1643 cm^{-1} for hydroxy and double bond functionality respectively which



Scheme 3 Exploration of **9a** for tamiflu **1**

strongly supported the structure of compound 13. The ^{1}H NMR spectrum showed multiplet at 5.90-5.82 ppm for two protons of double bond and the ^{13}C DEPT NMR spectrum of **13** showed the peaks at 77.4, 58.7, 57.4 and 31.3 ppm which revealed for the four methylene carbons. The HRMS spectrum showed the peak at 321.1962 which confirmed the molecular formula $C_{21}H_{24}N_2O$ of the compound **13**.

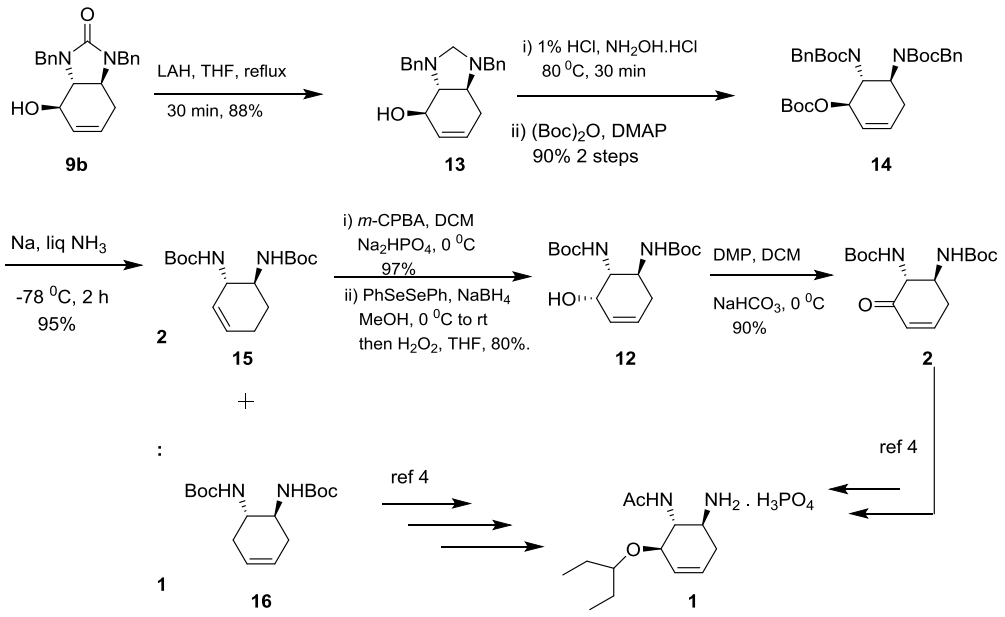
Further, the compound **13** was subjected to hydrolysis in 1% HCl and $NH_2OH.HCl$ to furnish diamine, which was treated with boc anhydride however to provide a mixture of desired diboc derivative as minor and triboc derivative **14** as major compound. By performing the boc protection in the presence of catalytic amount of DMAP the triboc derivative **14** was obtained in good yield. The ^{1}H spectrum showed the peak at 5.96 - 5.57 ppm as multiplet for two protons of double bond and the multiplet at 1.66 - 1.03 ppm for 27 protons which clearly supported the formation of the triboc derivative **14**. The ^{13}C NMR spectrum showed peaks at 156.4, 153.4 and 152.6 ppm for the three carbonyl carbons of triboc derivative **14**. The HRMS spectrum showed peak at 609.3530 which confirmed molecular formula $C_{35}H_{48}N_2O_7$ of the triboc compound **14** (Scheme 4).

Triboc compound **14** was subjected to Birch reaction condition at -78 ^{o}C in THF to give regioisomeric compounds **15** and **16** in ratio 2:1 respectively.

The IR spectrum of the compound **16** showed the band at 1675 cm^{-1} for the carbamate functionality. Its ^{1}H NMR spectrum showed the peak at 5.58 (s, 2 H) ppm assigned for the olefinic protons and peak at 1.44 (s, 18 H) ppm which strongly supported the diboc protection. The ^{13}C NMR spectrum of **16** showed the peaks at 156.4 and 125.1

corresponding to the carbons of carbamate and olefin groups. Its ^{13}C DEPT NMR showed the peak at 32.9 ppm was assigned to the methylene carbon. The HRMS spectrum showed the peak at 335.1942 $(M+Na)^+$ confirming the molecular formula $C_{16}H_{28}N_2O_4$ of compound **16**. The spectral data of compound **16** is in well agreement with those reported by Shibasaki.[1]

The conversion of the compound **15** to unsaturated enone is thoroughly described in the Chapter 1 Section 3.



Scheme 4 Exploration of **9b** for tamiflu **1**

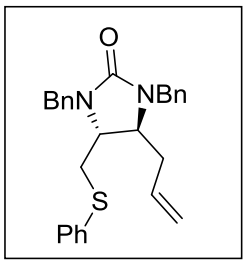
1.4.2 Conclusion

In conclusion, we have successfully achieved the formal synthesis of the tamiflu from the L-cysteine hydrochloride salt, which is natural renewable source, readily available, inexpensive and present in enantiomerically pure form. The novel stereospecific amidoalkylation methodology which provides vicinal *trans* diamine motif on urea hydrolysis is the essential feature of the tamiflu. The key feature of the strategy involves substituted cyclohexene as the main core of tamiflu, which was obtained efficiently using Grignard addition and ring closing metathesis (RCM). Both RCM diastereomers were successfully converted to neuraminidase inhibitory drug **1**. The synthetic approach is

practically simpler, avoids labile aziridine intermediate and complete process is free of hazardous azide reagent. Thus, the newly established synthetic method for the Oseltamivir phosphate is considered advantageous.

1.4.3 Experimental section

(4*S*,5*R*)-4-Allyl-1,3-dibenzyl-5-((phenylthio)methyl)imidazolidin-2-one (6)



To a solution of crude thiol **4** (30 gm, 85.11 mmol) in dry DMF (150 mL) was added cupric acetate (23.19 gm, 127.66 mmol), phenyl boronic acid (20.75 gm, 170.21 mmol) and pyridine (20 mL, 255.32 mmol) and reaction mixture was heated at 80 ^{0} C for 1 h. The reaction mixture was filtered through celite and celite was washed thoroughly with ethyl acetate (50 mL). Water (300 mL) was added and the compound was extracted with ethyl acetate (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **6** (28.82 gm, 79%) as a colourless syrup.

R*$_f$*: 0.5 (Pet. ether: ethyl acetate, 70:30).

MF: $C_{27}H_{28}N_2OS$, **MW:** 428.59.

Yield: 79%.

$[\alpha]_D^{25}$: +32.85 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2920, 1694, 1604, 1449.

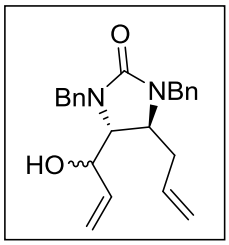
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.36-7.01 (m, 15H), 5.38-5.31 (m, 1H), 4.94-4.79 (m, 3H), 4.67 (dd, *J* = 4, 16 Hz, 1H), 4.01-3.89 (m, 2H), 3.32 (q, *J* = 5 Hz, 1 H), 3.23 - 3.18 (m, 1H), 3.02 (dd, *J* = 5, 12 Hz, 1H), 2.63 (dd, *J* = 8, 12 Hz, 1H), 2.12 (dd, *J* = 5, 8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 159.1, 137.2, 135.0, 132.0, 129.7, 128.9, 128.6, 128.5, 128.4, 128.1, 126.4, 119.1, 56.3, 54.8, 45.7, 45.3, 36.3, 36.1.

HRMS: Observed- 451.1812, calculated-451.1815.

(4*S*,5*R*)-4-Allyl-1,3-dibenzyl-5-(1-hydroxyallyl)imidazolidin-2-one (3)

To the phenyl sulfide **6** (20.00 gm, 46.66 mmol) solution in dry CCl_4 (150 mL) at 0 ^{0}C was added *N*-chlorosuccinimide (6.81 gm, 51.26 mmol) and the reaction mixture was stirred at room temperature for 2 h. Reaction was monitored by the TLC. After disappearance of the starting material, reaction mixture was cooled to 0 ^{0}C and filtered through the simple filter paper. Residue was washed with CCl_4 (3 x 50 mL) and the filtrate was concentrated under reduced pressure to obtain the chloro sulfide **7**. The crude chloro sulfide **7** was directly subjected for next reaction without any purification.



The crude chloro sulfide **7** (21 gm, 45.35 mmol) was hydrolyzed with CuO (14 gm, excess) and $CuCl_2.6H_2O$ (14 gm, excess) in acetone: water (25:1, 200 mL). The reaction mixture was refluxed for 20 min, filtered through the celite bed and the residue was washed with acetone (3 x 80 mL). Filtrate was concentrated under reduced pressure, water was added to the residue and compound was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish aldehyde **8**.

The crude aldehyde **8** (14 gm, 41.91 mmol) without any purification was treated with vinyl magnesium bromide (62.67 mL, 1M solution in toluene, 62.87 mmol) at -20 ^{o}C in dry THF (150 mL). Reaction mixture was stirred at same temperature for 20 min and quenched with saturated aqueous solution of NH_4Cl. The compound was extracted with DCM (3 x 150 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **3** (12.86 gm, 76%) as a yellow syrup.

R_f: 0.5 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{23}H_{26}N_2O_2$, **MW:** 362.47.

Yield: 76% (over three steps).

$[\alpha]_D^{25}$: +25.71 (*c* 1.4, $CHCl_3$).

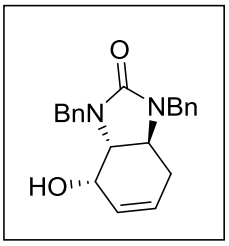
IR ($CHCl_3$, cm^{-1}): ν_{max} 3355, 2924, 1672, 1604, 1451, 1240.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.43-7.13 (m, 10H), 5.68-5.52 (m, 1H), 5.46-5.32 (m, 1H), 5.28-5.06 (m, 2H), 5.00-4.81 (m, 4H), 4.26-3.94 (m, 3H), 3.43-3.27 (m, 1H), 3.24-3.15 (m, 1H), 2.20-2.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 160.1, 159.9, 137.3, 137.0, 136.4, 132.2, 128.6, 128.54, 128.51, 128.4, 128.3, 127.5, 127.4, 119.1, 117.3, 117.1, 72.7, 70.8, 60.0, 59.4, 52.9, 51.6, 47.1, 46.4, 45.5, 45.4, 36.7, 36.6.

HRMS: Observed- 385.1880, calculated-385.1880.

(3a*R*,4*R*,7a*S*)-1, 3-Dibenzyl-4-hydroxy-1,3,3a,4,7,7a-hexahydro-2*H*-benzo[*d*] imidaz-ol-2-one (9a)



To a solution of allylic acohol **3** (5.00 gm, 13.81 mmol) in dry DCM (800 mL) was added Grubbs' Ist generation catalyst (227 mg, 0.276 mmol) and refluxed for 6 h. The reaction mixture was filtered through celite and thoroughly washed with DCM (3 x 60 mL). The filtrate was concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 15% ethyl acetate in pet. ether as an eluent to afford diastereomers **9a:9b** in 4:1 ratio (3.58 and 0.89 gm respectively, 97%).

R_f: 0.4 (pet. ether: ethyl acetate, 60:40).

MF: $C_{21}H_{22}N_2O_2$, **MW:** 334.42.

$[\alpha]_D^{25}$: +20.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3391, 2919, 1667, 1415.

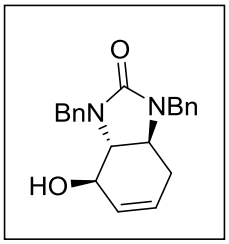
MP: 159-161 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.44-7.21 (m, 10H), 5.66-5.57 (m, 1H), 5.46 (d, *J* = 10 Hz, 1H), 4.75 (d, *J* = 15 Hz, 1H), 4.59-4.45 (m, 2H), 4.34 (d, *J* = 15 Hz, 1H), 4.16 (bs, 1H), 3.00-2.85 (m, 2H), 2.22-2.12 (m, 1H), 1.97-1.83 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 162.9, 138.3, 137.1, 131.0, 128.65, 128.62, 128.4, 128.3, 127.5, 127.4, 126.0, 71.5, 63.9, 54.8, 47.9, 47.4, 29.7.

HRMS: Observed- 357.1569, calculated-357.1573.

(3a*R*,4*S*,7a*S*)-1,3-Dibenzyl-4-hydroxy-1,3,3a,4,7,7a-hexahydro-2H-benzo[d]imidazol-2-one (9b)



R_f: 0.3 (pet. ether: ethyl acetate, 60:40).

MF: $C_{21}H_{22}N_2O_2$, **MW:** 334.42.

$[\alpha]_D^{25}$: +70.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3391, 2919, 1667, 1415.

MP: 178-180 ^oC ($CHCl_3$: pet.ether).

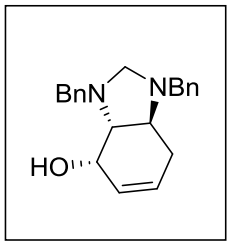
HRMS: Observed- 357.1569, calculated-357.1573.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.42-7.21 (m, 10H), 5.71 (d, *J* = 1.5 Hz, 1H), 4.68 (d, *J* = 15 Hz, 1H), 4.57-4.36 (m, 2H), 4.29 (d, *J* = 15 Hz, 1H), 4.08 (bs, 1H), 3.29 (dt, *J* = 4.6, 10 Hz, 1H), 2.89 (dd, *J* = 3.2, 11.2 Hz, 1H), 2.21 (td, *J* = 5, 15 Hz, 1H), 1.81 (dd, *J* = 3.2, 11.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 163.1, 137.7, 137.4, 129.0, 128.5, 128.3, 128.0, 127.5, 63.4, 62.6 50.8, 48.3, 47.9, 31.2.

(3a*R*,4*R*,7a*S*)-1,3-Dibenzyl-2,3,3a,4,7,7a-hexahydro-1*H*-benzo[*d*]imidazol-4-ol (10)

To a solution of allylic alcohol **9a** (2.00 gm, 5.98 mmol) in dry THF was added lithium aluminium hydride (1.36 gm, 35.88 mmol) at 0 ^oC and mixture was refluxed for 30 min. The reaction mixture was quenched with 15% NaOH solution and ice pieces. Sodium



sulphate was added, reaction mixture was filtered over simple filter paper and reaction mass washed with ethyl acetate (3 X 50 mL). The filtrate was concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **10** (1.72 gm, 89%) as colourless syrup.

R_f: 0.5 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{21}H_{24}N_2O$, **MW:** 320.44.

Yield: 89%.

$[\alpha]_D^{25}$: +62.5 (*c* 0.8, $CHCl_3$).

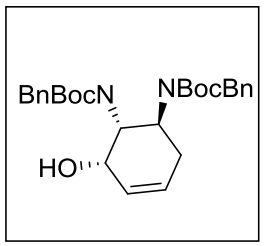
IR ($CHCl_3$, cm^{-1}): ν_{max} 3429, 1643, 1216.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.44-7.18 (m, 10H), 5.71-5.54 (m, 2H), 4.73 (bs, 1H), 4.57-4.45 (m, 1H), 3.93-3.54 (m, 4H), 3.45 (d, *J* = 12 Hz, 1H), 2.91-2.81 (m, 1H), 2.74 (dt, *J* = 4, 12 Hz, 1H), 2.27-1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 131.4, 129.2, 128.6, 128.4, 127.9, 127.4, 126.0, 75.6, 72.4, 71.6, 63.3, 59.8, 57.1, 30.8.

HRMS: Observed- 321.1962, calculated-321.1961.

Di-*tert*-butyl ((1*S*,2*R*,3*R*)-3-hydroxycyclohex-4-ene-1,2 diyl) bis (benzylcarbamate) (11)



To a solution of diamine **10** (1.50 gm, 4.68 mmol) in 1% HCl (30 mL) was added $NH_2OH.HCl$ (3.8 gm, excess) and mixture was heated at 80 ^oC for 30 min. The aqueous layer of reaction mixture was washed with ethyl acetate to remove organic impurities. Aqueous layer was basified with solid $NaHCO_3$ and compound was extracted with DCM (3 x 20 mL). The combined organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure to

furnish a crude diamine residue. Diamine was subjected for protection with neat boc anhydride (2.55 gm, 11.70 mmol) and the reaction mixture was stirred at room temperature for 4 h. Water was added to the reaction mass and the compound was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over flash silica gel, eluting with 5% ethyl acetate in pet. ether as an eluent to give diboc compound **11** (2.17 gm, 91%) as a colourless liquid.

R_f: 0.6 (Pet. ether: ethyl acetate, 80:20).

MF: $C_{30}H_{40}N_2O_5$, **MW:** 508.66.

Yield: 91%.

$[\alpha]_D^{25}$: -21.53 (*c* 2.0, $CHCl_3$).

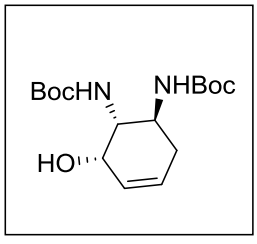
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 2974, 1692, 1605, 1167.

HRMS: Observed- 531.2827, calculated-531.2829.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.51-7.11 (m, 10H), 5.67-5.35 (m, 2H), 5.07-3.67 (m, 7H), 2.40-2.00 (m, 2H), 1.69-1.33 (m, 18H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.8, 155.8, 140.3, 140.1, 129.4, 128.6, 128.2, 126.4, 125.9, 125.8, 68.8, 47.1, 46.8, 30.6, 28.6, 28.4, 28.3.

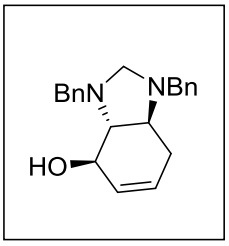
Di-*tert*-butyl ((1S,2R,3S)-3-hydroxycyclohex-4-ene-1,2-diyl)dicarbamate (12)



To a solution of diboc compound **11** (600 mg, 1.18 mmol) in THF (10 mL) and ammonia (10 mL) at -78 ^oC was added sodium metal (870 mg, 37.79 mmol) portionwise and stirred at same temperature for 2 h. The reaction mixture was quenched with solid ammonium chloride and the reaction mass brought to room temperature. Water (10 mL) was added to the residue and compound was extracted with ethyl acetate (3 x 15

mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compound **12** (167 mg, 85%). The characterization data of compound **12** is fully described in Chapter 1 section 3.

(3a*R*,4*S*,7a*S*)-1,3-Dibenzyl-2,3,3a,4,7,7a-hexahydro-1*H*-benzo[*d*]imidazol-4-ol (13)



To a solution of allylic acohol **9b** (500 mg, 1.50 mmol) in dry THF (8 mL) was added lithium aluminium hydride (340.47 mg, 8.97 mmol) at 0 ^{0}C and mixture was refluxed for 0.5 h. The reaction mixture was quenched with 15% NaOH solution and ice pieces were added. The sodium sulphate was added and reaction mixture was filtered over simple filter paper and reaction mass was washed with ethyl acetate (3 X 15 mL). The filtrate was concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **13** (422 mg, 88%) as a colourless syrup.

R*$_f$*: 0.5 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{21}H_{24}N_2O$, **MW:** 320.44.

Yield: 88%.

$[\alpha]_D^{25}$: +128.0 (*c* 1.5, $CHCl_3$).

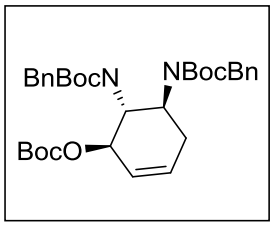
IR ($CHCl_3$, cm^{-1}): ν_{max} 3429, 1643, 1604, 1216.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.40-7.17 (m, 10H), 5.96-5.78 (m, 2H), 4.01 - 3.82 (m, 3H), 3.78-3.61 (m, 2H), 3.59-3.47 (m, 1H), 3.38 (d, *J* = 13.0 Hz, 1H), 2.84-2.64 (m, 2H), 2.41-2.23 (m, 1H), 2.12 - 1.89 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 138.2, 129.6, 128.7, 128.5, 128.46, 128.40, 127.5, 127.3, 70.2, 62.8, 59.3, 58.7, 57.4, 31.3.

HRMS: Observed- 321.1962, calculated-321.1961.

Di-tert-butyl ((1S,2R,3R)-3-((tert-butoxycarbonyl)oxy)cyclohex-4-ene-1,2 diyl-bis-(benzylcarbamate) (14)



To a solution of diamine **13** (300 mg, 1.56 mmol) in 1% HCl (10 mL) was added $NH_2OH.HCl$ (800 mg, excess) and mixture was heated at 80 ^{0}C for half hour. The aqueous layer of reaction mixture was washed with ethyl acetate to remove organic impurities. Aqueous layer was basified with solid $NaHCO_3$ and compound was extracted with DCM (3 X 10 mL). The combined organic layer was dried over sodium sulphate, filered and filtrate was concentrated under reduced pressure to furnish a crude diamine residue. Diamine was subjected for protection with neat boc anhydride (0.5 gm, 3.9 mmol) and the reaction mixture was stirred at room temperature for 4 h. Water was added to reaction mass and compound was extracted with ethyl acetate (3 X 15 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over flash silica gel, eluting with 5% ethyl acetate in pet. ether as the eluent to afford diboc compound **14** (513 mg, 90%) as colourless liquid.

R_f: 0.6 (Pet. ether: ethyl acetate, 90:10).

MF: $C_{35}H_{48}N_2O_7$, **MW:** 608.78.

Yield: 90% (over two steps).

$[\alpha]_D^{25}$: +128.5 (*c* 1.0, $CHCl_3$).

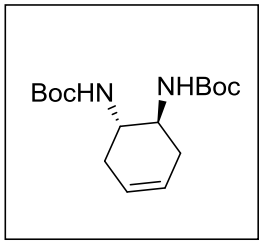
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 2974, 1692, 1605, 1167.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.47-7.09 (m, 10H), 6.03-5.57 (m, 2H), 5.40-3.52 (m, 7H), 2.76-1.82 (m, 2H), 1.68-1.12 (m, 27H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 156.4, 153.4, 152.6, 139.0, 132.8, 128.7, 128.2, 128.0, 127.8, 127.6, 126.8, 126.5, 126.0, 125.1, 121.7, 81.6, 81.3, 79.9, 72.7, 69.1, 54.8, 48.6, 47.6, 31.9, 28.5, 28.0, 27.8, 27.5, 22.7.

HRMS: Observed- 609.3530, calculated-609.3531.

Di-*tert*-butyl ((1*S*,2*S*)-cyclohex-3-ene-1,2-diyl)dicarbamate (16)



To a solution of triboc compound **6** (300.00 mg, 0.58 mmol) in THF (5 mL) and ammonia (10 mL) at -78 ^{o}C was added sodium metal (428 mg, 18.75 mmol) portionwise and stirred at same temperature for 2 h. The reaction mixture was quenched with solid ammonium chloride and the reaction mass brought to room temperature. Water (10 mL) was added to the residue and compound was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compounds **15** and **16** in ratio 2:1 (97 and 48 mg respectively, 95%).

The characterization data of compound **15** is described in Chapter 1 section 3.

The data for compound 16:

R*$_f$*: 0.5 (Pet. ether: ethyl acetate, 70:30).

MF: $C_{16}H_{28}N_2O_4$, **MW:** 312.41.

$[\alpha]_D^{25}$: -33.1 (*c* 0.6, $CHCl_3$), lit. -34.5 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1})**:** ν_{max} 3360, 2923, 1675, 1600, 1463, 1166.

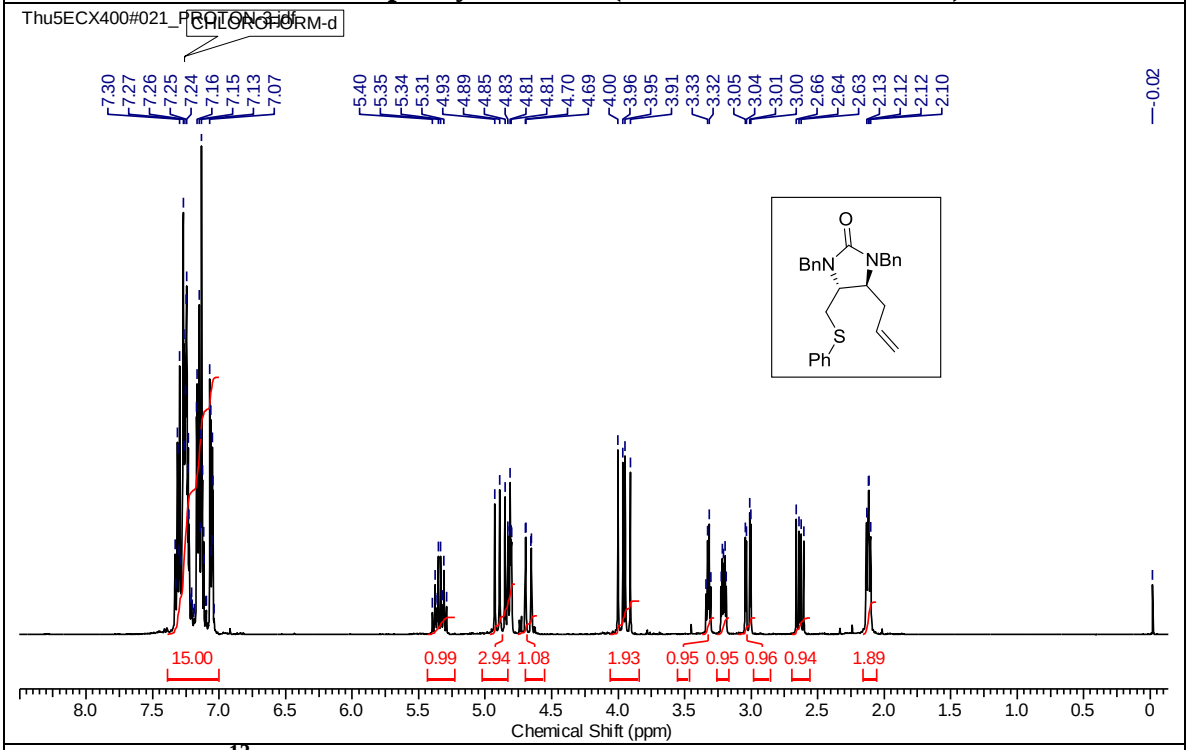
^{1}H NMR (500MHz, $CDCl_3$ + CCl_4): δ 5.58 (s, 2H), 4.90 (bs, 2H), 3.65 (bs, 2H), 2.48 (d, *J*= 16 Hz, 2H), 2.6 – 1.98 (m, 2H), 1.44 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): 156.4, 125.1, 79.2, 51.3, 32.9, 28.4.

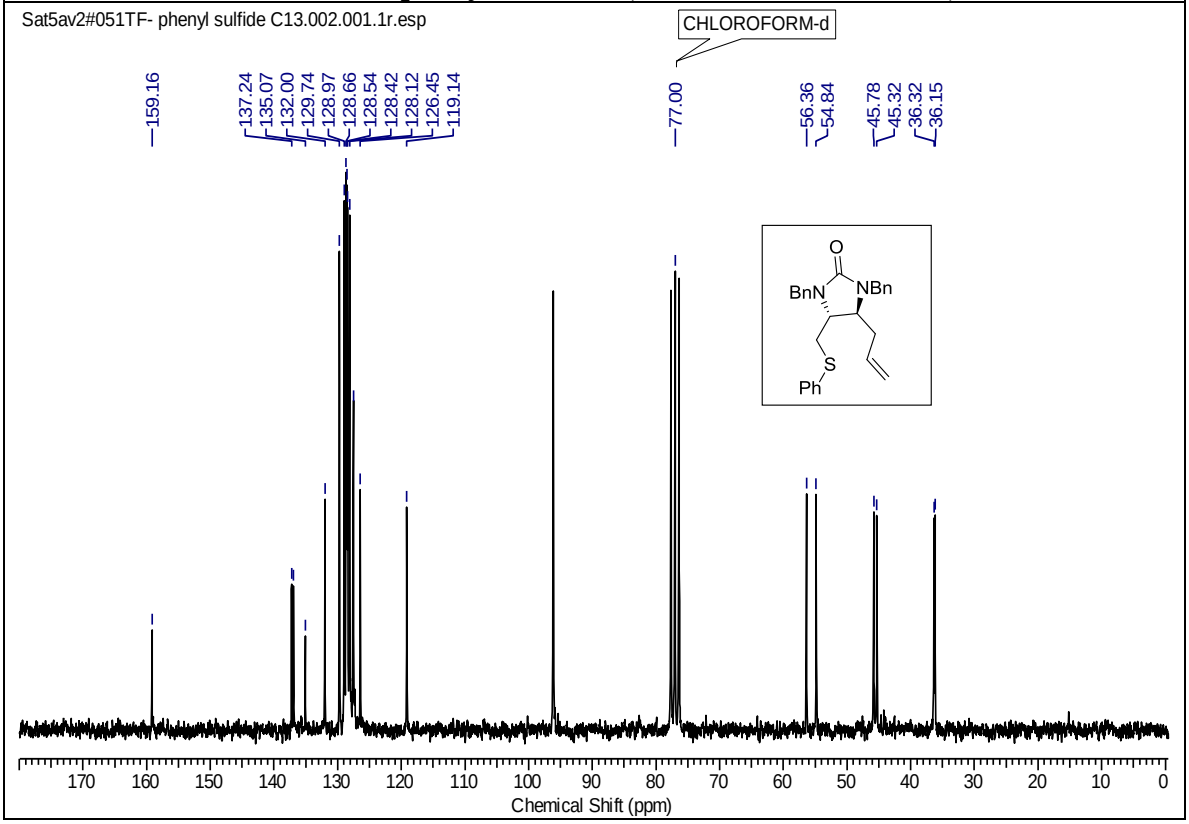
HRMS : Observed- 335.1942, calculated- 335.1940.

1.4.4 Spectral data

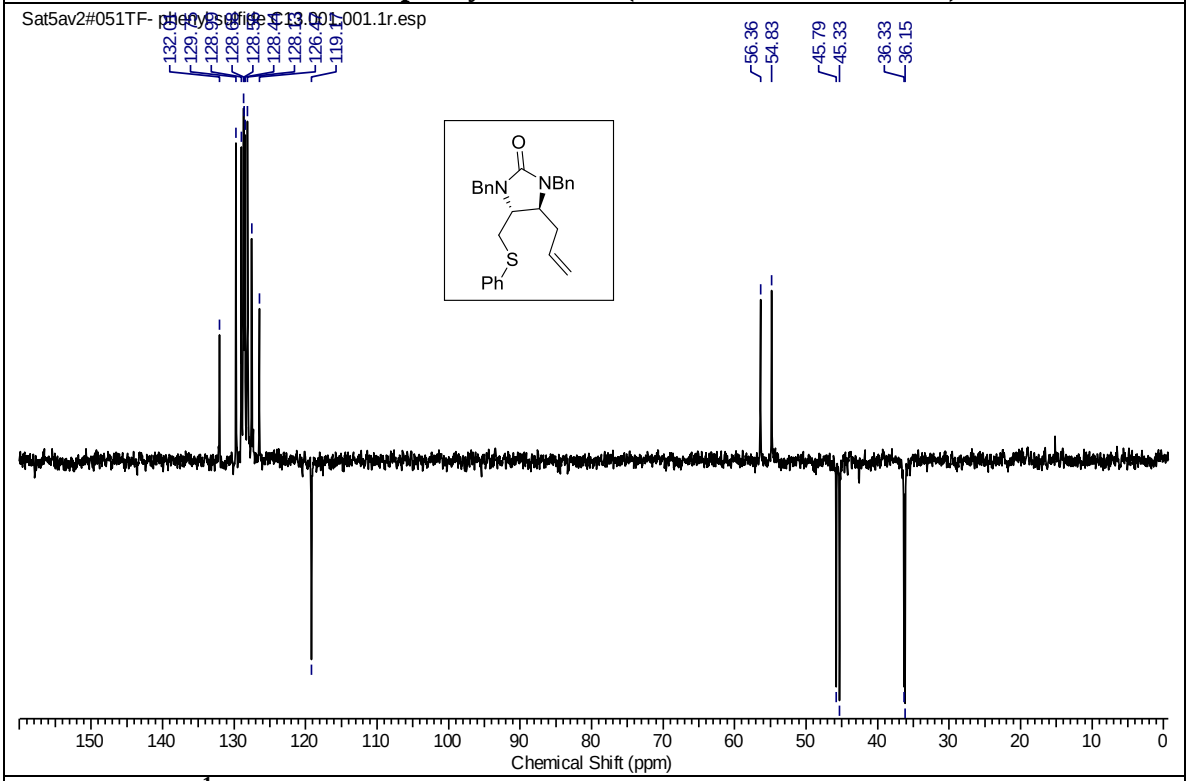
^{1}H NMR of phenyl sulfide 6 (400 MHz, $CDCl_3$ + CCl_4)



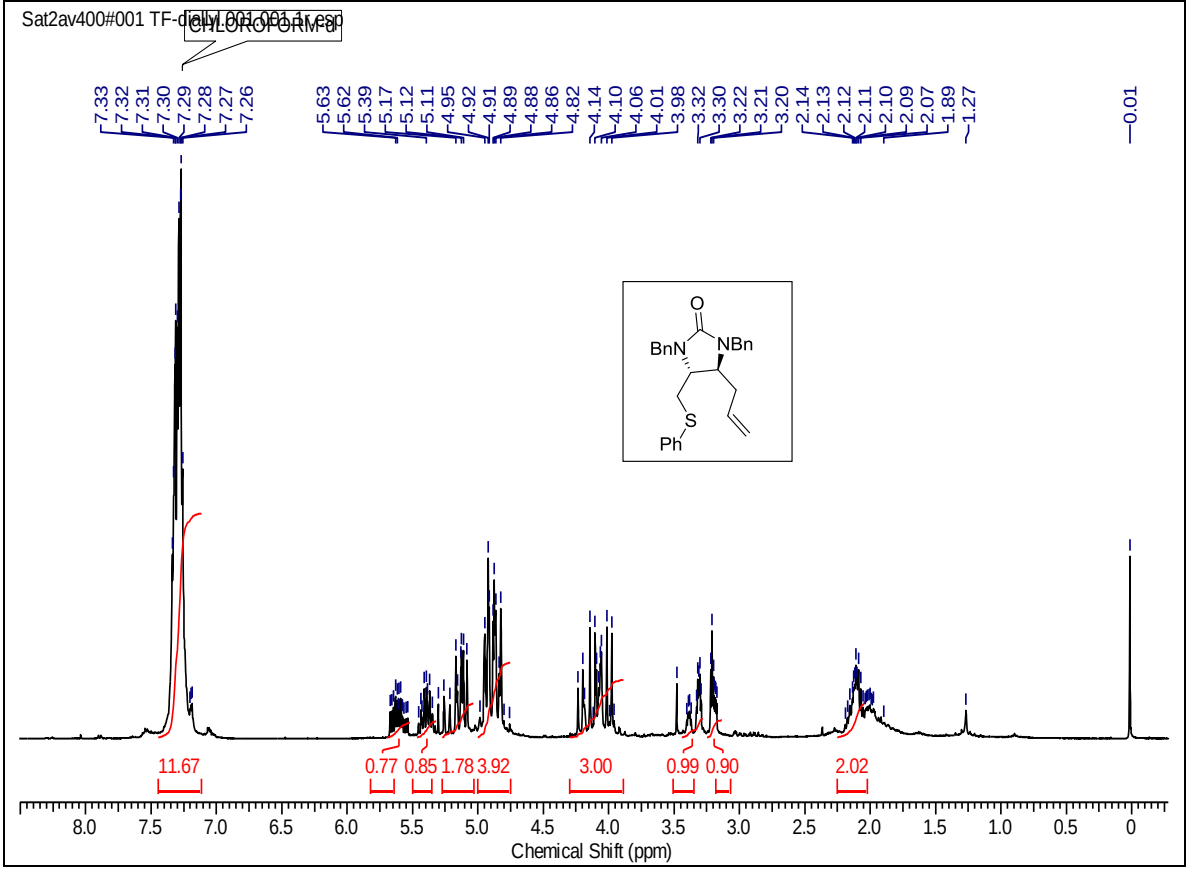
^{13}C NMR of phenyl sulfide 6 (50 MHz, $CDCl_3$ + CCl_4)



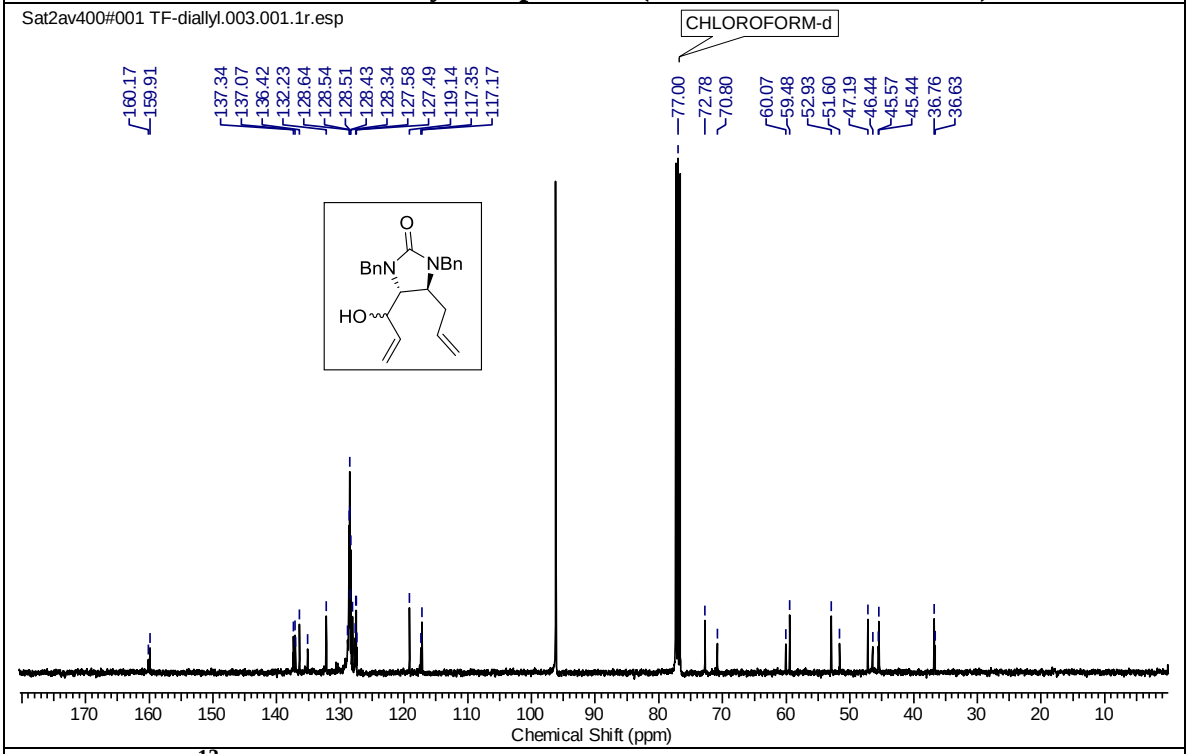
^{13}C NMR of phenyl sulfide 6 (50 MHz, $CDCl_3$ + CCl_4)



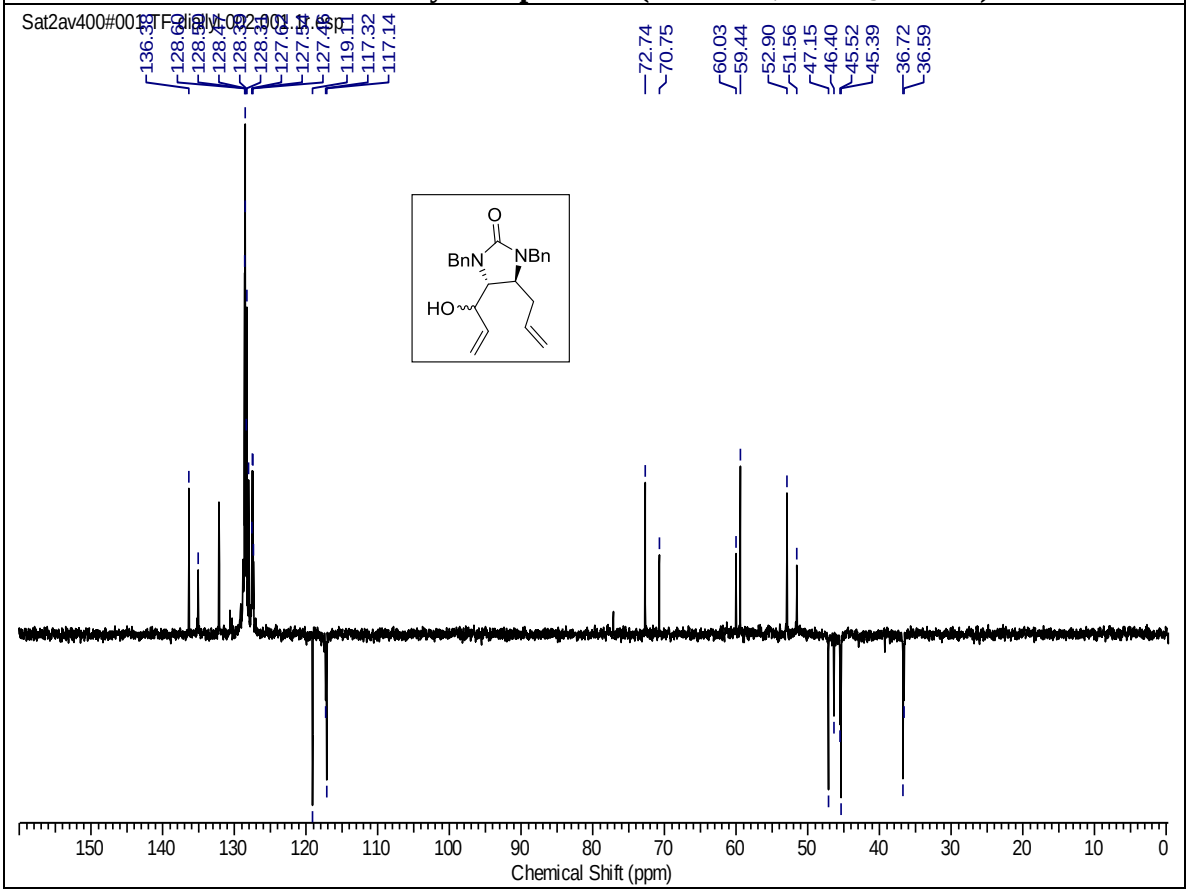
^{1}H NMR of diallyl compound 3 (400 MHz, $CDCl_3$ + CCl_4)



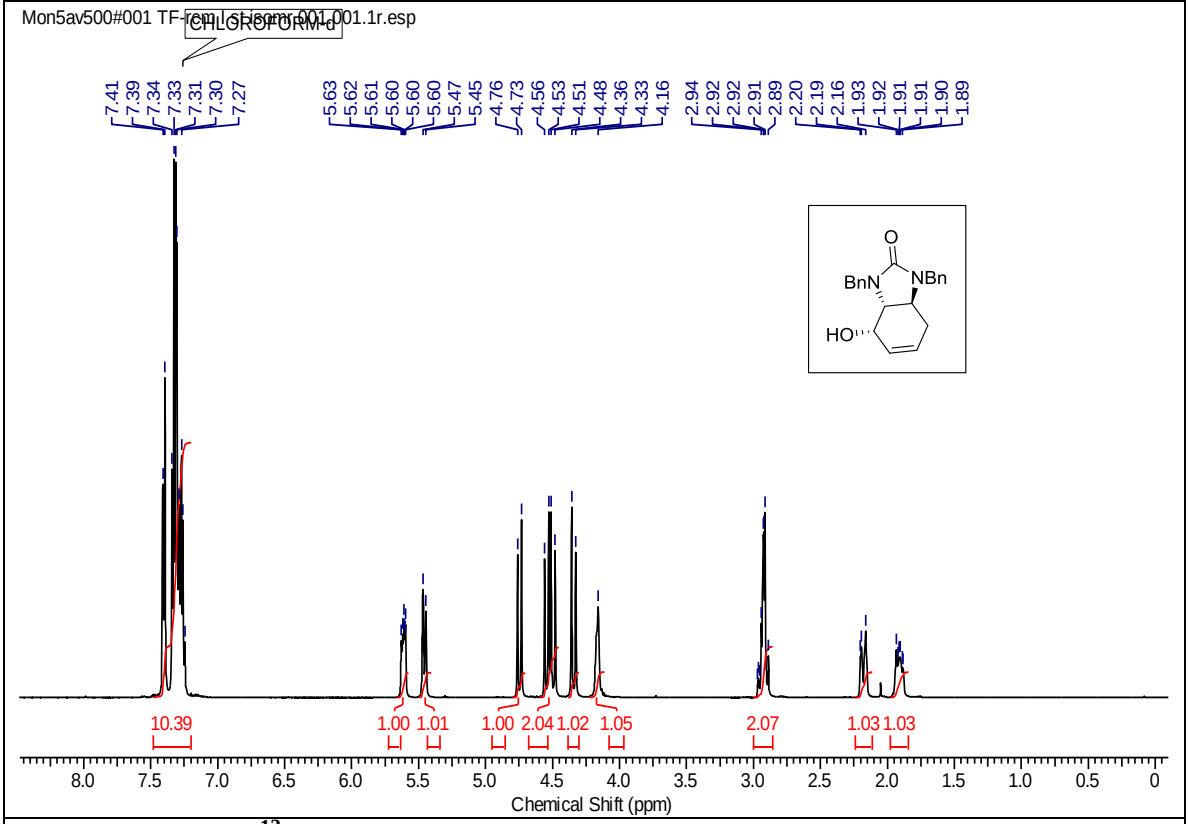
^{13}C NMR of diallyl compound 3 (100 MHz, $CDCl_3$ + CCl_4)



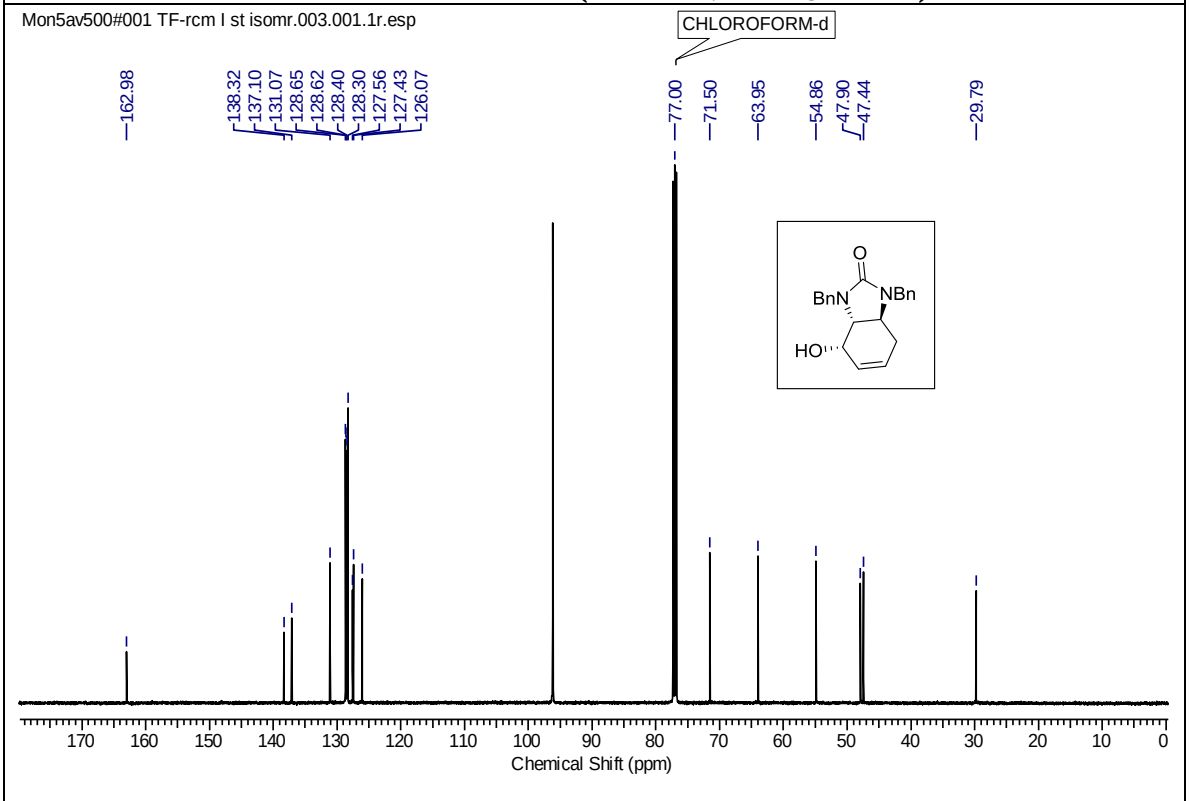
^{13}C NMR of diallyl compound 3 (100 MHz, $CDCl_3$ + CCl_4)



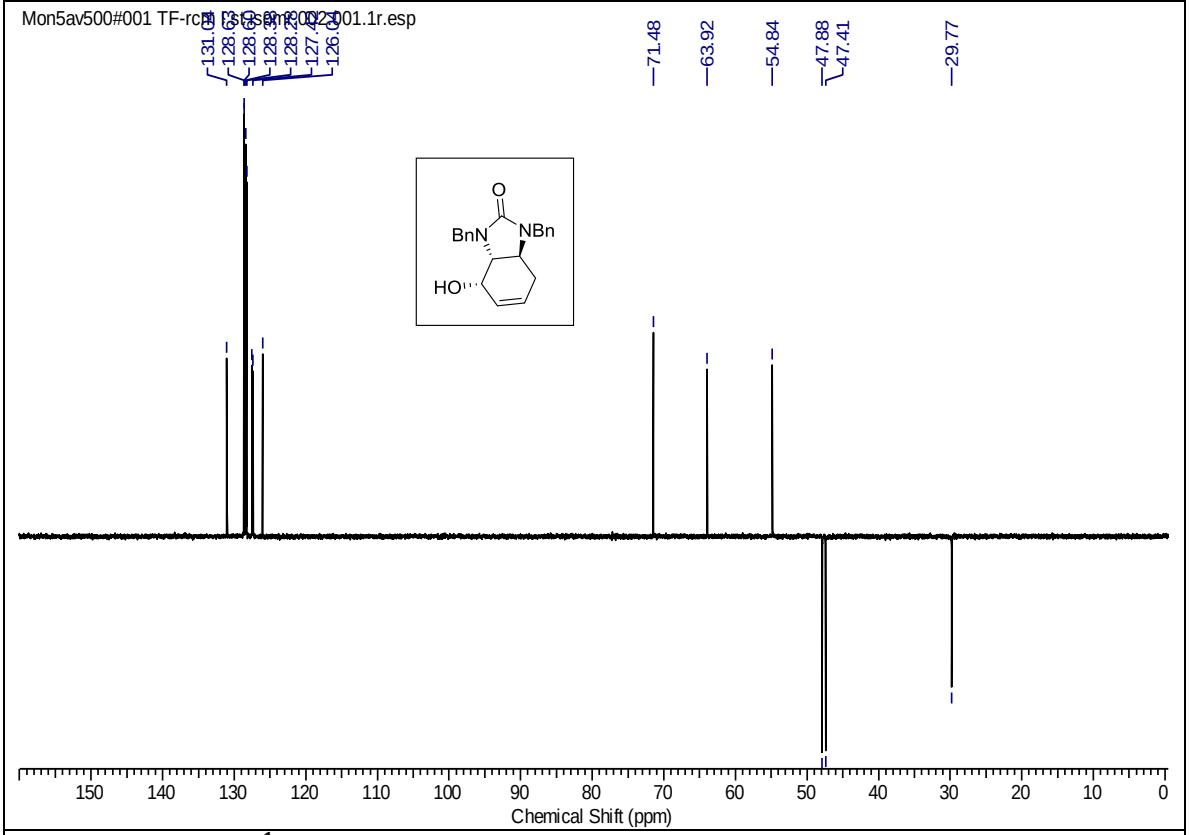
^{1}H NMR of alcohol 9a (500 MHz, $CDCl_3$ + CCl_4)



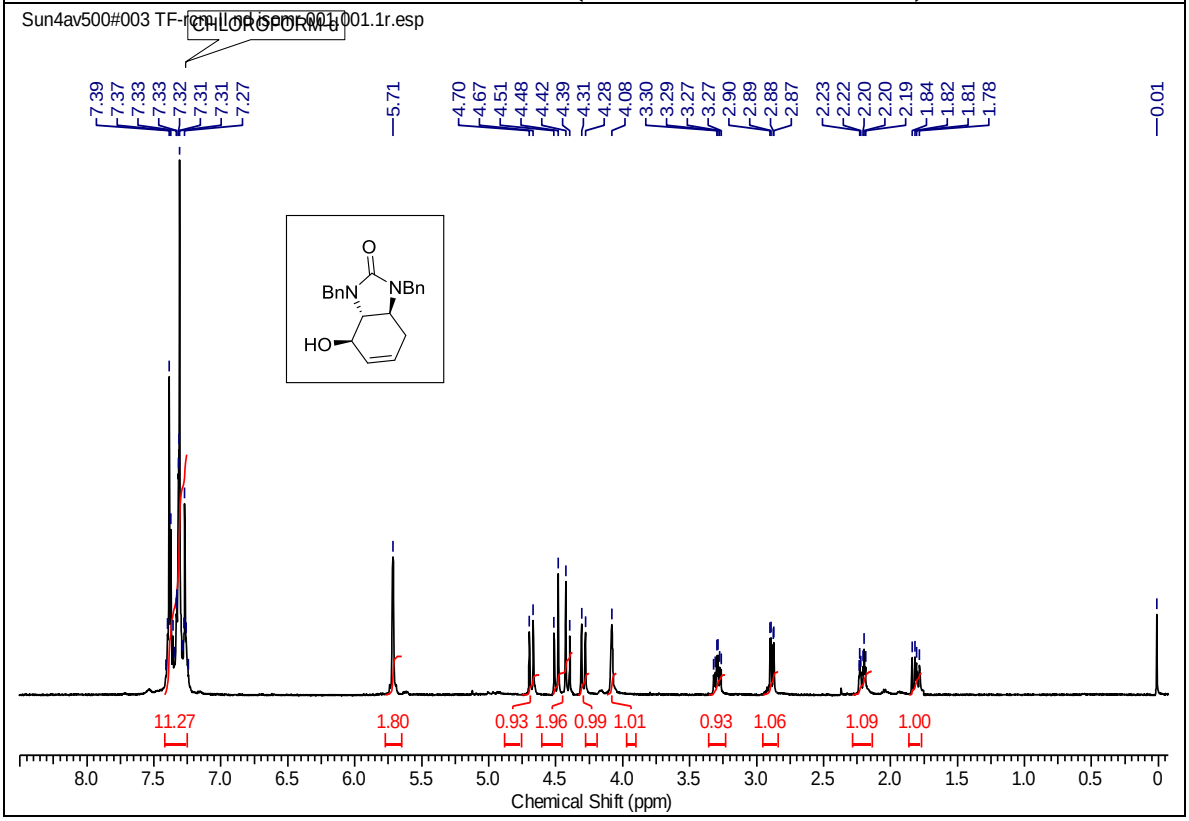
^{13}C NMR of alcohol 9a (125 MHz, $CDCl_3$ + CCl_4)



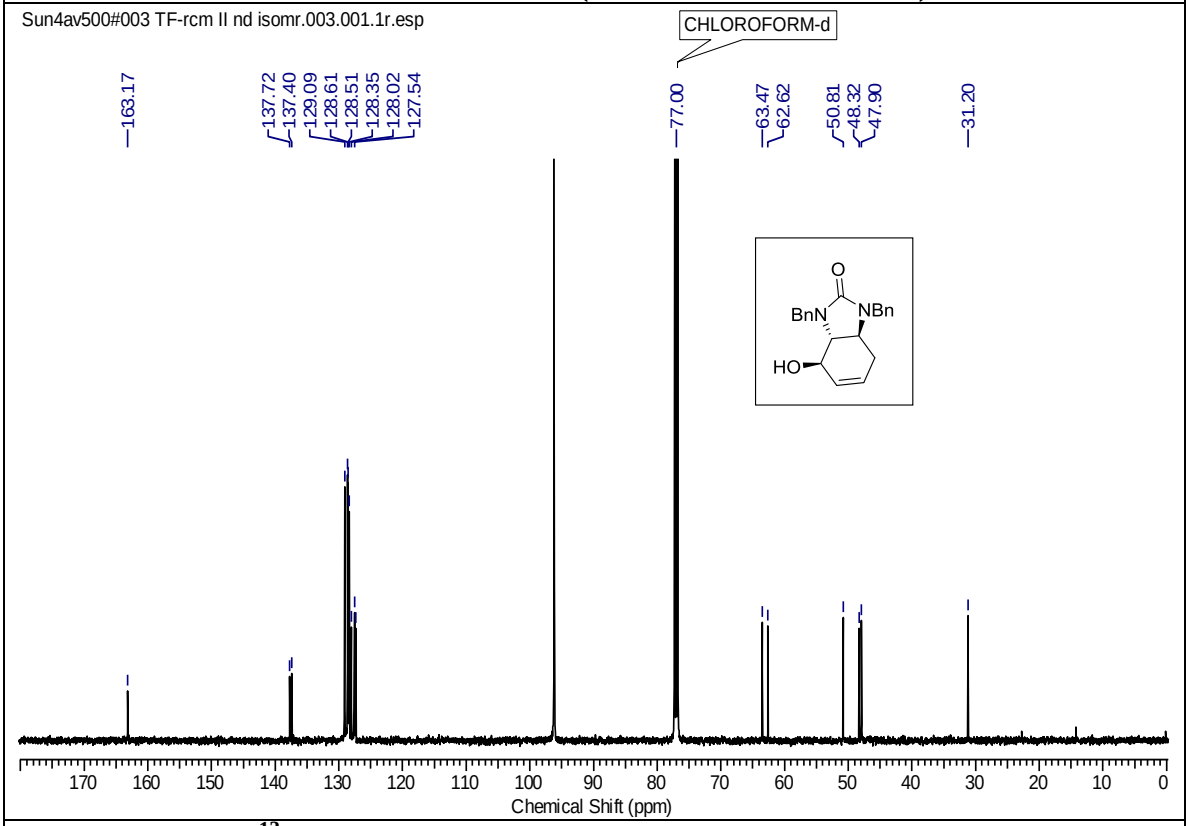
^{13}C NMR of alcohol 9a (125 MHz, $CDCl_3$ + CCl_4)



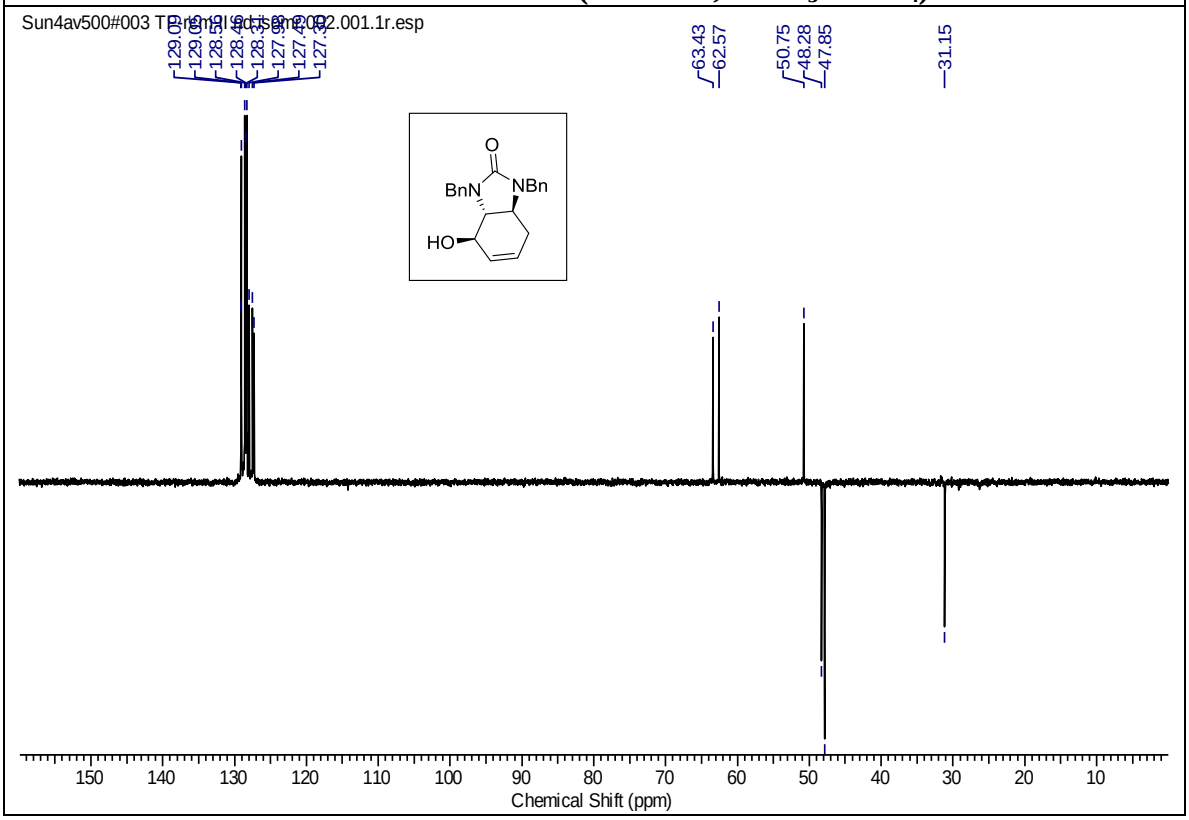
^{1}H NMR of alcohol 9b (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of alcohol 9b (125 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of alcohol 9b (125 MHz, $CDCl_3$ + CCl_4)



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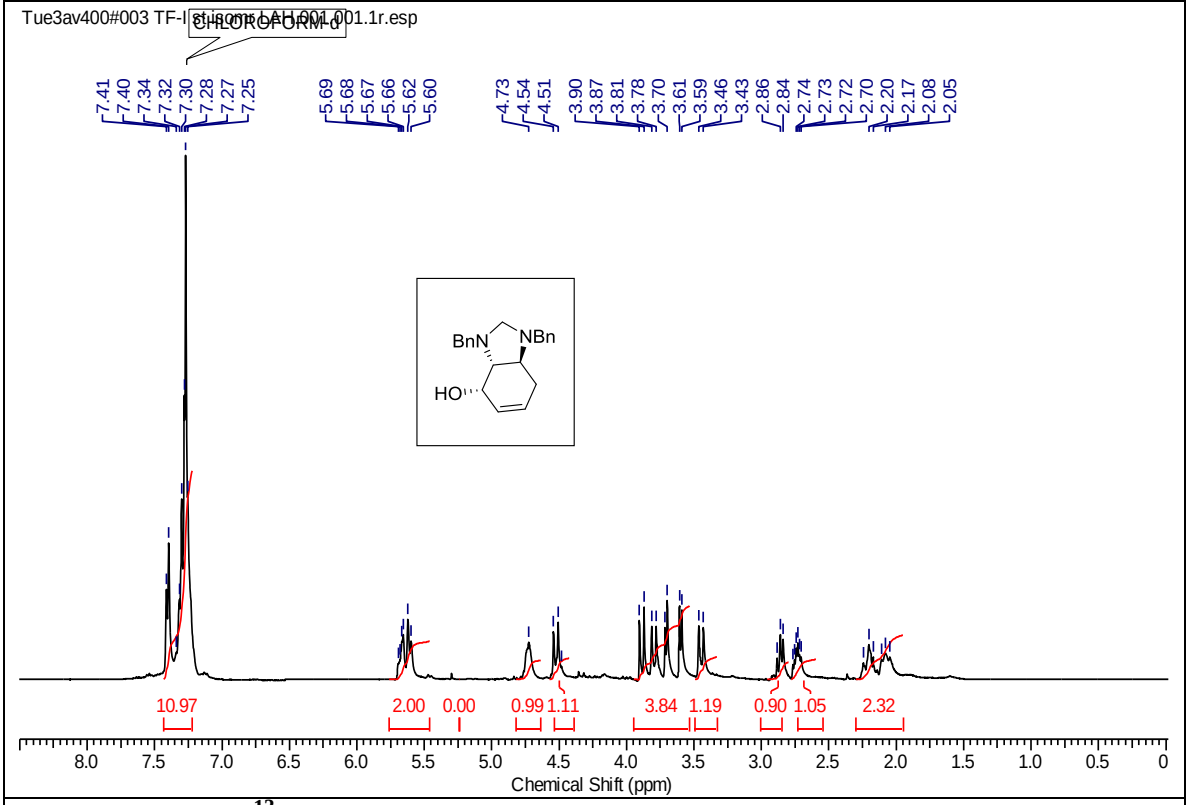

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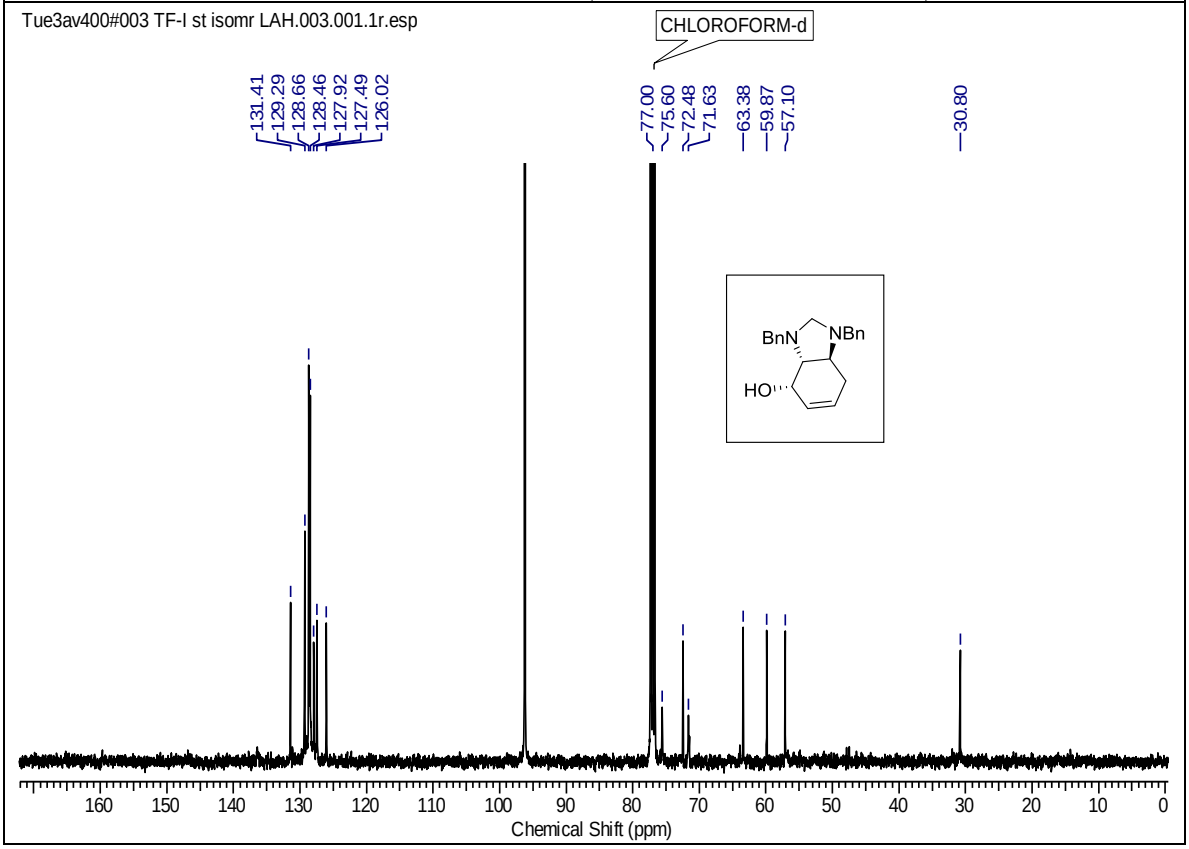
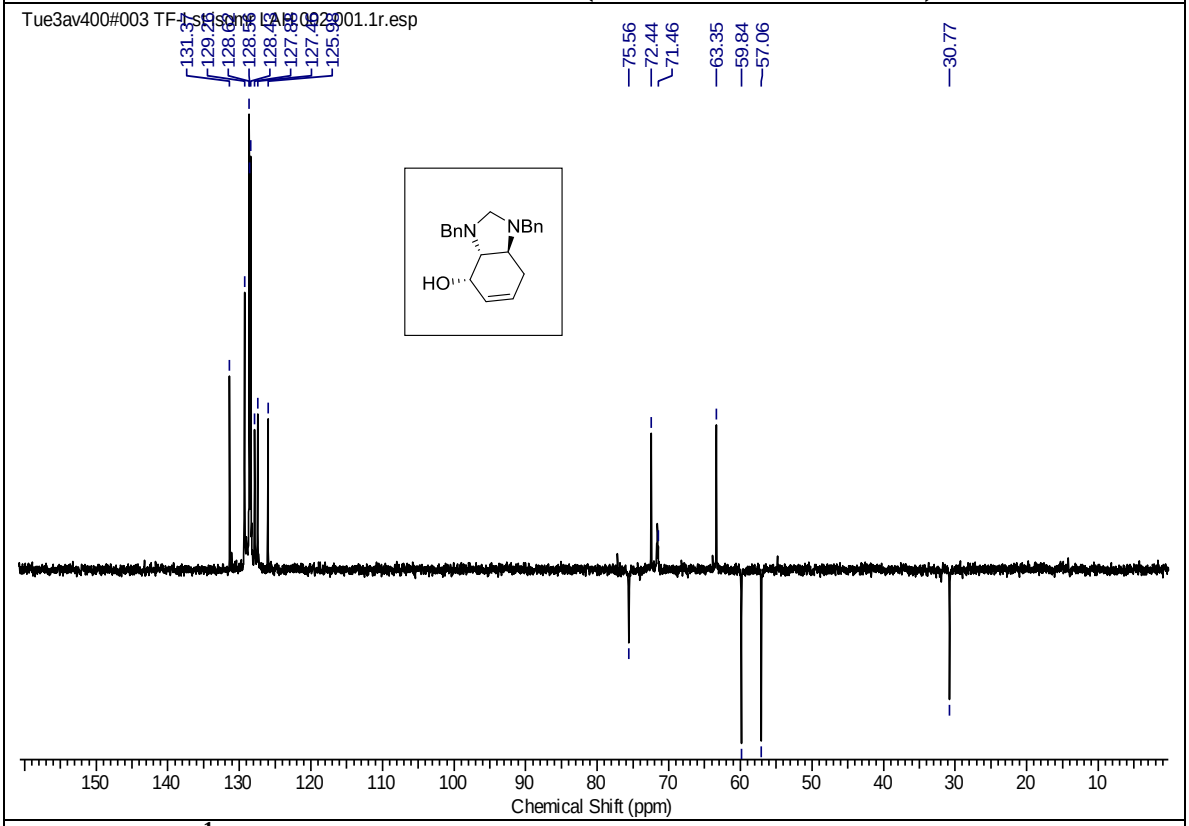
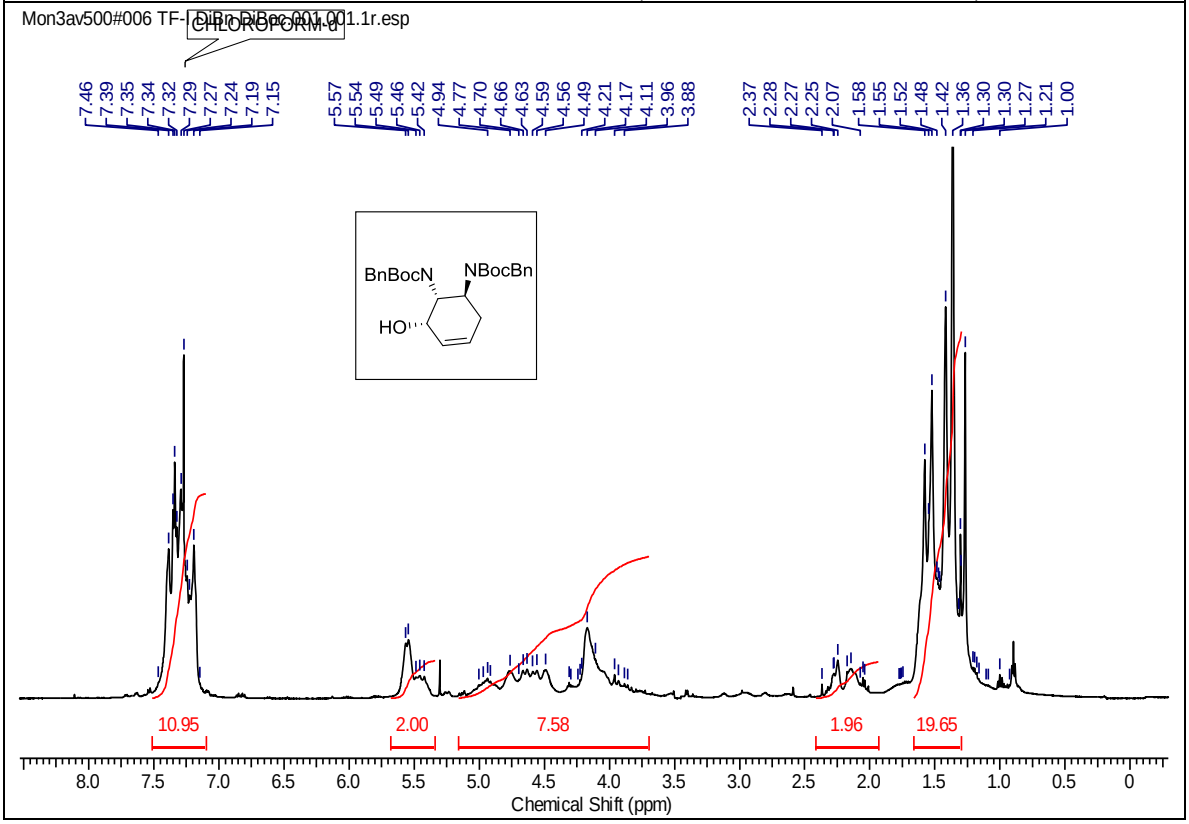


^{13}C NMR of diamine 10 (100 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR of diboc derivative 11 (500 MHz, $CDCl_3$ + CCl_4)



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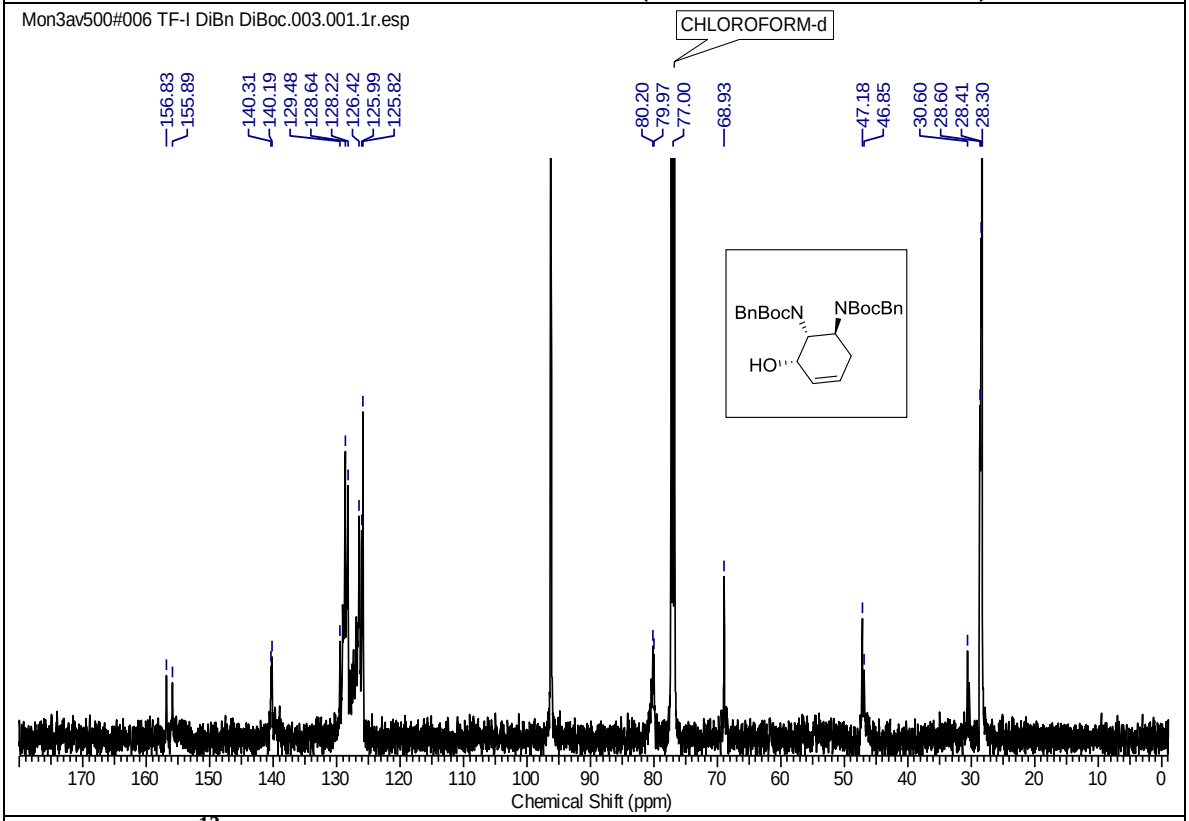
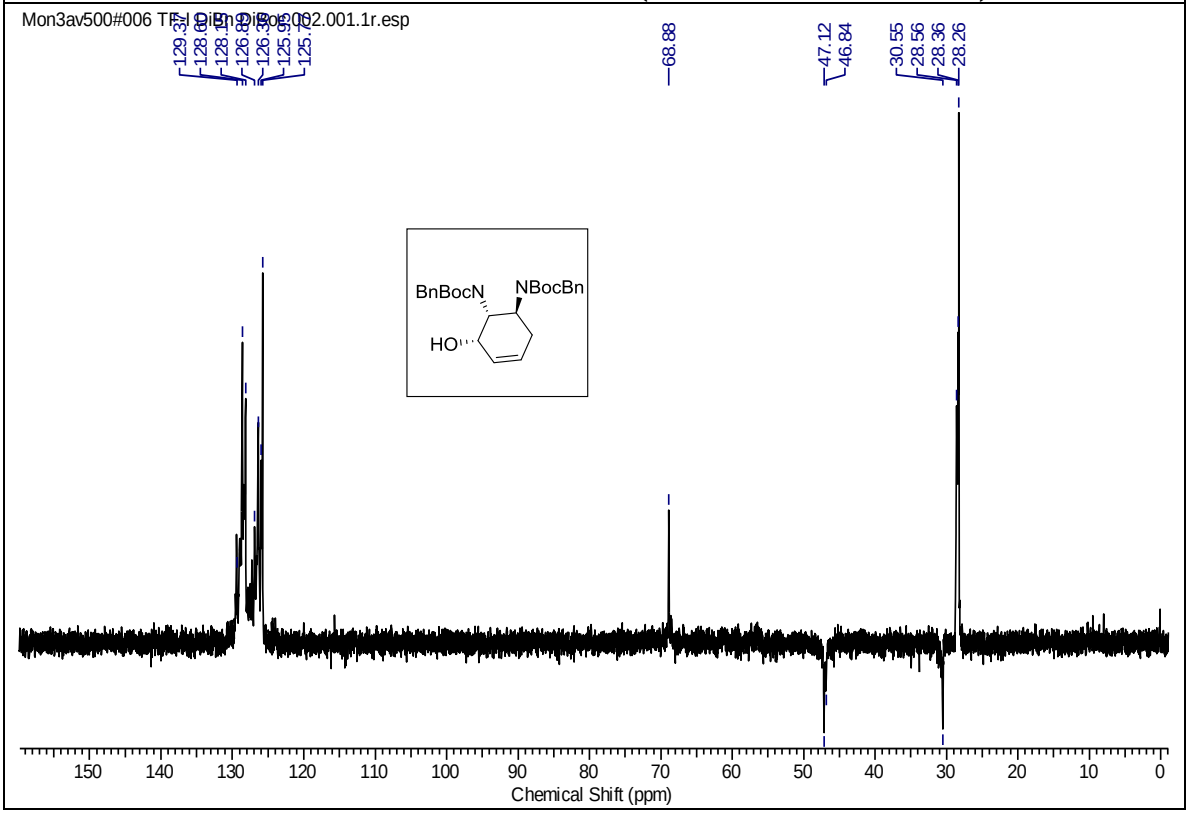
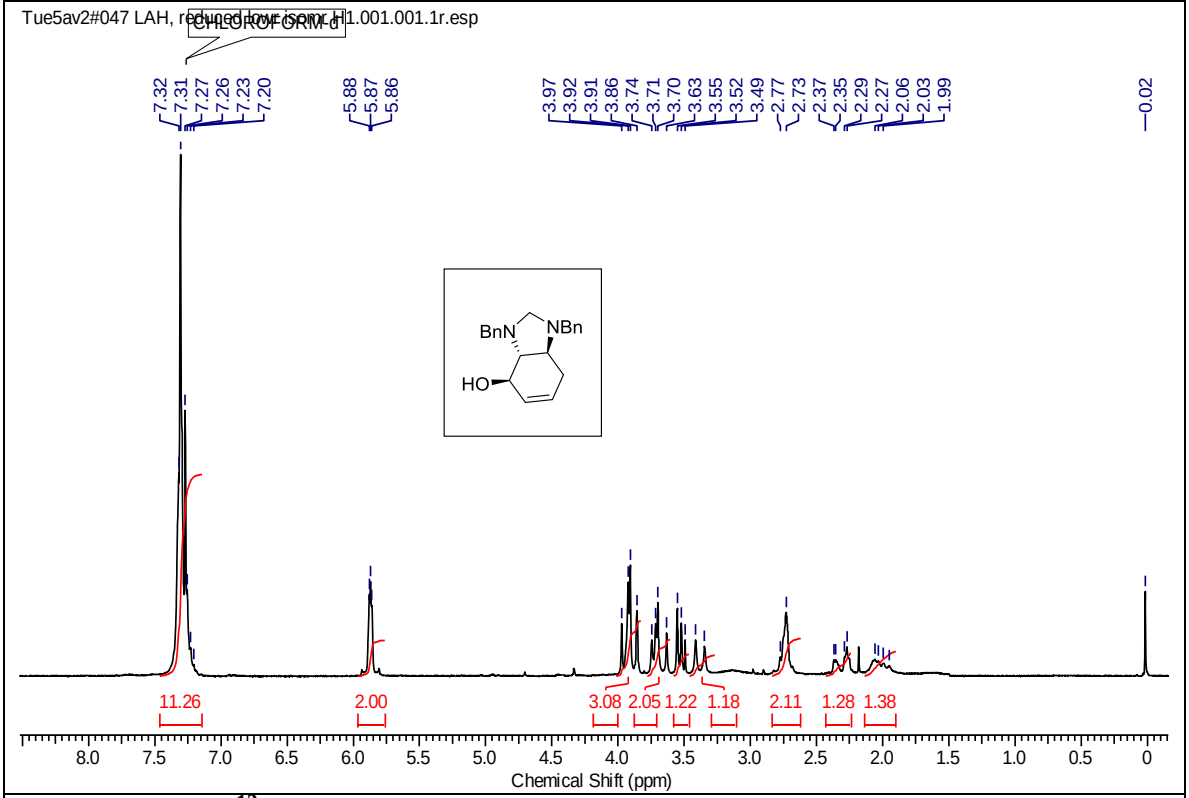


^{13}C NMR of diboc derivative 11 (125 MHz, $CDCl_3$ + CCl_4)



^{1}H NMR of compound 13 (200 MHz, $CDCl_3$ + CCl_4)



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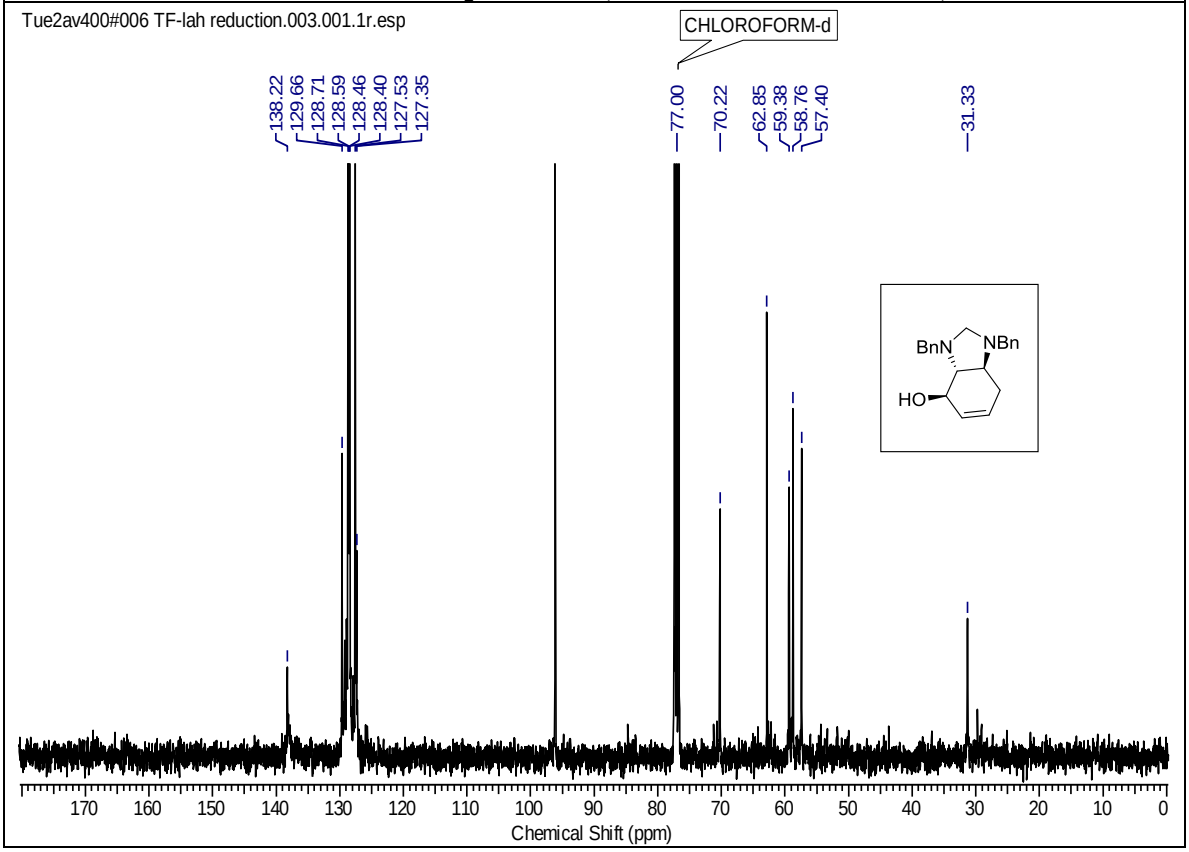
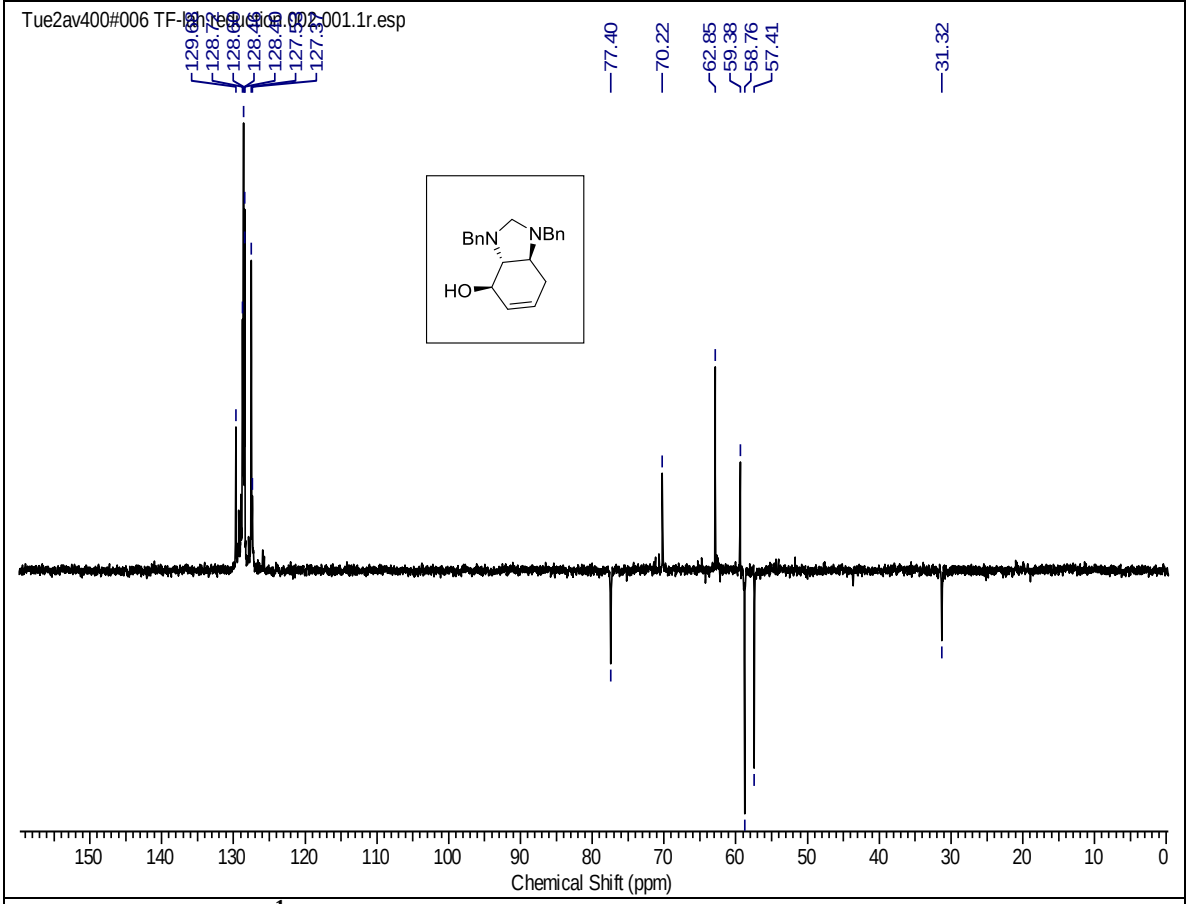
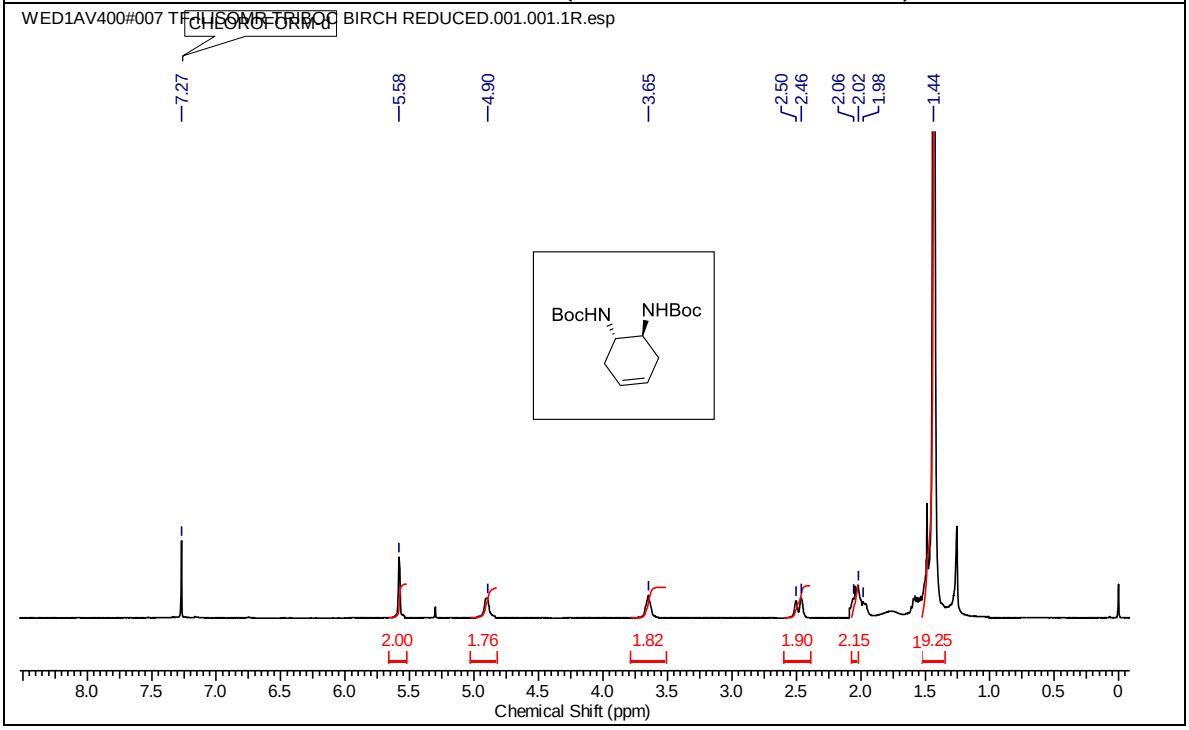


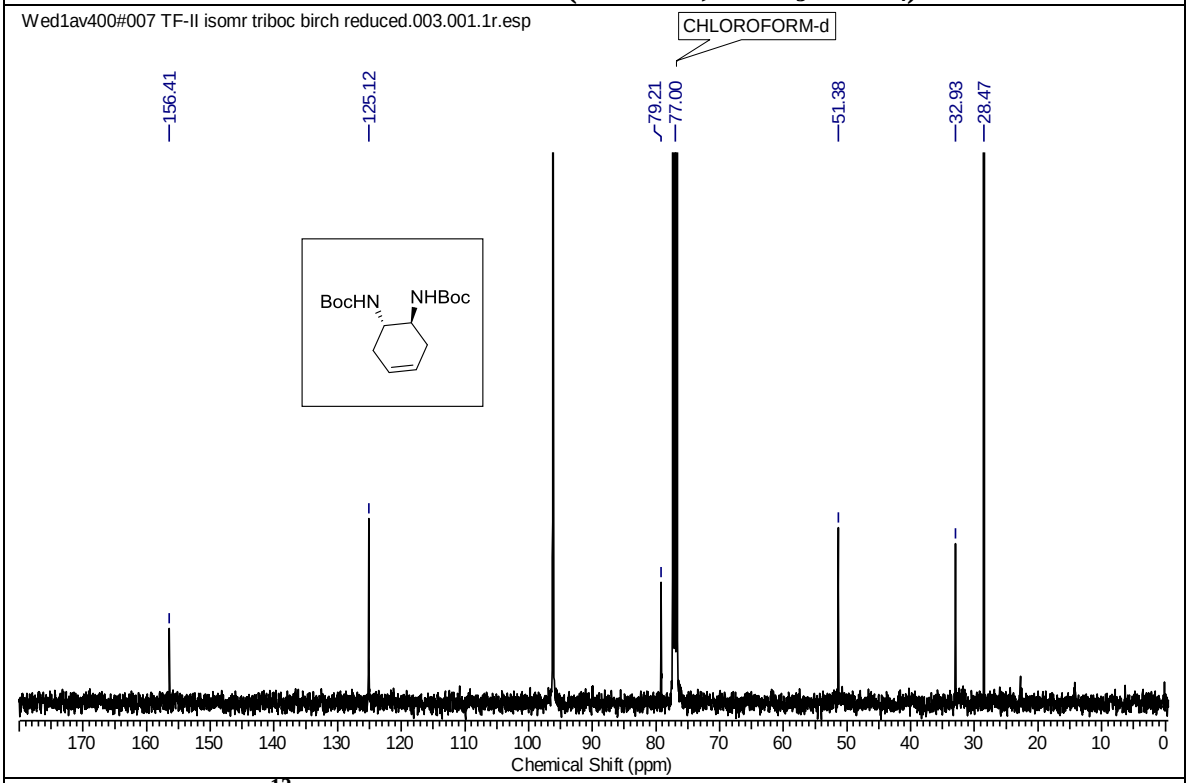
^{13}C NMR of compound 13 (100 MHz, $CDCl_3$ + CCl_4)



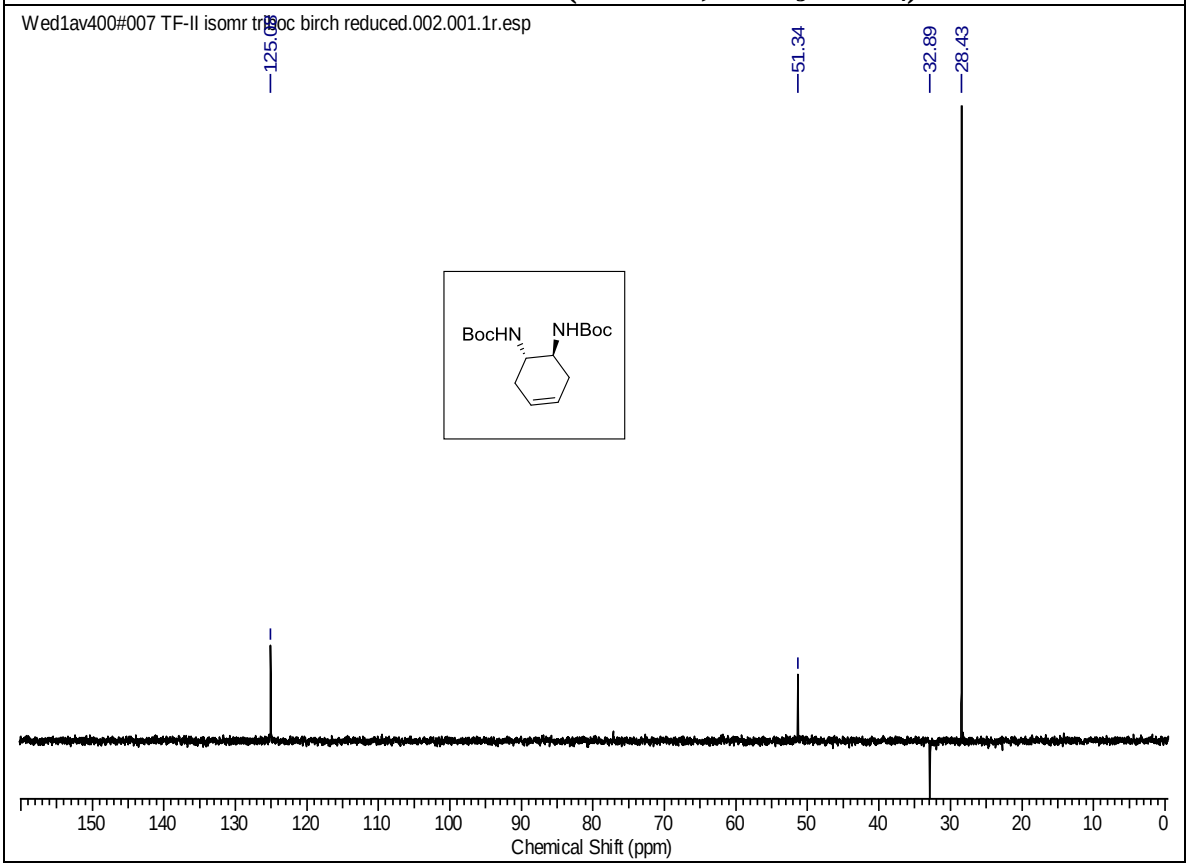
^{1}H NMR of olefin 16 (400 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of olefin 16 (100 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR of olefin 16 (100 MHz, $CDCl_3$ + CCl_4)



1.4.5 References

1) Fukuta, Y.; Mita, T., Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.
2) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.*, **2000**, 2, 2019.
3) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555.
4) Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.
5) Trnka, T. M.; Grubbs, R. H. *Accounts of Chemical Research* **2001**, *34*, 18.
6) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc*. **2003**, *125*, 11837.

Chapter 2

Aziridine based synthetic strategies

Section 1

Introduction to aziridine

2.1 Introduction of Aziridine

2.1.1 Introduction

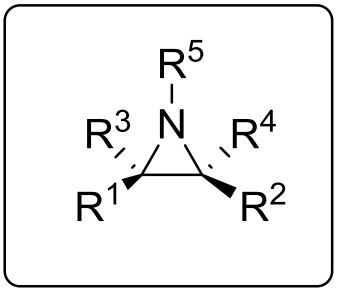


Fig 1 Aziridine

Aziridines are saturated three membered heterocycles containing one nitrogen atom and other two methylene bridges, which are also known as ethyleneimines (Fig 1). They theoretically can be obtained from cyclopropane by replacing one of the methylene groups with nitrogen. Aziridine was introduced as the smallest nitrogen containing heterocycle in 1888 by Gabriel. Since its discovery, it has been a synthetic target as well as useful building block in synthesis. The ring strain and unique reactivity of aziridine attracted synthetic chemists and they have extensively explored the various manipulations of aziridine containing compounds. The possible invertomers of aziridines are *cis* and *trans*, which are key synthons in the organic synthesis. These smallest heterocycles also exhibit synthetically very useful balance between stability and reactivity. Thus, they are often employed as versatile and selective intermediates.

Biological properties of aziridines

As powerful alkylating agents, aziridines have inherent in vivo potency, based on toxicity rather than specific activity. Several classes of aziridine containing natural products display selective potency, the best examples are mitosanes.[1] Mitosanes were isolated from soil extracts of *Streptomyces verticillactus*, which show both anti-tumour and anti-biotic activities. The aziridine ring is much essential for such biological activity and thus large amount of work has concentrated on derivatisation of these natural products with increased potency.

Mitosanes represent the first class of bioactive compounds to rely on bio-reductive activation to provide a means for DNA alkylation. FR and FK compound which are analogous to mitosanes show similar anti-cancer activity. Azinomycin, a structurally distinct class, possesses activity against wide range of cancer cells, tumour cells and exert cytotoxicity against human tumour cell lines. PBI class natural products, which contain aziridinyl quinone, represent another group of DNA-alkylating compounds (Fig 2).

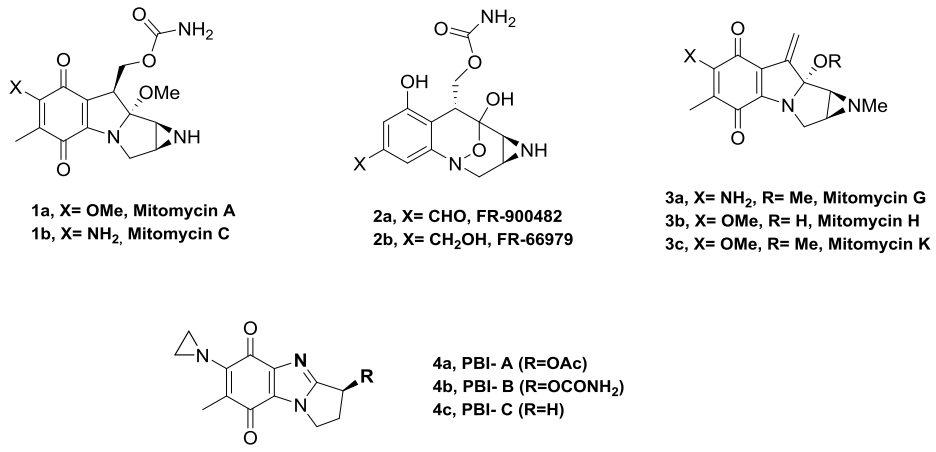
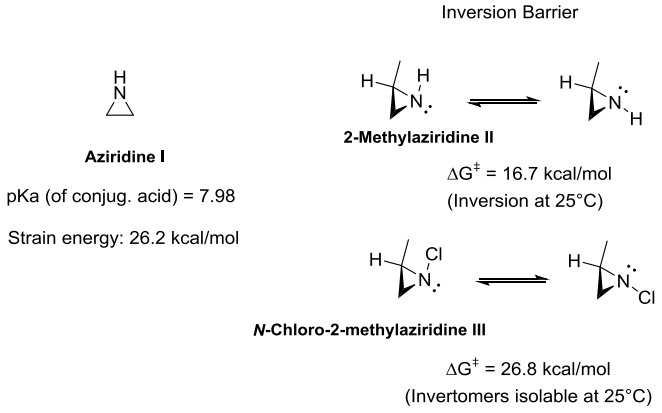


Fig 2 Aziridine ring-containing natural products

Physical properties of aziridines

The bond angle in the aziridine is approximately 60^{o}, less than hydrocarbons 109.5^{o}, which results in the angle strain as comparable to cyclopropane and epoxides. In general aziridines are less basic compared with acyclic amines (the aziridinium ion has p*K*a =

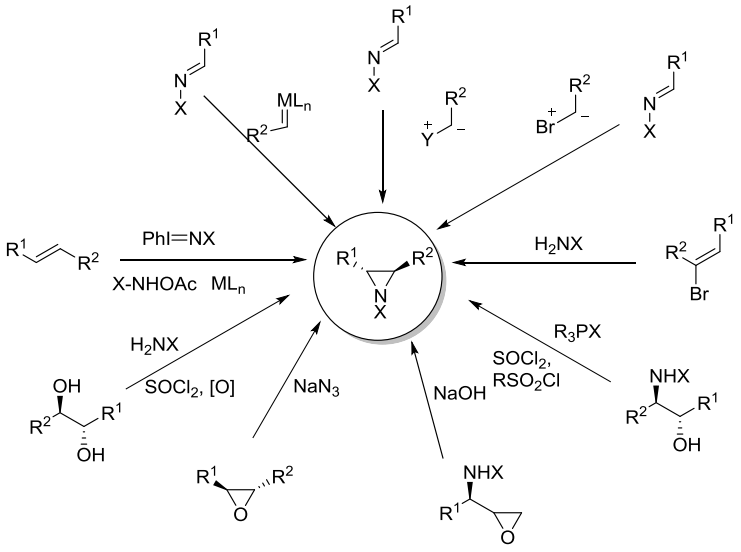


Scheme 1 Physical properties of aziridines

7.98) due to increased 's' character of the nitrogen lone pair. The increased 's' character results into increase in angle strain which is the barrier for the aziridine inversion. This inversion barrier can be enough for the separation of invertomers, for instance the *cis* and *trans* invertomers of *N*-chloro-2-methylaziridine described in Scheme 1.[2] The large inversion energy for aziridine is due to angle and torsional strains.

2.1.2 Synthesis of aziridines

It is certain that the chemistry of aziridine has been hindered by dearth of suitable methods available for aziridination compared with epoxidation. In other words, the methods for the preparation of aziridines are dwarfed by these available for preparation of epoxides, which are traditionally being mainstay from the alkenes. Reason for this incongruity is the inertness of N-O and N-N bonds compared to peroxide bond. Thus,



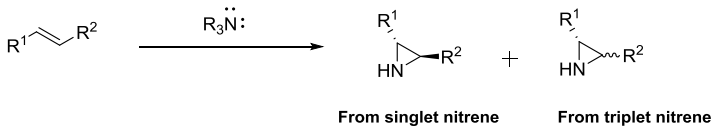
Scheme 2 Aziridines synthesis: Overview[3]

whereas alkenes react with peroxyacids and alkylhydroperoxides (in presence of Lewis acid), a parallel reactivity is not observed when alkenes are treated with the aza-analogues. The methods for aziridines preparation have been usually distinct from those for epoxides synthesis. Asymmetric aziridine formation method is still not generalized while asymmetric epoxidation is much generalized. Thus considering the importance of the smallest heterocycle inspired many organic groups to develop synthetic methodologies for the preparation of aziridines. Due to important features of the

aziridine, chemical communities have established the different ways of *N*-substituted and *N*-unsubstituted aziridine synthesis in achiral and chiral fashion. Also some efforts have been made for synthesis of *cis* and *trans* aziridines which is outlined in the Scheme 2.

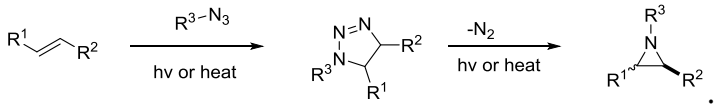
Addition of nitrene

It is the classical method for aziridination, featuring the addition of the nitrene to the unsaturated partner (Scheme 3). The limitations to the method (often involving alkoxycarbonylnitrenes) are well documented, with necessity for harsh reaction conditions and lack of stereoselectivity, which have limited the attractiveness of this methodology.[4]



Scheme 3 Addition of nitrene

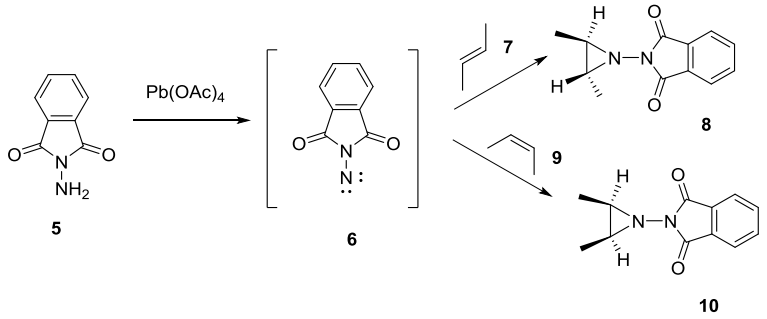
Typically such nitrenes were generated by thermal or photochemical decompositions of the corresponding azides, which led to the mixture of very active singlet nitrenes and more stable triplet nitrenes. The reaction of single nitrenes to 1, 2-disubstituted alkenes partner gives stereospecifically addition, while triplet nitrenes react in two step process with alkenes to furnish stereoselective products, in which N-C bond is formed in each step. The nature of the *N*-substituents in this case exerts powerful effect on exposing under this reaction conditions. When non-acyl azide undergo cycloaddition with alkene partner they furnished substituted triazoline, which is isolated in many instance and separately converted to the aziridine poor in stereoselectivity (Scheme 4).



Scheme 4 Addition of azide

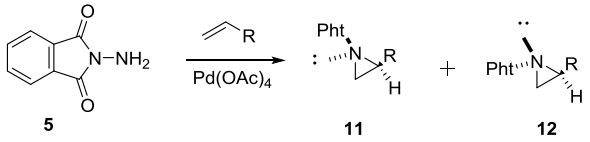
The useful modification of the method involves in situ generation of nitrene by the oxidation of hydrazine derivatives. This method provides the aziridines in more stereoselective manner than previous reported examples. Atkinson *et al* demonstrated that using hydrazine derivatives **5** led to the stereospecific addition to alkenes due to formation of *N*-nitrene **6**, which reacts only in singlet state. The *N*-amino phthalimide **5** in

presence of $Pb(OAc)_4$ generated singlet nitrene **6**, which underwent addition to both *cis*-alkene **9** and *trans*-alkenes **7** to provide stereospecific products **10** and **8** respectively. The primary reason was the high inversion barrier of phthalimide group (Scheme 5).[5]



Scheme 5 *N*-Nitrene addition on *cis* and *trans* alkene

In the case of mono-substituted olefin, the above reaction condition provides the diastereoselective addition products **11** and **12** at different temperature (Scheme 6).

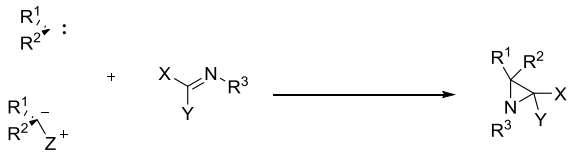


Scheme 6 Effect of temperature on *N*-nitrene addition

By addition to imines

Carbene and ylide method

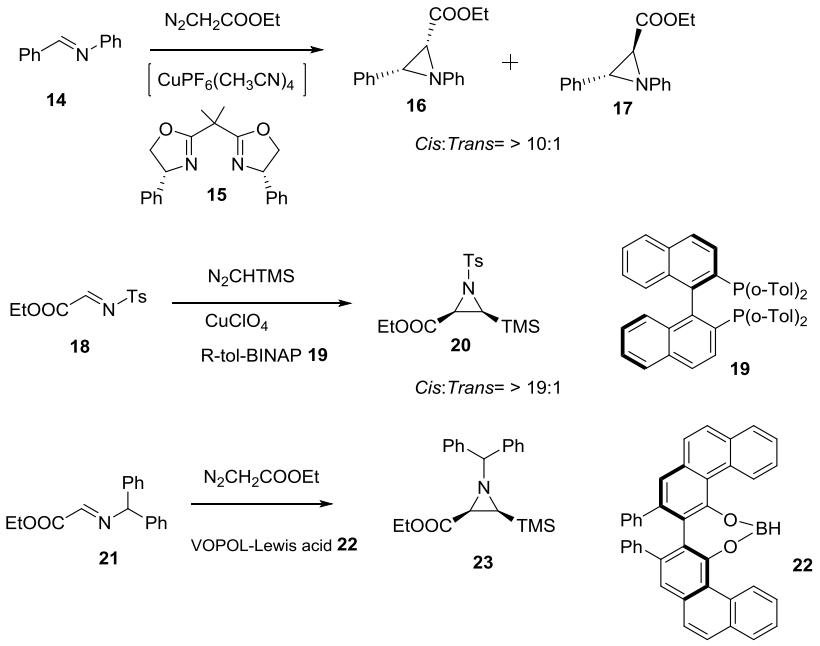
The addition of the carbines and ylides with imines provides aziridines through the formation of one C–N bond and one C–C bond as outlined in Scheme 6. The stereo chemical outcome of singlet and triplet carbene addition is similar to the nitrene reaction with alkene but the addition of ylide is in stereospecific way *via* S_N2 attack.



Scheme 7 Carbene addition to imine

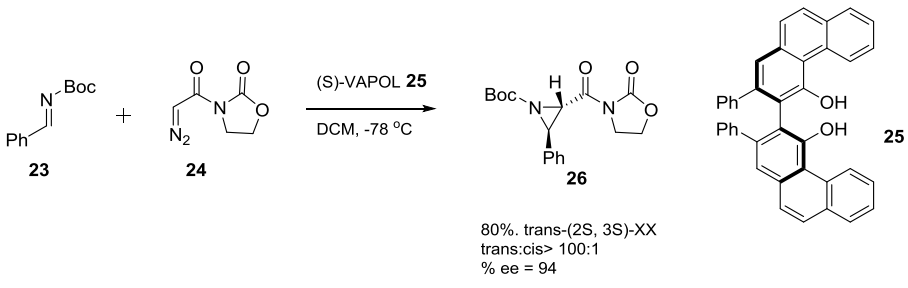
Jacobsen and Finney reported that metallocarbene derived from ethyl diazoacetate and copper-(I)-hexafluorophosphate added to *N*-arylaldimine **14** in presence of catalyst

derived from the Evans chiral bis(oxazoline) ligand **15** to afford acceptable diastereoselectivities (> 10:1) but enantioselectivity was low. Jorgensen using similar copper catalyst and **19** reported the better level of enantiocontrol, but falls short of standards of modern asymmetric transformation. Wulff *et al* utilized the axially-chiral boron Lewis acid **22** for asymmetric addition of ethyldiazoacetate to imine **21** and observed better enantioselective product **23** (Scheme 8).[6]



Scheme 8 Asymmetric aziridine synthesis

Huang *et al* has been recently published the first asymmetric catalytic reaction of diazo-compound **24** and *N*-Boc imine **23** in the presence of chiral polyborate as Bronsted acid (S)-VAPOL **25** gave trisubstituted aziridine **26** (Scheme 9).[7]

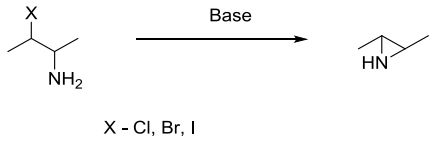


Scheme 9 Asymmetric synthesis of trisubstituted aziridine **26**

From 1, 2-aminoalcohols and 1, 2-aminohalides

Gabriel's aziridine synthesis[8]

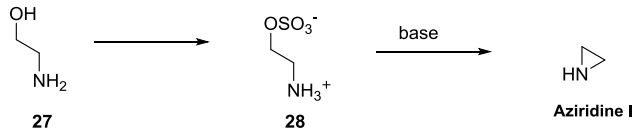
This is oldest method used for the aziridines synthesis. Gabriel who introduced aziridine as the three membered heterocyclic synthon in 1888 and demonstrated the synthesis of the aziridine from the ethanoamine in two step protocol. The 1, 2-aminoalcohol when treated with thionyl chloride resulted into halo-intermediate, which on alkali-mediated cyclisation to provide aziridine. The general example is described in Scheme 10.



Scheme 10 Gabriel's aziridine synthesis

Wenker's synthesis

In 1935, Wenker synthesized the first pure form of aziridine by heating ethanolamine **27** in presence of conc. sulfuric acid at higher temperature to afford compound **28**, which was termed as '*β*-aminoethyl sulfuric acid' (Scheme 11). The compound **28** was distilled out from aq. base to furnish aziridine, which was represented the first preparation of parent aziridine **I** in purest form. Afterwards different reaction conditions were utilized for the activation of hydroxy group of 1, 2-ethanolamines, enabling the preaparation of aziridines in achiral and enantiomerically pure form as the synthetic point of view.[9]



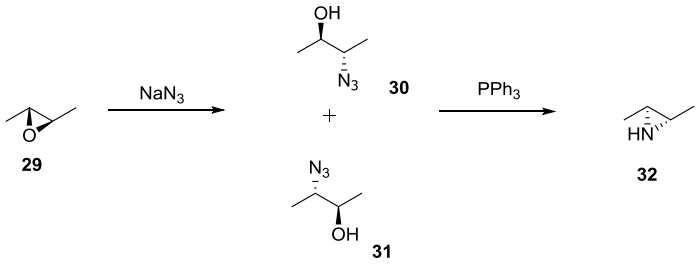
Scheme 11 Wenker's aziridine synthesis

These reaction conditions were not applied to wide range of aminoalcoholes, which led to mixture of cyclised and eliminated products if any *α*-substituents to hydroxy moiety were present. These are major limitations of this synthetic procedure for the preparation of aziridines. But some methods like Mitsunobu reaction by oxyphosphonium activation of

amino alcohols, which is extensively utilized in the organic transformations for aziridines synthesis.

From 1, 2-azidoalcohols

This method generally used for the asymmetric synthesis of aziridines from their readily available enantiopure *O*-analogs, epoxides. The enantiomerically pure epoxides, which could be obtained using the well documented asymmetric processes of epoxide preparation. The epoxides are the key precursor for the aziridines synthesis in multi-step procedure. Most useful procedure, the phosphine-mediated ring closing of 1, 2-azido alcohol (i.e. Staudinger reaction), which was derived from chiral epoxide **29** opening using azide as N-nucleophile afforded azidoalcohols **30** and **31** as regioproducts. Following the treatments of trialkyl/triarylphosphine furnished the *N*-unsubstituted aziridine product **32**. This is wildly used process for the aziridination, which gives the both asymmetric center smoothly and predictably from the chiral and achiral epoxides (Scheme 12).[10]

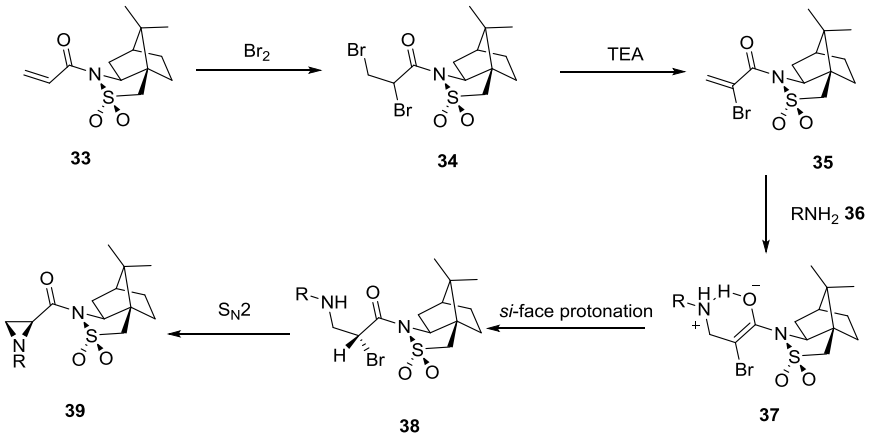


Scheme 12 Synthesis of aziridine from 1, 2-azidoalcohol

From α-bromoacrylates

Gabriel-Cromwell reaction

This is one of useful procedure for wide range of chiral aziridination. The aziridines were obtained by treatment of *α*-bromoacrylates with the wide range of amines following the reaction sequences conjugated addition of amines; proton transfer and S_N2 ring closing. The chiral *α*-bromoacrylates **35** on the similar addition of amine **36** led to aziridine **39** in chiral form (Scheme 13).[11] The unsubstituted chiral aziridine can be derived using ammonia as nitrogen source undergoes similar reaction sequences.

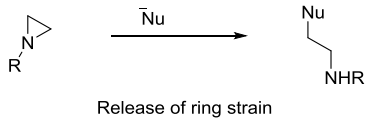


Scheme 13 Gabriel-Cromwell reaction

Reactions of aziridines

Ring-opening process

One of the most widely encountered reactions of aziridines is the nucleophilic ring opening. Aziridine having the Baeyer strain around 111 kJ mol^{-1} comparable to oxirane due to smallest cyclic nature and electronegativity of the nitrogen atom, which undergo ring opening under mild conditions with release of ring strain. The compared electronegativity of nitrogen is less compared with oxygen, thus ring-opening reaction of aziridine is less facile than the epoxide. But still there is requirement of an extensive exploration of the aziridine chemistry (Scheme 14). There are several features of these reactions which are worthy of consideration.[12]

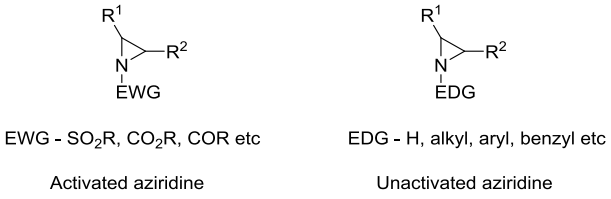


Scheme 14 Ring opening process

The nature of the *N*-substituents

The presence of the additional valency on the nitrogen atom in aziridines that of epoxides makes its chemistry comparatively complicated. The aziridine ring opening is carried using high basic and carbon-centered nucleophiles. The N-H bond of aziridines should be masked to avoid side reactions. The *N*-substituents should be stabilizes the anion

generated by ring opening. On the basis reactivity of the *N*-substituents aziridines have been devided into two type *i.e*. activated and unactivated aziridines. The activated aziridines having electon withdrawing groups like acyl, sulfonyl, carbonyl *etc* as substituents. These groups stabilize the negative charge on the nitrogen during the ring opening and also facilitate the nucleophilic ring opening. The unactivated aziridines are also known as simple aziridines, which having alkyl substituents on the nitrogen. Usually, these aziridines in presence of acid catalysts are prone to facile ring opening (Scheme 15).[13]



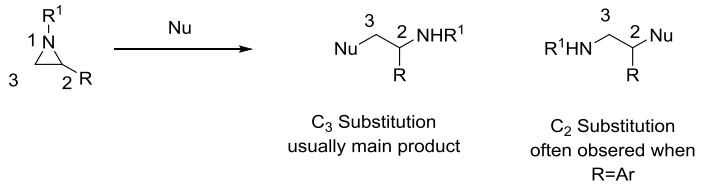
Scheme 15 Types of aziridines based on *N*-substituents

The inductive effect of *N*-substituent is responsible for kinetic activation and led to the polarization of C-N bond. The amide like anion produced after ring-opening is thermodynamically stabilized. If carbonyl is present as substituent the resonance stabilization is highly likely.

Regeoselectivity in ring-opening processes

Ring cleavage is most useful process for the 1, 2-functionalization of the aziridines as per

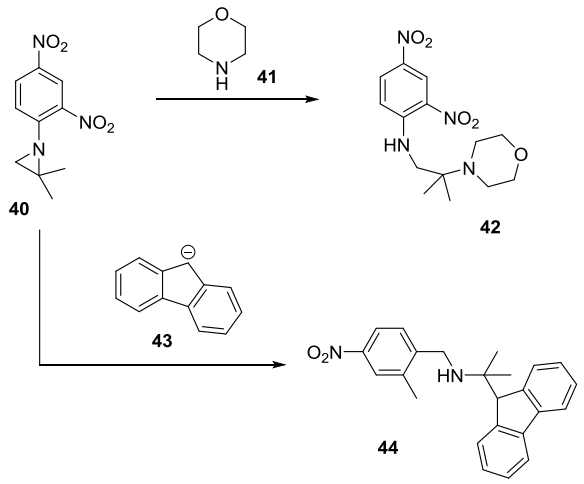
design. The nucleophilic aziridine ring opening process provides product selectivity similar to the epoxide ring opening. In the case of the unsymmetrically substituted aziridines were subjected to attack of nucleophiles led to the mixture of regioisomeric



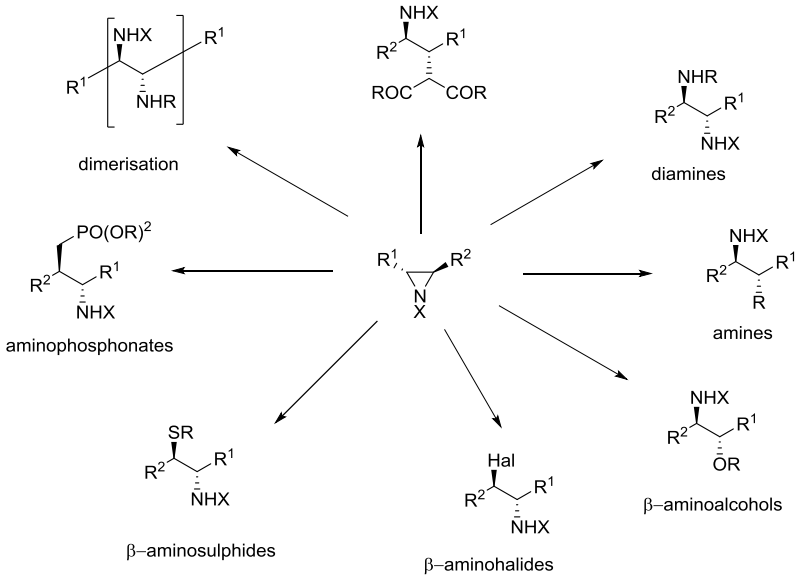
Scheme 16 Regeoselectivity in aziridine ring opening

ring opened products. Fundamentally the nucleophiles would preferentially direct the attack from the less crowding arm of aziridine considering the electronic factor as described in Scheme 16.[14]

Inconsistent reactivity profiles of aziridines are occasionally observed when nucleophiles either hindered **43** or a relatively weak Lewis base **41** or weakly activated aziridines. In this situation, attack at a quaternary 'C' atom is preferred over the less substituted 'C' atom (Scheme 17)



Scheme 17 Hindered nucleophilic ring opening

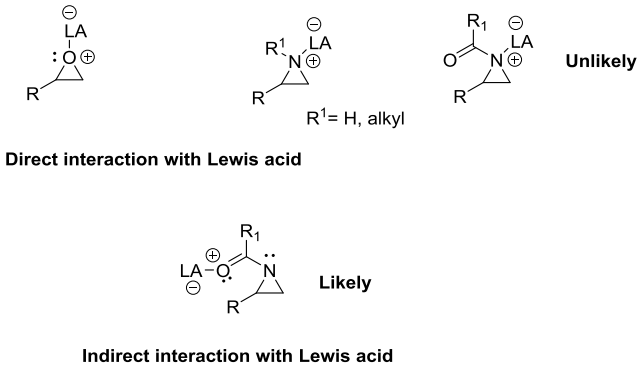


Scheme 18 Aziridine ring opening: Overview[3]

The nucleophilic aziridine ring opening provides the regioselective and stereoselective product. It is possible to synthesize the number of the functionalized compounds that show 1, 2-relation of incoming nucleophiles. The wide range of the nucleophiles *e. g*. carbon, oxygen, sulfur, nitrogen, halogen, hydrogen, phosphorous, silanes, selenols, cobalt, *etc*. have been utilised to synthesise 1, 2-functinalised compounds. The functionalizations of the aziridines by ring opening as outlined in the Scheme 18.[15]

Effect of Lewis acid

The non-bonding lone pair electrons acts as Lewis base, its mean presence of the Lewis acids enhances the rate of epoxide ring opening process by weakening the already strained C-O bond through coordinating. In aziridines, when alkyl as substituents on the



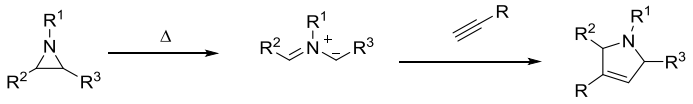
Scheme 19 Effect of Lewis acid

nitrogen atom then it can interact with Lewis acids and since the polar activating *N*-substituent is often required for efficient aziridine ring opening. The ring opening of aziridine is less facile as compared with epoxide by the use of Lewis acid. Nonetheless, the desirability of polar oxygenated *N*-substituent for ring-opening still allow for some use of this type of activation *via* coordination of oxygen lone pair to Lewis acid (Scheme 19).

Electrocyclic aziridine ring-opening

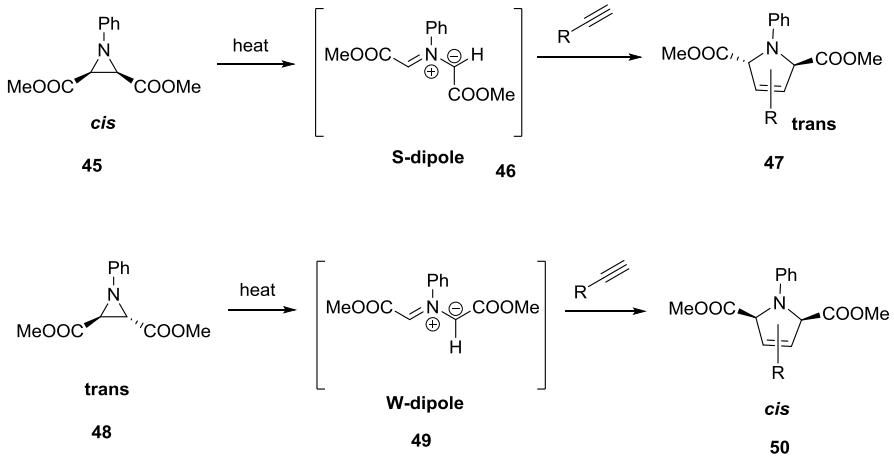
Aziridines are considered as the precursor of azidomethane ylide. On heating the aziridines rupture in stereospecifically to generate 1, 3-dipolar azidomethane ylides, which insitu were trapped with dipolarophiles to provide the substituted pyrrolidines

(Scheme 20).



Scheme 20 Pyrrolidines synthesis

The aziridine stereochemistry is maintained in the stereochemistry of the dipole such that *S*-dipole **46**, which is obtained from *cis*-aziridines **45** leading to *trans*-2, 5-substituted pyrrolidines **47**, where as the *W*-dipole **49** obtained from *trans* aziridines **48** leading to *cis*-2, 5-substituted pyrrolidines **50**. The *S*-dipoles reacts efficently with wide range of dipolarophiles with retention of geometry whilst *W*-dipoles react smoothly with reactive dipolarophiles such as acetylenedicarboxylates and maleimides (Scheme 21).



Scheme 21 *S* and *W* dipole reactivity

2.1.3 Application of aziridines in synthesis

The renewed interest in aziridination has fostered increased application in synthesis of variety of nitrogen containing bioactive natural products. Last 20 years have attracted organic chemists for the synthesis of aziridines and dealing with the preparation of small nitrogen containing heterocyclic compounds and its reactions. Aziridine moiety presents itself, or can serve as intermediates in strategies for the synthesis of natural products. The high strain and inherent potent abilities of aziridines led to stereo- and regioselective ring-opening reactions have been exploited in natural.

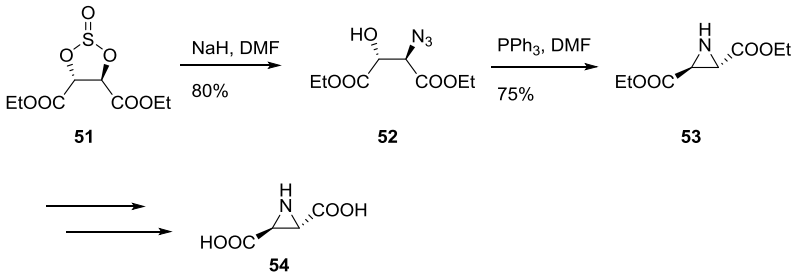
The aziridine based synthesis of natural products are categorized in two type *i.e.* synthesis of natural products containing aziridine units and synthesis of natural products involving the transformation of an aziridine moiety.

Synthesis of natural products containing aziridine units

Numbers of natural products possessing aziridine ring as unit possesses potent biological activity.

Synthesis of aziridine-2, 3-dicarboxylic acid

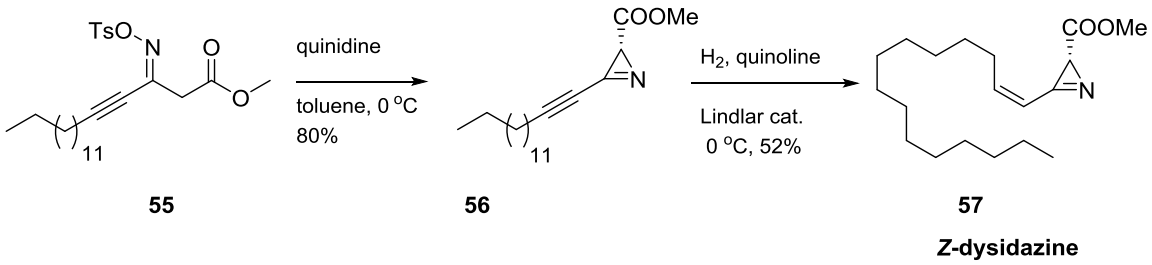
The C_2-symmetry compound **51**, which is metabolite of Streptomyces MD 398-A1.[16] The compound **51** was prepared from L-(+)-diethyl tartarate as chiral starting material in enantiopure form is described in Scheme 22.



Scheme 22 Aziridine-2, 3-carboxylic acid

Synthesis of (*Z*)-dysidazine

The first enantioselective synthesis of (*Z*)-dysidazine **57** reported by Molishki,[17] which was isolated from the marine sponge *Dysidea fragilis* shows antifungal activity. The intermediate **55** was converted into aziridine **56**, followed by Lindlar reduction afforded

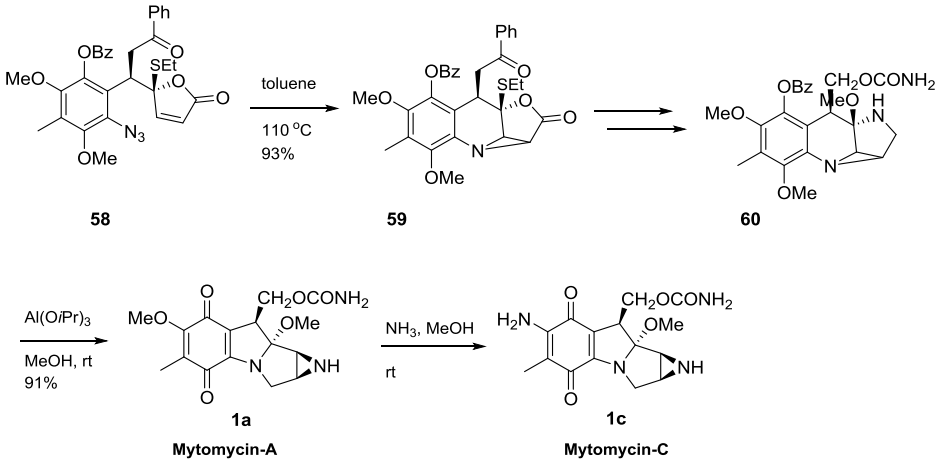


Scheme 23 (*Z*)-Dysidazine

(*Z*)-dysidazine **57** (Scheme 22).

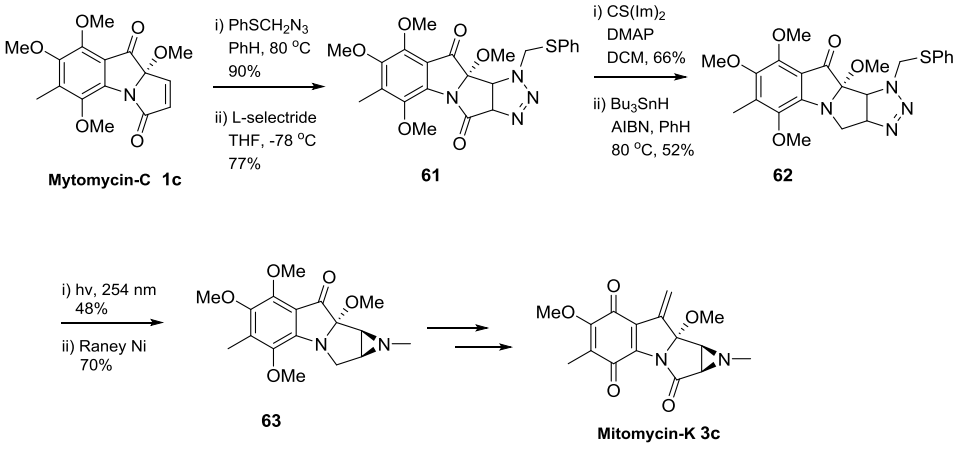
Synthesis of Mitomycins

This is the important class of aziridine ring containing natural products show very potent antibacterial and anticancer activities, which were extracted from the genus *Streptomyces*. Most efforts have been put by synthetic chemists for the synthesis of the natural products, which contains aziridine ring.



Scheme 24 Mitomycin A **1a** and C **1c**

Fukuyama and co-workers synthesized mitomycin A **1a** and mitomycin C **1c** which is briefly described in the Scheme 24.[18] The azide **58** on intramolecular cycloaddition at 110 ^{o}C provided aziridine **59**, followed by few reaction sequences compound **59** was



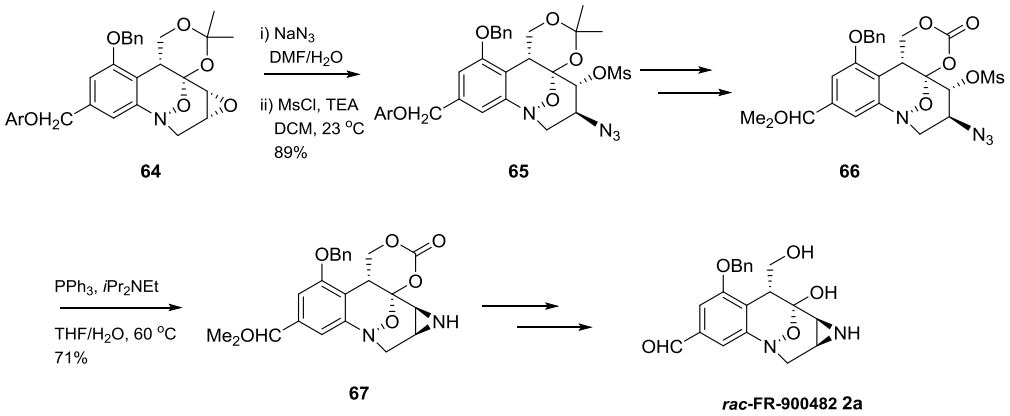
Scheme 25 Mitomycin K **3c**

converted into target compounds **1a** and **1c**.

Danishefsky and colleagues reported a short synthesis of mytomycin K **3c**. The *N*-methyl aziridine **63** was obtained from the olefin **1c** by 1, 3-dipolar cycloaddition of methylthiophenyl azide provided triazloine **61**, which on two step sequences afforded compound **62**. Compound **62** was irradiated at 254 nm to furnish aziridine **63** as key intermediate, which was converted to Mitomycin K **3c** in few steps (Scheme 25).

Synthesis of FR-900482

The FR-900482 **2a** is structurally related with Mitomycin C **1c** and show antitumor and antibiotic activities. Fukuyama has reported the first total synthesis of FR-900482 **2a**,



Scheme 26 *rac*-FR-900482 **2a**

which is outlined in Scheme 26.[19]

Epoxide **64** was opened with NaN_3, followed by the mesylation afforded azide **65**. The azide **65** was transformed to compound **66** using few reaction sequences, which was treated with PPh_3 in presence of base ended aziridine **67** as the key intermediate. The aziridine **67** was advanced to the target compound **2a** in few steps.

Synthesis of natural products involving the transformation of an aziridine moiety

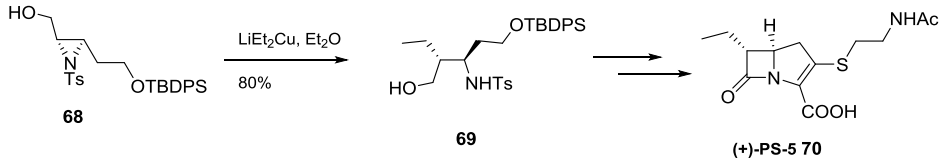
The aziridines are undergoing nucleophilic ring opening to release ring strain. Unactivated aziridines required acids to catalyze reaction *e.g.* unsubstituted or alkyl-substituted aziridines while activated aziridines are facile to the attack of nucleophiles.

Thus aziridines are useful and having the good potency in the synthesis of natural products.

Carbon-centered nucleophiles

Generally organometallic reagents are used as *C*-centered nucleophiles in the natural product synthesis through nucleophilic ring opening. Late 1980 have witnessed for its application in natural products synthesis using organocuprate or Grignard reagents to open *N*-alkyl aziridines in Lewis acids or *N*-tosyl aziridines with no need of Lewis acids.

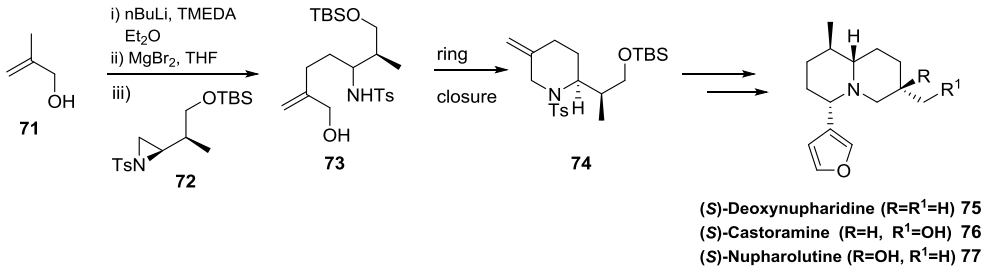
Organocopper reagents mediated ring opening has proved useful in the number of synthesis. First example reported by Tanner and co-workers of an enantioselective synthesis of (+)-PS-5 **70** described in Scheme 27.[20]



Scheme 27 (+)-PS-5 **70**

The aziridine **68** on $LiEt_2Cu$ addition afforded compound **69**, which provided target compound **70** in few reaction sequences.

The Grignard reagents have been also used in the natural products synthesis as like organocopper reagents. The allyl magnesium reagent obtained from the allylic alcohol **71** by deprotonation/transmetallation was reacted with *N*-sulfonyl aziridine **72** afforded compound **73**. Compound **73** was cyclised to the advanced intermediate piperidine **74**, which eventually provided nuphar alkaloids **75**, **76** and **77** (Scheme 28).[21]

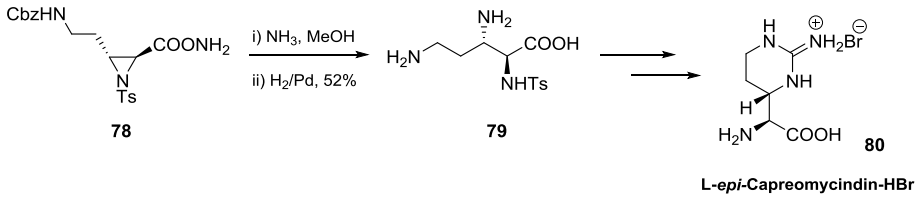


Scheme 28 Nuphar alkaloids

Nitrogen-centered nucleophiles

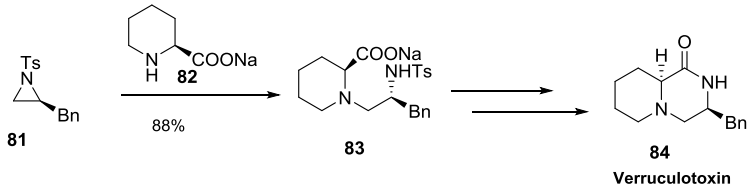
Amines and azides are representative example of nitrogen nucleophiles for the aziridine ring opening. They have attracted synthetic community for preparation of diamine containing compounds due to synthetic importance and their utility in pharmaceutical. The limited number of compounds bearing the diamine functionality as structural unit, made it less applicable.

Shiba and co-workers described the synthesis of L-epicapreomycidin-HBr **80** from the enantiopure *trans*-*N*-tosylaziridine-2-carboxylate **78** (Scheme 29). Azridine **78** was underwent S_N2 attack of ammonia to provide diamine **79** and followed by few steps derived L-epicapreomycidin-HBr **80**.[22]



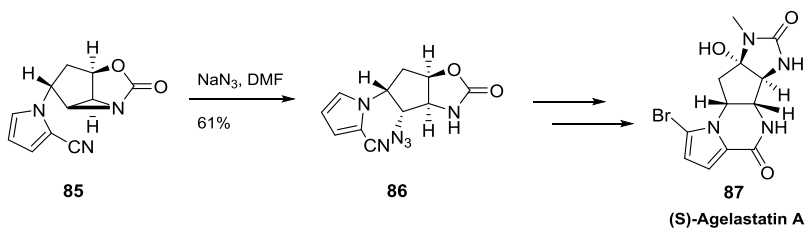
Scheme 29 L-*epi*-Capreomycindin-HBr **80**

The sodium pipecolinate **82** was also found as nucleophile, which was efficently reacted with mono-substituted enantiopure *N*-tosyl aziridine **81** to furnish piperidine adduct **83**. The adduct **83** was transformed to verruculotoxin **84** in few steps described in Scheme 30.[23]



Scheme 30 Verruculotoxin **84**

Yoshimitsu, Ino and Tanaka disclosed the synthesis of (-)-agelastatin A **87**, which involved sodium azide as nucleophile for aziridine opening. The sodium azide selectively opened the aziridine ring of the **85** to afford azide **86**, followed by *via* reaction sequences was transformed to (-)-agelastatin A **87** (Scheme 31).[24]



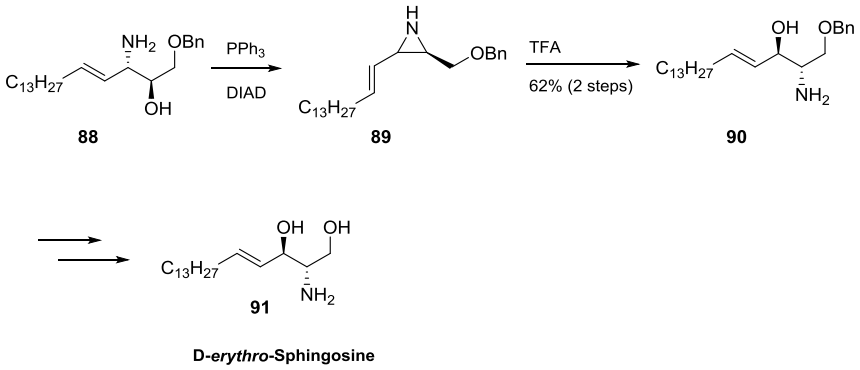
Scheme 31 (*S*)-Agelastatin A **87**

Oxygen-centered nucleophiles

It provides the method for direct access to amino alcohol unit that is ubiquitous in nature on oxygen nucleophilic aziridine ring opening.

The aziridine ring opening by oxygen nucleophiles are less active reaction compared to with epoxides. It requires aziridines to be activated by electron withdrawing groups as *N*-substituent or Bronsted or Lewis acids.

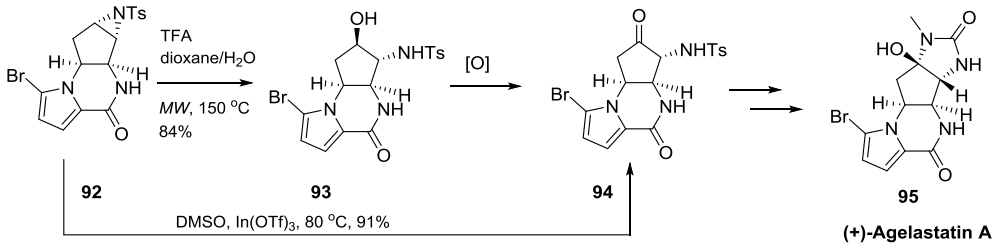
Generally water and strong Bronsted acids e.g. TsOH and TFA are used as nucleophiles for aziridine activation. Olofsson and Somfai synthesized D-erythro-sphingosine **91** in enantiomerically pure form. Aziridine **89** was prepared from the enantiopure 1, 2-amino alcohol **88**, followed by TFA mediated aziridine opening with water as nucleophile furnished compound **90**. Compound **90** was converted to target D-erythro-sphingosine **91** in few steps (Scheme 32).[25]



Scheme 32 D-*erythro*-Sphingosine **91**

Trost and Dong reported the synthesis of the non-natural (+)-agelastatin A **95** utilizing regio- and stereoselective hydrolytic ring opening of enantiopure aziridine **92** to afford alcohol **93**, which was oxidized to ketone **94**. Ketone **94** was obtained in one step from

the aziridine **92** in DMSO/indium triflate and followed by few reaction steps provided agelastatin A **95** (Scheme 33).[26]

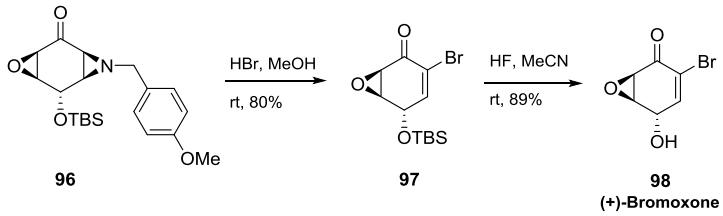


Scheme 33 (+)-Agelastatin A **95**

Halogen nucleophiles

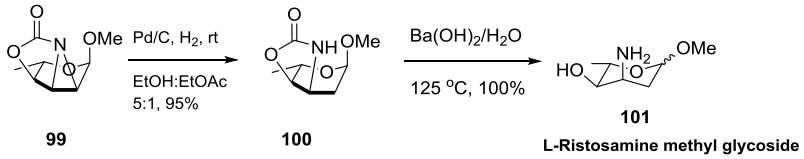
The uses of halogen as nucleophiles in natural product synthesis have been reported recently. Hydrogen bromide has used to generate *vicinal* bromo-amine from the aziridine ring opening.

Maycock and co-workers reported synthesis of (+)-bromoxone **98**, where they used 0.1 M HBr/MeOH for aziridine opening **96** in presence of epoxide unit to afford vinyl bromide **97**. The vinyl bromide 97 on TBS deprotection furnished target compound **98** as described in Scheme 34.[27]



Scheme 34 (+)-Bromoxone **98**

Reductions



Scheme 35 L-Ristosamine methyl glycoside **101**

Catalyst mediated reductive opening of aziridines provide high regioselective products. Mendlik *et al* reported palladium charcoal catalysed C-N bond cleavage of aziridine **99** to

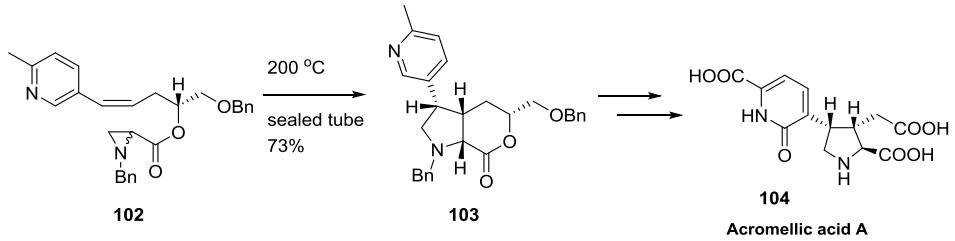
obtain carbamate **100,** which on hydrolysis provided L-ristosamine methyl glycoside **101** (Scheme 35).[28]

Cycloaddition reactions and rearrangements

Aziridines have been used as partner for cycloaddition reaction to obtain cyclic adducts in organic synthesis.

Aziridines in [3+2] cycloaddition

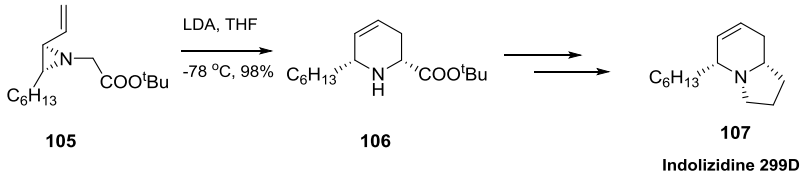
Aziridinyl esters are used as precursors of azomethine ylide, which react with olefin moiety in a [3+2] cycloaddition reaction to provide cyclic products and this reaction has been used as transformation for the synthesis of acromellic acid A **104** by Takano and co-



Scheme 36 Acromellic acid A **104**

workers (Scheme 36). The aziridine **102** was underwent thermal conditions afforded cycloadduct **103**, which was converted to acromellic acid A **104** following some reaction steps.[29]

Aziridines in [2+3]-Wittig rearrangements



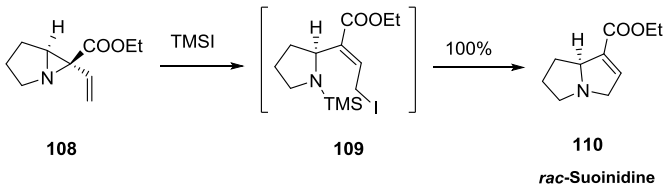
Scheme 37 Indolizidine 299D **107**

Somfai and co-workers demonstrated the application of the [2, 3]-Wittig rearrangement in enantioselective synthesis of indolizidine 299D **107**. Aziridine **105** was treated with LDA and the generated enolate underwent [2, 3]-Wittig rearrangement to furnish

piperidine derivative **106**. Compound **106** was converted into target compound **107** using few reaction conditions (Scheme 37). [30]

Aziridines in iodide-mediated rearrangement

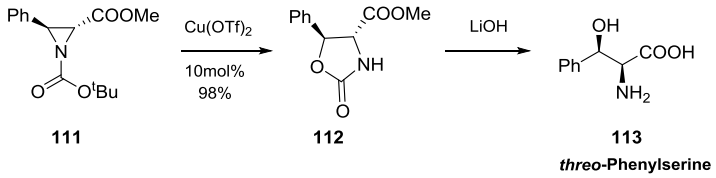
This is another method to rearrange the vinyl aziridines into pyrrolines by S_N2 ring opening of vinyl aziridine with iodine. First time this method was recognized by Hudlicky's and co-workers to accomplish the synthesis of *rac*-suoinidine **110**. The aziridine **108** was treated with TMSI to undergo S_N2' ring opening which afforded *rac*-suoinidine **110**, through intermediate **109** (Scheme 38).[31]



Scheme 38 *rac*-Suoinidine **110**

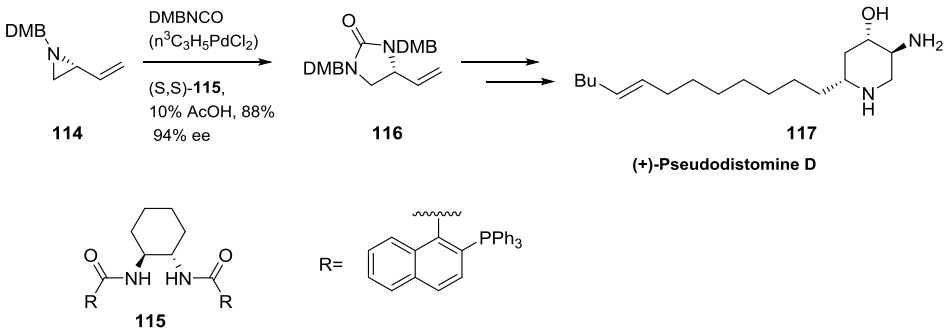
Aziridines in Miscellaneous rearrangements

The Lewis acid mediated aziridine rearrangement provide the retention of configuration e.g. *N*-acyl aziridine rearranged to oxazolidin-2-one. Tomasini synthesized *threo* phenylserine **113** from *N*-acyl aziridine **111** with retention of the configuration is outlined in Scheme 39.[32]



Scheme 39 *threo*-Phenylserine **113**

Trost and Fandrick reported total synthesis of (+)-pseudodistomine D **116**. They have used palladium (0) catalyst for the insertion of isocyanate to aziridine **114** in the presence of chiral ligand **115** provided enantioselective imidazolidin-2-one **116**. Urea **116** was converted to (+)-pseudodistomine D **117** in few steps (Scheme 40).[33]



Scheme 40 (+)-Pseudodistomine **117**

2.1.4 References

1) (a) Kasai, M.; Kono, M. *Synlett*, **1992**, 778; (b) Remers, W. A. *The Chemistry of Antitumour Antibiotics*, Wiley-Interscience, 1979, *1*, 242; (c) Remers, W. A.; Dorr, R. T.; Alkaloids*: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley, New York, **1988**, *6*, 1.
2) Antolini, L.; Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F. *J. Chem. Soc. Chem. Commun.* **1991**, 538.
3) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006,** *39*, 194.
4) (a) McCoull W. M.; Davis, F. A. *Synthesis* **2000**, 1347; (b) Atkinson, R. S.; Malpass, J. R. *J. Chem. Soc., Perkin Trans.* **1977**, *1*, 2242.
5) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.
6) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676; (b) Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans.* **1999**, *1*,2293; (c) Antilla, J. C.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4518.
7) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892.
8) Gabriel, S. *Chem. Ber.* **1888**, *21*, 1049.
9) (a) Wenker, H. *J. Am. Chem. Soc*. **1935**, *57*, 2328; (b) Leighton, P. A.; Perkins, W. A.; Renquist, M. L. *J. Am. Chem. Soc.* **1947**, *69*, 1540; (c) Kashelikar, D. V.; Fanta, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4927; (d) Brois, S. J. *J. Org. Chem.* **1962**, *27*, 3532; (e) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129.
10) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
11) (a) Nagel, D. L.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911; (b) Tarburton, P.; Woller, P. B.; Badger, R. C.; Doomes, E.; Cromwell, N. H. *J. Heterocycl. Chem*. **1977**, *14*, 459; (c) Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett*. **1994**, *35*, 1653; (d) Cardillo, G.; Gentilucci, L.; Tomasini, C.; Visa Castejon-Bordas, M. P. *Tetrahedron: Asymmetry* **1996**, *7*, 755; (e) Filigheddu, S. N.; Taddei, M. *Tetrahedron Lett*. **1998**, *39*, 3857; (f) Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* **1994**, *35*, 1653.
12) Padwa, A. *In Comprehensive Heterocyclic Chemistry III, Ed. Elsevier, Oxford* **2008**, *1*, 1.

13) Stankovic, S.; Dhooghe, S.; Catak, M.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H. J. *Chem. Soc. Rev.* **2012**, *41*, 643.

14) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.

15) (a) Dalili, S.; Caiazzo, A.; Yudin, A. K. *Organomet. Chem.* **2004**, *689*, 3604; (b) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160; (c) Caiazzo, A.; Dalili, S.; Yudin, A. K. Synlett **2003**, 2198; (d) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597.

16) Breuning, A.; Vicik, R.; Schirmeister, T. *Tetrahedron Asymmetry* **2003**, *14*, 3301.

17) Skepper, C. K.; Dalisay, D. S.; Molinski, T.F. *Org. Lett.* **2008,** *10*, 5269.

18) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881.

19) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.

20) Tanner, D.; Somfai, P. *Tetrahedron*, **1988**, *44*, 619.

21) (a) Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.*, **2003**, *5*, 3427; (b) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J . Org. Chem.* **2005**, *70*, 207.

22) Teshima, T.; Konishi, K.; Shiba, T. *Bull. Chem. Soc. Japan.* **1980**, *53*, 508.

23) Martens, J.; Scheunemann, M. *Tetrahedron Lett.* **1991**, 32, 1417.

24) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 5457.

25) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514.

26) (a) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054; (b) Trost, B. M.; Dong, G. B. *Chem. Eur. J.* **2009**, *15*, 6910.

27) Barros, M. T.; Matias, P.M.; Maycock, C. D.; Ventura, M. R. . *Org. Lett.* **2003**, *5*, 4321.

28) Mendlik, M. T.; Tao, P.; Hadad, C. M.; Coleman, R. S.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 8059.

29) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*.

30) Ahman, J.; Somfai, P. *Tetrahedron*, **1995**, *51*, 9747.

31) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart , L.D.; Beal, C. *J. Am. Chem. Soc.***1986**, *108*, 3755.

32) Tomasini, C. Vecchione, A. *Org. Lett.* **1999**, *1*, 2153.

33) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823.

Section 2

Lactone based strategy towards Tamiflu and shortest synthesis of major building block of mitomycinoids

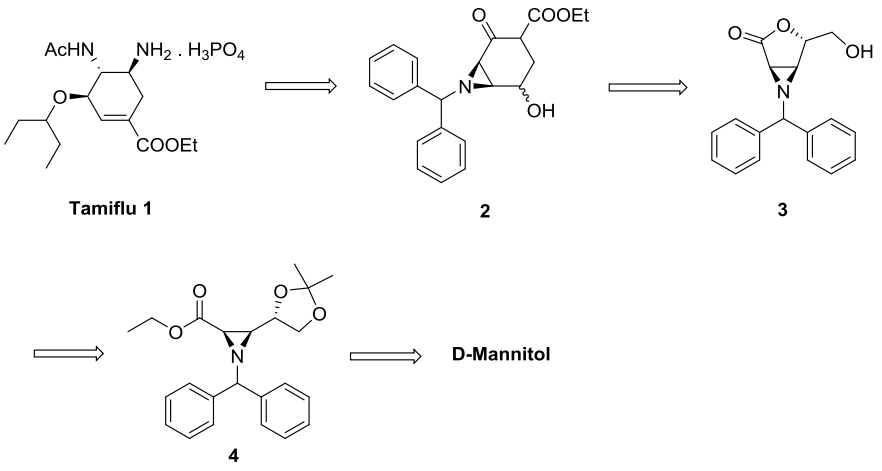
2.2.1 Present work

2.2.1.1 Objective

A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity as well as versatile template that could be used as platform to achieve the neuraminidase inhibitor from readily available starting materials. With these objectives, in mind an efficient route for tamiflu **1** from D-mannitol as a starting material, which is available in enantiopure form, was undertaken and the results are discussed in this section.

2.2.1.2 Retrosynthetic analysis

It was envisioned that the oseltamivir phosphate (Tamiflu) **1** can be accessed from the key intermediate **2**, which could be obtained from the aziridine lactone **3** using appropriate chemical transformations. The aziridine lactone **3** can be derived from the 2-carboxylate aziridine **4**, which could be derived from the cheap and abundant chiral source D-mannitol as shown in the Scheme 1.

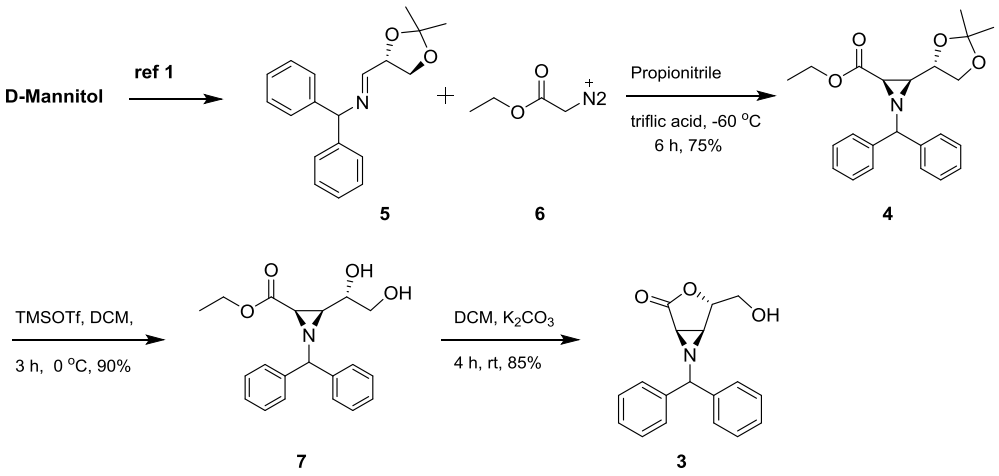


Scheme 1 Retrosynthetic analysis for Tamiflu **1**

2.2.1.3 Results and discussion

The synthesis began with 2-carboxylate aziridine **4**, which can be easily obtained from the D-mannitol using reported procedure.[1] The acetonide deprotection of **4** was carried out using TMSOTf in DCM at 0 ^{o}C to afford dihydroxy ester **5** in 90% yield.[2] The IR

spectrum showed bands at 1736, 3588 and 3369 cm^{-1} for ester and primary and secondary hydroxy functionalities respectively. The ^{1}H NMR spectrum showed a multiplet at δ 3.73-3.63 (m, 1 H) ppm corresponding to one proton of –CHOH while peak at δ 3.44-3.28 (m, 1 H) and 3.23-3.06 (m, 1 H) ppm were assigned to two protons of -CH_2OH group. Also the peaks at δ 4.23 (q, *J* = 8 Hz, 2 H) and 1.30 (t, *J* = 8 Hz, 3 H) ppm were observed in ^{1}H NMR spectrum for ethyl ester functionality. The ^{13}C NMR spectrum showed peaks at δ 77.4 and 64.7 ppm which were related to carbons of -CHOH and -CH_2OH groups and peaks in ^{13}C DEPT NMR spectrum at δ 61.3 and 14.1 ppm were due to -CH_2 and -CH_3 carbons of ethyl ester functionality. The HRMS spectrum showed the peak at 364.1516 $(M+Na)^+$ which confirmed the molecular formula $C_{20}H_{23}NO_4$ of dihydroxy aziridine **7**.

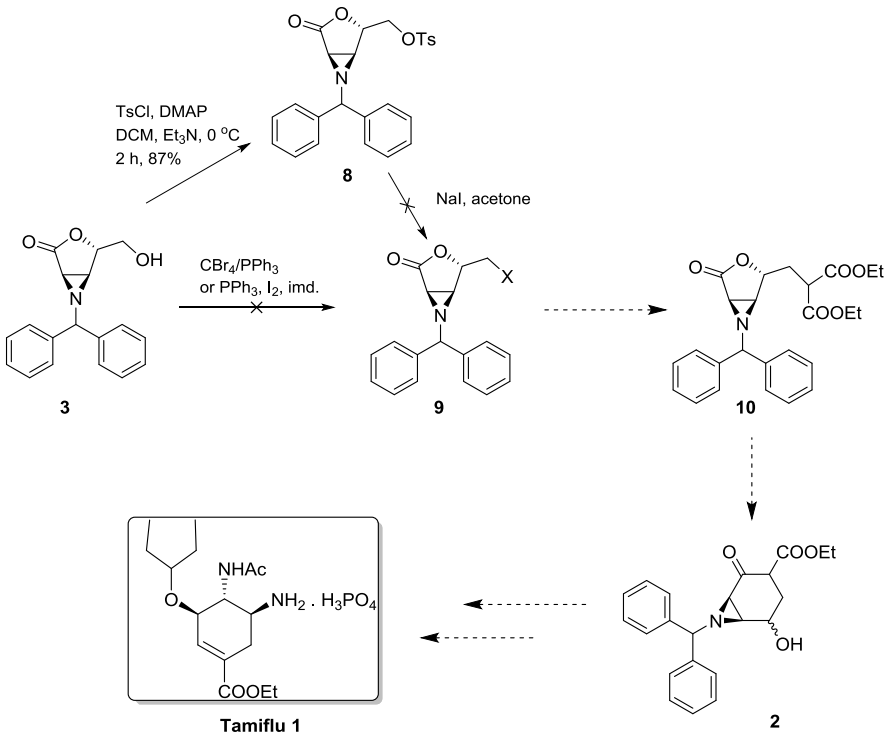


Scheme 2 Synthesis of Lactone **3**

The dihydroxy aziridine **7** was stirred with K_2CO_3 in DCM at room temperature for 3 h to furnish the five membered lactone **3** in 85% yield. The IR spectrum of lactone **3** showed the bands at 1773 cm^{-1} and 3445 cm^{-1} indicating the presence of the five membered lactone and hydroxy functionality respectively. The ^{1}H NMR spectrum showed a multiplet at δ 4.48-4.46 (m, 1H) ppm for –CHOH proton as well as peaks at δ 3.89-3.79 (m, 1H) and 3.67-3.64 (m, 1H) ppm corresponding to the two protons of – CH_2OH group. The ^{13}C peaks at δ 172.3 and 81.1 ppm corresponding with the carbonyl carbon of lactone and carbon of –CHOH group. The ^{13}C DEPT NMR spectrum showed the peak at δ 62.2

ppm for the methylene carbon of $–CH_2OH$ group. The HRMS peak was observed at 318.1100 $(M+Na)^+$ confirmed the molecular formula $C_{18}H_{17}NO_3$ of the lactone **3**.

The lactone aziridine **3** and its analogous are very important motifs for the pharmaceutical activities and are also used as magical precursors for the synthesis of the bioactive compounds. The lactone aziridine skeletons are ready for desired substitutions using proper chemical tools.[3]



Scheme 3 Attempt towards synthesis of tamiflu **1** from lactone **3**

Further lactone **3** was treated with tosyl chloride, TEA and cat. DMAP in dry DCM at 0 ^oC to room temperature to furnish tosyl derivative **8** in 87%. The IR spectrum of tosylate **8** showed the disappearance of band at 3445 cm^{-1} indicating the formation of tosyl derivative. The peaks in ^1H NMR spectrum at δ 4.28 - 4.05 (m, 2 H) ppm corresponding to methylene protons of $–CH_2OTs$ group and peak at δ 2.46 (s, 3 H) ppm related to the methyl protons of tosyl functionality. The ^{13}C NMR spectrum showed the peaks at δ 170.2 and 21.7 ppm corresponding to the lactone carbonyl carbon and methyl group of tosyl functionality respectively. In ^{13}C NMR DEPT spectrum peak at δ 68.0 ppm was

assigned to methylene carbon of $–CH_2OTs$ group. The HRMS spectrum showed the peak at 472. 1188 $(M+Na)^+$ which confirmed the molecular formula $C_{25}H_{23}NO_5S$ for tosyl derivative.

2.2.1.5 Shortest synthesis of major building block of mitomycinoids

There are several classes of aziridine-containing natural products, amongst which mitosane and mitosene compounds are best known for their inbuilt powerful alkylating ability.[4] They are isolated from soil extracts of *Streptomyces lavendulae* and show both antitumor and antibacterial activity. Mitomycin C is the most potent of this family and is registered antineoplastic drug supplied by Bristol-Myers Squibb Co.

It can be seen that mitomycinoids are actually naturally occurring pro-drugs that must be activated in vivo. These extraordinary antitumor activities along with mitomycinoid's unique structural features have attracted the interest of synthetic community and as a result several approaches and few total syntheses have been published. We have been deeply fascinated by those synthetic programs involving a highly functionalized four-carbon building block.

Aziridine was introduced as the smallest nitrogen containing three membered heterocycle in 1888 by Gabriel.[5] Aziridines are highly useful intermediates for the preparation of nitrogen containing compounds. Their value is reflected by the numerous studies that have been conducted to optimize their preparation and to enhance the scope of their applications in the total synthesis of natural and/or biologically active products.[6] Among the large varieties of substituted aziridines described, aziridine 2-carboxylate holds a prominent position as a synthon for the synthesis of nitrogen containing bioactive molecules.[7]

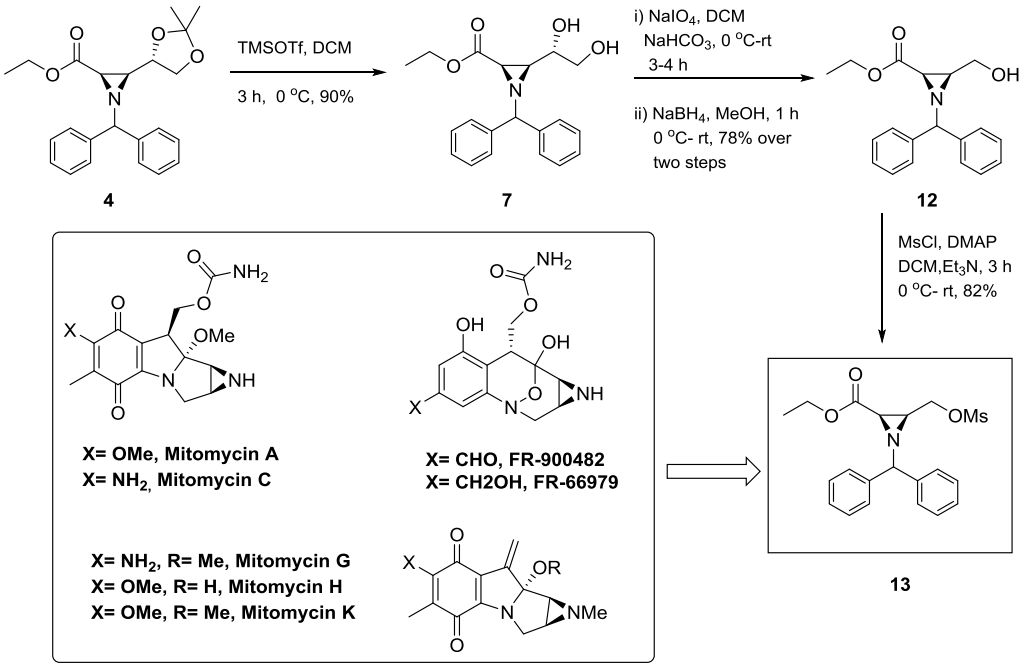
Thus *cis*-aziridine-2-carboxylate **4** was chosen as the key synthon for synthesis of mesyl aziridine[8] from D-mannitol as chiral raw material.

2.2.1.6 Results and discussion

The synthesis was started from the *cis*-2-carboxylate aziridine **4**, which was converted into the diol **7** which is already discussed in Scheme 2. The diol **7** was subjected for the

$NaIO_4$ cleavage in DCM/$NaHCO_3$ to afford crude aldehyde. The crude aldehyde without purification was subjected for chemoselective reduction using $NaBH_4$ in MeOH to obtain alcohol **12** in 78% yield over two steps. The IR spectrum of hydroxy compound **12** showed the bands at 3439 and 1733 cm^{-1} corresponding to hydroxy and ester functionality. The ^1H NMR spectrum showed the peaks at δ 4.20 (q, *J* = 8 Hz, 2 H) and 1.28 (t, *J* = 8 Hz, 3 H) ppm for the five protons of ethyl ester while peak at δ 3.70 (d, *J* = 6 Hz, 2 H) ppm related with two protons of $–CH_2OH$ group. The ^{13}C NMR spectrum showed the peak at δ 169.1 ppm corresponding to the ester carbonyl carbon and ^{13}C DEPT NMR spectrum showed the peaks at δ 61.1 and 60.2 ppm for the methylene carbons of $–CH_2OH$ and ethyl ester group while peak at δ 14.2 ppm corresponded to methyl carbon of ethyl ester. The LCMS spectrum showed the peak at 334.18 $(M+Na)^+$ confirming the molecular formula $C_{19}H_{21}NO_3$ of the hydroxy compound **12**.

Further the hydroxy compound **12** was subjected to mesylation using TEA as base, mesyl chloride and cat. DMAP in dry DCM to afford mesylate **13** in 82% yield. The IR spectrum of mesylate **13** showed the peak at 1734 cm^{-1} indicating the ester functionality while disappearance of 3439 cm^{-1} band of hydroxy group indicated the formation of



Scheme 4 Synthesis of mesylate **13**

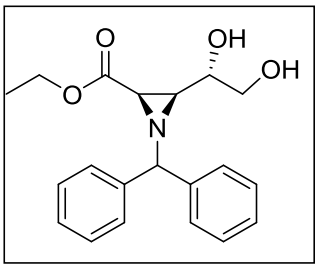
mesyl derivative. The ^{1}H NMR showed the peaks at δ 4.39 - 4.34 (m, 2 H) related with methylene protons of –CH_2OMs while δ 4.20 (q, *J* = 7.2 Hz, 2 H) and 1.27 (t, *J* = 8 Hz, 3 H) ppm peaks revealed the presence of methyl and methylene protons of ethyl ester respectively. The peak at δ 2.76 (s, 3 H) ppm in ^{1}H NMR spectrum was assigned for the methyl protons of mesyl functionality. The ^{13}C NMR spectrum showed the peak at δ 168.3 ppm for the ester carbonyl and DEPT ^{13}C NMR showed the peaks at δ 67.2 and 61.1 ppm assigned for methylene carbon of –CH_2OMs and ethyl ester respectively while peak at δ 37.12 ppm indicated the methyl carbon of mesyl functionality. The peak observed at 412.09 $(M+Na)^+$ in MS (ESI) spectrum confirmed the molecular formula $C_{20}H_{23}NO_5S$ of the mesylate **13**.

2.2.2 Conclusion

In conclusion, the successful synthesis of five membered lactone aziridine as key intermediate has been achieved. The lactone can be explored for the tamiflu using suitable chemical transformations. The synthesis of major building block of the mitomycinoid alkaloids has been accomplished in very short and robust way in high yield. The synthesis involved the simple reaction conditions, inexpensive and abundant chiral D-mannitol as raw material.

2.2.3 Experimental Section

Ethyl (2*R*, 3*S*)-1-benzhydryl-3-((*S*)-1,2-dihydroxyethyl)aziridine-2-carboxylate (7)



To a stirred, ice-cold solution of the aziridine acetonide **4** (15 gm, 39.37 mmol) in anhydrous DCM (150 mL) under nitrogen atmosphere, was added TMSOTf (8.1 mL, 51.18 mmol) dropwise at 0 ^{o}C. The resulting solution was stirred at the same temperature for 3 h and the reaction mixture was quenched with solid $NaHCO_3$. Water was added and the compound was extracted with DCM (3 X 80 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet. ether as an eluent to afford compound **7** (12.08 gm, 90%) as a white solid.

***Rf*:** 0.3 (Pet. ether: ethyl acetate, 40:60).

MF: $C_{20}H_{23}NO_4$, **MW:** 341.41.

Yield: 90%.

$[\alpha]_D^{25}$: +101.6 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 3588, 3369, 2927, 1736, 1603, 1454, 1371, 1193.

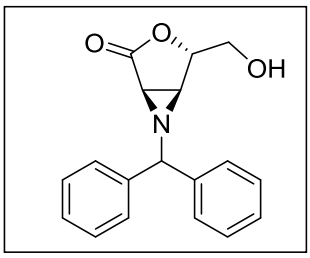
MP : 122-124 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.52 - 7.18 (m, 10H), 4.23 (q, *J* = 8 Hz, 2H), 3.74 (s, 1H), 3.73 - 3.63 (m, 1H), 3.44 - 3.28 (m, 1 H), 3.23 - 3.06 (m, 1H), 2.64 - 2.52 (m, 1H), 2.44 (d, *J* = 8 Hz, 1H), 2.21 (t, *J* = 8 Hz, 1H), 1.30 (t, *J* = 8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 169.5, 142.1, 141.7, 128.5, 128.3, 127.9, 126.9, 77.3, 64.6, 61.1, 46.8, 42.5, 14.0.

HRMS: Observed- 364.1516 $(M+Na)^+$, Calculated-364.1519.

(1*R*, 4*S*, 5*S*)-6-Benzhydryl-4-(hydroxymethyl)-3-oxa-6-azabicyclo-[3.1.0]-hexan-2-one (3)



The diol **7** (4 gm, 11.73 mmol) was dissolved in DCM (40 mL) and K_3CO_3 (3.2 gm, 23.44 mmol) added at room temperature. Further, the reaction mixture was stirred for 3-4 h and progress of reaction was monitored with TLC. The reaction mixture was filtered through simple filter paper, washed with DCM (3 X 30 mL) and filtrate was concentrated under reduced pressure. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet. ether as an eluent to afford compound **3** (2.94 gm, 85%) as colourless syrup.

Rf: 0.2 (Pet. ether: ethyl acetate, 40:60).

MF: $C_{18}H_{17}NO_3$, **MW:** 295.34.

Yield: 85%.

$[\alpha]_D^{25}$: +42.00 (*c* 1.0, $CHCl_3$).

MP : 112-114 ^oC.

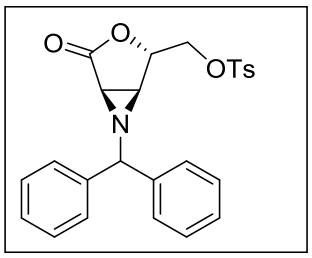
IR ($CHCl_3$, cm^{-1}): νmax 3445, 2928, 2850, 1773, 1580, 1150, 1080, 833.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.46 - 7.22 (m, 10H), 4.47 (t, *J* = 3.2 Hz, 1H), 3.91 - 3.78 (m, 1H), 3.75 (s, 1H), 3.65 (dd, *J* = 2.7, 12.5 Hz, 1H), 3.02 (d, *J* = 4.4 Hz, 1H), 2.94 (bs, 1H), 2.80 (d, *J* = 4.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 172.39, 142.0, 141.5, 128.8, 128.6, 127.2, 126.8, 81.12, 74.5, 62.2, 44.3, 40.7.

HRMS: Observed- 318.1100 $(M+Na)^+$, Calculated-318.1101.

(1*S*, 2*S*, 5*R*)-6-Benzhydryl-4-oxo-3-oxa-6-azabicyclo-[3.1.0]-hexan-2-yl)-methyl-4-methyl benzenesulfonate (8)



To a stirred solution of lactone **3** (1.5 gm, 5.08 mmol) in dry DCM at 0 ^{o}C was added TEA (2.1 mL, 15.25 mmol), tosyl chloride (1.44 gm, 7.62 mmol) and DMAP (62 mg, 0.5 mmol). Reaction mixture was stirred for 2 h at room temperature and completion of the reaction was monitored with TLC. Water was added to the reaction mixture and the compound was extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **8** (1.94 gm, 87%) as a colourless syrup.

Rf: 0.6 (Pet. ether: ethyl acetate, 75:25).

MF: $C_{25}H_{23}NO_5S$, **MW:** 449.52.

Yield: 87%.

$[\alpha]_D^{25}$: +36.36 (*c* 1.1, $CHCl_3$).

MP : 146-148 ^{o}C.

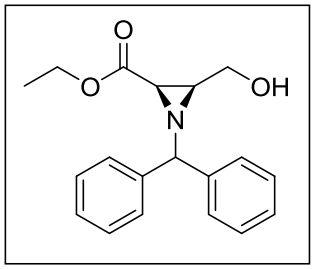
IR ($CHCl_3$, cm^{-1}): νmax 3340, 2928, 2850, 1764, 1580, 1150, 1080.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.43 - 7.22 (m, 12H), 4.55 (t, *J* = 3.4 Hz, 1H), 4.28 - 4.05 (m, 2H), 3.76 (s, 1H), 3.08 (d, *J* = 4.3 Hz, 1H), 2.84 (d, *J* = 4.3 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 170.2, 141.7, 141.2, 130.0, 128.7, 128.0, 127.1, 126.8, 74.7, 68.0, 43.9, 40.2, 21.7.

HRMS: Observed- 472.1188 $(M+Na)^+$, calculated-472.1189.

Ethyl (2*R*, 3*S*)-1-benzhydryl-3-(hydroxymethyl)aziridine-2-carboxylate (12)



To a solution of diol **7** (2 gm, 5.86 mmol) in DCM (20 mL) was added solid $NaHCO_3$ (1.5 gm, 17.58 mmol) and sodium metaperiodate (2.51 gm, 11.73 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 3-4 h and completion of reaction was monitored by TLC. The reaction mass was quenched using ethylene glycol (0.01 mL), extracted with DCM (3 X 20 mL), washed with brine, dried over anhydrous sodium sulphate and filtered. The combined organic layer was concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of crude aldehyde (1.9 gm, 6.11 mmol) obtained above in MeOH (15 mL) was added sodium borohydride (0.24 gm, 7.37 mmol) at 0 ^oC. The reaction mixture was stirred for 1 h at room temperature then quenched with saturated aq. solution of ammonium chloride (10 mL). The solvent was evaporated under reduced pressure and crude residue obtained was extracted with ethyl acetate (3 X 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated to give a crude residue which was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet ether as an eluent to afford compound **12** (1.42 gm, 78% over two steps) as a colourless syrup.

Rf: 0.4 (Pet.ether: ethyl acetate, 65:35).

MF: $C_{19}H_{21}NO_3$, **MW:** 311.38.

Yield: 78% (over two steps).

$[\alpha]_D^{25}$: +63.80 (*c* 0.7, $CHCl_3$).

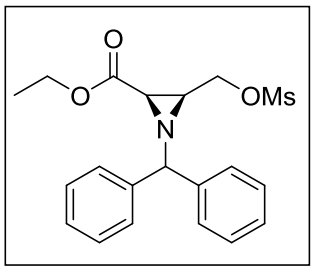
IR ($CHCl_3$, cm^{-1}): νmax 3439, 1733, 1599, 1454, 1196.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.50 - 7.18 (m, 10H), 4.20 (q, *J* = 8 Hz, 2H), 3.79 (s, 1H), 3.70 (d, *J* = 6 Hz, 1H), 2.44 - 2.27 (m, 1H), 1.28 (t, *J* = 8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 159.3, 137.4, 137.1, 135.2, 132.2, 129.9, 129.1, 128.8, 128.7, 128.6, 128.3, 127.7, 126.6, 119.3, 77.2, 56.5, 55.0, 45.9, 45.5, 36.5, 36.3.

HRMS (ESI): Observed-334.1834, calculated-334.1840.

Ethyl (2*R*, 3*S*)-1-benzhydryl-3-(((methylsulfonyl)oxy)methyl)aziridine-2-carboxylate (13)



To a stirred solution of alcohol **12** (1 gm, 3.21 mmol) in dry DCM (10 ml) at 0 ^{o}C was added TEA (1.3 mL, 9.64 mmol), mesyl chloride (0.4 mL, 4.82 mmol) and DMAP cat. (125 gm, 0.32 mmol). Reaction mixture was stirred for 3 h at room temperature and completion of the reaction was monitored with TLC. Water was added to the reaction mixture and the compound was extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compound **13** (1.02 gm, 82%) as a colourless syrup.

Rf: 0.5 (Pet.ether: ethyl acetate, 65:35).

MF: $C_{20}H_{23}NO_5S$, **MW:** 389.47.

Yield: 82% (over two steps).

$[\alpha]_D^{25}$: +42.00 (*c* 0.2, $CHCl_3$).

MP : 77-79 ^{o}C.

IR ($CHCl_3$, cm^{-1}): νmax 3027, 1734, 1492, 1360, 1201.

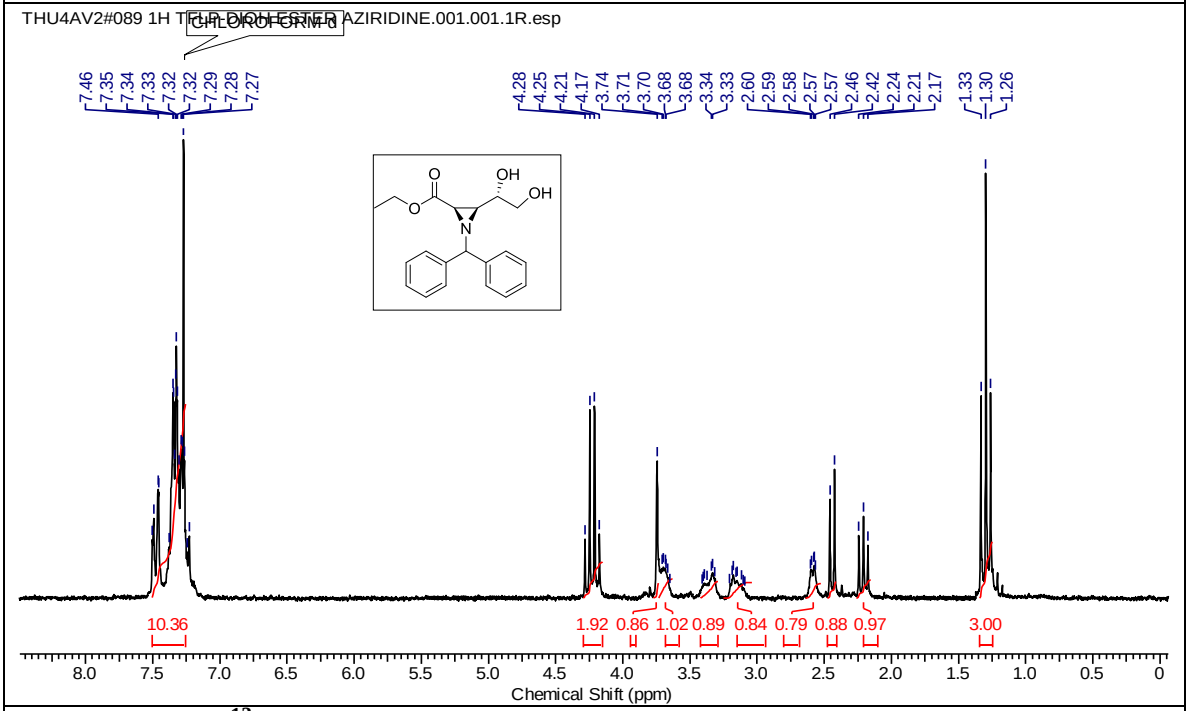
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.50 - 7.19 (m, 10H), 4.39 - 4.34 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 1H), 2.76 (s, 3H), 2.56 - 2.39 (m, 2H), 1.27 (t, *J* = 8 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 168.3, 141.9, 141.5, 128.5, 127.5, 126.9, 67.1, 61.32, 43.1, 41.9, 37.06, 14.1.

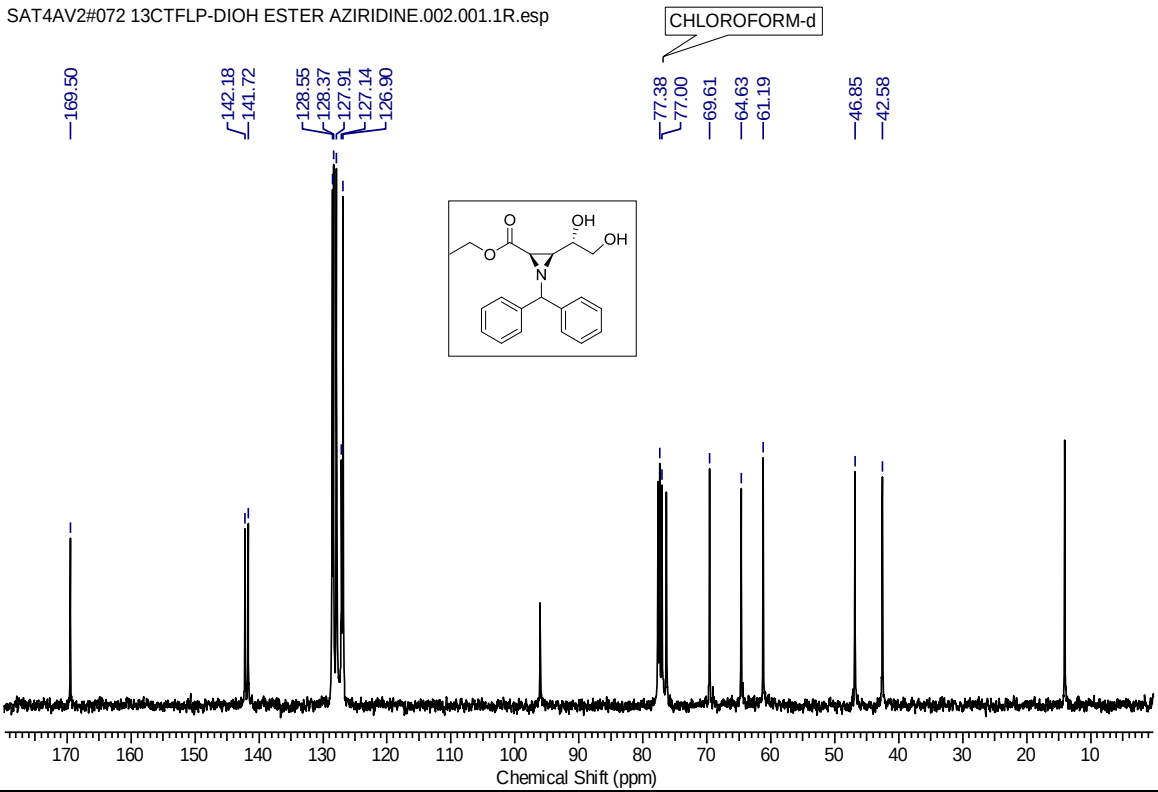
HRMS (ESI) : Observed-412.0925, calculated- 412.0927.

2.2.4 Spectral Data

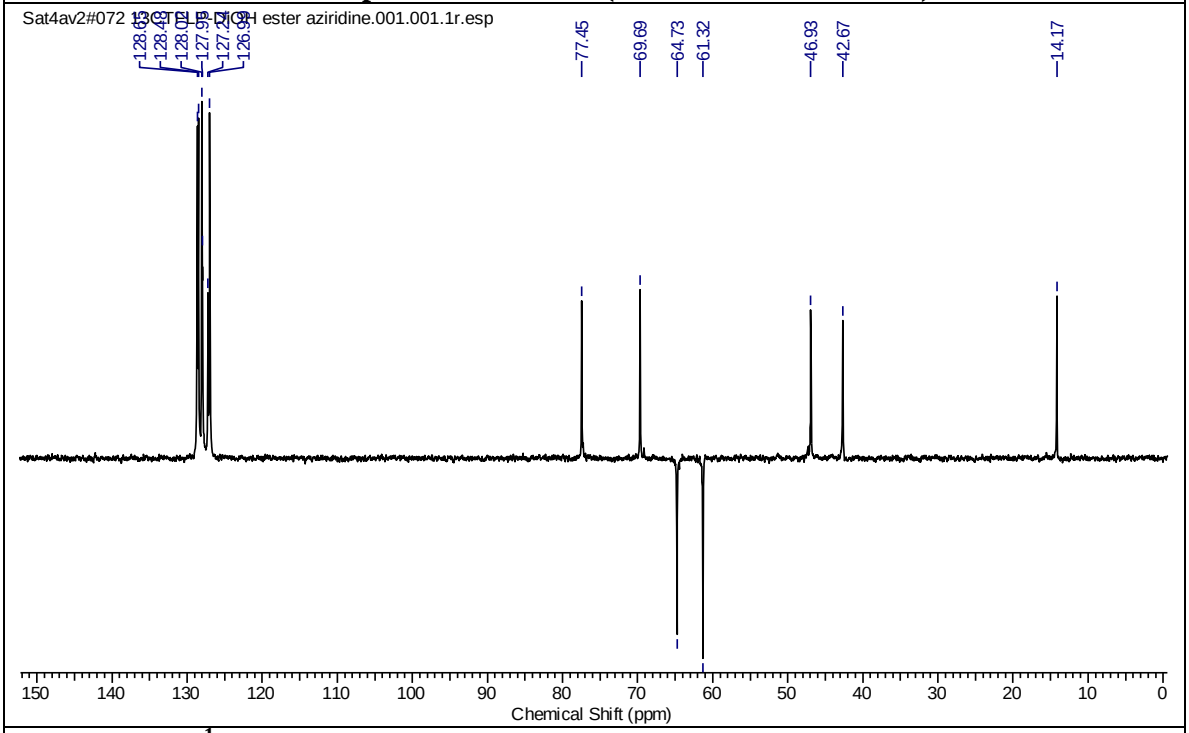
^{1}H NMR spectrum of diol 7 (200 MHz, $CDCl_3$ + CCl_4)



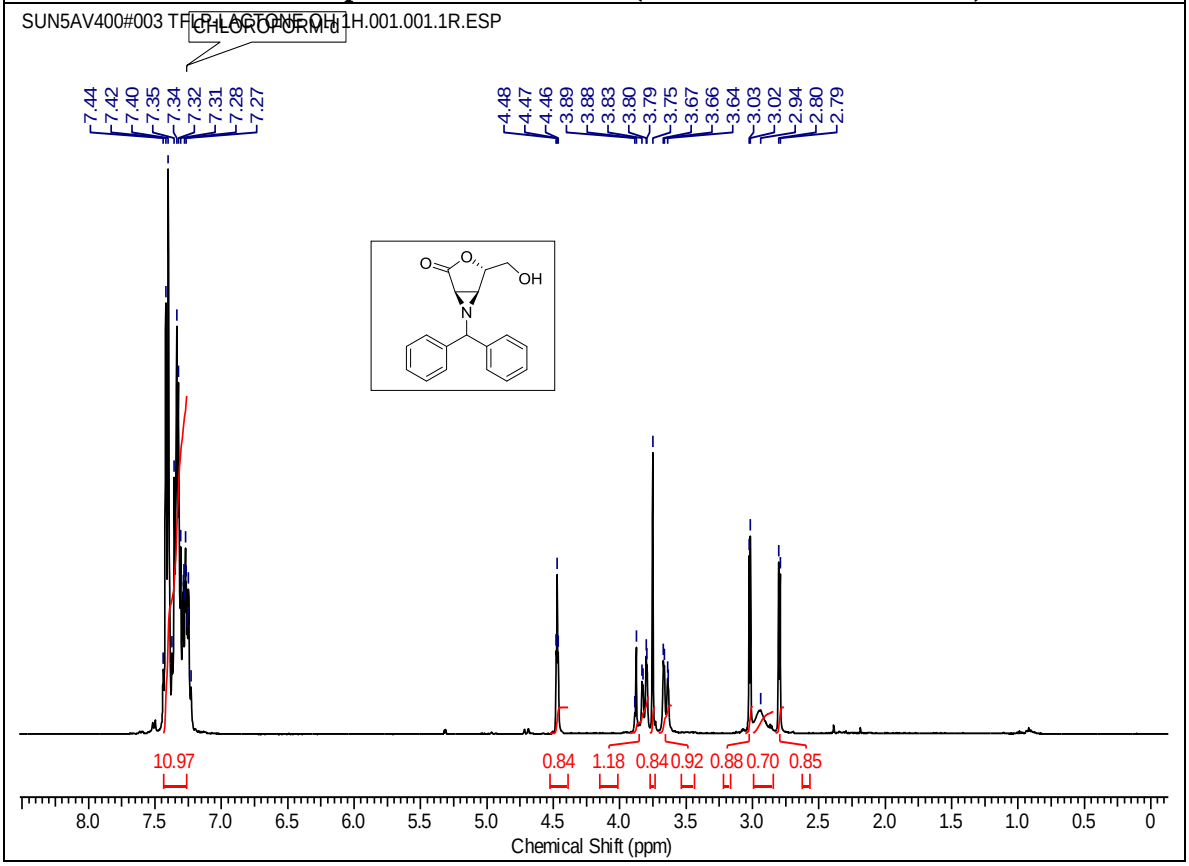
^{13}C NMR spectrum of diol 7 (50 MHz, $CDCl_3$ + CCl_4)



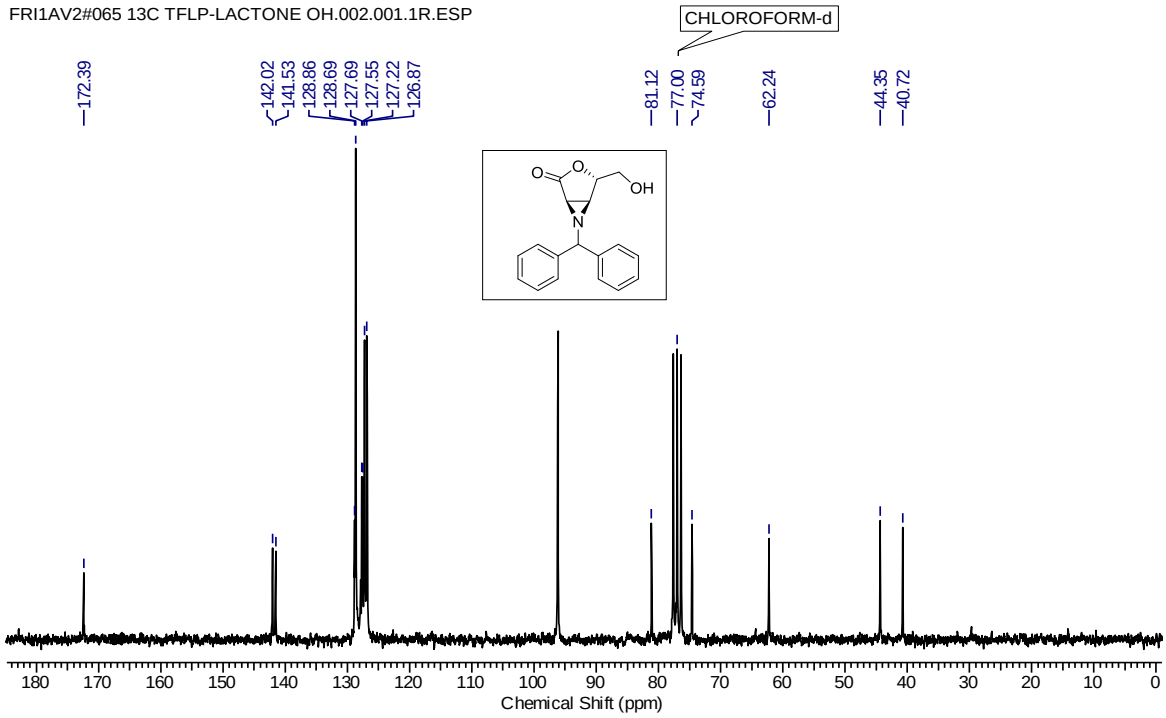
DEPT spectrum of diol 7 (50MHz, $CDCl_3$ + CCl_4)



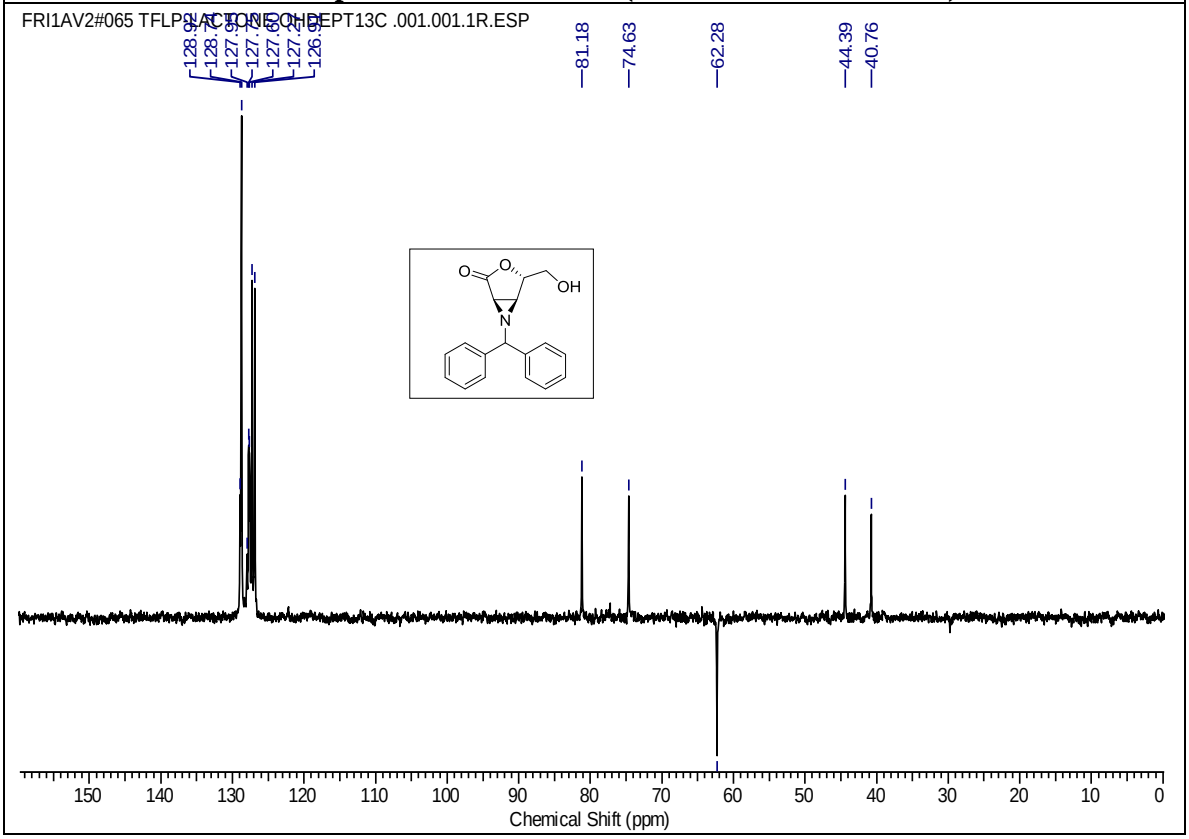
^{1}H NMR spectrum of lactone 3 (400 MHz, $CDCl_3$ + CCl_4)



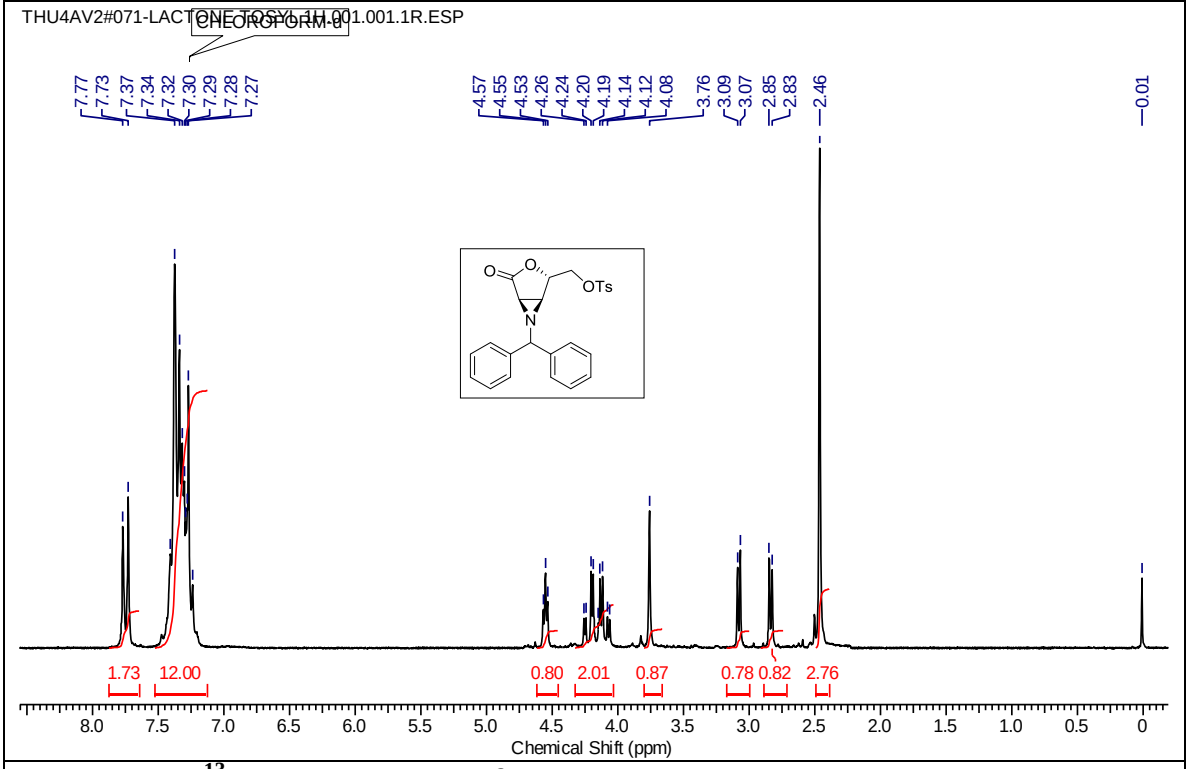
^{13}C NMR spectrum of lactone 3 (50 MHz, $CDCl_3$ + CCl_4)



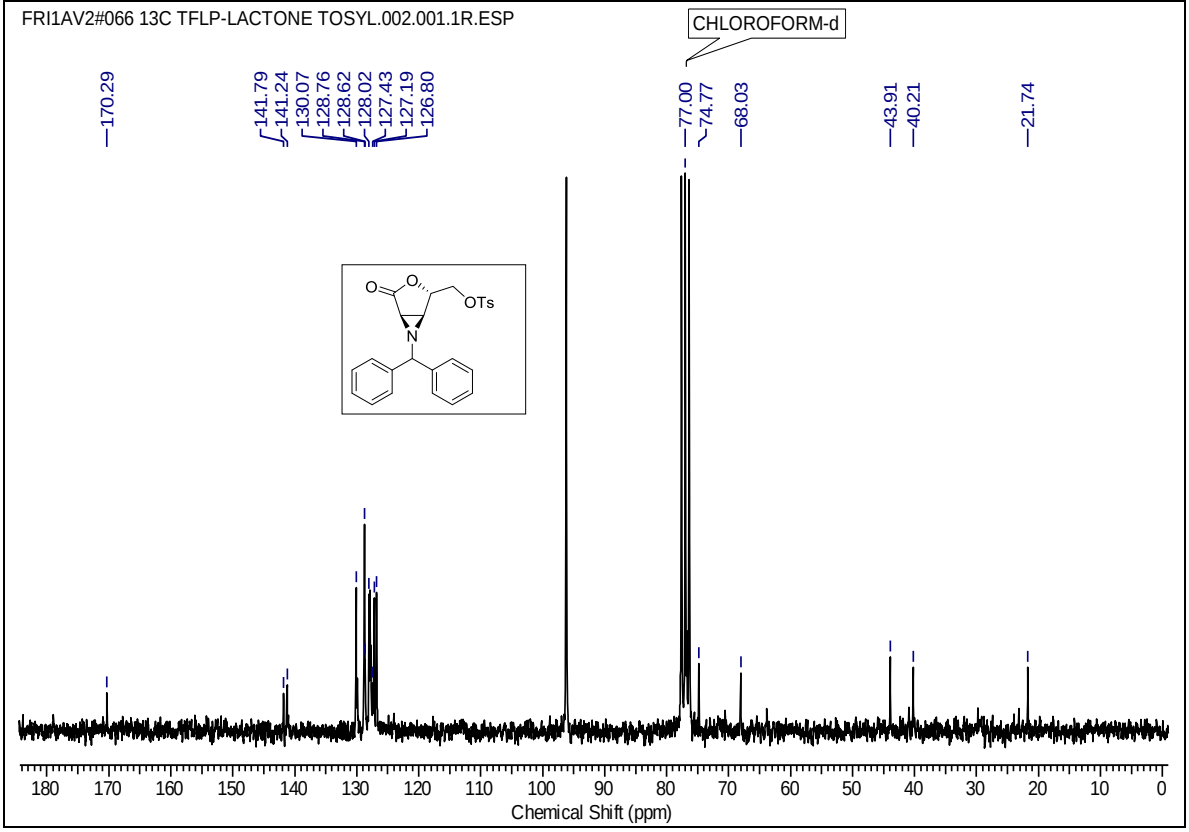
DEPT spectrum of lactone 3 (50 MHz, $CDCl_3$ + CCl_4)



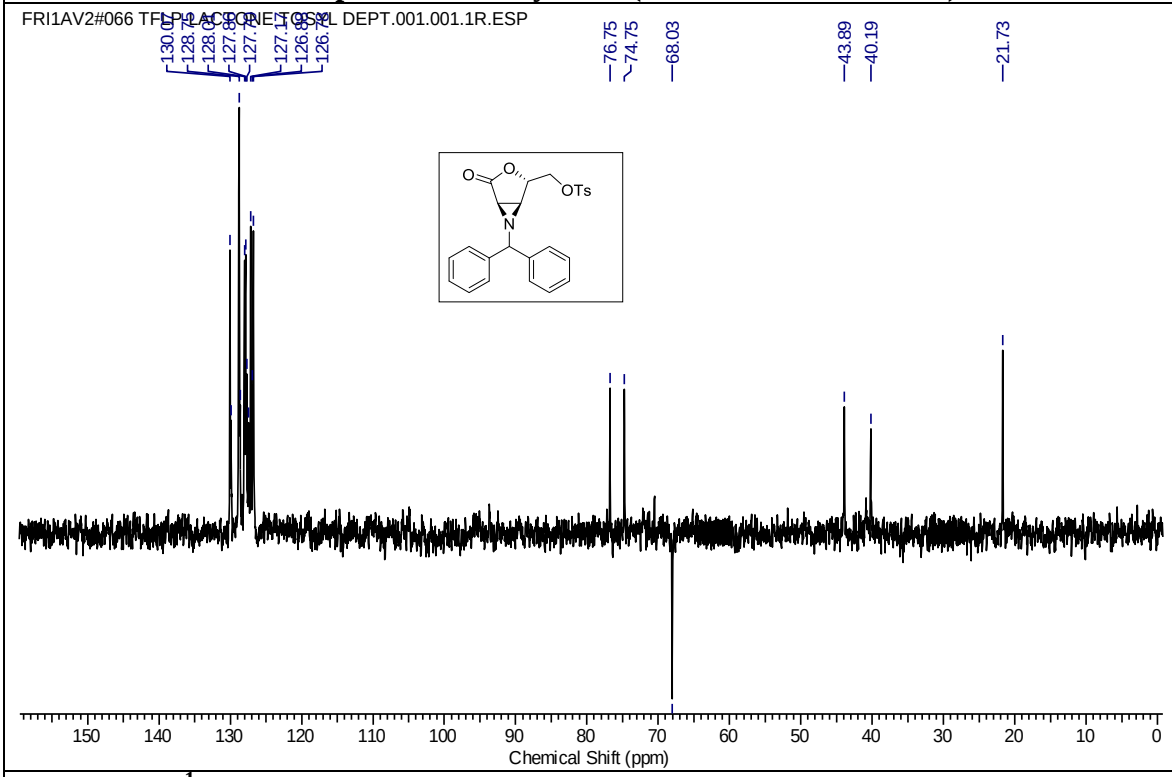
^{1}H NMR spectrum of tosylate 8 (200 MHz, $CDCl_3$ + CCl_4)



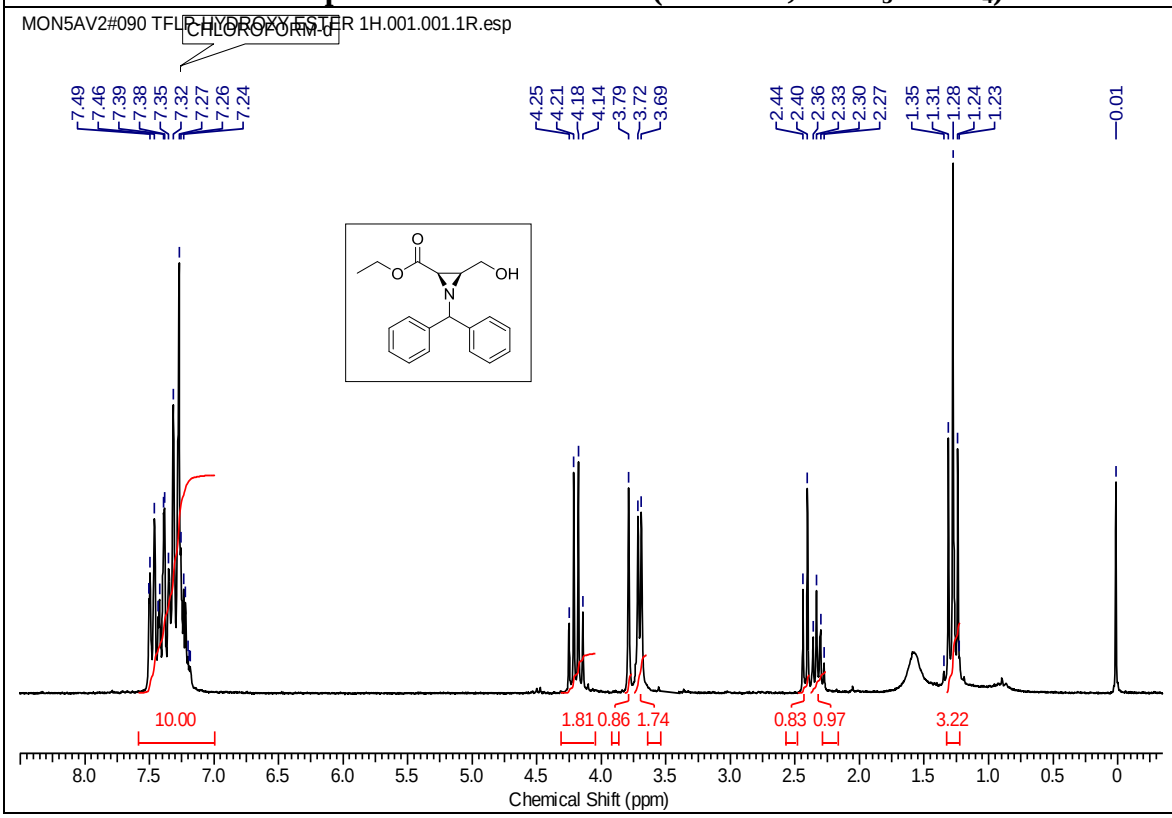
^{13}C NMR spectrum of tosylate 8 (50 MHz, $CDCl_3$ + CCl_4)



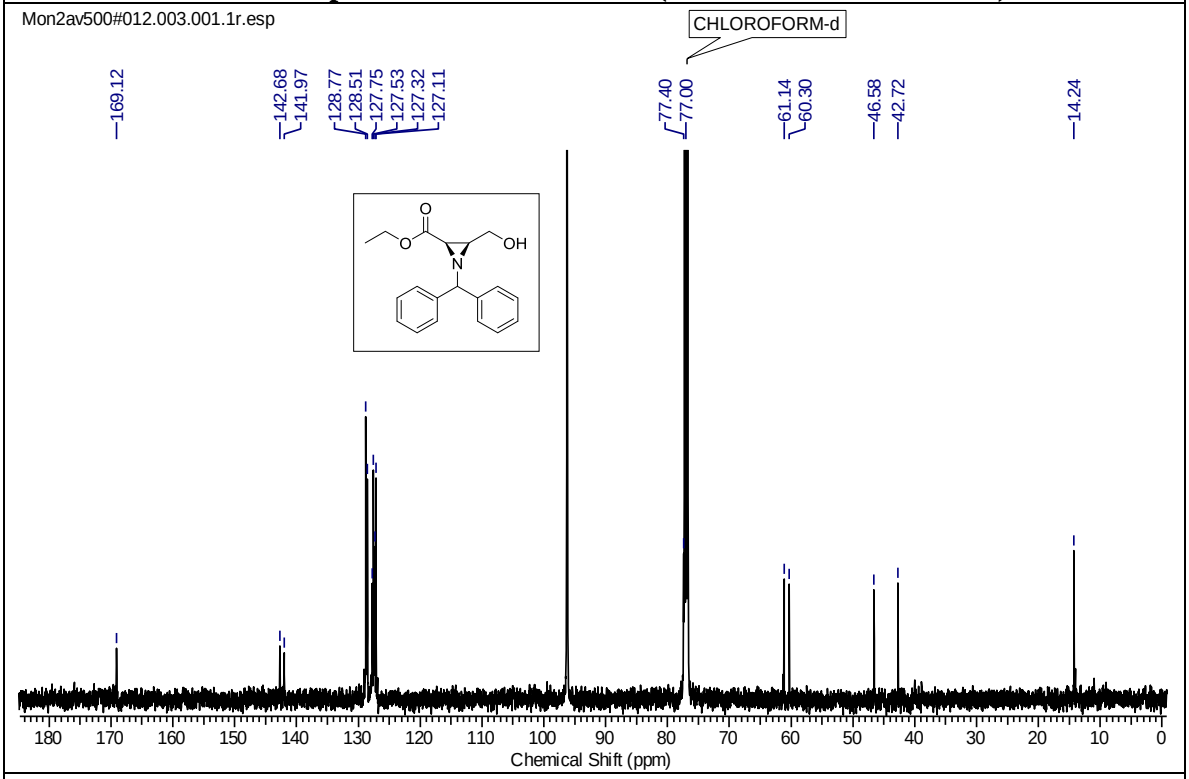
DEPT spectrum of tosylate 8 (50MHz, $CDCl_3$ + CCl_4)



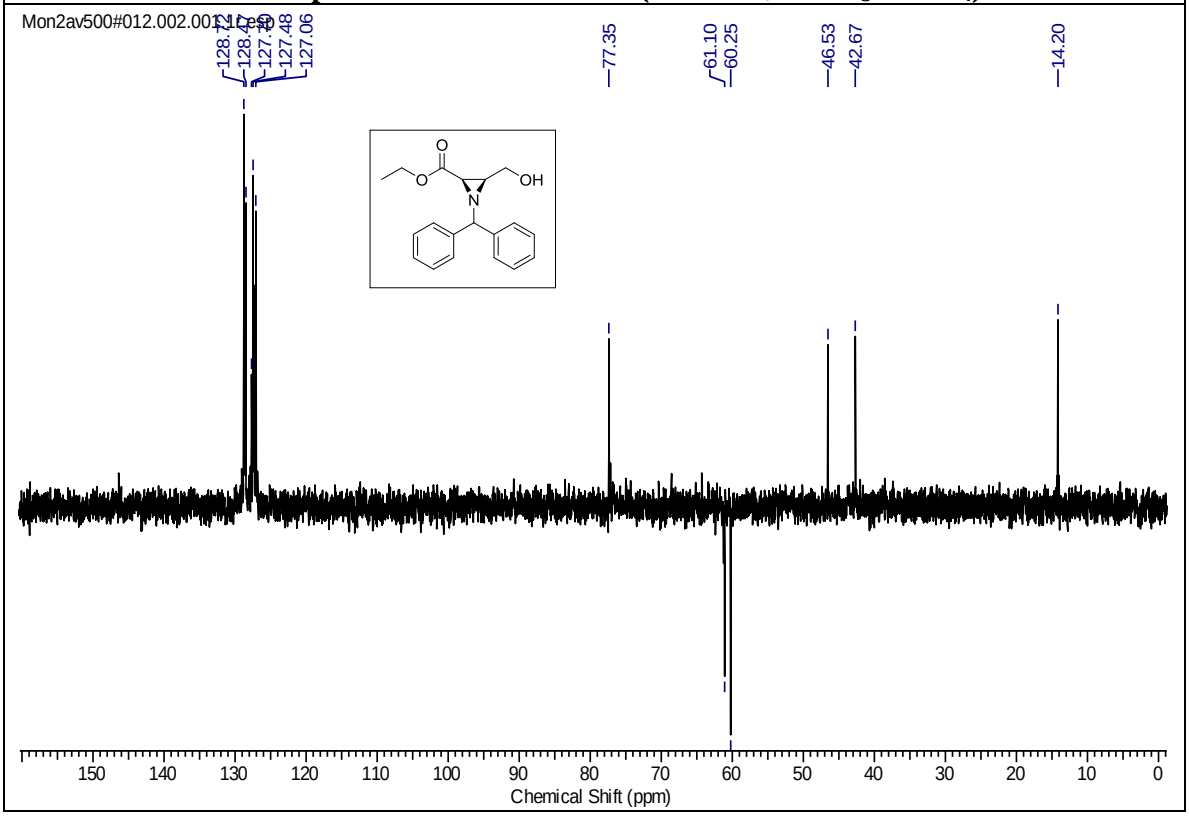
^{1}H NMR spectrum of aziridine 12 (200 MHz, $CDCl_3$ + CCl_4)



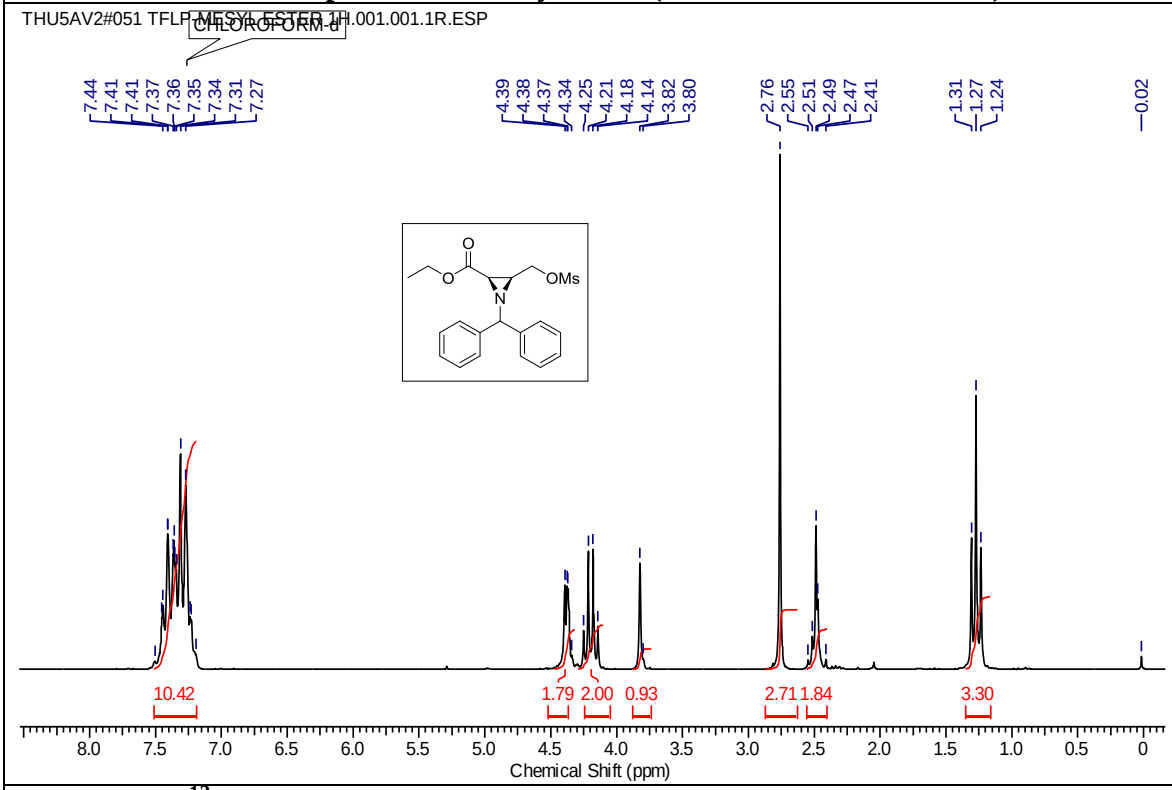
^{13}C NMR spectrum of aziridine 12 (125 MHz, $CDCl_3$ + CCl_4)



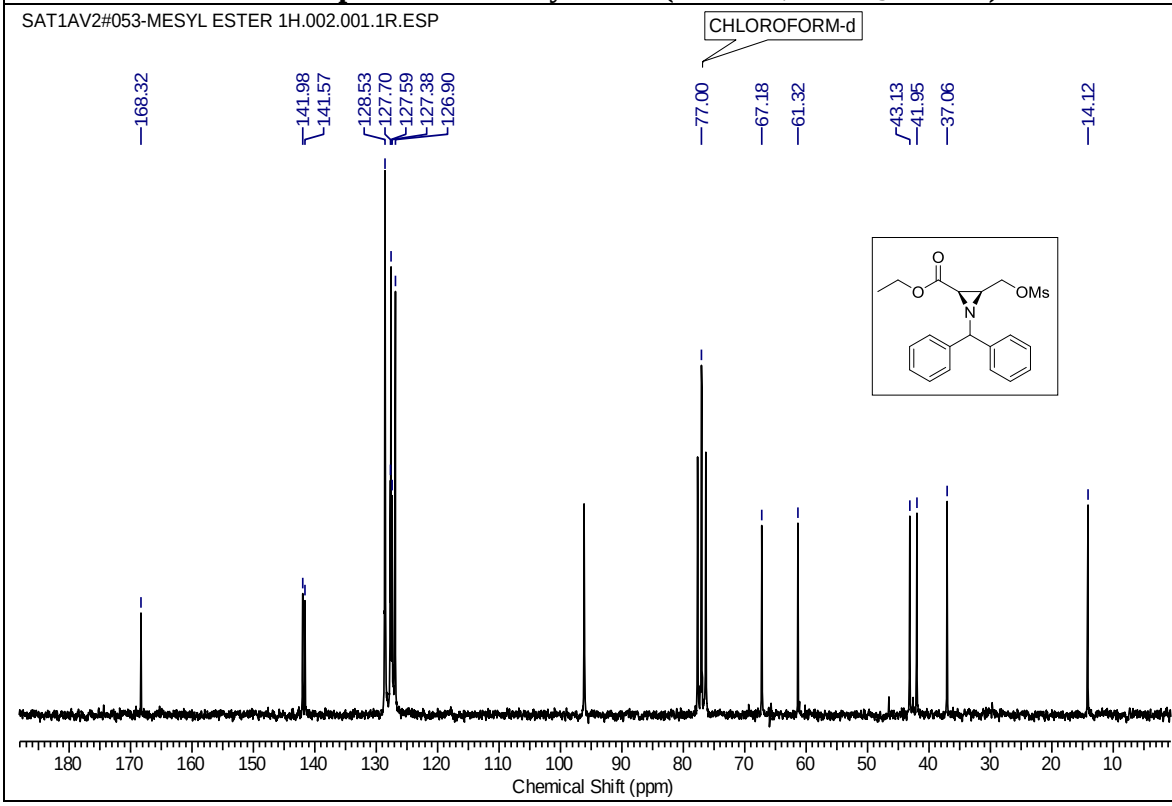
DEPT spectrum of aziridine 12 (125MHz, $CDCl_3$ + CCl_4)



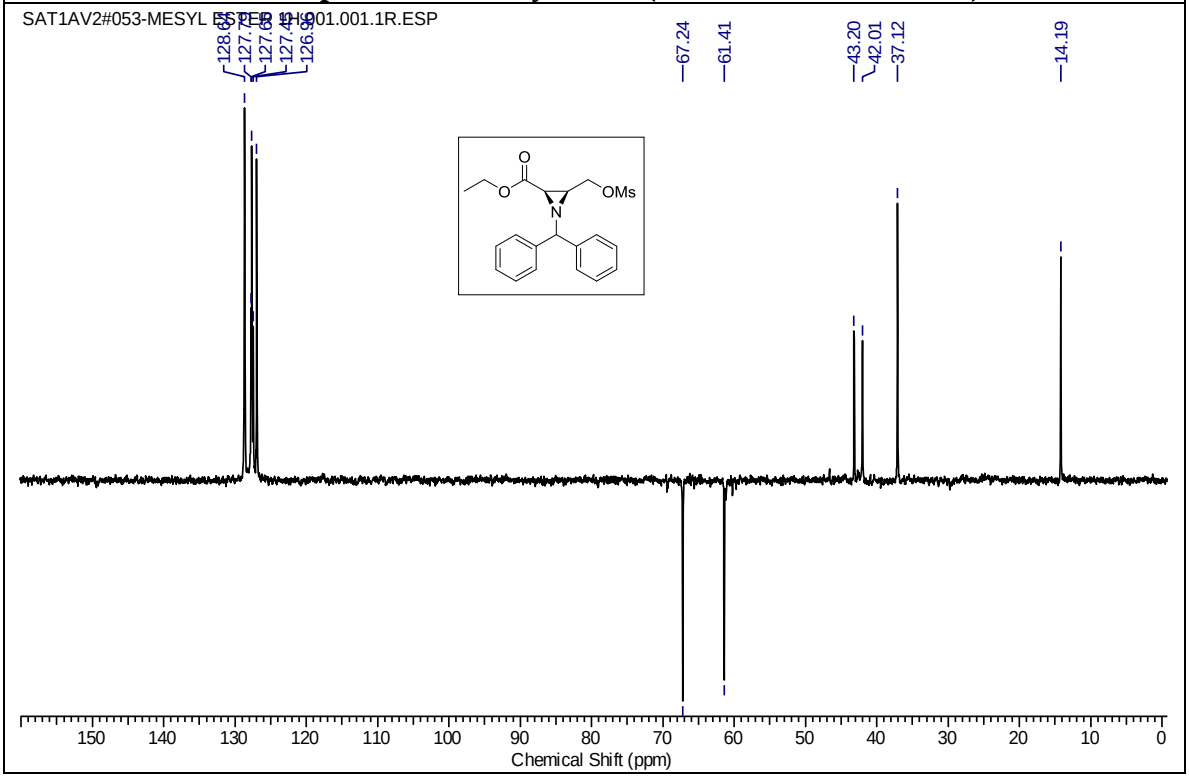
^{1}H NMR spectrum of mesylate 13 (200 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR spectrum of mesylate 13 (50 MHz, $CDCl_3$ + CCl_4)



DEPT spectrum of mesylate 13 (50 MHz, $CDCl_3$ + CCl_4)



2.2.5 References

1) Williams, A. l.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.
2) Poon, K. W. C.; Lovell, K. M.; Dresner, K. N.; Datta, A. *J. Org. Chem.* **2008**, *73*, 752.
3) Kale, A. S.; Deshmukh, Abdul Rakeeb, A. S. Synlett **2005**, 2370.
4) (a) Kasai, M.; Kono, M. *Synlett*, **1992**, 778; (b) Remers, W. A. *The Chemistry of Antitumour Antibiotics*, *Wiley-Interscience* **1979**, *1*, 242; (c) Remers, W. A.; Dorr, R. T.; Alkaloids*: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley, New York, **1988**, *6*, 1.
5) Gabriel, S. *Chem. Ber.* **1888**, *21*, 1049.
6) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (b) McCoull, W.; Davis, F. A. *Synthesis* **2002**, 1347; (c) Stamm, H. *J. Prakt. Chem.* **1999**, *341*, 319; (d) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160; (e) Sweeney, J. B.; Cantrill, A *Tetrahedron* **2003**, *59*, 3677; (f) Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J. R. *Synthesis* **2002**, 2211; (g) Hou, X. L.; Fan, R. H.; Dai, L. X. *J. Org. Chem.* **2002**, *67*, 5295; (h) Hu, X. E. Tetrahedron Lett. **2002**, *43*, 5315.
7) (a) Yadav, J. S.; Reddy, B. V. S.; Shesha, Rao, M.; Reddy, P. N. *Tetrahedron Letters* **2003**, *44*, 5275; (b) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135; (c) Tranchant, M. J.; Dalla, V.; Jabin, I.; Decroix, B. *Tetrahedron Lett*. **2002**, *58*, 8425; (d) Atkinson, R. S.; Draycott, R. D.; Hirst, D. J.; Parratt, M. J.; Raynham, T. M. *Tetrahedron Lett.* **2002**, *43*, 2083; (e) Zwanenburg, B.; Ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93.
8) Fernandez-Megia, E.; Montaos, M. A.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 6780.

Section 3

Formal synthesis of Tamiflu using *cis*-aziridine as the key precursor and RCM

2.3.1 Present work

2.3.1.1 Objective

The literature study revealed that there is always considerable mortality and morbidity rates due to influenza infection and it continues to be a threat to the health of human as well as other animals and birds. Last decade's drug designing and development studies on the neuraminidase inhibitors led to discovery of Oseltamivir phosphate (Tamiflu®) and Zanamivir (Relenza®) as effective drugs.[1] Tamiflu is widely used for the treatment and prevention of both human influenza (H1N1) as well as avian influenza (H5N1) infections. It is available as a capsule or powder for liquid suspension with good bioavailability, which is well absorbed by gastrointestinal track and hydrolyzed to its caboxylate active form.

Aziridine has been extensively explored for the construction of stereogenic centers containing nitrogen compounds. The literature reports revealed that aziridines are less explored for the synthesis for oseltamivir phosphate. There is only one report of synthesis of tamiflu, which involved the chiral aziridine as chiral building block.[2] Enantiomerically pure aziridines have been considered to be prominent precursors in the synthesis of natural and unnatural biologically active compounds due to their inherent ability to undergo regio and chemoselective nucleophilic ring opening reactions as well as cycloaddition pathways.[3]

Our group is engaged in the synthesis of the natural products from the aziridine chiral synthon and development of synthetic methodologies based on the aziridine chemistry.[4]

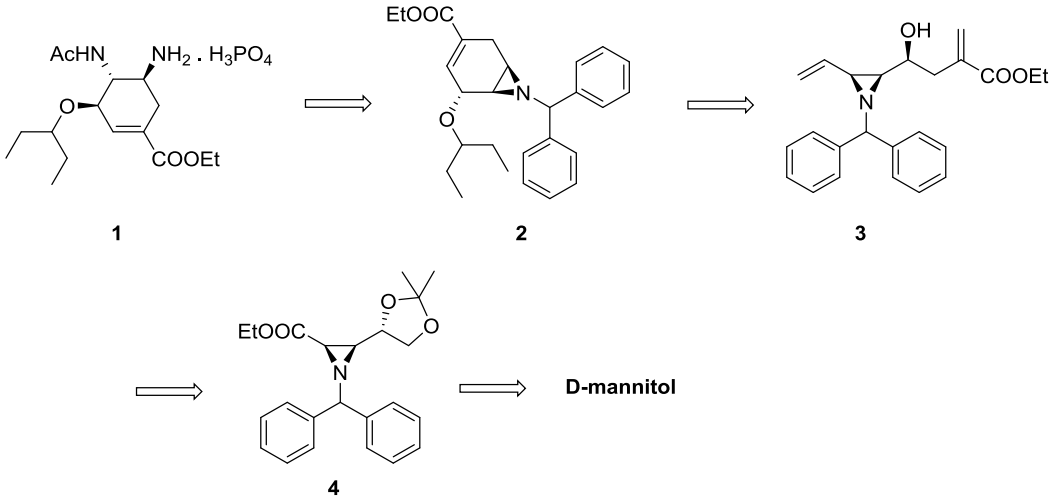
The present work was undertaken in the view of the exploration of the aziridine chemistry for the synthesis of the neuraminidase inhibitor drug. The reported chiral pool approaches for tamiflu are associated with low yields and lengthy routes or involve usage of potentially hazardous chemicals such as azides. In this context, there is a need of convenient and efficient route for its enantiopure synthesis.

In the present section an alternative approach based on chiral pool strategy is described. The current novel route for oseltamivir phosphate (Tamiflu) synthesis involved the use of aziridine-2-carboxylate as chiral synthon derived from D-mannitol which is abundant and inexpensive starting material.

2.3.1.2 Retrosynthetic analysis

Owing to their ring strain, aziridines are very prone to nucleophilic ring opening reactions with various nucleophiles with predictable chemo and regio selectivity to *trans*-diamine compounds.

The aziridine ring can be used to access the diamine as per the existing stereochemistry in tamiflu by proper chemical tools. Taking account of this, as shown in Scheme 1, it was thought that *trans*-vicinal diamine skeleton of the tamiflu **1** can be obtained from aziridine **2,** a key precursor, which could be obtained by intramolecular RCM of bis olefin **3**. Compound **3** in turn could be obtained from the aziridine **4** by DIBAL-H reduction, one carbon Wittig olefination, acetonide deprotection, diol cleavage and Barbier addition. The aziridine **4** is the key synthon readily available from D-mannitol (Scheme 1).

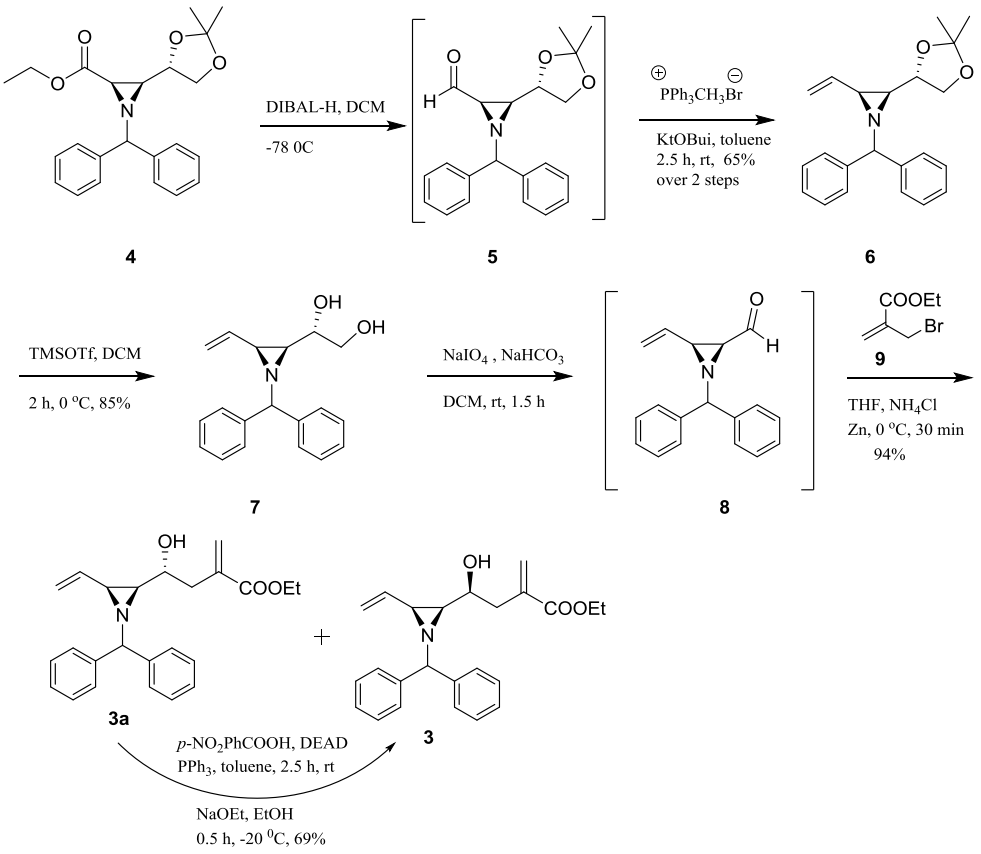


Scheme 1 Retrosynthetic analysis for tamiflu **1**

2.3.1.3 Results and discussion

The present section describes the total synthesis of oseltamivir phosphate **1** (Scheme 2). The *cis*-aziridine ester **4** can be synthesized from D-mannitol diacetonide and was converted to **6** in two steps using the reported procedure.[5] The *cis*-aziridine ester **4** was subjected to the DIBAL-H reduction at -78 ^{o}C in DCM to furnish the aldehyde **5**. The crude aldehyde without purification was subjected for the one carbon homologation using

the Wittig conditions[6] wherein to the one carbon Wittig salt dissolved in dry toluene was added potassium *t*-butoxide at room temperature and after 1 h compound **5** in dry THF was added to afford the olefin **6**. The band in IR spectrum at 1636 cm^{-1} indicates the presence of double bond functionality. The ^{1}H NMR spectrum showed the peaks at δ 7.42-7.12 (m, 10 H) for aromatic protons while peaks at δ 5.91-5.74 (m, 1 H) and 5.43-5.22 (m, 2 H) ppm were assigned to three protons of terminal olefin. The ^{13}C NMR spectrum showed the peaks at δ 26.7 and 25.3 ppm for two methyl carbons of acetonide protecting group and ^{13}C DEPT NMR spectrum showed the peak at δ 118.5 for the methylene of terminal olefin. The peak observed at 336.1957 $(M+H)^{+}$ in HRMS spectrum confirmed the molecular formula $C_{22}H_{25}NO_2$ of olefin compound **6**.



Scheme 2 Synthesis of RCM precursor **3**

The next task was to obtain the diene **3**. Accordingly, the olefin **6** was treated with TMSOTf in DCM at 0 °C to furnish the diol **7** in 85% yield.[7] The strong bands at 3640, 3451 cm^{-1} in IR spectrum indicated the presence of two hydroxy groups and 1638 cm^{-1} for olefin functionality. The disappearance of the peaks for two methyl groups at δ 1.31

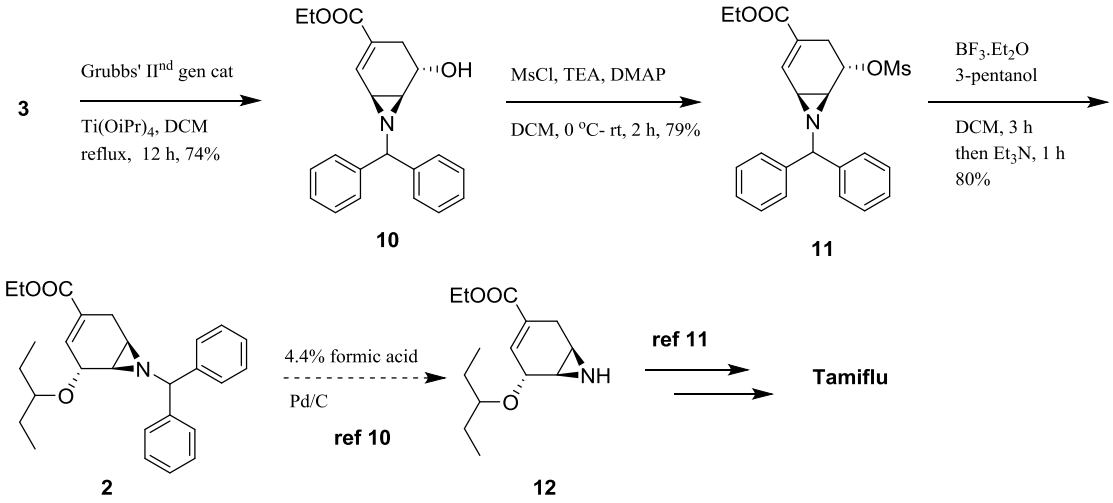
(s, 3 H) and 1.23 (s, 3 H) ppm in ^{1}H NMR supported the formation of diol **7**. The ^{13}C NMR spectrum showed the peaks at δ 118.8 and 64.9 ppm for the methylene carbon of terminal olefin and $–CH_2OH$ group. The HRMS spectrum showed the peak at 296.1643 $(M+H)^+$ which confirmed the molecular formula $C_{19}H_{21}NO_2$ of the dihydroxy olefin **7**.

The diol **7** was treated with $NaIO_4$ and $NaHCO_3$ in DCM at room temperature to afford aldehyde **8**, which was directly subjected for the addition of ethyl 2-(bromomethyl)-acrylate **9** in presence of Zn powder in THF/NH_4Cl to furnish the diastereomers **3a**:**3** in ratio 3:2 with 92% yield (Scheme 2).[8] The isomer **3a** was inverted to desired isomer **3** using Mitsunobu reaction conditions, *p*-nitrobenzoic acid and DEAD in toluene at room temperature for 1 h, to provide ester which on basic hydrolysis with NaOEt/EtOH gave **3** in 69% over two steps.

The IR spectrum showed the bands at 3451 and 1638 cm^{-1} indicating the presence of the hydroxy and olefin functionalities. The peaks in ^{1}H NMR spectrum at δ 6.16 (d, J = 1 Hz, 1 H) and 5.49 (s, 1 H) ppm were assigned to two protons of unsaturated ester while the peaks at δ 4.18 (q, J = 8 Hz, 2 H) and 1.30 (t, J = 8 Hz, 3 H) ppm corresponded to the five protons of ethyl ester. The peak at δ 166.7 in ^{13}C NMR spectrum indicated carbonyl carbon of ester and DEPT NMR spectrum showed the peaks at δ 127.1 and 118.8 ppm for the two methylene carbons of unsaturated ester and terminal olefin respectively, while the peaks δ 60.5 and 14.2 ppm related to methylene and methyl carbons of ethyl ester. The peak observed at 378.2065 $(M+H)^+$ in HRMS spectrum confirmed the molecular formula $C_{24}H_{27}NO_3$ of the diene **3**.

Further the diene **3** on RCM using the Grubbs' II gen catalyst in presence of $Ti(iPrO)_4$ under reflux in dry DCM furnished the cyclohexene aziridine **10** in 74% yield.[9] The IR spectrum showed the bands at 1710 and 1637 cm^{-1} for carbonyl of ester functionality. The ^{1}H NMR spectrum exhibited peaks at δ 7.44-7.20 (m, 11H) ppm for the ten aromatic protons and one *β*-proton of unsaturated ester. The ^{13}C NMR spectrum showed the peak at δ 166.5 ppm for carbonyl carbon of ester and peak at 136.4 ppm for carbon of unsaturated ester. The disappearance of the peaks at δ 127.1 and 118.8 ppm in ^{13}C DEPT spectrum confirmed the formation of cyclic compound **10**. The HRMS spectrum showed the peak at 350.1748 $(M+H)^+$ which confirmed the molecular formula $C_{22}H_{23}NO_3$ of cyclohexene aziridine **10**.

The next step of mesylation of hydroxy aziridine **10** was carried out using mesyl choride, TEA and cat. DMAP in DCM at 0 ^{o}C to afford the mesylate derivative **11** in 79% yield. The IR bands at 1709 and 1645 cm^{-1} indicated presence of ester and double bond functionality. ^{1}H NMR spectrum showed the peak at δ 2.94 (s, 3H) ppm for the methyl protons of mesyl group. The ^{13}C NMR spectrum exhibited peak at δ 165.9 ppm corresponding to carbonyl carbon of ester while peaks at δ 139.3, 128.7, 128.5, 127.6, 127.3, 127.1 and 126.9 ppm for aromatic carbons. The ^{13}C DEPT NMR spectrum showed the peak at δ 38.8 for the methyl carbon of mesyl functionality. The peak at 428.1524 $(M+H)^{+}$ in HRMS spectrum corresponded to the molecular formula $C_{23}H_{25}NO_5S$ of the mesylate **11**. The characterization data of mesyl **11** was in full agreement with the data reported by Ishiwata and coworkers.[10]



Scheme 3 Synthesis of aziridine **2**

Further, the mesylate **11** was treated with 3-pentanol in DCM at room temperature in presence of $BF_3.Et_2O$ followed by addition of TEA after 3 h to afford the reaziridination product **2** in 80% yield. The IR spectrum of **2** showed the band at 1712 cm^{-1} for the ester carbonyl. ^{1}H NMR spectrum showed the peak at δ 6.78-6.76 (m, 1H) ppm for *β*-proton of unsaturated ester while peaks at δ 1.46-1.32 (m, 4 H), and 0.86-0.80 (m, 6 H) ppm were assigned to the four methylene protons and six protons of two methyl groups respectively of pentyl group. The peaks at δ 166.9 and 134.2 ppm in ^{13}C NMR spectrum were present for the carbonyl and olefinic –CH carbon and ^{13}C DEPT NMR spectrum showed the peaks at δ 26.5 and 24.3 ppm for two methylene carbons while peaks at δ 9.8 and 9.6

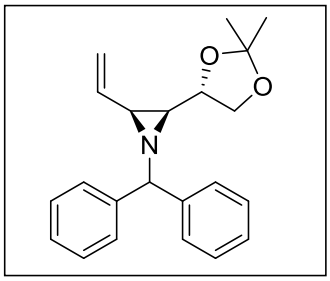
ppm corresponding to methyl carbons supported the iso-pentyl group. The peak observed at 420.2535 $(M+H)^+$ in HRMS spectrum confirmed the molecular formula $C_{27}H_{33}NO_3$ of the aziridine **2**. The spectral data of aziridine **2** was in agreement with the data reported by Ishiwata and coworkers.

2.3.2 Conclusion

In conclusion, a very short and practical formal synthesis of the tamiflu has been accomplished starting from the economical and abundant chiral material D-mannitol. *Cis*-aziridine as a key building block is utilized in the synthesis to fix the desired stereocenter of the neuraminidase inhibitor drug oseltamivir phosphate. In the strategy, we had advantages of the Wittig olefination and Barbier reaction for acyclic diene precursor for RCM, which was converted to cyclohexene core of tamiflu by means of well-organized ring closing metathesis (RCM). The undesired stereoisomer of Barbier reaction was converted into desired isomer using Mitsunobu conditions. The synthetic route is concise, uses inexpensive reagents throughout the synthesis and involves high yielding reaction steps.

2.3.3 Experimental section

(2*S*, 3*S*)-1-Benzhydryl-2-((*S*)-2, 2-dimethyl-1, 3-dioxolan-4-yl)-3-vinylaziridine (6)



To a stirred solution of *cis* aziridine 2-carboxylate **4** (10 gm, 26.24 mmol) in dry DCM (100 mL) was added DIBAL-H (33.65 mL, 26.24 mmol, 1M solution in toluene) at -78 ^{o}C slowly over period of 15 min and the reaction mixture was stirred at same temperature for 20 min. Reaction was quenched by careful addition of pre-cooled (-78 ^{o}C) MeOH (25 mL) and allowed to warm to 0 ^{o}C. Roche's salt (saturated solution of sodium potassium tartarate, 30 mL) was added and stirred for 0.5 h. The compound was extracted with DCM (3 x 80 mL) and combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude aldehyde **5**, which was used as such for next reaction.

To a stirred solution of methyltriphenylphosphonium bromide (28.5 gm, 79.88 mmol) in dry toluene (90 mL) was added K^{t}OBu (7.54 gm, 66.57 mmol) portion wise and stirred at room temperature for 1 h. The crude aldehyde **5** (9.4 gm, 26.62 mmol) in dry THF (50 mL) was added dropwise to the reaction mixture and stirred at room temperature for 1.5 h. Reaction mixture was quenched by addition of saturated aq. solution of NH_4Cl and the compound was extracted with DCM (3 x 80 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford olefin **6** (5.71 gm, 65%) as a yellow syrup.

Rf: 0.7 (Pet. ether: ethyl acetate, 80:20).

MF: $C_{22}H_{25}NO_2$, **MW**: 335.45.

Yield: 65% .

[*α*]$^{25}_{D}$: +41.33 (*c* 1.5, $CHCl_3$).

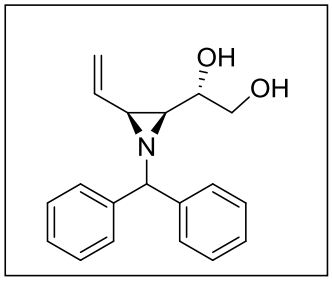
IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 2970, 1638, 1598, 1453, 1370, 1213, 1054.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.42 - 7.12 (m, 10H), 5.91 - 5.74 (m, 1H), 5.43 - 5.22 (m, 2H), 3.80 - 3.59 (m, 3H), 2.85 (dd, *J* = 6, 8.0 Hz, 1H), 2.32 (t, *J* = 6 Hz, 1H), 1.87 (dd, *J* = 6, 8 Hz, 1H), 1.31 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 143.2, 142.5, 133.3, 128.4, 128.1, 128.0, 127.0, 126.8, 118.5, 109.1, 77.9, 68.1, 46.7, 45.9, 26.7, 25.3.

HRMS: Calculated- 336.1958, Observed-336.1957 $(M+H)^+$.

(*S*)-1-((2*S*, 3*S*)-1-Benzhydryl-3-vinylaziridin-2-yl)-ethane-1, 2-diol (7)



To a stirred, ice-cold solution of the aziridine acetonide **6** (6 gm 14.92 mmol) in anhydrous DCM (70 mL) under nitrogen atmosphere, was added TMSOTf (4.8 mL, 29.85 mmol) dropwise at 0 ^oC. The resulting solution was stirred at the same temperature for 2 h and the reaction mixture was quenched by addition of solid $NaHCO_3$. Water (50 mL) was added and the compound was extracted with DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **7** (4.4 gm, 85%) as colourless syrup.

Rf: 0.3 (Pet. ether: ethyl acetate, 50:50)

MF: $C_{19}H_{21}NO_2$, **MW**: 295.38.

Yield: 85% .

$[\alpha]_D^{25}$: +112.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 3451, 2927, 1638, 1453, 1096.

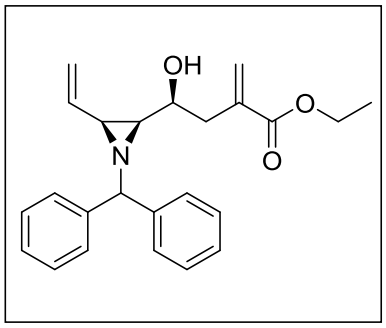
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.20 (m, 10H), 5.85-5.92 (m, 1H), 5.43 - 5.39 (m, 1H), 5.29 (dd, *J* = 1, 10 Hz, 1 H), 3.73 (s, 1H), 3.52 - 3.47 (m, 1H), 3.27 (d, *J* =

10 Hz, 1H), 3.13 (dd, *J* = 5, 10 Hz, 1H), 2.38 - 2.35 (m, 1H), 2.16 (bs, 1H), 1.97 (dd, *J* = 5, 10 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 143.0, 142.2, 133.9, 128.6, 128.2, 128.1, 127.9, 127.1, 127.0, 118.8, 78.0, 69.8, 64.9, 46.3, 46.2.

HRMS: Calculated- 296.1645, Observed- 296.1643 $(M+H)^+$.

Ethyl-(*S*)-4-((2*S*,3*S*)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (3)



To the solution of diol **7** (3.3 gm, 11.18 mmol) in DCM (40 mL) was added sodium metaperiodate (5.4 gm, 22.37 mmol). The reaction mixture was stirred at room temperature for 1.5 h and completion of reaction was monitored by TLC. The reaction mass was quenched using ethylene glycol (0.01 mL), extracted with DCM (3 X 30 mL), washed with brine, dried over anhydrous sodium sulphate and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde **8** which was used as such for next reaction.

To the solution of crude aldehyde **8** (3.1 gm, 11.78 mmol) from above reaction in THF (40 mL) was added ethyl 2-(bromomethyl) acrylate **9** (1.8 mL, 12.96 mmol), activated zinc powder (3 gm, 47.14 mmol) and saturated aq. solution of NH_4Cl (5 mL) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for additional 10 min. The reaction mixture was filtered through a simple filter paper and thoroughly washed with ethyl acetate (3 X 30 mL). Water was added to the filtrate and the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated to give a crude residue that was purified by flash chromatography (pet. ether-ethyl acetate, 9:1) to afford **3a:3** in 3:2 ratio (2.76 gm, 94%) as colourless syrup.

To the solution of **3a** (500 mg, 1.326 mmol) in toluene (10 mL) was added triphenyl phosphine (870 mg, 3.315 mmol), *p*-nitrobenzoic acid (560 mg, 3.315) and DEAD (0.6 mL, 3.315 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 2.5 h and progress of reaction was monitored by

TLC. To the reaction mass, water (20 mL) was added and the compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was as such subjected for next reaction.

The crude product (570 mg, 1.08 mmol) was dissolved in absolute ethanol (10 mL) and to the solution was added NaOEt (81 mg, 1.19 mmol) at -20 ^{o}C. The reaction mixture was stirred further for 0.5 h at same temperature. Several drops of CH_3COOH were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 15% ethyl acetate in pet. ether to provide the product **3** (345 mg, 69% yield over two steps) as colourless syrup.

Ethyl 2-((*S*)-((2*S*, 3*S*)-1-benzhydryl-3-vinylaziridin-2yl)-4-hydroxy)methyl)acrylate (3)

Rf: 0.6 (Pet. ether: ethyl acetate, 70:30)

MF: $C_{24}H_{27}NO_3$, **MW**: 377.48.

$[\alpha]_D^{25}$: +32.0 (*c* 1.5, $CHCl_3$).

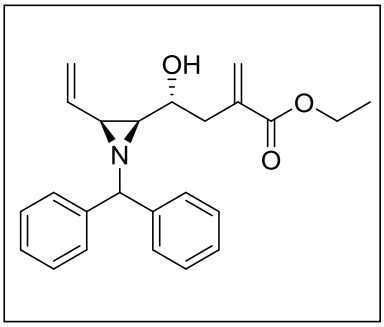
IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 3434, 2925, 1715, 1626, 1153.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.41-7.21 (m, 10H), 6.16 (d, *J* = 1 Hz, 1H), 5.85-5.76 (m, 1H), 5.49 (s, 1H), 5.36 - 5.18 (m, 2H), 4.18 (q, *J* = 8 Hz, 2H), 3.77 (s, 1H), 3.65 - 3.60 (m, 1H), 2.36 - 2.29 (m, 2H), 2.24 - 2.19 (m, 1H), 1.92 (t, *J* = 8 Hz, 1H), 1.81 (bs, 1H), 1.30 (t, *J* = 8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 166.7, 143.5, 142.3, 136.7, 134.2, 128.8, 128.2, 127.8, 127.7, 127.4, 127.1, 126.9, 118.8, 77.7, 67.6, 60.6, 49.6, 47.1, 37.8, 14.2.

HRMS: Observed- 378.2065 $(M+H)^+$, calculated- 378.2064.

Ethyl(*R*)-4-((2*S*,3*S*)-1-benzhydryl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylene butanoate (3a)



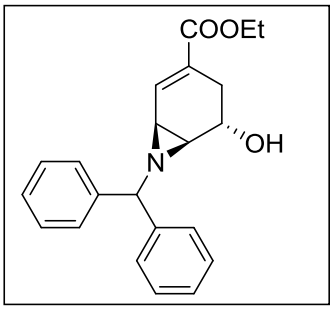
Rf: 0.5 (Pet. ether: ethyl acetate, 70:30).

[α]$^{25}_{D}$: +13.33 (*c* 1.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.42 - 7.16 (m, 10H), 6.11 (d, *J* = 2 Hz, 1H), 6.01 - 5.84 (m, 1H), 5.41 - 5.21 (m, 3H), 4.34 - 4.11 (m, 3H), 3.76 (s, 1H), 3.64-3.54 (m, 1H), 2.92 (bs, 1H), 2.32 (t, *J* = 6 Hz, 1H), 2.22 – 2.10 (m, 2H), 1.93 (t, *J* = 6 Hz, 1H), 1.34 (t, *J* = 6 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 167.9, 143.3, 142.6, 137.3, 134.4, 128.4, 128.2, 128.0, 127.6, 127.5, 127.0, 126.8, 118.2, 77.9, 69.0, 60.9, 49.1, 46.3, 37.6, 14.1.

Ethyl(1S,5S,6S)-7-benzhydryl-5-hydroxy-7-azabicyclo-[4.1.0]hept-2-ene-3-carboxylate (10)



To the solution of the olefin compound **3** (500 mg, 1.32 mmol) in dry DCM (400 mL) was added titanium tetraisopropoxide (0.23 mL, 0.66 mmol) and Grubbs' 2nd generation catalyst (45 mg, 0.05 mmol). The reaction mixture was refluxed for 12 h and the completion of the reaction was monitored with TLC. The reaction mixture was filtered through celite bed and thoroughly washed with DCM (3 X 50 mL). The solvent was evaporated under reduced pressure to furnish the crude product, which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **10** (342 mg, 74%) as colourless syrup.

Rf: 0.3 (Pet ether: ethyl acetate, 70:30)

MF: $C_{22}H_{23}NO_3$, **MW**: 349.43.

MF: $C_{27}H_{33}NO_3$, **MW**: 419.57.

Yield: 74% .

[α]$^{25}_{D}$: - 128.75 (*c* 1.6, $CHCl_3$).

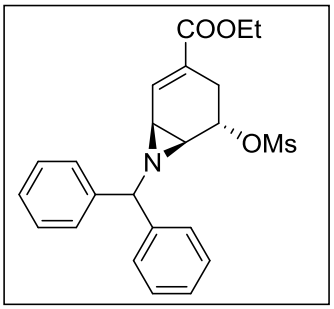
IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 3428, 2925, 1710, 1637, 1495, 1249, 1249.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.44-7.20 (m, 11H), 4.35 (t, *J* = 5 Hz, 1H), 4.26-4.18 (m, 2H), 4.18 – 4.43 (m, 1H), 3.79 (s, 1H), 2.79 (d, *J* = 20 Hz, 1H), 2.56-2.51 (m, 1H), 2.42-2.51 (m, 1H), 2.24 (t, *J* = 5 Hz, 1H), 1.32 (t, *J* = 10 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 166.5, 143.0, 142.8, 136.4, 128.5, 128.4, 127.3, 127.2, 127.1, 76.5, 63.9, 60.6, 46.7, 35.8, 30.2, 14.3.

HRMS: Calculated- 350.1751, Observed- 350.1748 $(M+H)^+$.

Ethyl (1*S*,5*S*,6*S*)-7-benzhydryl-5-((methylsulfonyl)oxy)-7-azabicyclo[4.1.0]hept-2-ene-3-car boxylate (11)



To a solution of alcohol **10** (150 gm, 0.42 mmol) in DCM (3 mL) was added triethylamine (0.3 mL, 2.15 mmol) followed by mesyl chloride (0.04 mL, 0.47 mmol) and DMAP (cat.) at 0 ^oC. The reaction mixture was allowed to stir at room temperature for 2 h under nitrogen atmosphere. The completion of reaction was monitored by TLC and reaction mixture was poured in cold ice water. The compound was extracted with DCM (3 X 5 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet. ether as an eluent to afford compound **11** (144 mg, 79%) as colourless syrup.

Rf: 0.4 (Pet. ether: ethyl acetate, 70:30).

MF: $C_{23}H_{25}NO_5S$, **MW**: 427.51.

Yield: 79% .

[α]$_D^{25}$: - 4.44 (*c* 0.9, $CHCl_3$).

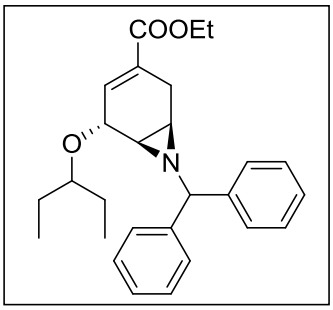
IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 3026, 2925, 1709, 1645, 1359, 1263.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.30-7.20 (s, 11H), 5.28-5.27 (m, 1H), 4.24-4.17 (m, 2H), 3.81 (s, 1H), 3.02 (d, *J* = 20 Hz, 1H,), 2.94 (s, 3H), 2.64-2.57 (m, 2H), 2.35 (t, *J* = 5 Hz, 1H), 1.31 (t, *J* = 5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 165.9, 142.3, 139.3, 128.7, 128.5, 127.6, 127.3, 127.1, 126.9, 76.3, 73.4, 60.8, 44.2, 38.8, 36.1, 27.7, 14.3.

HRMS: Observed- 428.1524, calculated- 428.1526 $(M+H)^+$.

Ethyl (1*R*,5*R*,6*R*)-7-benzhydryl-5-(pentan-3-yloxy)-7-azabicyclo[4.1.0]hept-3-ene-3-carbox- ylate (2)



Mesyl compound **11** (0.05 gm, 0.11 mmol) was dissolved in 3-pentanol (2 mL) and dry DCM (1 mL). To the reaction mixture was added $BF_3.Et_2O$ (0.083 mL, 0.58 mmol) dropwise and stirred at room temperature for 3 h. Then TEA (0.25 mL, 1.75 mmol) was added to the reaction mixture and stirred for 1 h at room temperature. Reaction mixture was concentrated under reduced pressure to remove low boiling impurities. To the remaining residue, water (3 mL) was added. The compound was extracted with DCM (3 X 5 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude product, which was purified by column chromatography over silica gel, eluting with 10% ethyl acetate in pet. ether as an eluent to afford compound **2** (49 mg, 80%) as a colourless syrup.

Rf: 0.6 (Pet. ether: ethyl acetate, 80:20).

MF: $C_{27}H_{33}NO_3$, **MW**: 419.57.

Yield: 80% .

$[\alpha]_D^{25}$: - 4.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}**)**: ν_{max} 2968, 2876, 1712, 1660, 1493, 1302, 1248, 1080.

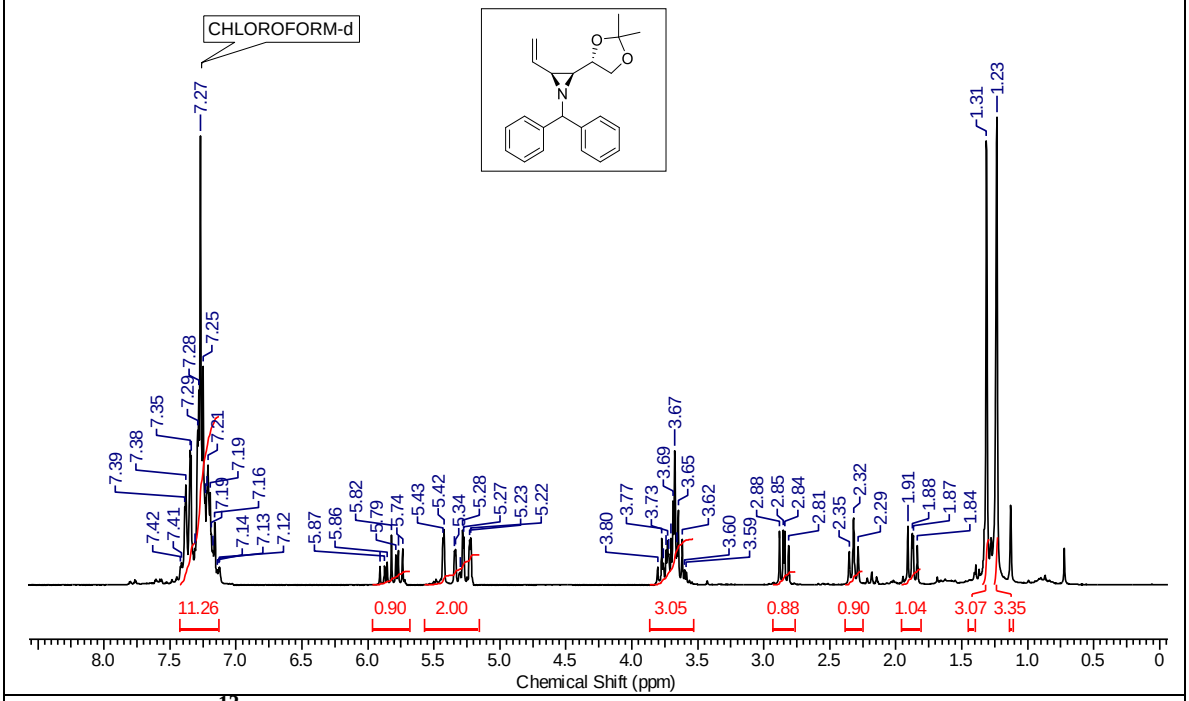
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.20 (m, 10H), 6.78-6.76 (m, 1H), 4.19 (q, *J* = 5 Hz, 2 H), 4.05 (bs, 1 H), 3.70 (s, 1 H), 3.13-3.10 (m, 1 H), 2.72 - 2.68 (m, 1 H), 2.61 - 2.55 (m, 1 H), 2.14 - 2.12 (m, 1H), 1.96 (d, *J* = 5 Hz, 1H), 1.46 - 1.32 (m, 4H), 1.31 (t, *J* = 5 Hz, 3H), 0.86-0.80 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 166.9, 143.4, 143.0, 134.2, 128.3, 127.6, 127.2, 127.0, 82.1, 77.7, 69.8, 60.6, 39.8, 38.2, 26.5, 26.4, 14.3, 9.8, 9.7.

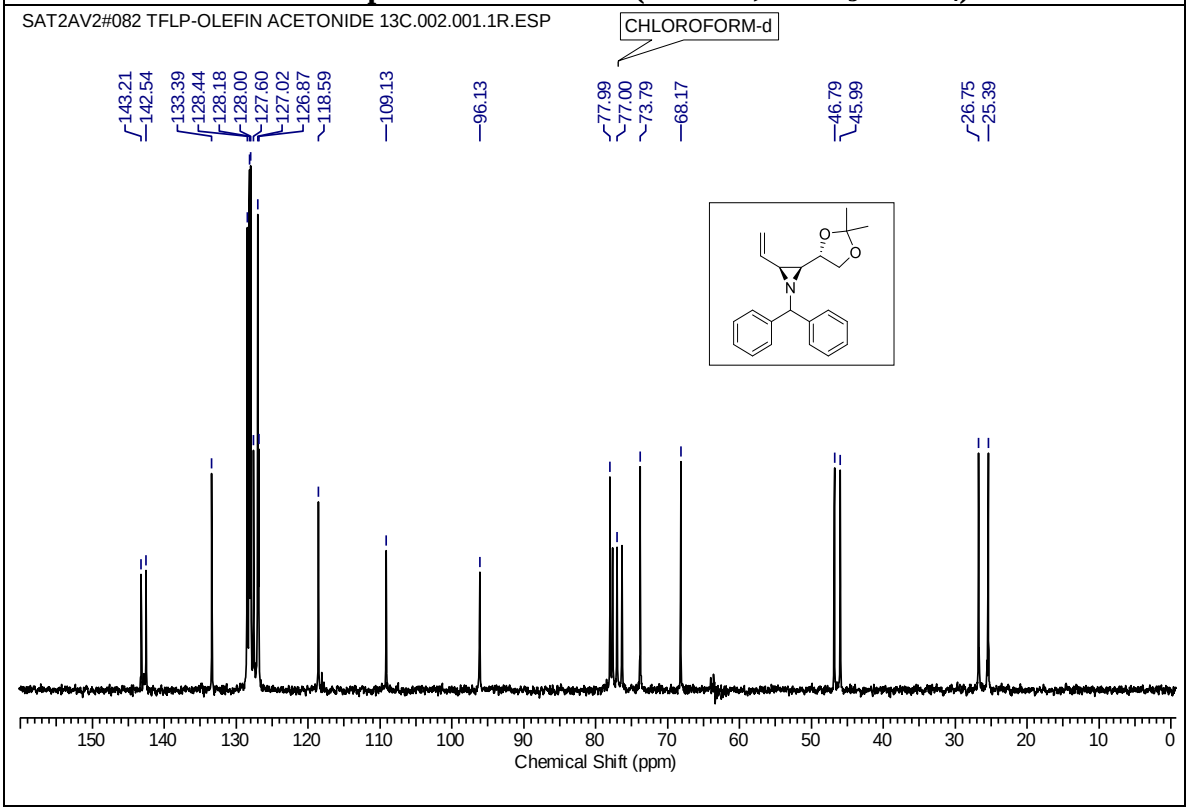
HRMS: Observed- 420.2535, calculated- 420.2533 $(M+H)^+$.

2.3.4 Spectral Data

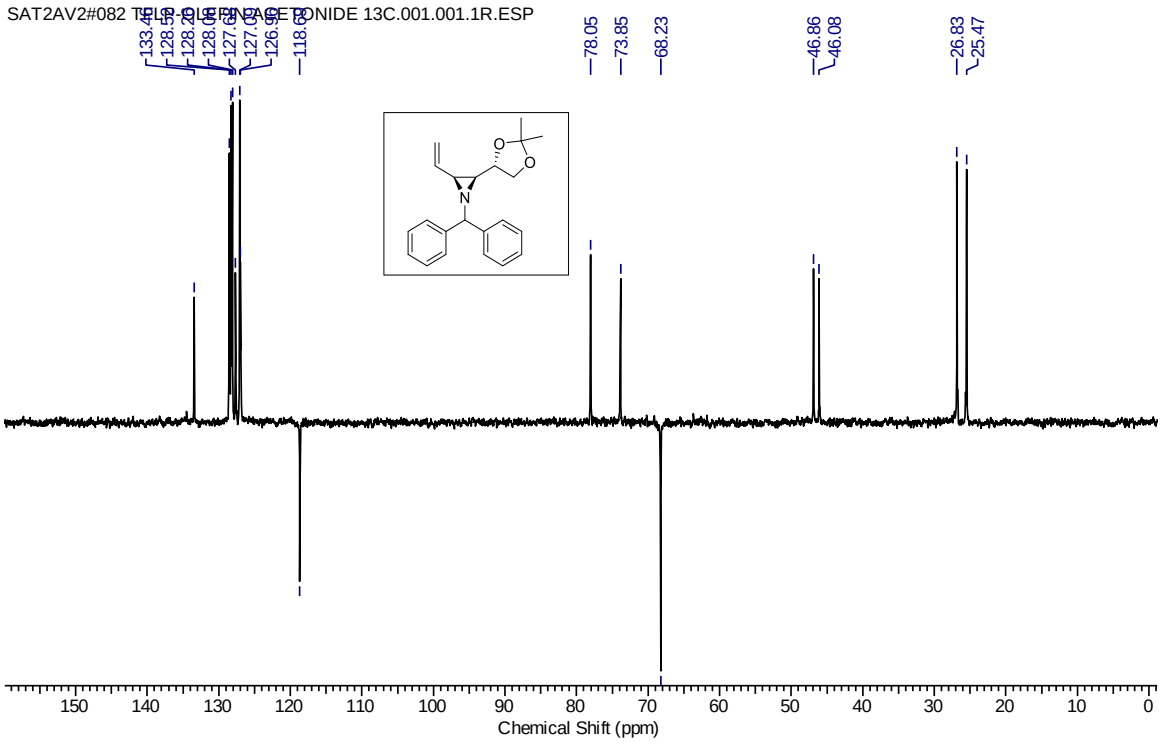
^{1}H NMR spectrum of olefin 6 (200 MHz, $CDCl_3$ + CCl_4)



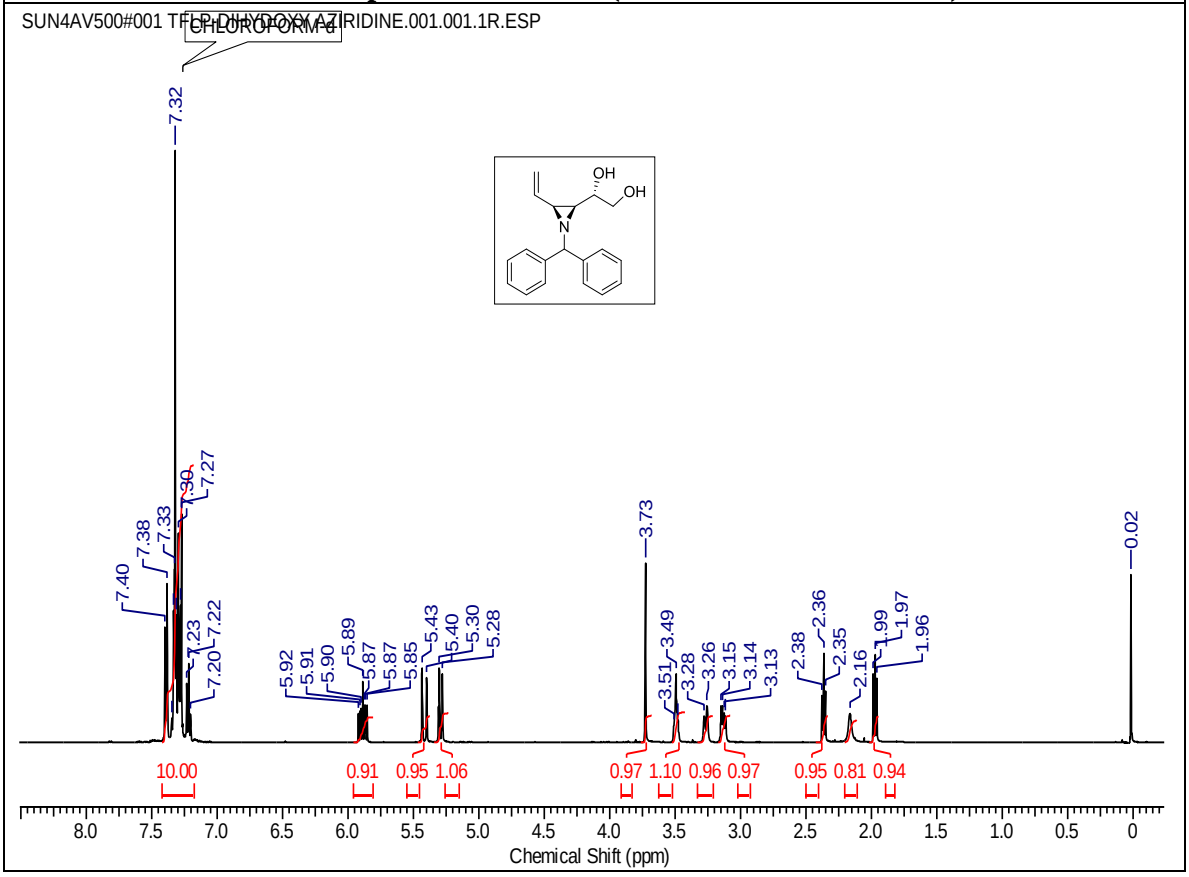
^{13}C NMR spectrum of olefin 6 (50 MHz, $CDCl_3$ + CCl_4)



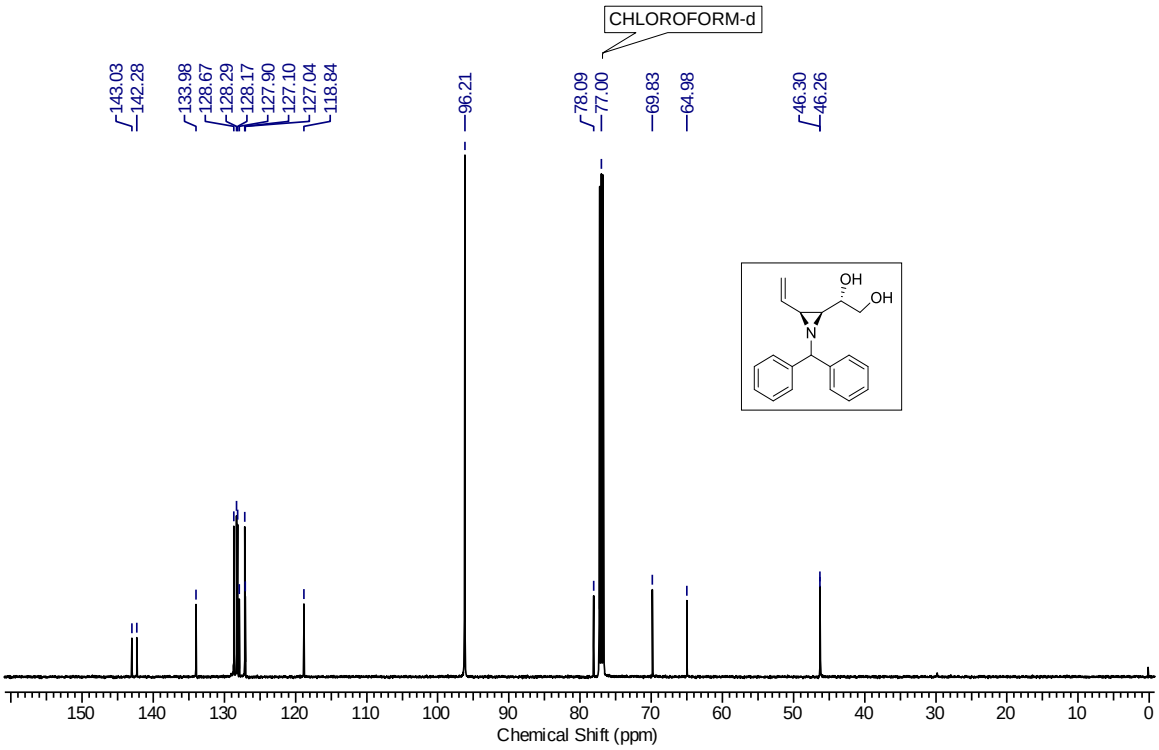
^{13}C NMR spectrum of olefin 6 (50 MHz, $CDCl_3$ + CCl_4)



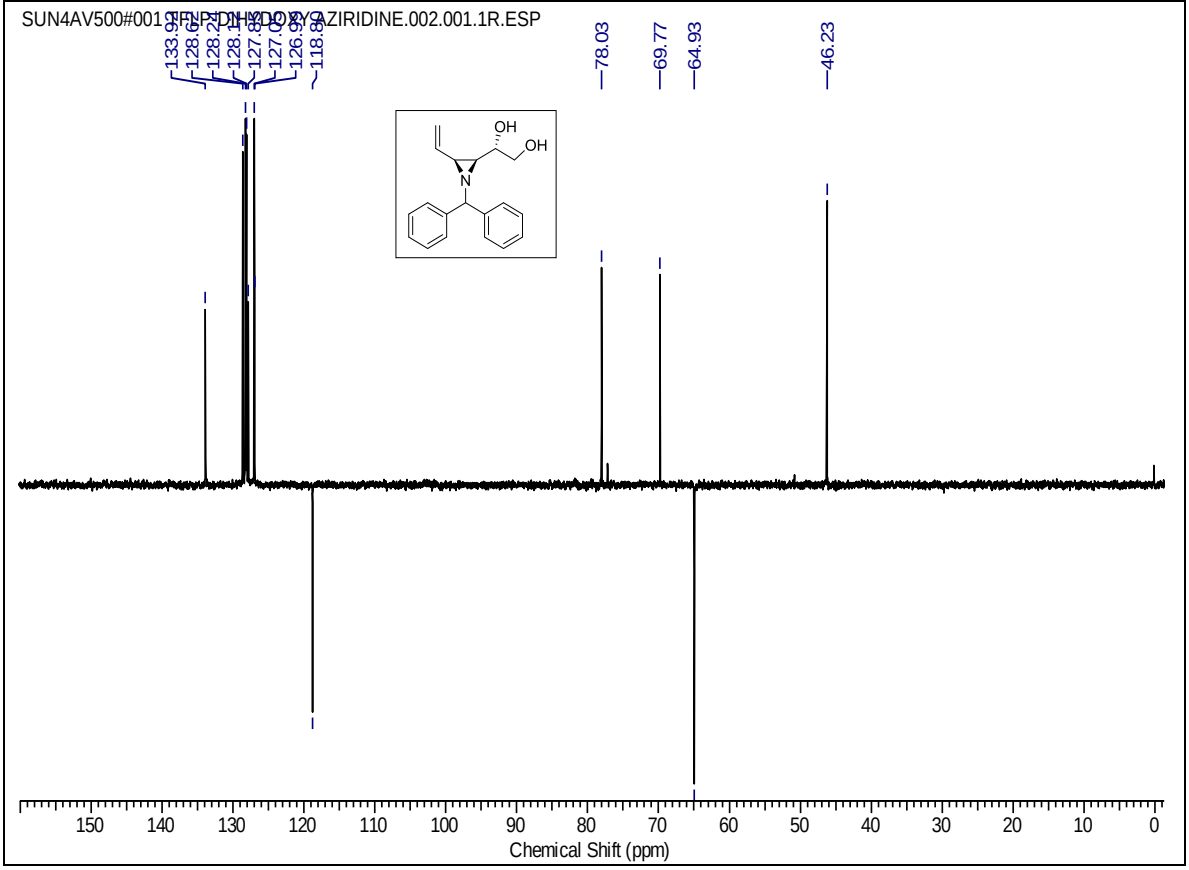
^{1}H NMR spectrum of diol 7 (500 MHz, $CDCl_3$ + CCl_4)



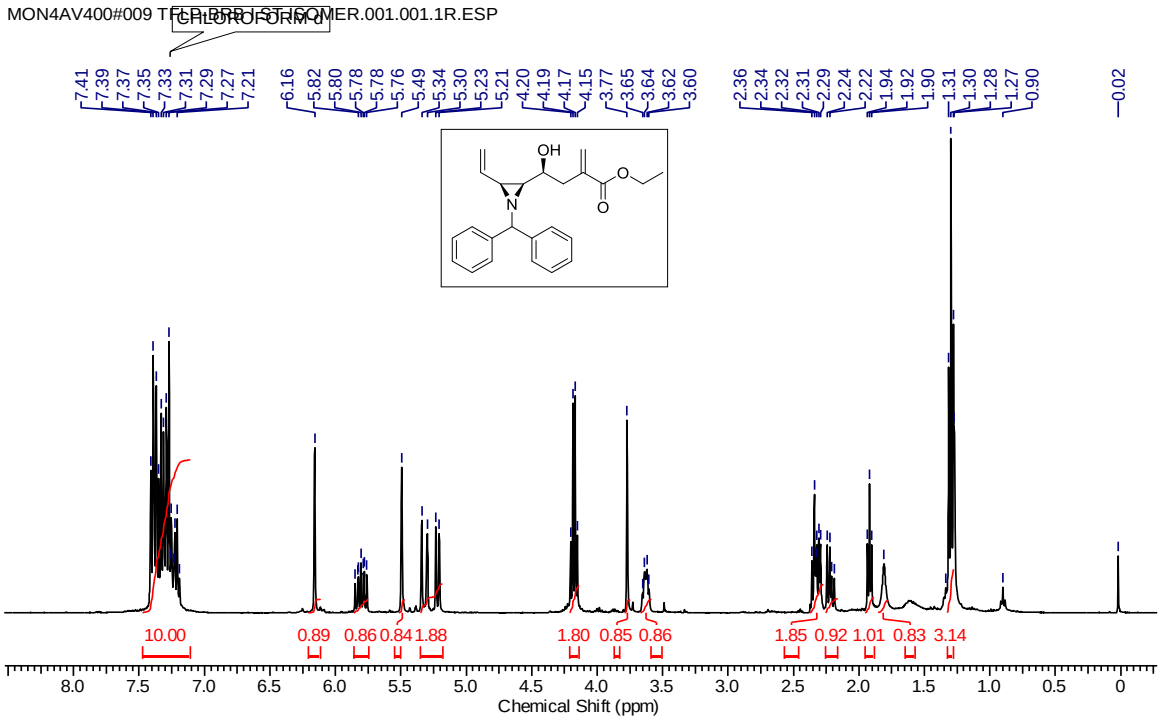
^{13}C NMR spectrum of dol 7 (125 MHz, $CDCl_3$ + CCl_4)



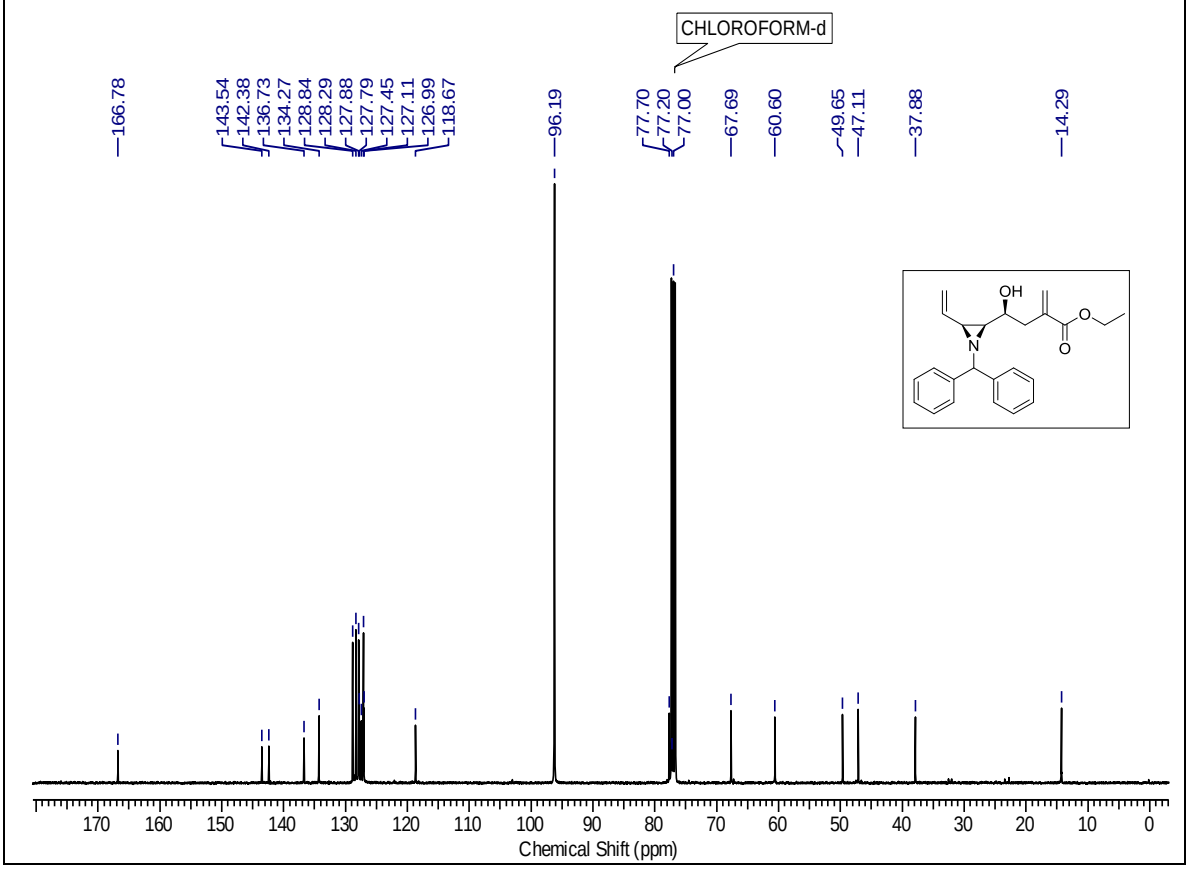
^{13}C NMR spectrum of diol 7 (125 MHz, $CDCl_3$ + CCl_4)



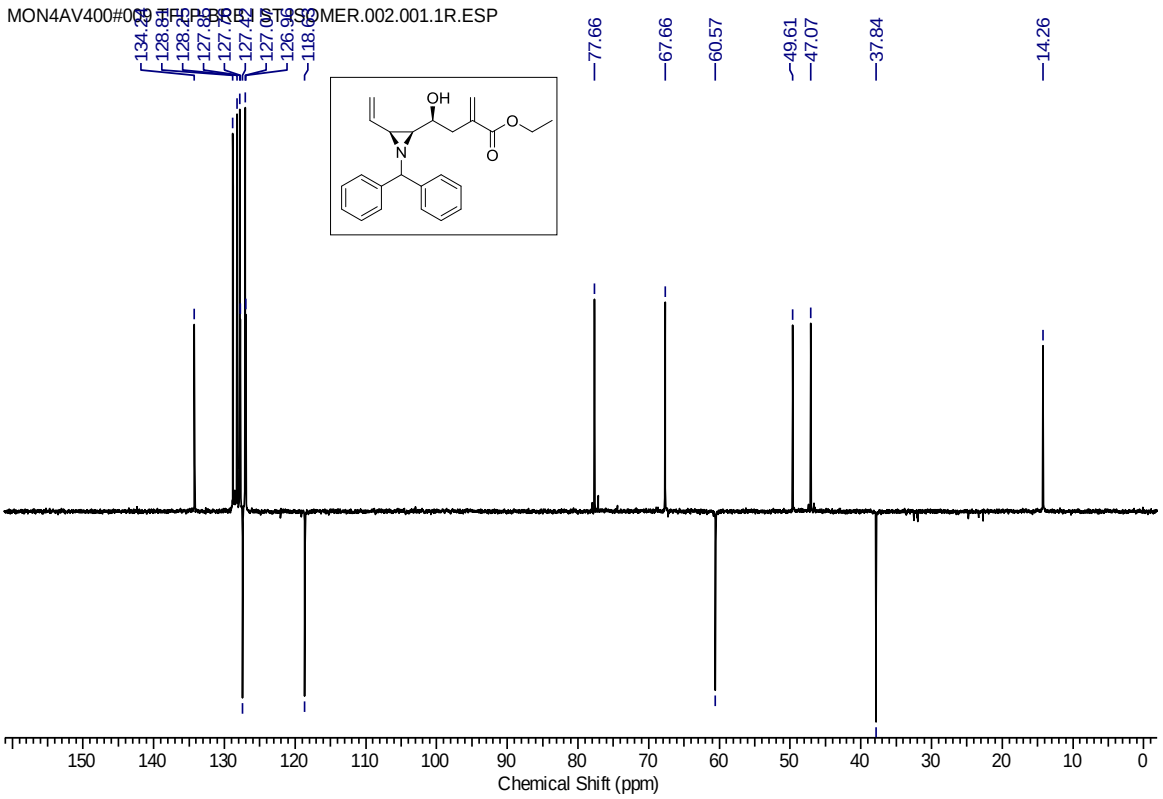
^{1}H NMR spectrum of compound 3 (400 MHz, $CDCl_3$ + CCl_4)



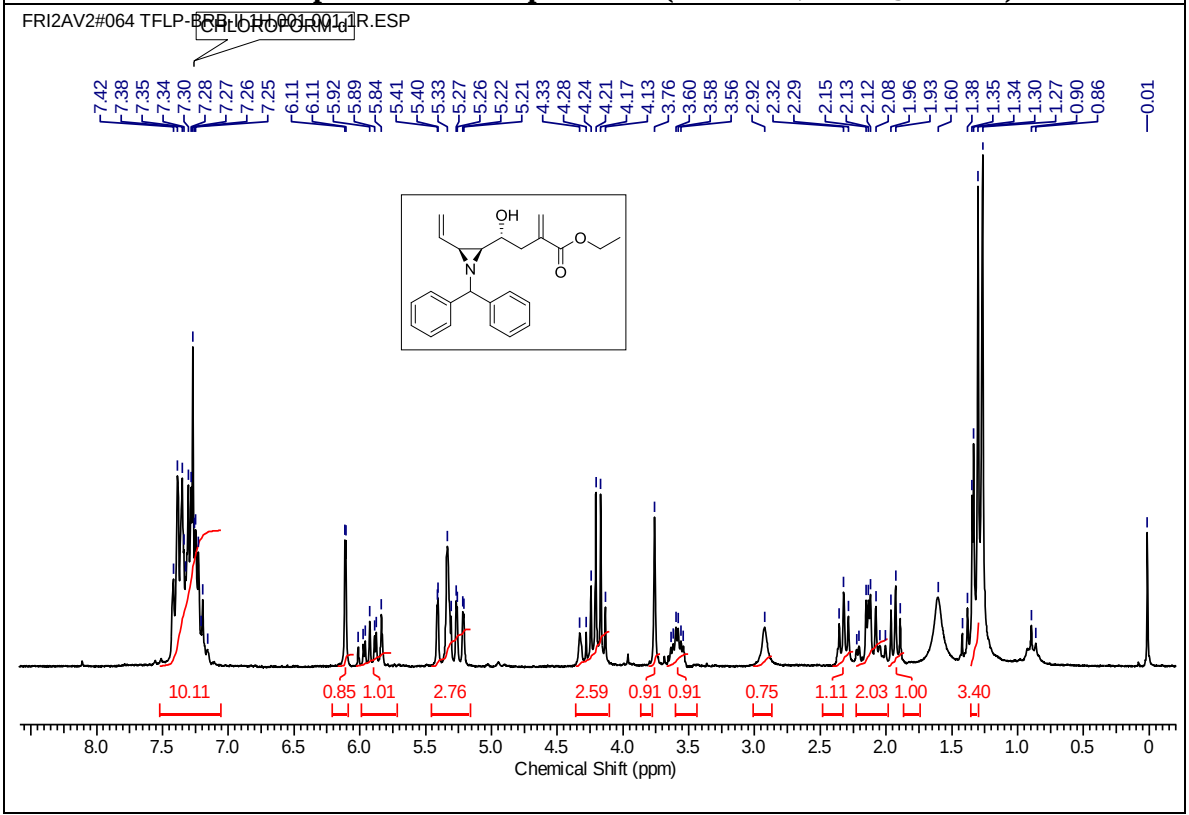
^{13}C NMR spectrum of compound 3 (100 MHz, $CDCl_3$ + CCl_4)



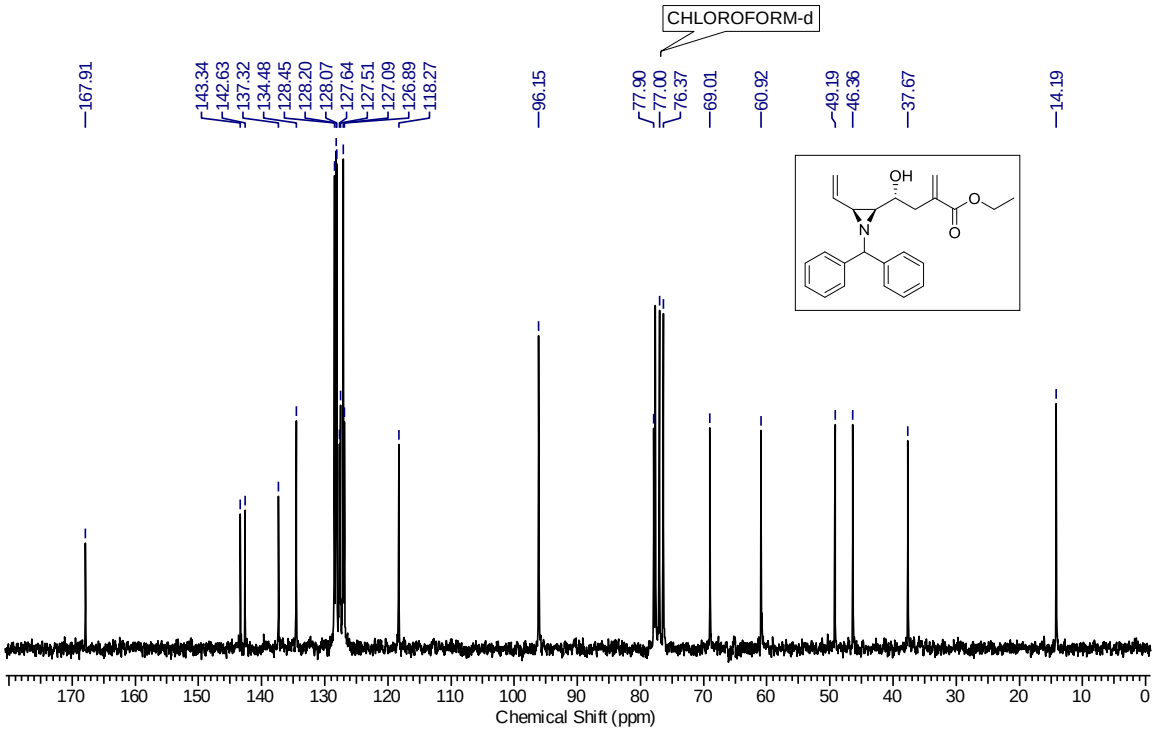
^{13}C NMR spectrum of compound 3 (100 MHz, $CDCl_3$ + CCl_4)



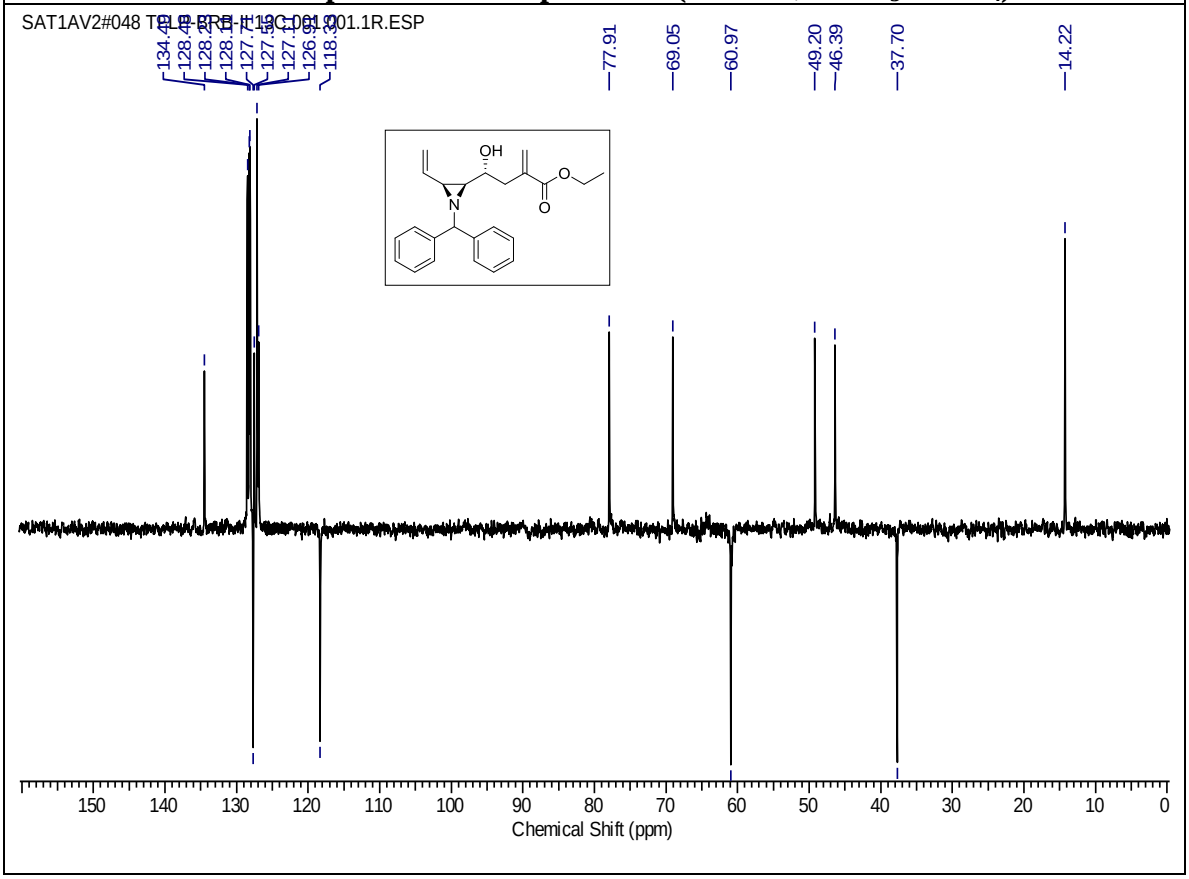
^{1}H NMR spectrum of compound 3a (200 MHz, $CDCl_3$ + CCl_4)



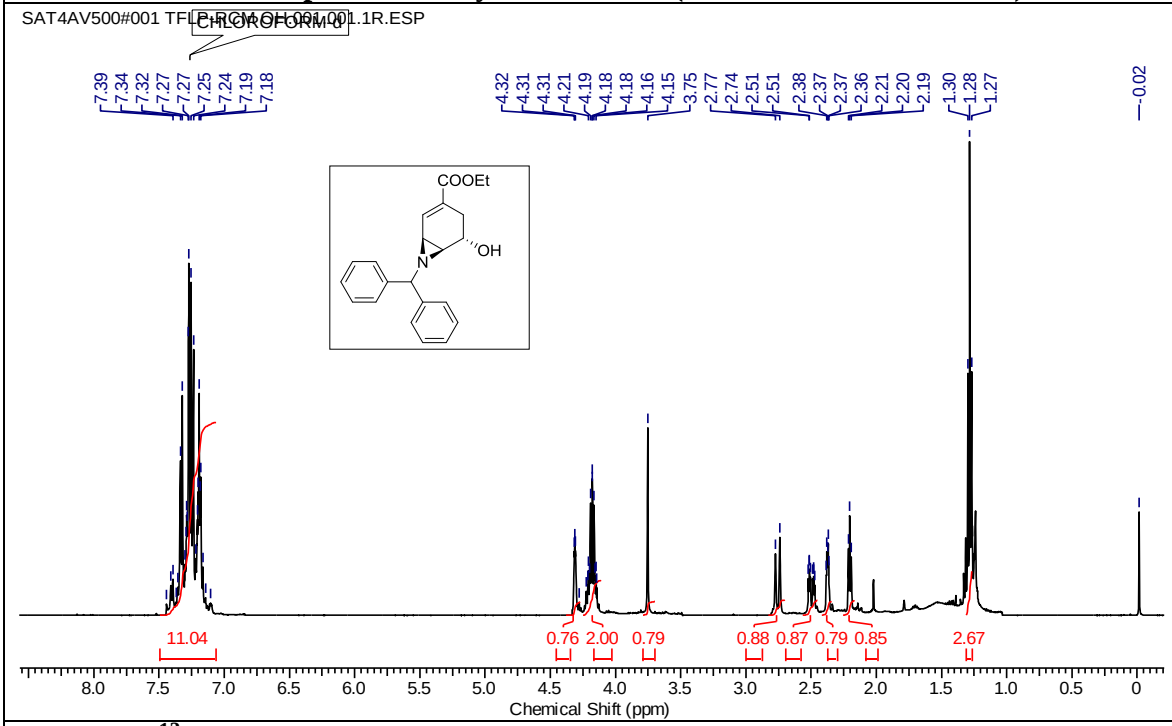
^{13}C NMR spectrum of compound 3a (50 MHz, $CDCl_3$ + CCl_4)



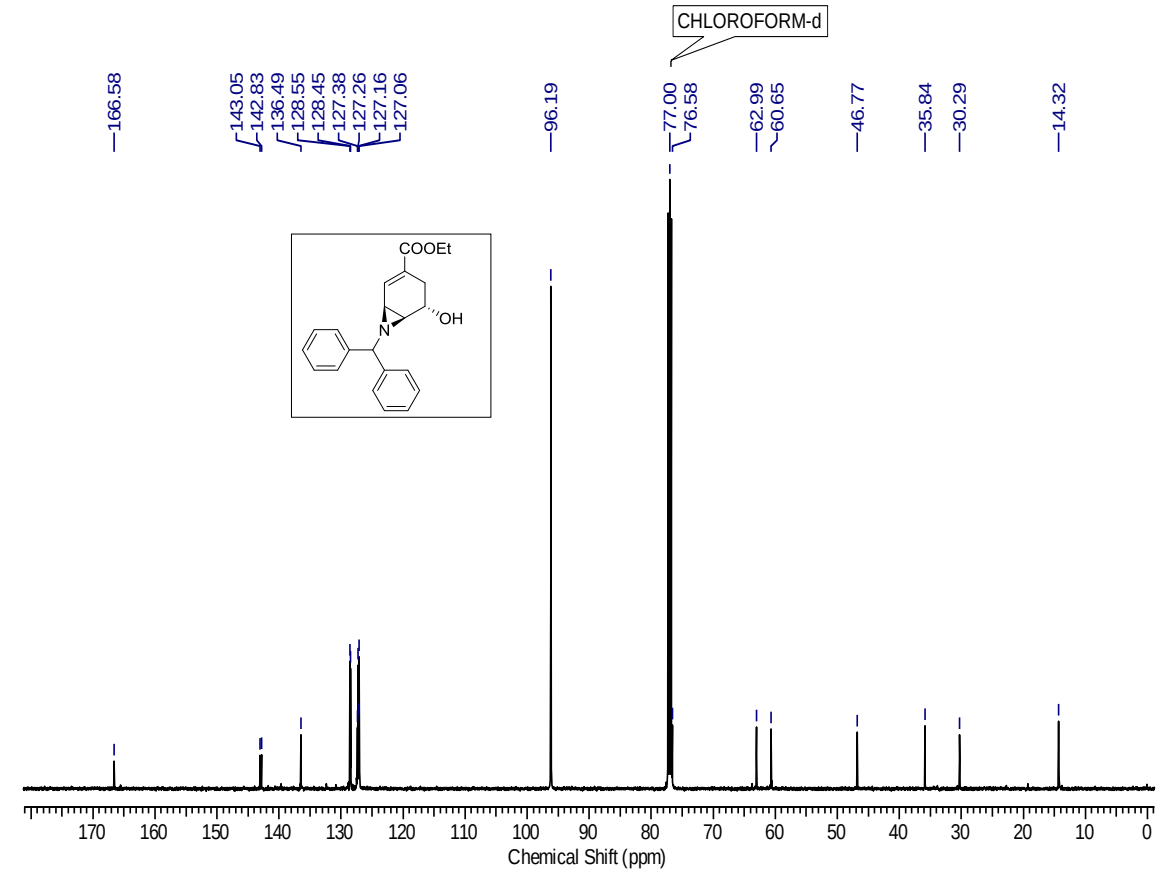
^{13}C NMR spectrum of compound 3a (50 MHz, $CDCl_3$ + CCl_4)



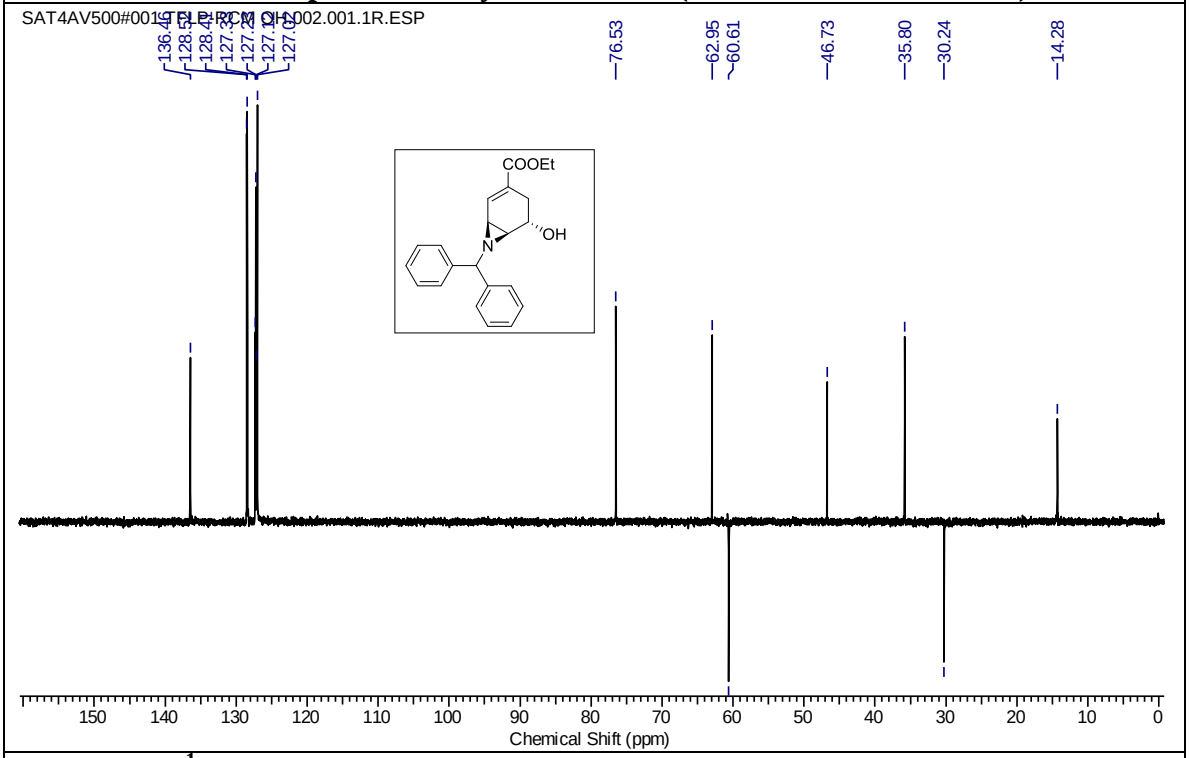
^{1}H NMR spectrum of cyclohexene 10 (500 MHz, $CDCl_3$ + CCl_4)



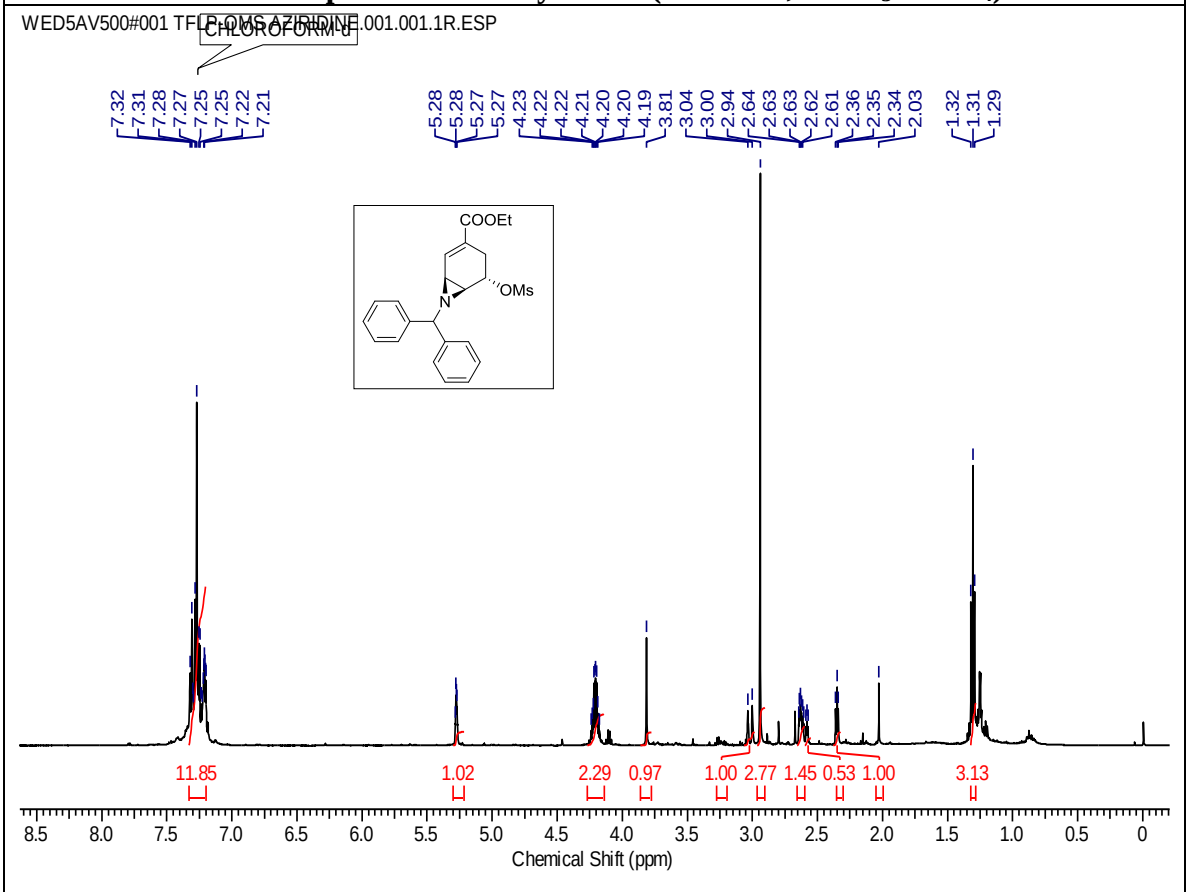
^{13}C NMR spectrum of cyclohexene 10 (125 MHz, $CDCl_3$ + CCl_4)



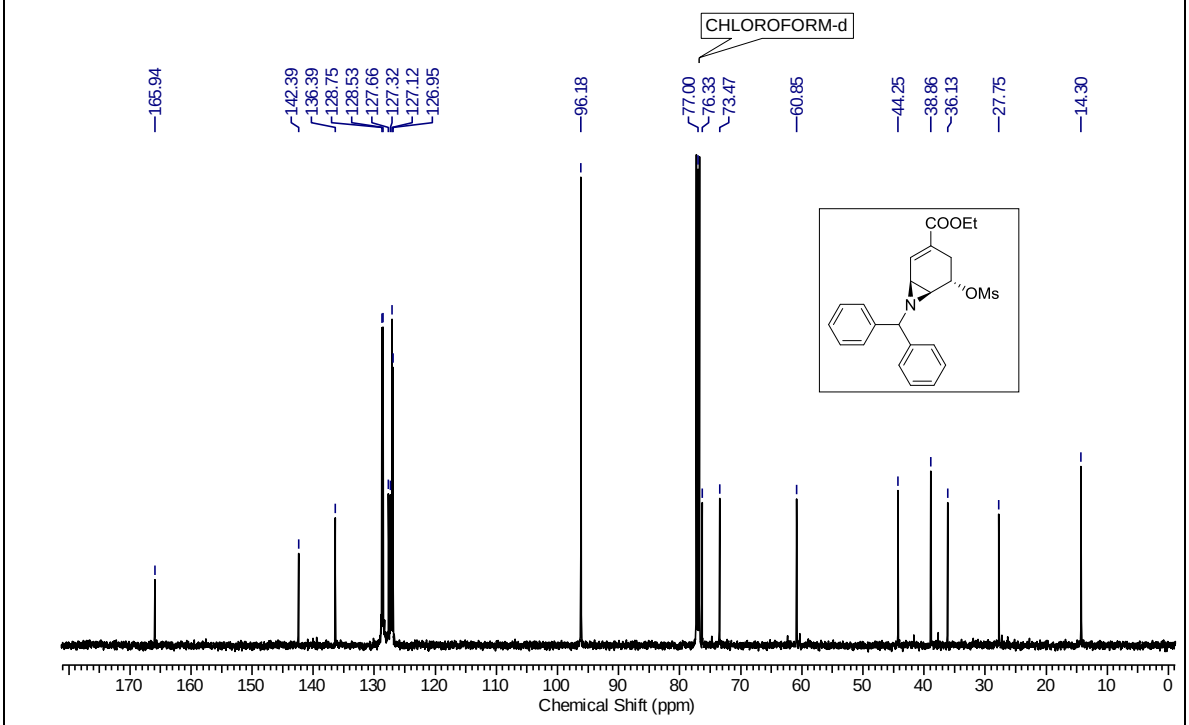
^{13}C NMR spectrum of cyclohexene 10 (125 MHz, $CDCl_3$ + CCl_4)



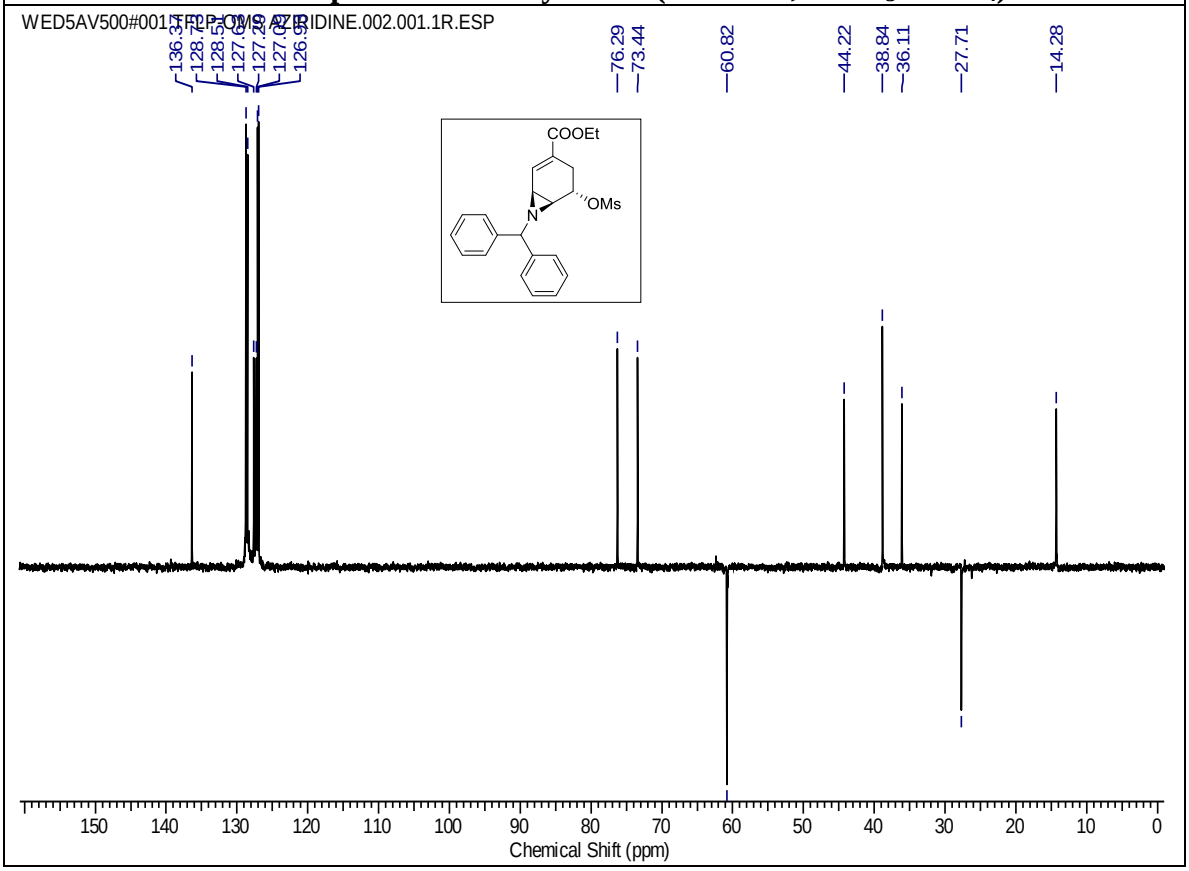
^{1}H NMR spectrum of mesylate 11 (500 MHz, $CDCl_3$ + CCl_4)



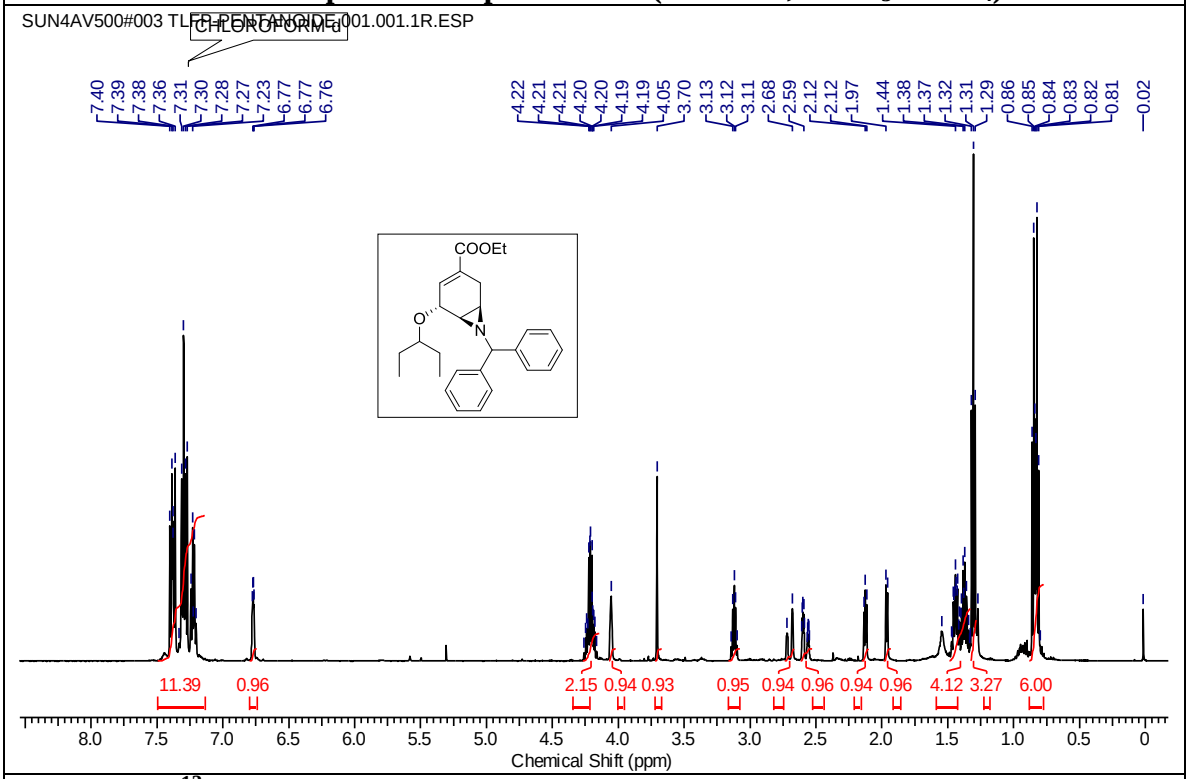
^{13}C NMR spectrum of mesylate 11 (125 MHz, $CDCl_3$ + CCl_4)



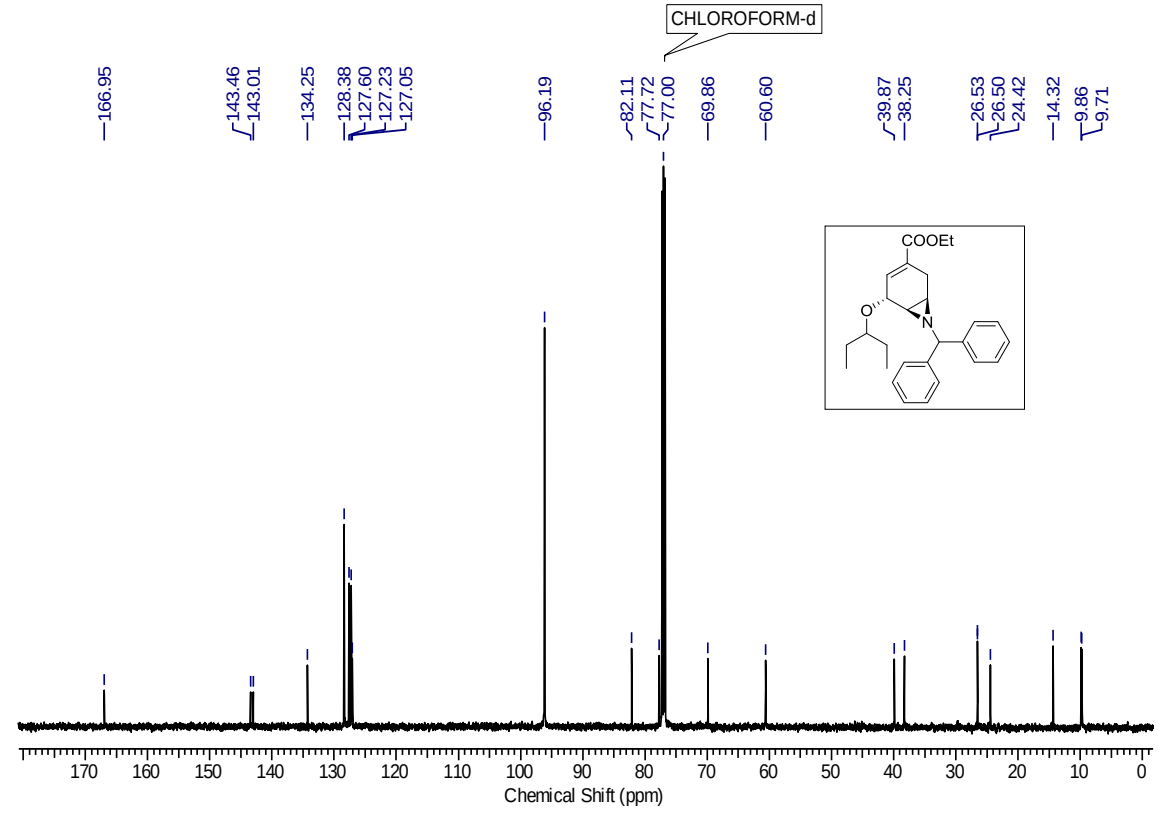
^{13}C NMR spectrum of mesylate 11 (125 MHz, $CDCl_3$ + CCl_4)



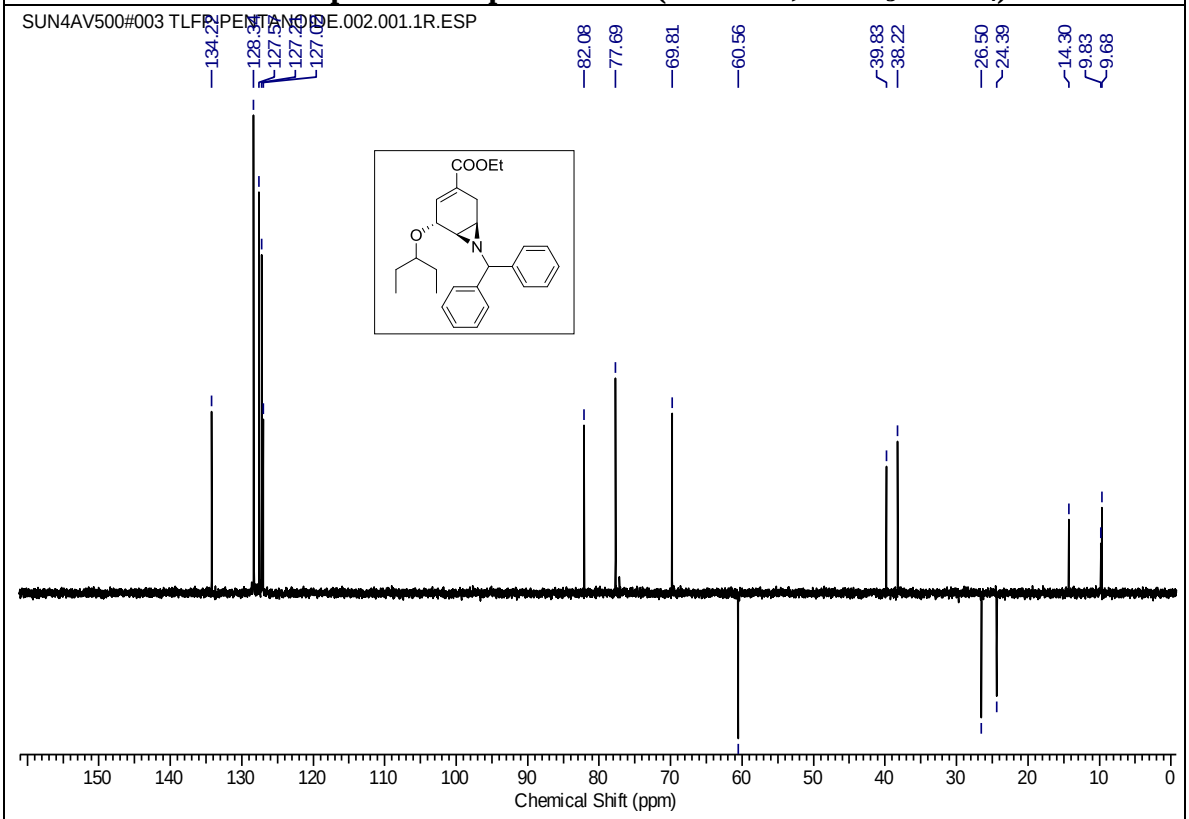
^{1}H NMR spectrum of pentanide 2 (500 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR spectrum of pentanide 2 (125 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR spectrum of pentanide 2 (125 MHz, $CDCl_3$ + CCl_4)



2.3.5 References

1) (a) Burch, J.; Corbett, M.; Stock, C. *Lancet. Infect. Dis.* **2009**, *9*, 537; (b) Magano, J. *Chem. Rev.* **2009**, *109*, 4398; (c) Magano, J. *Tetrahedron* **2011**, *67*, 7875.
2) Oh, H. Se.; Kang, H. Y. *J. Org. Chem.* **2012**, *77*, 8792.
3) (a) Stankovic, S.; Dhooghe, S.; Catak, M.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H. *J. Chem. Soc. Rev.* **2012**, *41*, 643; (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
4) Khairnar, L. B. *Ph.D. Thesis*, **2012**, Pune University, INDIA.
5) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.
6) (a) Wittig, G.; Schollkopf, U. *Chemische Berichte* **1954**, *87*, 1318; (b) Wittig, G.; Haag, W. *Chemische Berichte* **1955**, *88*, 1654; (c) Tapolcsanyi, P.; Wolfling, J.; Mernyak, E.; Schneider, G. *Monatshefte fur Chemie* **2004**, *135*, 1129.
7) Poon, K. W. C.; Lovell, K. M.; Dresner, K. N.; Datta, A. *J. Org. Chem.* **2008**, *73*, 752.
8) (a) Barbier, P. *Compt. Rend.* **1899**, *128*, 110; (b) Rawat, V.; Dey, S.; Sudalai, A. *Org.*
9) *Biomol. Chem.* **2012**, *10*, 3988.
10) Trnka, T. M.; Grubbs, R. H. *Accounts of Chemical Research* **2001**, *34*, 18.
11) Ishiwata, K.; Terashima, S.; Ujita, K. *EP1229022 B1* or *EP1229022 A4* or *EP1229022 A1*, Aug 7, **2002**.
12) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H. W.; Zhang, L. J.; Chen, X. W.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem*. **1998**, *41*, 2451.

Chapter 3

Synthetic studies towards Biotin

Section 1

Introduction to Biotin

3.1 Introduction of Biotin

3.1.1 Introduction

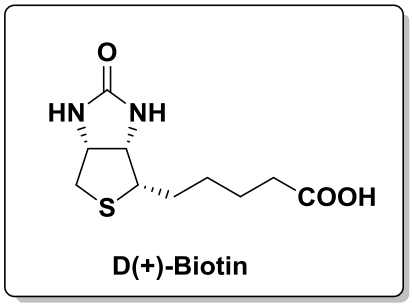


Fig 1: Biotin 1

Biotin is also known as Vitamin-H or coenzyme, which is very important component of all living cells. It was first isolated from the egg yolk in 1936 as growth factor for yeast. [1] A few years later it was also isolated from beef liver [2] and from milk concentrate.[3] First total synthesis and structural confirmation of biotin have been reported by Merck. It has unusual fused bicyclic skeleton of ureido and tetrahydrothiophene ring with valeric acid as side chain. It also possesses three contiguous chiral centers on thiophene ring and all are cis to each other.

Commonly biotin is consumed from a wide range of food in the diet. The rich sources with high contents of biotin are Swiss chard, raw egg yolk, liver, Saskatoon berries, leafy green vegetables and peanuts. Biotin is also provided in supplementary form and found in most pharmacies. Biotin plays very important role in some biological processes like fatty acid synthesis, branched chain amino acid catabolism and glucogenesis.

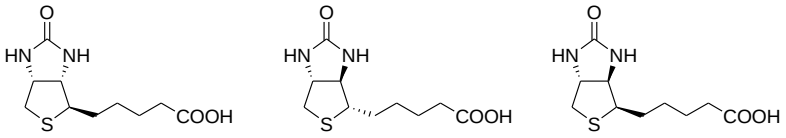
The symptoms of biotin deficiency are hair loss, which includes loss of eyelashes and eyebrows as well as weak, brittle nails. Its deficiency is very rare and mild and could be tackled by supplementation. Due to its academic and commercial importance it attracts attention of synthetic chemists and biologists.

3.1.1.1 Structure determination

In 1941 the empirical formula of the biotin was established as $C_{10}H_{16}N_2O_3S$ and just after

one year in 1942 full structure was reported by du Vigneaud.[4, 5] The structure of the biotin was confirmed by first total synthesis in Merck Laboratories by Harris and coworkers in 1945.[6] Later on after more than two decades the absolute configuration was established by using X-ray crystallographic analysis.[7]

Biotin contains two five membered rings fused together (ureido and thiophene ring) and it has three contiguous chiral centers, therefore totally four diastereomeric racemic forms are possible i.e. (+)-biotin, *epi*-biotin, *allo*-biotin and *epi*-*allo*-biotin and their enantiomeric forms. Among these strereomeric forms only D-(+)-biotin is naturally occurring, biologically active compound and other forms are biologically inactive isomers.



***epi*-Biotin 1A** ***allo*-Biotin 1B** ***epi-allo*-Biotin 1C**

Fig 2 Possible diastereomers of biotin

The crystal structure of the biotin was determined by two groups in 1976 and was in accurate agreement with previous one reported. [8] According to the data, the ureido ring is planar in nature and thiophene ring is in the envelope form. In the solution also the thiophene ring exists in envelope form which was shown by Glassel and Marquet.[9] The valeric acid side chain is not observed totally in extended form but is found twisted and there is a strong interaction between C6 and N3.

3.1.1.2 Biosynthesis

Biotin is sulphur-containing heterocyclic monocarboxylic acid. The fungi and bacteria synthesize biotin by metabolic pathway, which has been thoroughly investigated. Biotin is made from alanine and pimeloyl-CoA precursors *via* three enzymes by classical biochemical reactions. [10-13] The pimeloyl-CoA could be produced by a modified fatty acid pathway from the malonyl thioester. The 7,8-diaminopelargonic acid (DAPA) amino transferase is unusual in using S-adenosyl methionine (SAM) as the NH_2 donor. The ureido ring formation is catalysed by dethiobiotin synthase *via* DAPA carbamate

activated with ATP. The last step of the biosynthesis involves the conversion of dethiobiotin to biotin. Marquet and coworkers solved the clarification of the mechanism for the conversion of dethiobiotin to biotin. Biotin synthase reductively cleaves S-adenosyl methionine (SAM) into a deoxyadenosyl radical, a first radical formed on dethiobiotin is trapped by the sulfur donor, which was found to be the iron-sulfur (Fe-S) center contained in the enzyme. The recent study clearly demonstrated that the C4 pro hydrogen of dethiobiotin is replaced by the sulfur at C3 with the retention of the configuration.

3.1.1.3 Biotin deficiency

The biosynthesis of biotin is done by the intestinal flora and its deficiency is very rare and mild, which is due to consumption of two or more of the several raw egg whites. The avidin protein binds extremely strongly to the biotin making it unavailable. The symptoms can be reversed by giving biotin in 150-300 μg/dose as per requirement. Recently in a small number of young children genetic defect in biotin metabolism has been found, which is due to carboxylase deficiency dependent on biotin. Johnson *et al* reported that diet which is biotin deficient led to sudden unexpected death of young broiler chickens when exposed to stress. The low level of biotin in liver led to disorder in chickens. In condition of biotin insufficiency a similar disorder, triggered by mild stress may occur in the human infants. By the radiochemical technique, biotin content of 204 livers obtained from infants at autopsy was measured. The level of biotin in liver of infants died was significantly lower than those in livers of infants of similar age died of explicable cause.

In poultry, biotin is needful vitamin for normal growth, feed conversion and reproduction as well as healthy skin, feathers and bones. Biotin deficiency in poultry led to slow growth rate, impaired feed conversion, decreased feed intake, perosis and leg-weakness, poor feathering and dermatitis. In broilers, biotin deficiency causes breast blisters, fatty liver and kidney syndrome, parrot beak and death. Swine suffered from the biotin deficiency causes reduced growth rate, hair loss, dermatitis, furry tongue, food tensions, stiff-legged gait, squatness and hind-leg spasms.[14] Recovery from the deficiency of biotin is done by taking biotin as a feed additive for poultry and swine.

3.1.1.4 Uses

Biotin is used in pharmaceutical preparation of ointments, tonics *etc*. it's essentially used in poultry for the rapid growth of chicks and healthy hatching of eggs.

In recent years a use of strong biotin avidin complex has emerged in biochemistry as an important and versatile method for isolation, localization, and immunoassay, drug delivery.[15a] It has been recently recognized that biotin finds use in cosmetic [15b] and it is administered orally for brittle nails and hair fall.

Avidin-Biotin system in immunochemistry [16]

One of the most useful interactions in immunochemistry involves the specific binding of water-soluble vitamin: biotin, to the egg white protein avidin. Avidin is a tetramer consisting of four identical subunits of molecular weight 15,000. Each subunit has a high affinity binding site for biotin with a dissociation constant of approximately 10-15 M. This binding is unaffected at extreme pH of buffer salts or even chaotropic agents, such as guanidine hydrochloride (up to 3 M). Due to the strength of the avidin and biotin interaction, the researcher used it as a unique tool in immunoassays, receptor studies, and immunocytochemical staining and protein isolation.

This avidin-biotin system is perfectly useful for binding or sandwich system for association of antigen-antibody interaction. The biotin molecule can be easily activated and coupled with either antigens or antibodies, usually with complete retention of activity. Subsequently avidin can be conjugated with enzymes, fluorochromes, ferritin or colloidal markers and used as high affinity secondary reagents, which can increase the sensitivity of an assay. In addition, since only one conjugate preparation is required for many different assays, the avidin-biotin system can be very attractive for use in immunological procedures. The following are some of the biotin derivatives in use.

Biotin derivatives as gelators of organic solvents [17]

Gelling compounds are useful in recovery of spilled oil, disposal of used cooking oil and in drug delivery. These compounds have ability to form stable gels with a variety of organic solvents.

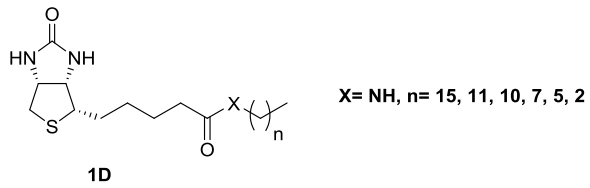


Fig 3

Biotin derivatives as anti HIV protease inhibitors [18]

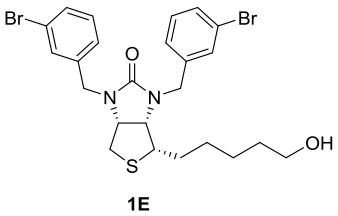


Fig 4

Biotin based bis-*N*-alkylated derivatives were synthesized and evaluated for activities against HIV-1 protease. Derivative **1E** is most potent inhibitor, it has Ki of 0.50 mM and antiviral IC90 of 7mM. The (+)-biotin analogues have good translations from enzymic Ki to antiviral cell assay IC90. The biotin derivatives are used for the different applications *eg*. *N*-hydroxyl succinimidobiotin as a sulfosuccinimidobiotin, N-iodoacetyl-N-biotinylhexylenediamine, biotinhydrazide, immobilized biotin and biotin cellulose.

3.1.2 Literature Review

Biotin consists of a bi-heterocyclic core and a carboxybutyl side chain. The heterocyclic system comprises of a cyclic urea and a tetrahydrothiophene ring. Biotin has three contiguous stereocenters and all are in *cis* fashion on thiophane ring.

A continuous endeavor over a period of more than 60 years has now resulted in more than 40 original contributions on the total synthesis of biotin. Many of the earlier syntheses known were lengthy which involve number of steps, without any stereochemical control. Then there was a drought of published information for about 20 years when no significant progress in biotin synthesis was made. However, the recent recognition of the importance of biotin in poultry, biochemistry, supplementary for diabetes patient and pharmaceutical formulations, revived the interest in this molecule

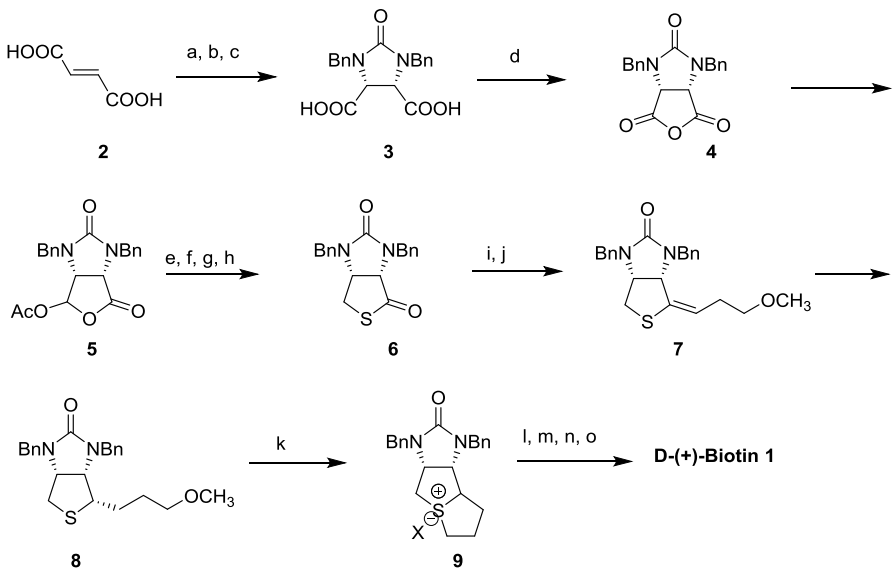
and it is evident from a boom in number of international patents published on biotin (around 50) between 1970-2000. The above figure excludes the application of biotin in biochemistry and related subjects.

The synthesis of biotin has been extensively reviewed by R. B. Tejwani, Amar Gopal, Ramakrishna G and (Ms) Soni P. B. of this laboratory in their theses; [19] as well as is reviewed by De Clercq in 1997 [20] and current section outlines some of the elegant attempts of biotin synthesis.

Hoffmann-La Roche's lactone-thiolactone approach (*Pat*. 2, 489232, Nov. 22, **1949**; *Chem. Abstr.* **1951**, *45*, 184) [21, 22]

Goldberg and Sternbach reported the first total synthesis of (+)-biotin **1** in 1946 from the fumaric acid as cheap, inexpensive and economical starting material as outlined in the Scheme 1.

Fumaric acid **2** was converted to the cyclic anhydride **4** in four steps which involved bromination of fumaric acid to give meso-dibromosuccinic acid, double substitution of latter with benzyl amine, treatment phosgene in alkali and anhydride **4** formation upon treatment of **3** in $(Ac)_2O$. Anhydride **4** was reduced in presence of acetic acid to give



Scheme 1

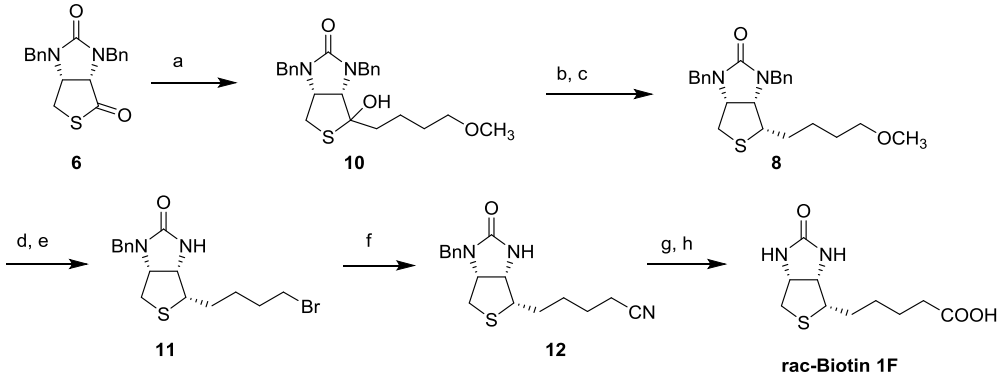
Reagents and conditions: *(a) Br_2; (b) $PhCH_2NH_2$, EtOH; (c) $COCl_2$, KOH; (d) Ac_2O; (e)*

Zn, Ac_2O, HOAc; (f) H_2S, HCl; (g) KSH, EtOH; (h) Zn, HOAc; (i) $ClMg(CH_2)_3OCH_3$; (j) HOAc; (k) H_2, cat.; (l) HBr; (m) Silver D-camphorsulfonate, followed by fractional crystallization; (n) $NaCH(COOEt)_2$; (o) 48% HBr.

compound **5**, which on treatment with H_2S followed by reduction with Zn furnished thiolactone **6**. Thiolactone **6** on Grignard addition underwent dehydration to afford olefin **7**. The catalytic reduction of olefin **7** provided compound **8** with the all C2, C3 and C4 in *cis* fashion. The ether **8** on treatment with HBr gave thiophanium salt **9**, which was resolved with camphorsulfonate followed by two steps sequence afforded D-(+)-biotin **1**.

Hoffmann-La Roche's 2nd approach (*US Pat.* 2,489235, Nov. 22, **1949**; *Chem. Abstr.* **1951**, *45*, 186**)** [23]

Goldberg and Sternbach have reported the modified synthetic strategy for biotin from the thiolactone **6** shown in the Scheme 2. Thiolactone **6** was treated with Grignard reagent of 4-methoxybutyl bromide to form alcohol **10**, which was subjected to the dehydration followed by the catalytic hydrogenation to provide compound **8**. Bromide **11** was obtained from compound **8** by mono-debenzylation with Na/liq ammonia and hydro bromic acid treatement to furnish bromide **11**. The bromide **11** was converted into rac-biotin **1F** by a reaction sequence involving nucleophilic displacement of bromide with KCN, followed by basic hydrolysis and subsequent Na/liq NH_3.



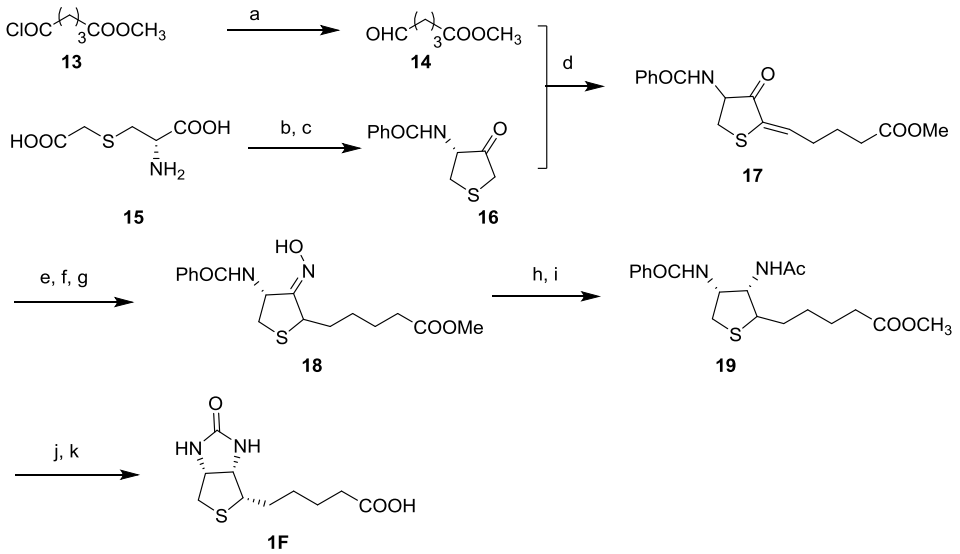
Scheme 2

Reagents and conditions: *(a) $CH_3O(CH_2)_4Br$, Mg, ether, PhH; (b) HOAc, reflux; (c) H_2,*

Pd/C, MeOH; (d) Na, liq NH_3; (e) HBr, HOAc, 90 °C; (f) KCN, H_2O; (g) NaOH, H_2O/MeOH; (h) Na, liq NH_3.

Easton approach (*J. Am. Chem. Soc.* **1944,** *70*, 1756**)** [24]

Easton *et al* in 1944 reported the synthesis of biotin **1F** which is summarized in Scheme 3, which involved L-cystine and chloroacetic acid as the starting materials. The L-cystine was treated with Na/liq NH_3 and coupled with chloroacetic acid to furnish amino acid **15**. Acid **15** was benzoylated and on esterification in MeOH/HCl furnished ester, which was treated with NaOMe and the sodium salt thus obtained was hydrolyzed and decarboxylated in AcOH/HCl/H_2O to furnish compound **16**. Chloride **13** was obtained from the glutaric acid *via* anhydride formation followed by conversion into monoester acid and subsequently to its corresponding acid chloride **13**. The resultant acid chloride **13** on Rosenmund reduction afforded aldehyde **14**. The crude aldehyde **14** was condensed with ketone **16** to afford ketone ester **17** and was converted to its oxime with NH_2OH followed by reduction with zinc dust in Ac_2O/AcOH to give compound **19**. The ester **19** on reduction with Pd-H_2, hydrolysis using $Ba(OH)_2$, subsequent H_2SO_4 treatment and reaction with phosgene gave *rac*-biotin **1F**.



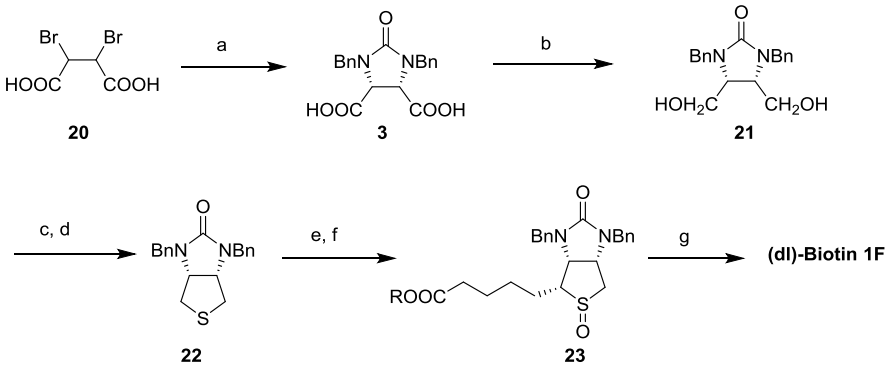
Scheme 3

Reagents and conditions: *(a) Pd, H_2; (b) BzCl then MeOH, HCl; (c) NaOR; (d) HCl, H_2O, HOAc, (e) Pd, H_2; (f) Piperidine, HOAc; (g) NH_2OH, py; (h) Zn, HOAc, Ac_2O; (i)*

Pd, H_2; (j) $Ba(OH)_2$ then H_2SO_4; (k) $COCl_2$, $NaHCO_3$.

Marquet's approach (*Tetrahedron Lett*, **1975**, 827, *J. Am. Chem. Soc*. **1978**, *100*, 1558**)** [25]

The Marquet's group reported a conceptually simple total synthesis of rac-biotin **1F** that is based on the stereoselective alkylation of sulfoxides as shown in Scheme 4. The synthesis started with the dibromo-fumaric acid **20** which was converted into diacid **3** *via* reaction with benzylamine followed by phosgene treatement to provide acid **3**. Acid **3** in four step reaction sequence was converted to sulfide **22** in high yield. The sulfide **22** this was oxidized with $NaIO_4$ to a diastereomeric mixture of sulfoxide with *trans* isomer predominating and subjected to reaction with *tert*-butyl W-iodovalerate in presence of MeLi/HMPA to furnish a single stereoisomer **23**. The compound **23** was converted into rac-biotin **1F** in a three step sequence involving reduction of sulfoxides ester hydrolysis followed by debenzylation by refluxing in HBr.



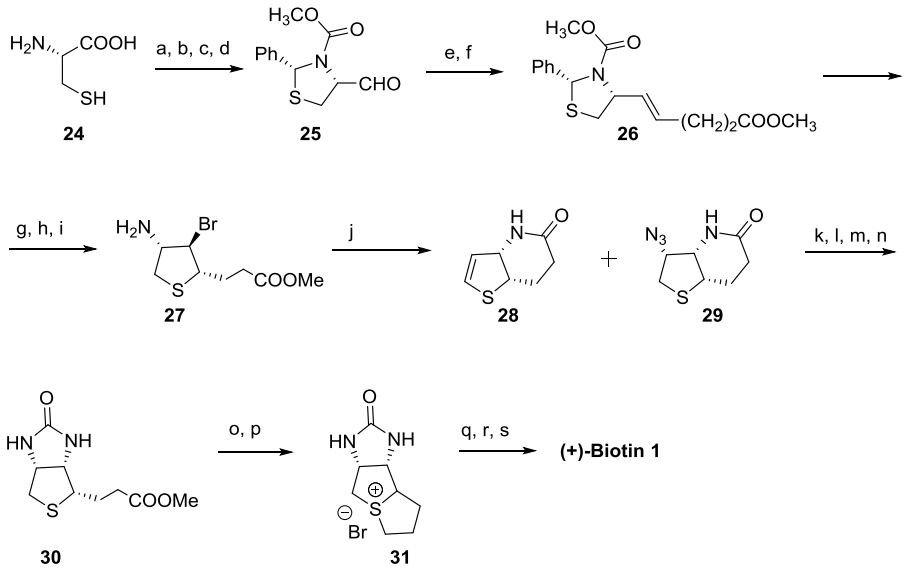
Scheme 4

Reagents and conditions: *(a) ref 21; (b) $LiAlH_4$, THF; (c) MsCl, DCM, TEA; (d) Na_2S; (e) $NaIO_4$; (f) MeLi, THF, $I(CH_2)_4COOtBu$; (g) $TiCl_3$, H^+.*

Confalone approach (*J. Am. Chem. Soc.* **1975**, *97*, 5936**)** [26]

Confalone and co-workers reported an interesting approach in which bromination of olefin **26** resulted in a stereospecific rearrangement as depicted in Scheme 5. L-cystine **24** was converted into aldehyde **25** which on Grignard addition and treatment with trimethyl orthoformate in propionic acid resulted into olefin **26**. The stereospecific bromination of olefin **26** with Py.HBr salt was provided stereospecific sulfide **27** in good yield. The sulfide **27** was refluxed in acetic acid and LiN_3 treatment afforded bromo eliminated

compound **28** and azide **29** in 4:1 ratio respectively. The azide **29** in nine additional steps was converted into biotin **1** which involved thiophanium bromide **31** as intermediate.

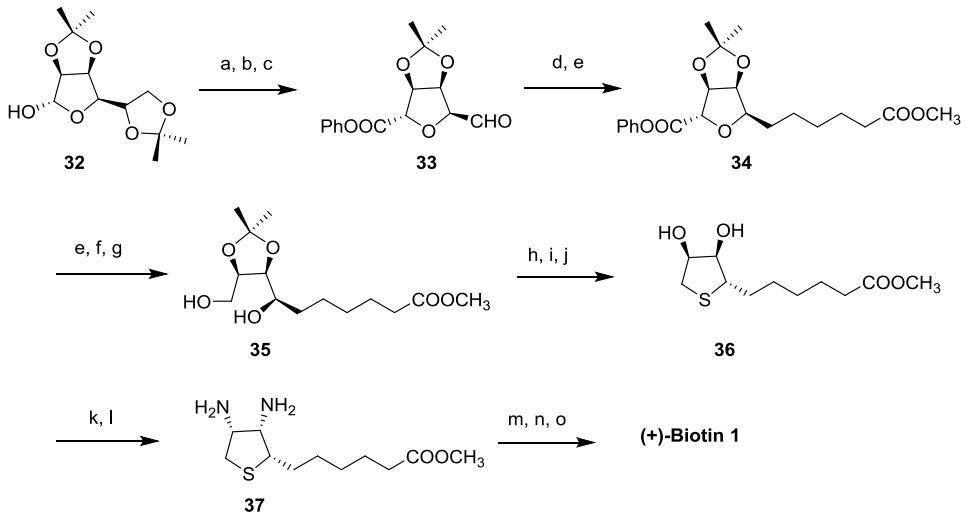


Scheme 5

Reagents and conditions: *(a) PhCHO; (b) $ClCOOCH_3$; (c) BH_3, THF, 25 ^oC; (d) CrO_3.pyridine; (e) $ClMgCH_2=CH_2$, DCM, -70 ^oC; (f) $HC(OMe)_3$, CH_3CH_2COOH, PhH, 85 ^oC; (g) $C_5H_5NHBr.Br_2$, MeOH; (h) HBr, HOAc, 25 ^oC, 20 h; (i) HOAc, reflux, 3 h; (j) LiN_3, DMF, 140 ^oC, 3.5 h; (k) Catalytic hydrogenation; (l) $Ba(OH)_2$, reflux, 20 h; (m) $COCl_2$, $NaHCO_3$, H_2O; (n) MeOH, H^+; (o) $LiBH_4$, THF, reflux; (p) HBr, HOAc, reflux; (q) $NaCH(COOEt)_2$, (r) $Ba(OH)_2$; (s) H_2O, reflux.*

Ohrui's approach (*Tetrahedron Letters* **1975**, 2765) [27]

Ohrui and Emoto started the series in 1975 which as summarized in Scheme 6. The di-*O*-isopropylidene protected R-D-mannofuranose **32** was subjected to benzoate formation of anomeric alcohol. Selective hydrolysis of the 5, 6-isopropylidene group, followed by oxidative cleavage resulted into aldehyde **33**. The aldehyde **33** subsequently on Wittig reaction and catalytic hydrogenation afforded **34**. The ester **34** on treatment with MeOH in presence of base generated hemiacetal, which was reduced to diol **35**. Thiophane formation and hydrolysis of **35** led to diol **36**, which was converted to diamine **37** using inversion protocols. Finally amine **37** was converted to (+)-biotin **1** on basic hydrolysis followed by treatement with phosgene.

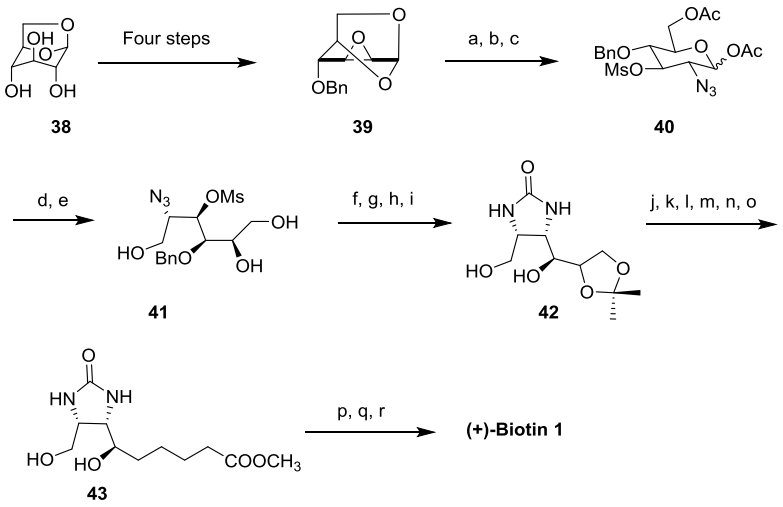


Scheme 6

Reagents and conditions: *(a) PhCOCl, py; (b) HOAc, H_2O; (c) $NaIO_4$, CH_3COCH_3/H_2O; (d) $Ph_3PCHCH_2CHCHCOOCH_3$, DCM; (e) H_2, Pd/C, MEOH; (f) $NaOCH_3$, MeOH; (g) $NaBH_4$; (h) CH_3SO_2Cl; (i) Na_2S, HMPA, 100 ^oC; (j) 90% HCOOH, 20 ^oC; (k) CH_3SO_2Cl; (l) NaN_3, HMPA, 80 ^oC; (m) PtO_2, $MeOH/Ac_2O$; (n) $Ba(OH)_2$, H_2O, 140 ^oC; (o) $COCl_2$.*

Ogawa's approach (*Carbohydrate. Res.* **1977**, *57*, C31)[28]

Ogawa and co-workers reported the approach towards biotin starting from D-glucose as per Scheme 7. Glucose was converted to triol **38**, which on the four-step reaction sequence resulted into compound **39**. The compound **39** was reacted with NaN_3 followed by mesylation afforded the corresponding mesylate, which on treatement with acetic anhydride in presence of $BF_3.Et_2O$ furnished to azide **40**. The azide **40** was subjected for the acidic hydrolysis in HCl/MeOH and $NaBH_4$ reduction to give **41**. For introduction second nitrogen, compound **41** was reacted with dimethoxypropane and then treated with LiN_3, followed by Lindlar reduction and treatment with phosgene to provide urea **42**. This on six-step transformation provided diol **43**. The sulfur was introduced by dimesylation of diol **43**, followed by Na_2S and treatment with base to furnish (+)-biotin **1**.

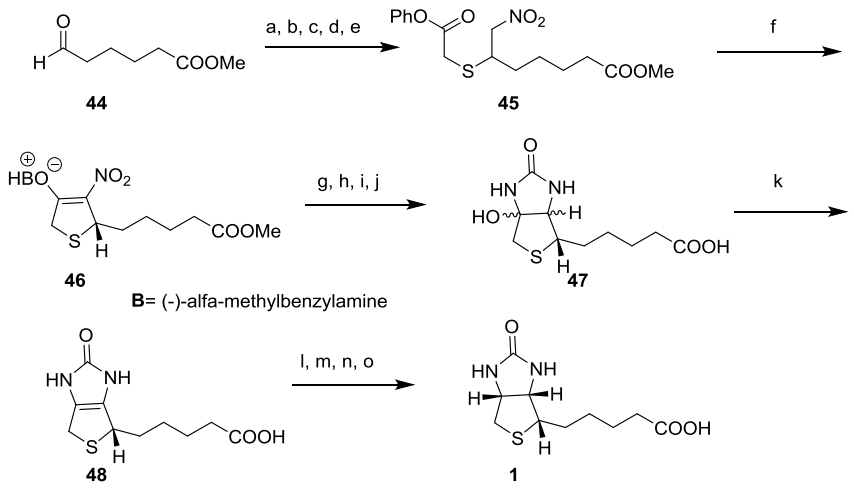


Scheme 7

Reagents and conditions: *(a) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH/H_2O$, 120 °C; (b) MsCl; (c) $BF_3.Et_2O$, Ac_2O; (d) HCl, MeOH; (e) $NaBH_4$, $B(OH)_3$, EtOH; (f) $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH; (g) LiN_3, DMF, 80 °C; (h) H_2, Lindlar, EtOH; (i) $COCl_2$; (j) Ac_2O, py; (k) $AcOH/H_2O$, 70 °C; (l) $NaIO_4$, $EtOH/H_2O$; (m) $Ph_3PCHCHCHCOOCH_3$, DCM; (n) H_2, Pd/C, MeOH; (o) CH_3ONa, MeOH; (p) CH_3SO_2Cl, C_5H_5N, -10 °C; (q) Na_2S, DMF, 100 °C; (r) NaOH.*

White and co-workers approach (*J. Am. Chem. Soc.* **1978**, *100*, 7423-7424**)** [29]

The interesting feature of White and coworker's synthesis is that they avoided diastereomer formation problem which was earlier encountered and described in Scheme 8. Aldehyde **44** on C-C bond formation reaction led to α-nitro ester, which on thioacetic acid treatment, salt formation with (-)-α-methylbenzylamine, treatment with dicyclohexylamine followed by reaction with thionyl chloride and phenol provided compound **45**. It was further reacted with (-)-α-methylbenzylamine leading to salt **46**. The urea ring was constructed from salt **46** by reduction of nitro group obtained amino ketone, which on treatment with KNCO followed by NaOH and acidic treatment provided compound **47**. The compound **47** was converted to (+)-biotin *via* treatment with acidic methanol followed by reaction with acetic anhydride, hydrogenation and basic hydrolysis to furnish **1**.

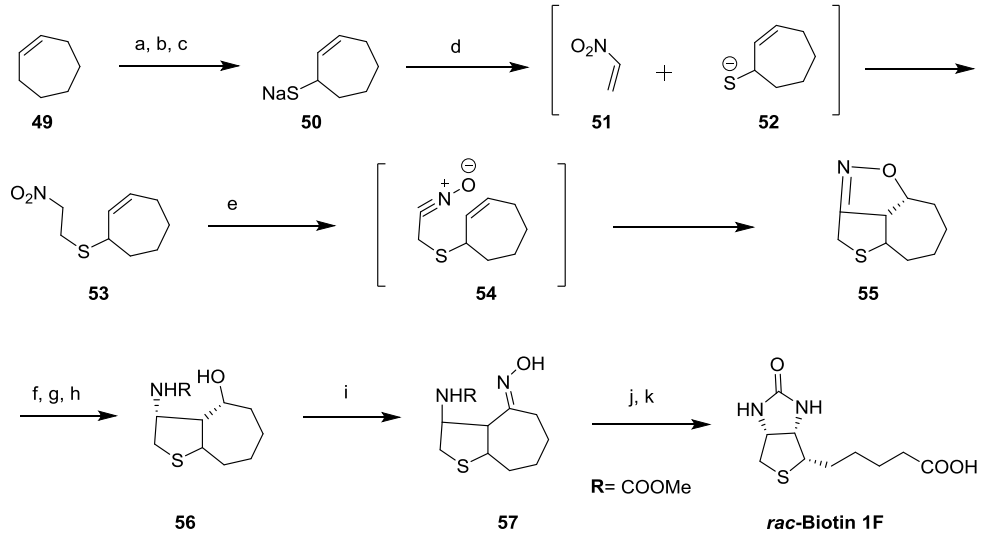


Scheme 8

Reagents and conditions *(a)CH_3NO_2; (b) $SHCH_2COOH$; (c) (+)-α-Methylbenzylamine ((+)-R-MBA), EtOAc; 30% yield, >97% ee after recrystallization; (d) Dicyclohexylamine; (e) PhOH, $SOCl_2$, pyridine (cat.); (f) (-)-α-Methylbenzylamine, EtOAc; (g) Pd/C (10%), HOAc/HCl; (h) KNCO, H_2O; (i) NaOH; (j)H^+; (k) HOAc, stripping at 55 °C; (l) MeOH, H^+; (m) Ac_2O, 110 °C; (n) H_2 (550 psi), 5% Pd/C (10% loading), Ac_2O, 85 °C; (o) NaOH, MeOH.*

Wilson's approach (*J. Am. Chem. Soc.* **1978**, *100*, 6291-6292**)** [30]

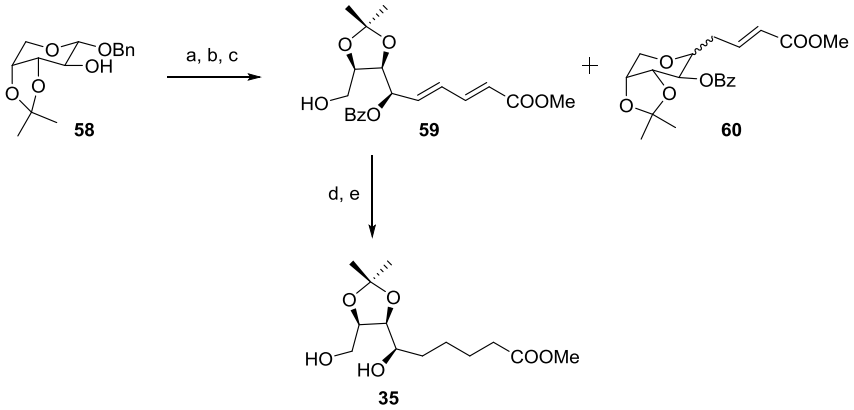
Wilson's approach involved the stereospecific cycloaddition of an olefinic nitrile oxide to provide amino alcohol **56** which is outlined in Scheme 9. Synthesis was started with cycloheptene **49**, which was converted to compound **50** by allylic bromination, displacement of bromo with thioacetic acid followed by treatment with NaOEt/EtOH to afford **50**. Mercaptide **50** was treated with 1-nitro-2-acetoxy ethane wherein nitroethylene **51** and mercaptanion **52** were generated insitu which underwent Michael addition to furnish sulfide **53**. The sulfide **53** was treated with phenyl isocyanate to form nitrile oxide **54** which underwent intramolecular [3+2] and cycloaddition resulted into stereospecific cycloadduct **55**. The compound **55** on LAH reduction and treatment with methylchloroformate afforded alcohol **56**. The alcohol **56** was converted to oxime **57** *via* oxidation of alcohol **56** to ketone followed by oxime formation with $NH_2OH.HCl$. The oxime **57** in few steps was converted to biotin **1F**.



Scheme 9

Reagents and conditions: *(a) NBS, AIBN, $CC1_4$, reflux, 1.5 h; (b) AcSH, CH_3CN, TEA, 0 ^oC, 3 h; (c) NaOEt/EtOH, reflux, 15 min; (d) $NO_2CH_2CH_2OAc$, EtOH, 0 ^oC, 3 h; (e) PhNCO, PhH, TEA (cat.), 25 ^oC, 24 h; (f) $LiAlH_4$, Et_2O, reflux, 4 h; (g) MeOH, CH_3OCOC1, 10% $NaHCO_3$, 25 ^oC, 0.5 h; (h) Me_2SO/Ac_2O (3:2), 25 ^oC, 18 h; (i) EtOH/Py (25:1), $NH_2OH.HCI$, reflux, 0.5 h; (j) PPA, 100 ^oC, 15 min; (k) $Ba(OH)_2$, H_2O, reflux, 20 h, $COCl_2$, 0 ^oC.*

Vogel's approach (*Liebigs Ann. Chem.* **1980**, 1972**)** [31]



Scheme 10

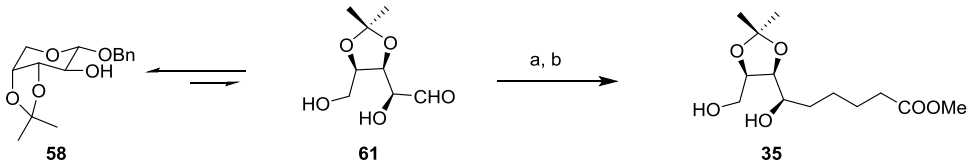
Reagent and conditions: *(a) PhCOCl, py; (b) H_2, Pd/C, dioxane; (c) $Ph_3PCHCHCHCOOCH_3$, DCM; (d) H_2, Pd/C; (e) $NaOCH_3$, MeOH (65% yield)*

Vogel and co-workers reported the synthesis of (+)-biotin by the use of D-arabinose as

starting material. The hemiacetal **58** was obtained from D-arabinose, which was subjected to Wittig olefination, reduction and benzoate removal which resulted in diol **35** in low yield, due to the formation of tertahydropyran **60** due to Michael addition of the free hydroxy group to unsaturated system of **59** (Scheme 10).

Schmidt's approach (*Synthesis* **1982**, 747) [32]

In 1982 the drawback in Wittig reaction of Vogel approach was overcome by Schmidt and Maier using the same starting material *i.e* D-arabinose as summarized in Scheme 11. The 3, 4-O-isopropylidine derivative **58** was obtained from D-arabinose. The dihydroxy aldehyde **61** form of compound **58** under Wittig reaction in presence of benzoic acid and catalytic hydrogenation afforded dihydroxy compound **35** in 39% yield.



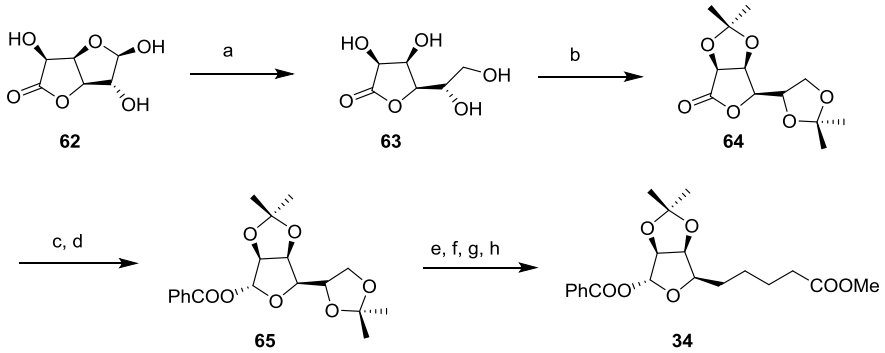
58 61 35

Scheme 11

Reagent and conditions: *(a) $Ph_3PCHCHCHCOOCH_3$, PhCOOH; (b) H_2, Pd/C.*

Ravindranathan's approach (*Carbohydr. Res.* **1984**, *134*, 332**)** [33]

A modified synthetic strategy for D-(+)-biotin from D-glucose was reported by Ravindranathan and co-workers in 1984 which is outlined in Scheme 12. The synthesis.



62 63 64 65 34

Scheme 12

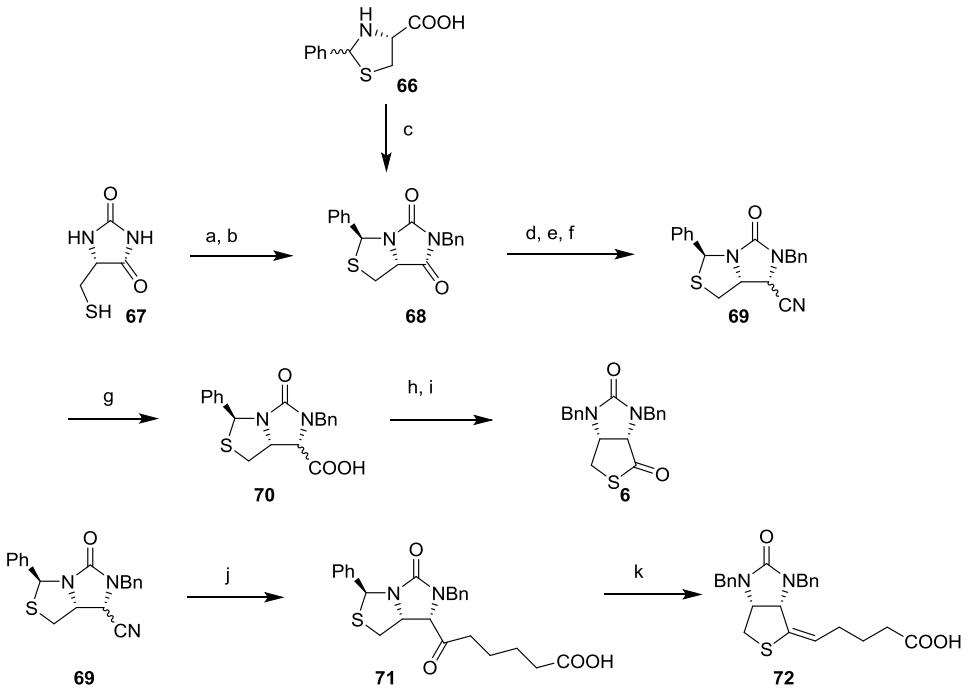
Reagents and conditions: *(a) H_2, Raney Ni; (b) $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH; (c)*

$NaBH_4$, MeOH, 0 ^oC; (d) PhCOCl, C_5H_5N; (e) MeOH, HCl; (f) $NaIO_4$, acetone/H_2O, 0 ^oC; (g) $Ph_3PCHCHCHCOOCH_3$, DCM; (h) H_2, Pd($NaBH_4$).

started from D-glucurono-6,3-lactone **62**, which was reduced to L-gulono-1,4-lactone **63**. Lactone **63** was subjected for the acetonide protection to result in formation of compound **64**, which on $NaBH_4$ reduction and treatement with benzoyl chloride/py resulted into diacetonide **65**. The diacetonide **65** in four steps was converted to ester **34** as an Ohrui intermediate for D-(+)-biotin.

Poetsch and Casutt's approach (*Chimia* **1987**, *41*, 148) [34]

Poetsch and Casutt have reported the shortest enantiospecific sequence to (+)-biotin and it involved synthesis of nitrile **69** as the crucial intermediate as shown in Scheme 13. Nitrile **69** was obtained from hydantoin **68**, which was obtained from acid **66** and thiol **67** in one and two steps respectively. Hydantoin **68** was converted to nitrile **69** via selective



Scheme 13

Reagents and conditions: *(a) PhCHO, $POCl_3$, $PhCH_3$; (b) $PhCH_2Cl$, K_2CO_3, DMF, 79%; (c) $PhCH_2NCO$, acetone, HCl, DCM, 85%; (d) $NaBH_4$, THF/H_2O; (e) 1,1'-*

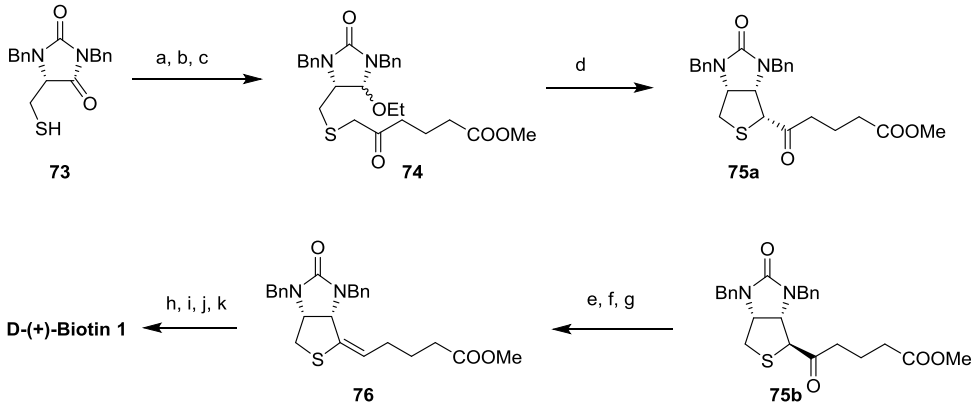
Carbonyldiimidazole, THF; (f) CH_3I, DMF; KCN, DMF, 78%; (g) KOH, EtOH, H_2O, 91%; (h) Zn, AcOH; (i) N,N'-Dicyclohexylcarbodiimide, py, p-TsOH; 70%; (j) $Br(CH_2)_4Br$, Mg, THF, CO_2, HCl, 65%; (k) Zn, AcOH; piperidine, AcOH, 70%.

reduction and cyanide introduction. Thiolactone **6** was obtained from nitrile **69** in two steps involving basic hydrolysis, and reductive cleavage to thiol acid, which was further cyclized to known thiolactone **6**.

The nitrile **69** was directly subjected to Grignard addition leading acid **71**, which was converted to biotin precursor **72** *via* reductive opening followed by treatment with piperidine acetate/AcOH provided olefin **72**.

Speckamp, Poetsch and Casutt's approach *(Angew. Chem. Int. Ed. Engl*. **1995**, 34) [35]

Speckamp, Poetsch and Casutt have reported jointly the intramolecular condensation of silyl enol ether with the *N*-acyliminium intermediate to effect the ring closure of sulfide **74** to thiophane nucleus **75a** and **75b** from the known intermediate **73** (Scheme 14). Intermediate **73** was prepared from the readily available L-cysteine, which was reduced with DIBAL-H leading to *cis-trans* hydroxy imidazolidinone in 10:1 ratio followed by coupling with α-chloro ketone to give sulfide, which was transformed to ethoxy derivative **74**. The key cyclisation reaction was performed by use of ethyl(trimethyl)acetate/TBAF to generate enol ether followed by on addition of TMSOTf leading formation of diastereomers **75a** and **75b** in ratio 3:2. The diastereoisomers **75a** and **75b** are formed due to the chair and boat confirmations respectively, of the transition



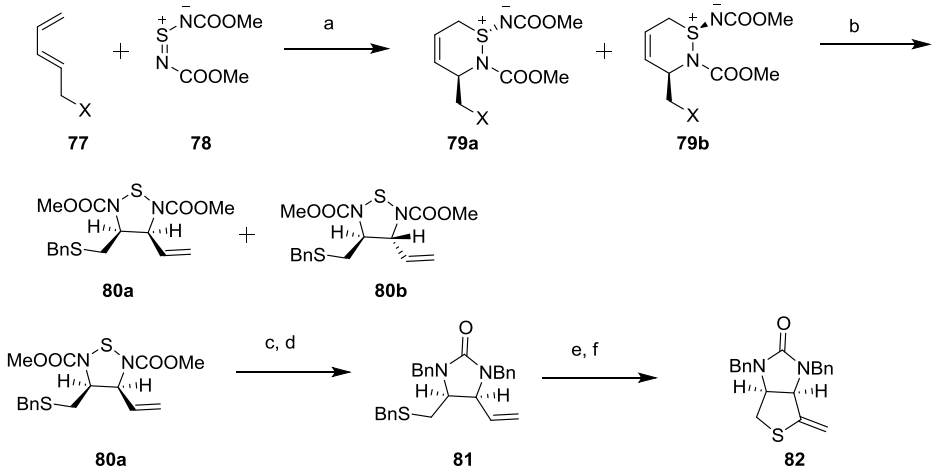
Scheme 14

Reagents and conditions: *(a) DIBAL-H, THF, -70 ^{o}C, 1 h; (b) $MeO_2C(CH_2)_3$-C(O)CH_2Cl, TEA, 4 h; (c) H_2SO_4/EtOH, methyl orange, pH=3.1, 0 ^{o}C, 2 h; (d) 2.1 equiv of (TMS)CH_2CO_2Et, 0.03 equiv of TBAF, THF, -78 ^{o}C to 25 ^{o}C, 18 h, then 1.5 equiv of TMSOTf, DCM, -78 ^{o}C, 1 h; (e) $NaBH_4$, MeOH, 25 ^{o}C; (f) $MeSO_2Cl$, TEA, DCM; (g) DBU, 60 ^{o}C, 2 h; (h) KOH/MeOH, 2 h; (i) H_2 (10 bar), 10% Pd/C, 2-propanol, 50 ^{o}C, 18 h; (j) 48% HBr, 100 ^{o}C, 2 h. (k) DBU, TBAF.*

state of *N*-acyliminium intermediate. For the completion of biotin synthesis, mixture was reduced with $NaBH_4$ the resultant alcohol was mesylated followed by elimination with DBU and saponification to afford olefin **76**. Conversion of the olefin **76** to biotin conversion was carried out in a usual way.

Weinreb's approach (*J. Org. Chem.*, ***1988,*** *53*, 1116-1118) [36]

Weinreb *et al* reported the stereoselective approach to biotin using novel strategy for synthesis of unsaturated vicinal diamines. Cycloaddition of diene **77** and dienophile sulfur diimide **78** led to epimeric mixture of **79a** and **79b** in 7.7:1 ratio. The epimeric



Scheme 15

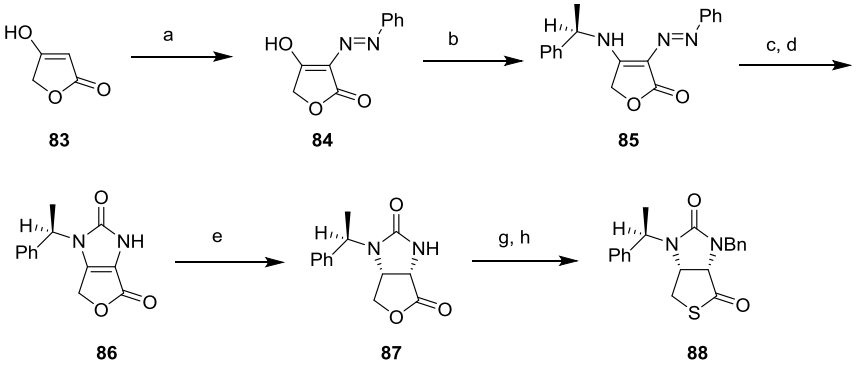
Reagents and conditions: *(a) Toluene, rt; (b) toluene, Δ; (c) $NaBH_4$, MeOH; (d) NaH, THF, BnBr; (e) Dioxane, Br_2, MeCN, 88%; (f) DBU, benzene: DCM, Δ.*

mixture was directly refluxed in toluene and it underwent stereospecific [2+3]-sigmatropic rearrangement to provide thiadiazolidines **80a** and **80b** in 7.7:1 ratio in quantitative yield. The thiadiazolidine **80a** was reduced with $NaBH_4$ to furnish

dicarbamate, which was treated with BnBr/NaH to afford cyclised dibenzyl urea **81**. The urea **81** on treatment with bromine/dioxane complex eventually provided single cyclised product, which on DBU treatment afforded olefin **82** (Scheme 15).

Lonza's approach (*Eur. Pat. Appl. EP* 0, 270, 076, 8th June **1988**; *Chem. Abstr.* **1988**, *109*, 128718b**)** [37]

An interesting asymmetric approach was developed by chemists at Lonza which is summarized in Scheme 16. The synthesis started from tetronic acid **83**, which was treated with diazonium salt, to effect the formation of diazo compound **84**. The diazo compound **84** was converted into urea **86** via reaction with (*S*)-1-phenylethylamine followed by reduction to give **85** and subsequently imidazolone ring formation with ethyl chloroformate. Reduction of **86** with rhodium on aluminium oxide in DMF lead to diastereomer **87** in 54% yield with desired (3S, 4R)-configuration while **87** on treatment with Pd/C in AcOH led to *ent*-**87**. The lactone **87** was subjected for benzyl protection followed by thioacetic acid treatement to afford thiolactone **88**.



Scheme 16

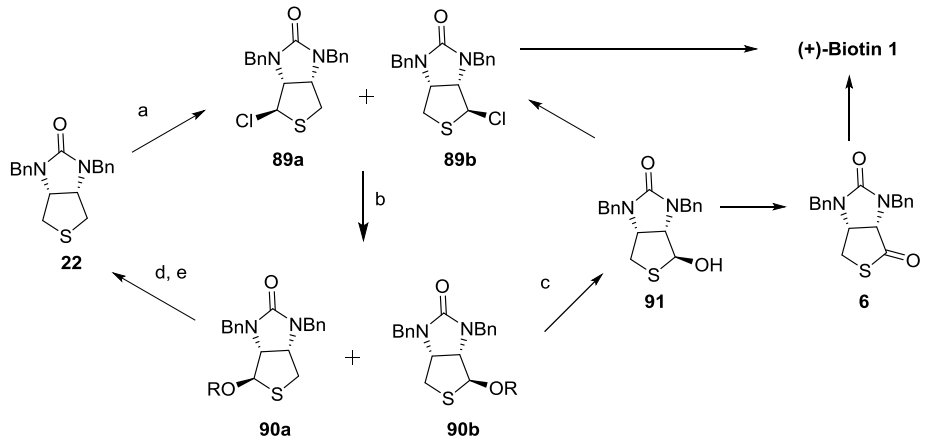
Reagents and conditions: *(a) $PhNH_2$, $NaNO_2$, HCl; (b) (R)-$PhCH(NH_2)CH_3$, $B(OEt)_3$, $PhCH_3$, 80 ^oC; (c) H_2, Pt/C, EtOAc, 40 bar; (d) $ClCO_2Et$, TEA, THF; TEA, CH_3CN, reflux; (e) H_2, Rh/Al_2O_3, DMF, 40 bar; (f) NaH, DME, $PhCH_2Br$; (g) CH_3COSK,*

$CH_3CON(CH_3)_2$, 150 ^oC.

Bihovsky's approach (*Tetrahedron* **1990**, *46* 7661-1616**)** [38]

Bihovsky and Bodepudi were successful to resolve the alcohol **91** as outlined in Scheme

17. The sulfide **22** was treated with NCS and it led to the formation of rac-α-chlorosulfide **89a** and **89b**, which were treated with optically active secondary alcohols. The most efficient alcohol was (+)-mandelic acid which provided the diastereomeric mixture which could be readily separated by crystallization. Acid hydrolysis of **90b** led to (+)-alcohol **91**, which on oxidation provided (+)-thiolactone **6**. The ent-**90b** was treated with trimethyl silane/TFA to afford sulfide **22**. Thiolactone **6** and α-chlorosulfide **89b** led to biotin following different reaction sequences.

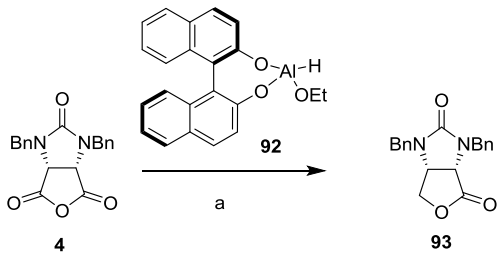


Scheme 17

Reagents and Conditions: *(a) NCS; (b) R-OH= (S)-(+)-mandelic acid, 75%; diastereomer separation by crystallization; CCl_4, reflux, 33% isolated with R= -CH(Ph)COOH; (c) H_2SO_4/dioxane; (d) HCl, $CHCl_3$; (e) Et_3SiH, CF_3COOH.*

Matsuki's approach (*Tetrahedron Letters* **1993**, *34*, 1167**)** [39]

Matsuki and co-workers developed efficient asymmetric strategies in the context of the original Hoffmann-La Roche for the highly enantioselective reduction of *meso*-1,2-



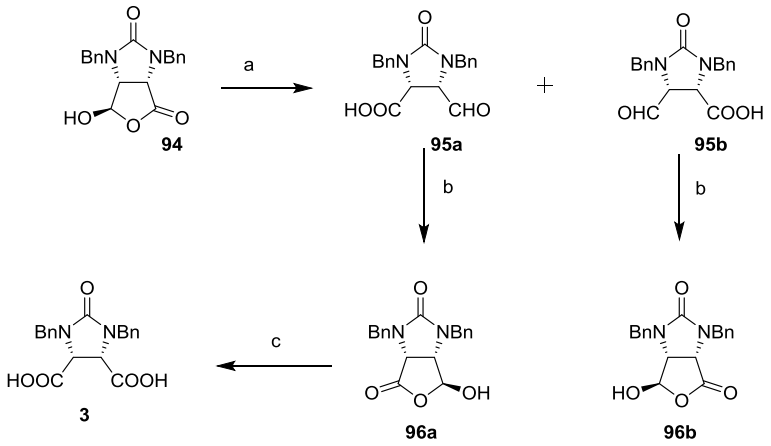
Scheme 18

Reagent and conditions: *(a) (R)-BINAL-H, -78 ^{o}C to rt, THF, 76%.*

dicarboxylic anhydride to yield optically active lactones using Noyori's lithium aluminium hydride-ethanol-1,1'-bis-2-naphthol complex (BINAL-*H*) **92**. When *meso*-anhydride **4** was subjected to reduction it provided desired lactone **93** in 76% yield with 90% *ee*, which was enriched to 95% *ee* by recrystallyzation from benzene/cyclohexane (Scheme 18).

Senuma's approach (*Chem. Pharm. Bull.* **1990**, *38*, 882**)** [40]

Senuma and co-workers in 1990 have reported an alternative method for the industrial resolution of hydroxy lactone **94** as shown in Scheme 19. For the resolution optically active amine was used. Thus the reaction of *rac*-lactone **94** with cinchonidine afforded desired amine salt in 45% yield with purity >98. The salt on acidification underwent cyclisation to 42% of hydroxy lactone **96b**. The mother liquor of salt on evaporation followed by acidification furnished **96a** in 36% yield. The undesired enantiomer **96a** was converted to meso diacid **3** by facile oxidation with $NaClO_2$. In the search of more practical and inexpensive resolving agent for industrial use, they also tried optical resolution of *rac*-**94** with various *N*-alkyl-D-glucamines.

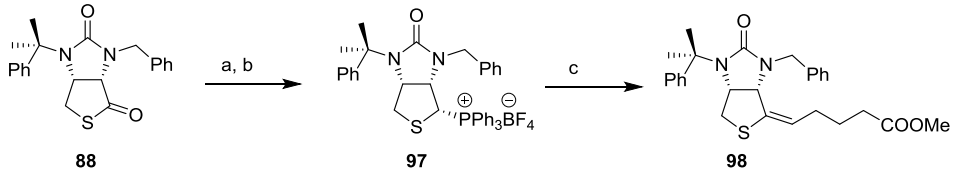


Scheme 19

Reagents and conditions: *(a) Cinchonidine: 45% of precipitated salt or N-butyl-D-glucosamine derivative: 46% of precipitated salt; (b) HCl; (c) $NaClO_2$.*

Eyer's approach (*Chem. Abstr*. **1991**, *114*, 81435**)** [41]

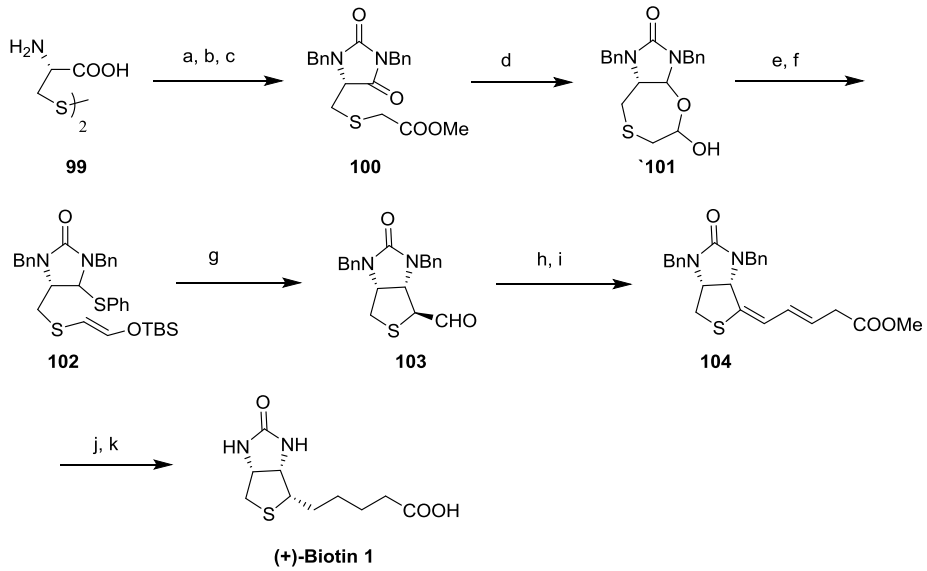
Eyer *et al* have developed an alternative Wittig reaction starting from the thiolactone **88** which is summarized in Scheme 20. Thiolactone **88** was subjected to the DIBAL-H reduction to corresponding hydroxy derivative, which on treatement with $PPh_3.HBF_4$ was directly converted to phosphonium salt **97**. The salt **97** was treated with base followed by methyl-5-oxopentanoate to afford olefin **98** in good yield.



Scheme 20

Reagents and conditions: *(a) $(Me_2CHCH_2)_2AlH$, $PhCH_3$, -70 ^oC; (b) Ph_3PHBF_4, CH_3CN, reflux; (c) KOtBu, THF; $OHC(CH_2)_3CO_2Me$, THF.*

Chavan's 1st approach (*US patent* 5, 274, 107; *Chem. Abstr*. **1994**, *120*, 217097t; *J. Org. Chem*. **2001**, *66*, 6197-6201**)** [42a]



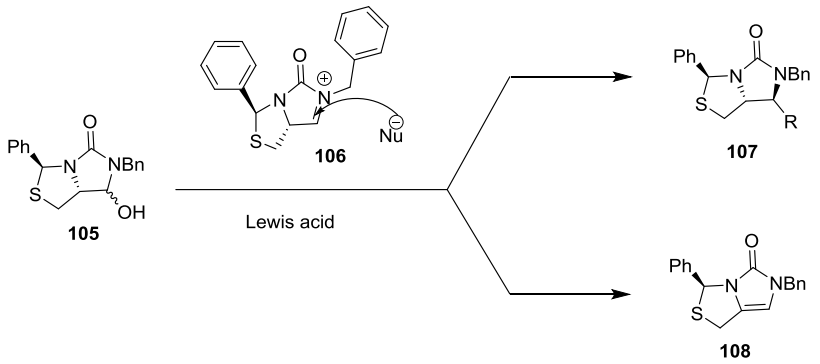
Scheme 21

Reagents and conditions: *(a) Ref 42b; (b) (i) BnNCO, DCM, rt, 1 h; (c) pTSA, rt, 6 h, 90% (two steps); (d) DIBAL-H, Tol, -78 ^oC, 2 h, 72%; (e) PhSH, pTSA, 0 ^oC, 5 min, 70%; (f) DBU, TBSCl, DCM, reflux, 2 h, 92%; (g) p-Nitrobenzaldehyde, DCM, TBSOTf, 5 min, 95%; (h) $Ph_3PCHCHCHCOOCH_3$, DCM, rt, 12 h, 89%; (i) 1 M NaOH, MeOH, 0 ^oC, 12 h, 97%; (j) 10%Pd-C/H_2 (3 atm), 8 h, 92%; (k) 48% HBr, reflux, 2 h, 80%.*

The hydantoin **100** can be easily obtained from cystine/cysteine. Reduction of keto ester **100** was carried out with DIBAL-H to afford lactol **101**. Lactol **101** was converted into thermodynamically stable aldehyde **103** *via* reaction with thiophenol followed by TBDMSCl/DBU treatment and TBDMSOTf in presence of *p*-nitrobenzyldehyde as thiophenol scavenger. Aldehyde **103** was subjected to four-carbon Wittig reaction and on base mediated deconjugation provided olefin **104**. The olefin **104** on catalytic reduction, followed by debenzylation with HBr furnished D-(+)-biotin **1** (Scheme 21).

Chavan's 2nd approach (*J. Org. Chem.* **2005**, *70*, 1901-1903**)** [43]

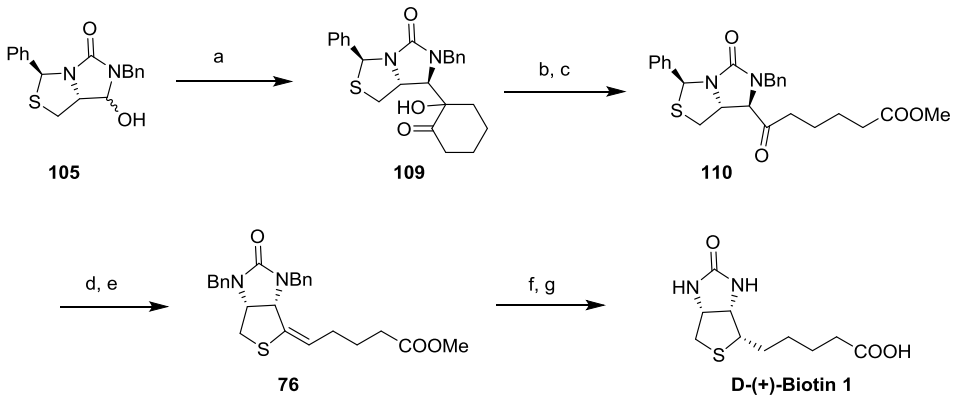
From this laboratory in 2005 a short and efficient synthesis of D-(+)-biotin was reported involving the stereospecific amidoalkylation of hydroxy imidazothiazolone methodoly. Hydroxy compound **105** was readily obtained from the L-cysteine.HCl using reported procedure. The hydroxy compound **105** was subjected to the crucial stereospecific



Scheme 22

amidoalkylation protocol using appropriate nucleophile to provide stereospecific *trans* products **107** in almost quantitative yield. The specific nucleophilic addition follows preferentially path A which led to specific product with *trans* fashion due to convex face accessibility for nucleophilic attack which is shown in Scheme 22.

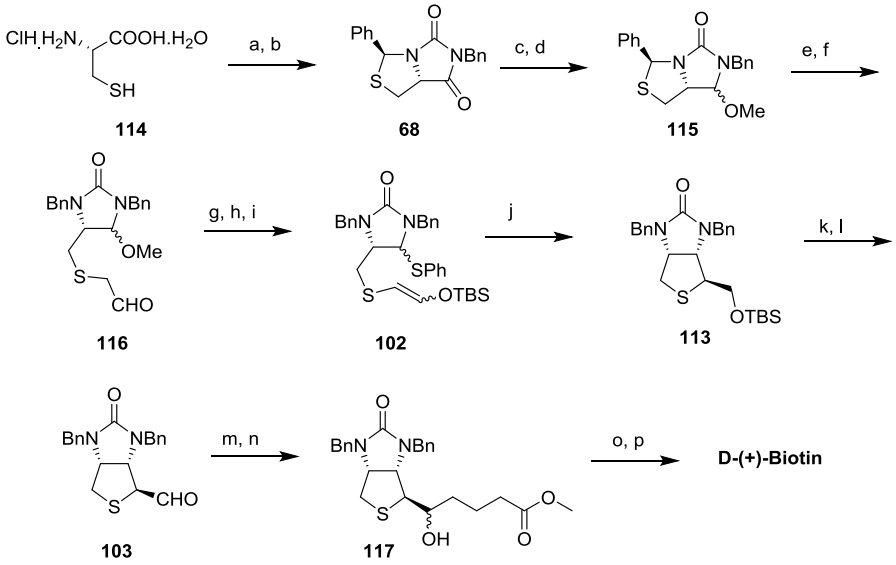
The α-hydroxy ketone **109** was prepared using appropriate nucleophile, which was subjected to Baeyer-Villiger oxidation and the resultant acid on esterification furnished keto ester **110**. Olefin **76** was obtained from keto ester **110** *via* C-S bond cleavage with Zn/AcOH followed by thiol cyclisation in piperidine/AcOH and dehydration. Olefin **76** on stereospecific hydrogenation and debenzylation in HBr led to D-(+)-biotin **1** (Scheme 23).



Scheme 23

Reagents and conditions: *(a) 1,2-Bis(trimethylsilyloxy)cyclohexene (1.5 equiv), $BF_3.OEt_2$, DCM, 98%; (b) 70% TBHP, KOH-MeOH, 15 min; (c) CH_2N_2, 10 min, 70%; (d) Zn/AcOH, 80 ^oC, 5 h; (e) AcOH/ piperidine, 100 ^oC, 90 min, 70%; (f) H_2/Pd-C, MeOH, 200 psi, 100%; (g) 47% HBr, 5 h, 78%.*

Chavan's 3rd approach (*Tetrahedron* **2005**, *61*, 9273–9280) [44]

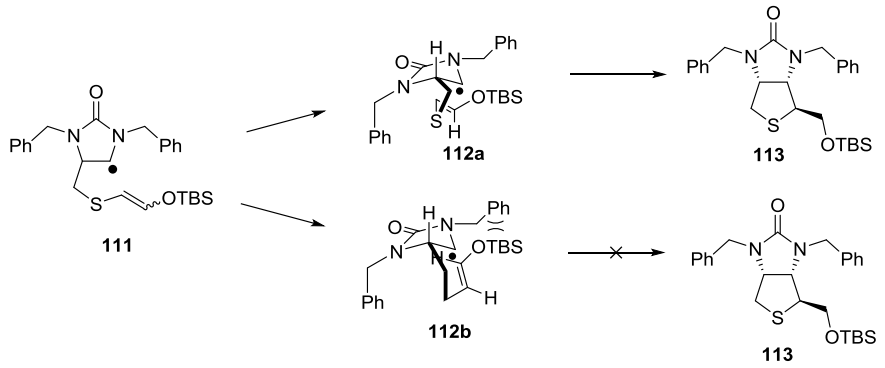


Scheme 24

Another approach was reported in 2005 starting from the L-cysteine which involved the stereospecific outcome of radical cyclisation of compound **102** which led to fused system **113**. The synthesis started from L-cysteine hydrochloride salt **114** which was converted to ketone **68** using known procedure. Reduction of ketone **68** with $NaBH_4$ resulted into hydroxyl compound, which on treatment with MeOH/*p*TSA led to compound **115**. Compound **115** on treatment with Zn cleaved the C-S bond; and crude thiol thus obtained was alkylated using ethyl chloroacetate to

afford compound ***116***. Sulfide ***116*** on DIBAL-H reduction furnished aldehyde and the crude aldehyde was converted to enol **102** with TBSCl/DBU. Enol **102** was subjected to the crucial step by reaction with Bu_3SnH and catalytic AIBN leading to single cyclised product **113** (Scheme 24). The exclusive formation of 113 happens due to steric and electronic factor of acylimido radical as well as electronegative nitrogen destabilizing transition step **112b** as shown in Scheme 25.

Compound **113** was converted to aldehyde **103** *via* TBS deprotection followed by Swern oxidation. The acid side chain was introduced by treating **103** with 1, 3-propane dimagnesium bromide, quenching with CO_2 and esterifying resultant acid by diazomethane treatement providing ester **117**. Ester **117** was converted to D-(+)-biotin **1** via hydroxy mesylate, which was eliminated in DBU followed by stereospecific catalytic reduction and HBr treatment to furnish target molecule **1** (Scheme 24).



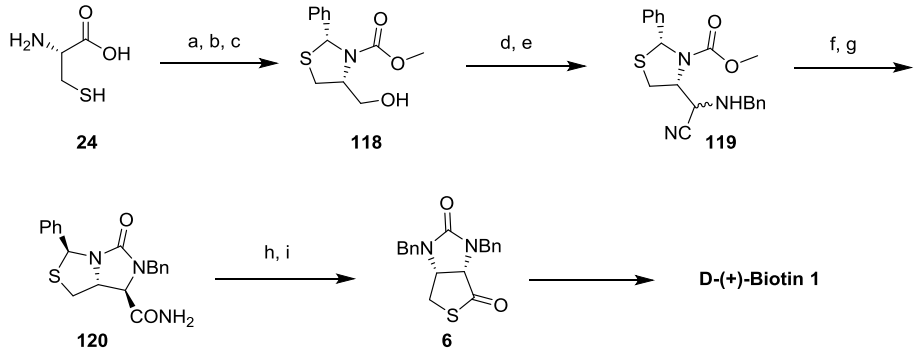
Scheme 25

Reagent and conditions: *(a) PhCHO, KOAc, MeOH:H_2O (1:1), rt, 6 h, 98%; (b) BnNCO, DCM, 60 min, conc. HCl, 60 min, reflux, 90 min, 90%; (c) $NaBH_4$, MeOH, 0 ^oC to rt, 1 h, 99%; (d) MeOH, pTSA (cat.), 15 min, 98%; (e) PhSH, pTSA (cat.), DCM 10 min, 93%; (f) DIBAL-H, toluene,-78 ^oC, 2 h, 78%; (g) TBSCl, DCM, DBU, reflux, 30 min, 80%. (h) $BF_3.Et_2O$, $CHCl_3$, rt, 2 h, 75%; (i) $(COCl)_2$, DMSO, DCM, TEA,-78 ^oC to rt, 2.5 h, 61%; (j) Bu_3SnH, AIBN, benzene, reflux, 4 h, 53%.; (k) Mg, $BrCH_2CH_2CH_2Br$, THF, 12 h, then cooled to -15 ^oC, CO_2, 2 h, rt; (l) CH_2N_2, 15 min, 76% (two steps); (m) MsCl, TEA, DCM, 0 ^oC to rt, 3 h; (n) DBU, 60 ^oC, 12 h, 80% (two steps); (o) 10% Pd/C, H_2, 200 psi, 65 ^oC, 6 h, 99%; (p) HBr (47%), reflux, 5 h, 75%.*

Seki's approach (*Synthesis* **2003,** 15, 2311**)** [45]

Seki's approach started from L-cysteine **24**, which was converted to alcohol **118** using reported procedure. Alcohol **118** was oxidized to aldehyde using Swern oxidation

conditions followed by imine formation with benzyl amine and TMSCN addition leading to compound **119**. The nitrile **119** on amidation and subsequent cyclisation provided amide **120**. Amide **120** upon reduction with zinc, hydrolysis and cyclisation afforded the thiolactone **6** as a key intermediate for (+)-biotin **1** (Scheme 26).

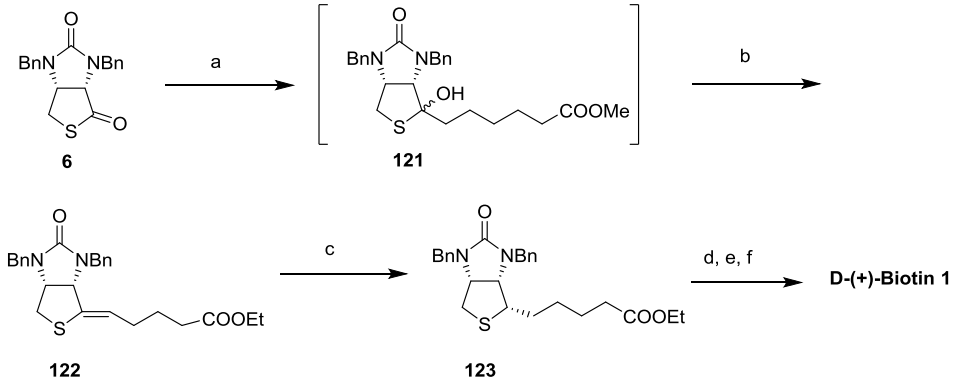


Scheme 26

Reagents and conditions: *(a) PhCHO, H_2O, EtOH, 96%; (b) (i) $SOCl_2$, EtOH (ii) $Ca(BH_4)_2$, EtOH, quant.; (c) $ClCO_2Me$, Na_2CO_3, THF, H_2O; (d) SO_3.py, TEA, DMSO; (e) (i) $BnNH_2$, DCM, MS (4 Å) (ii) TMSCN; (f). H_2O_2, K_2CO_3, DMSO; (g) DMF, 100 ^oC, 2 h, 60%; (h) (i) Zn, AcOH, 100 ^oC (ii) HCl, H_2O, AcOH, 110 ^oC, 87%; (i) DCC, p-TSA, py, toluene, 75%.*

Seki's 1st approach (*Tetrahedron Letters* **2000**, *41*, 5099**)** [46]

In 2000 Seki *et al* reported a facile synthesis of D-(+)-biotin **1** by using Fukuyama coupling of carbonyl compounds. The synthesis started with thiolactone **6**, which was treated with zinc reagent in presence of $PdCl_2(PPh_3)_2$ to afford alcohol **121**. The alcohol



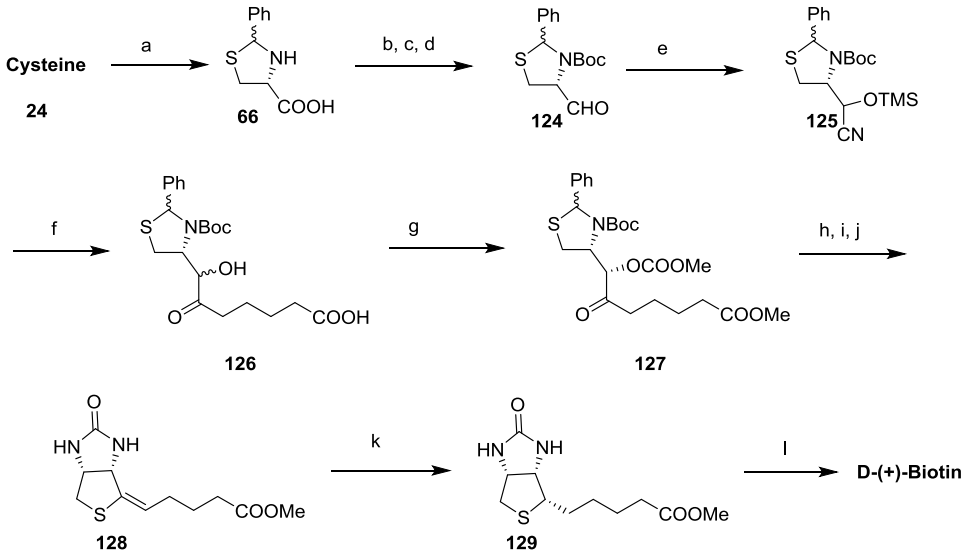
Scheme 27

Reagent and conditions: *(a) $IZn(CH_2)_4CO_2Et$ (3 equiv.), $PdCl_2(PPh_3)_2$ (10 mol%), THF, toluene, DMF, 20 ^oC, 35 h; (b) pTSA, toluene, 20 ^oC, 18 h; (c) H_2 (70 atm)/Pd-C, EtOH, 100 ^oC, 3 h; c: (d) 48% aq. HBr, reflux, 48 h; (e) $ClCO_2Et$, NaOH; (f) HCl.*

121 without purification, on *p*TSA treatement led to olefin **122**. Later on the thiolactone **6** coupling was modified by using zinc reagent in presence of Pd/C to give olefin **122** in 94% yield. The final task was achieved *via* the usual catalytic hydrogenation and debenzylation to furnish D-(+)-biotin **1** (Scheme 27).

Seki's 2nd approach (*J. Org. Chem.* **2002,** *16*, 5527**)** [47]

In 2002, Seki and co-workers reported (+)-biotin synthesis with 25% overall yield in 11 steps from L-cysteine **24** as summarized in Scheme 28. The aldehyde **124** was obtained from L-cysteine **24** by using reported method. Aldehyde **124** was subjected to novel and highly stereoselective cyanosilylation in presence of Lewis base which led to contiguous



Scheme 28

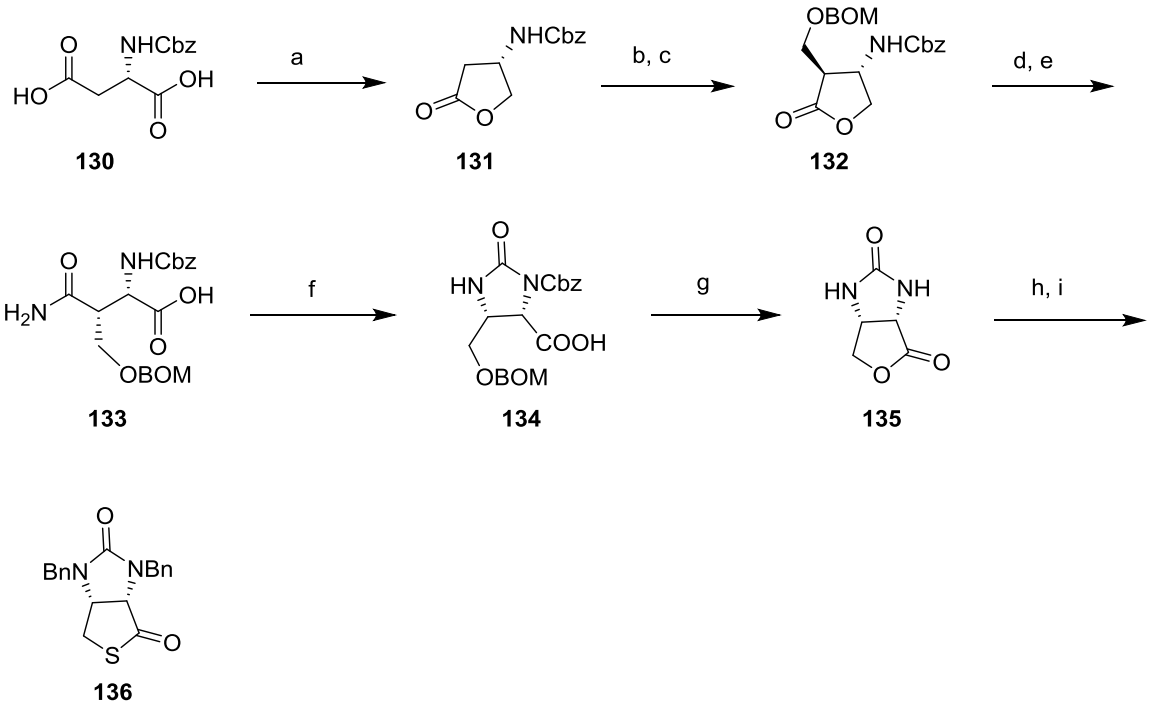
Reagents and conditions: *(a) PhCHO, AcOK, EtOH, H_2O, 96%; (b) (i) $SOCl_2$, EtOH (ii) $Ca(BH_4)_2$, EtOH, quant; (c) $(Boc)_2O$, Na_2CO_3, THF, H_2O, 88%; (d) SO_3.py, DMSO/toluene (5:1), TEA, 2 h, 95%, >99 de; (e) TMSCN, DCM, n-Bu_3P, 96%, de=92:8; (f) (i) Mg, 1,4-dibromobutane, n-Bu_2O, 76%; (ii) CO_2; (iii) Aq. citric acid; (g) (i) Me_2SO_4, K_2CO_3, DMF, (ii) crystallization from AcOEt-hexane, 73%; (iii) $ClCO_2Me$, TEA, DMAP, THF, quant. (h) HCl-AcOEt, (i) KNCO, TEA, THF, 75%; (j) $Pd(OAc)_2$,*

$NaHCO_3$, DMF; (k) H_2, $Pd(OH)_2/C$, quant; (l) (i) NaOH, MeOH, H_2O; (ii) $MeSO_3H$, xylene, 84%.

chiral center formation to provide cyanohydrin **125**. The side chain was introduced by treating cyanohydrin **125** with Grignard reagent derived from 1,4-dibromobutane and quenched with dry ice (CO_2) followed by acid treatment to provide acid **126**. Acid **126** on esterification afforded ester, which was treated with methylchloroformate to give ester **127**. Compound **127** on HCl/EtOAc treatment followed by potassium cyanate treatment, palladium acetate and base mediated cyclisation furnished olefin **128**. Finally olefin **128** was converted to D-(+)-biotin **1** *via* catalytic hydrogenation, ester hydrolysis with NaOH/MeOH/H_2O followed by debenzylation with methanesulfonic acid in xylene.

Seki's 3nd approach (*Synthesis* **2002,** *3*, 361-364**)** [48]

Seki reported synthesis from L-aspartic acid **130** as chiral synthon for (+)-biotin **1** as described in Scheme 29. Aspartic acid **130** was transformed to butanolide **131**, which on aldol reaction with formaldehyde resulted in the *trans*-substituted butanolide **132**



Scheme 29

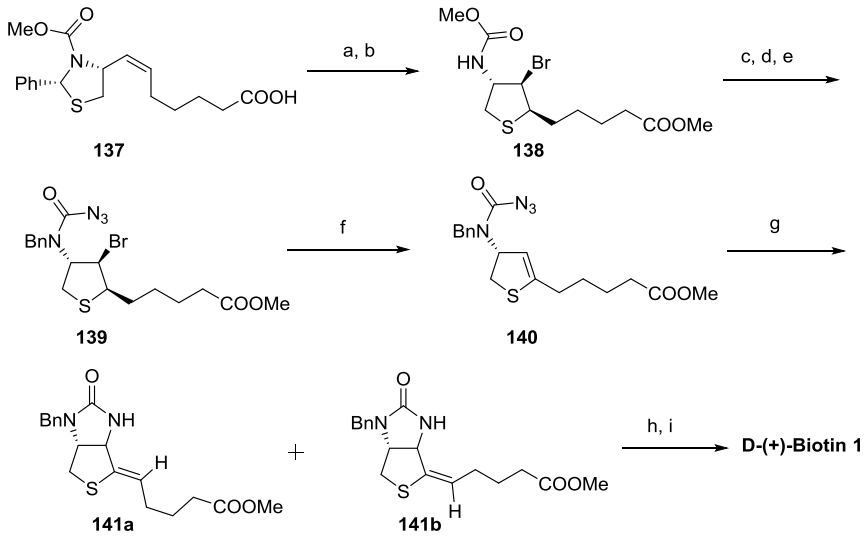
Reagents and conditions: (*a) (i) Ac_2O, (ii) $NaBH_4$, THF, (iii) HCl, 95%; (b) (i) LDA,*

THF, (ii) HCHO, -78 ^{o}C, 62%, trans/cis = 12:1; (c) BOMCl, i-Pr$_2$NEt, THF, quant; (d) NH$_4$OH, MeOH, 58%; (e) Jones' reagent, acetone, 76%; (f) NaOCl, NaOH, H$_2$O, 70%; (g) H$_2$, Pd(OH)$_2$/C, MeOH, 80%; (h) BnBr, NaH, DMF, 84%; (i) AcSK, DMF, 92%.

stereoselectively. The L-asparagine derivative **133** was obtained from lactone **132** by protection of hydroxy, followed by amidation and oxidation. Compound **133** on Hoffmann degradation provided urea **134** and subsequent hydrogenation of urea **134** led to lactone **135**, followed by potassium thioacetate treatement to afford thiolactone **136** as a key intermediate of biotin **1**.

De Clercq's approach I (*Tetrahedron Letters* **1993**, *34*, 4365) [49]

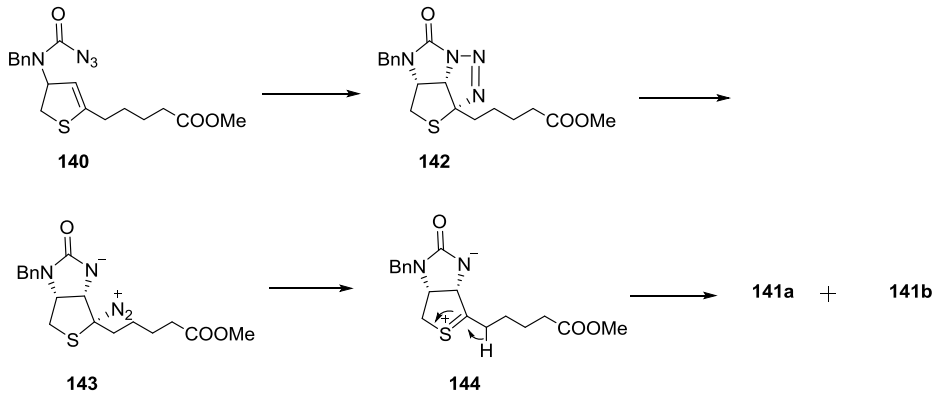
De Clercq in 1993 and 1994 described two different approaches based on thermal 1, 3-dipolar cycloaddition of carbamoyl azide and alkene. The olefin **137** was subjected to the esterification and stereospecific rearrangement protocol to provide compound **138**. It was converted to carbonyl azide by carbamate deprotection, imine formation with benzyldehyde, *in-situ* reduction, treatment with phosgene and with NaN_3 to get carbamoyl azide **139**. The bromide **139** on DBU elimination afforded olefin **140**, which on intermolecular 1,3-dipolar cycloaddition at high temperature resulted into mixture of (*E*)-olefin **141a** and (*Z*)- olefin **141b**, which was further converted into D-(+)-biotin **1** in a usual way (Scheme 30).



Scheme 30

Reagents and conditions: *(a) CH_2N_2, Et_2O, 0 ^oC, 99%; (b) Br_2, $CHCl_3$, H_2O, rt, 65%; (c) HBr, HOAc, 85%; (d) PhCHO, $NaCNBH_3$, THF, H_2O, rt; (e) $COCl_2$, DBU, DCM, 0 ^oC, NaN_3, acetone/H_2O, rt, 54%; (f) DBU, THF, reflux, 95%; (g) Autoclave, DCM, 150 ^oC, 3h, 78%; (h) H_2 (4 bar), $Pd(OH)_2$/C, EtOAc, rt; (i) HBr (48%), reflux, 78%.*

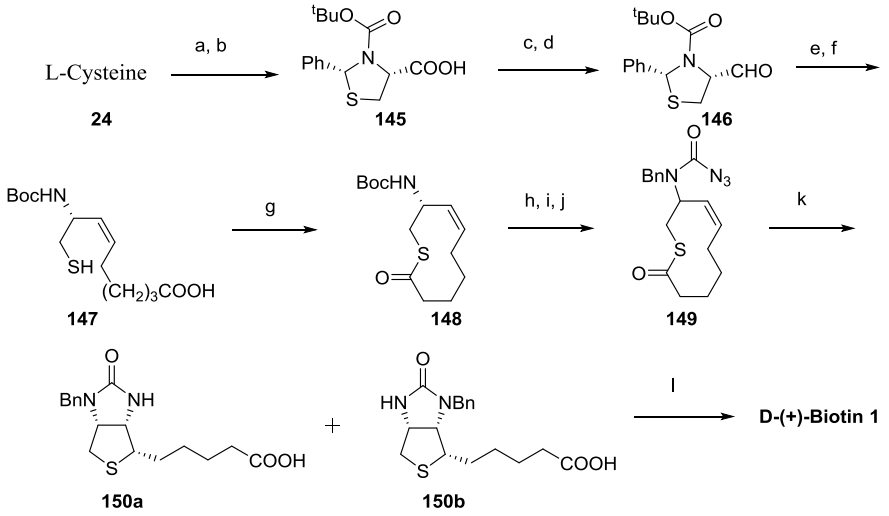
The mechanism of 1, 3-dipolar cycloaddition is depicted in Scheme 31, which involves triazoline formation **142** and nitrogen extrusion to provide *E*-olefin **141a** and *Z*-olefin **141b**.



Scheme 31

De Clercq's approach II (*Tetrahedron Letters* **1994**, *35*, 2615) [50]

The second approach of De Clercq for biotin based on previous strategy was reported in 1994 as described in Scheme 32. It involved obtaining the key intermediate carbomyl



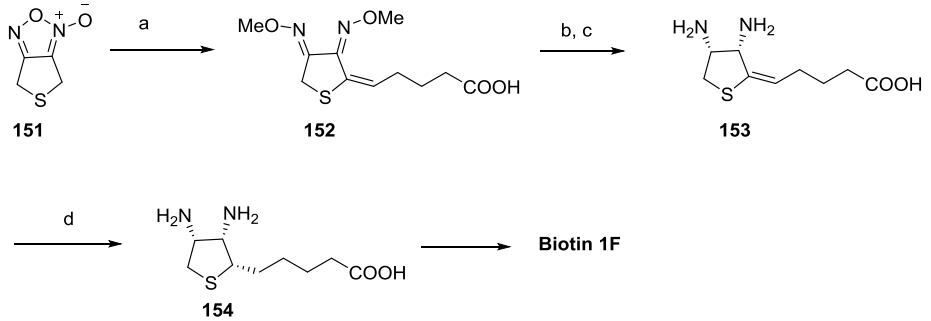
Scheme 32

Reagents and conditions: *(a) PhCHO, KOAc, H_2O, EtOH, rt; (b) $(Boc)_2O$, NaOH, H_2O, dioxane; (c) Me_2S/BH_3, THF; (d) $(COCl)_2$, DMSO, -60 ^oC, TEA; (e) $Ph_3P(CH_2)_5COOH]Br$, 2 equiv of LDA, THF, rt, 1 h; (f) Na, liq NH_3; H_3O^+; (g) $PhOP(O)Cl_2$/DMF, DCM, rt; (h) HCl, Et_2O, 0 ^oC; (i) PhCHO, $NaCNBH_3$, THF/H_2O (pH) (4), 0 ^oC; (j) $COCl_2$, DBU; NaN_3, acetone/H_2, rt; (k) H_2O, autoclave, 145 ^oC, 2 h; (l) HBr (48%), reflux, 2 h.*

azide **149**. The synthesis started with L-cysteine **24**, which was converted to aldehyde **146** through acid **145** by usual way. The aldehyde **146** was subjected for Wittig reaction followed by Birch reduction to provide olefin **147**. The olefin 147 was converted to carbamoyl azide **149** via four-step sequence. The azide **149** at 145 ^oC afforded the two 1,3-dipolar cycloadduct as a mixture of monobenzylated biotin **150a** and **150b**. The mixture on HBr treatment provided D-(+)-biotin **1**.

Kurimoto's approach (*JP* 06, 263, 752, Sept 20, **1994**; *Chem. Abstr.* **1995**, *122*, 81011s**)** [51]

Kurimoto and co-workers have reported short and enantioselective synthesis of (+)-biotin **1** in 1995 which is outlined in Scheme 33. The synthesis started with **151**, which was converted to olefin **153** *via* introduction of side chain by treatment with LDA/5-oxopentanoic acid, reduction with hydrazobenzene and methylation. The olefin **153** was reduced with BH_3/THF and norephedrine to afford *cis*-diamine **154**, which was converted to biotin using reported procedure.

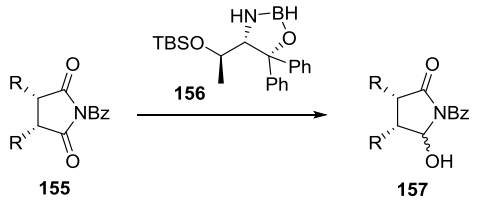


Scheme 33

Reagents and conditions: *(a) LDA, $OHC(CH_2)_3CO_2H$; (b) PhNHNHPh; (c) Methylation; (d) BH_3/THF, norephedrine.*

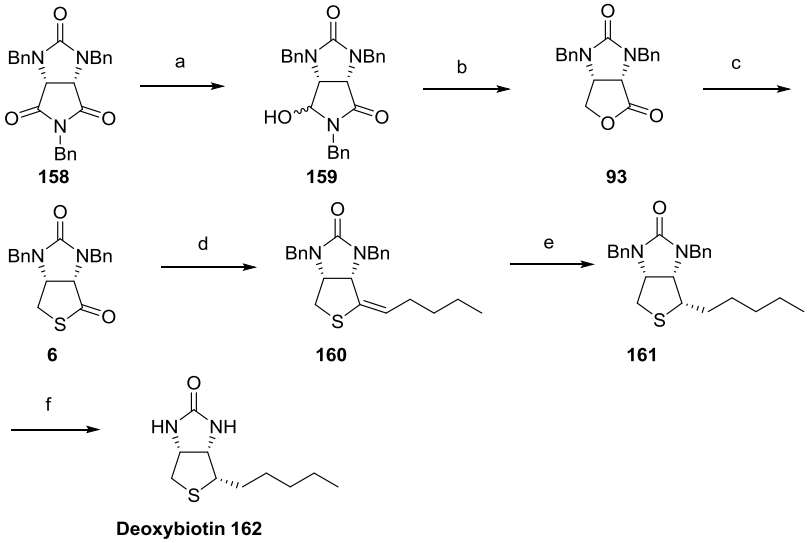
Shimazu's approach (*Tetrahedron Letters* **1999**, *40*, 8873**)** [52]

Shimazu's and co-workers in 1999 have reported the stereocontrolled reduction of meso-imides **155** using oxazaborolidine **156** as shown in Scheme 34.



Scheme 34

Using this protocol the strategy for the synthesis of (+)-deoxybiotin **162**was developed in an enantio controlled manner in good yield. The hydroxy lactam **159** was reduced with $NaBH_4$ to afford hydroxy amide **159**, which on subsequent treatment with H_2SO_4 provided lactone **93**. Lactone **93** was converted to thiolactone **6** using known procedure. The valeric side chain was introduced on Grignard addition on the thiolactone **6**, followed by AcOH treatment, furnished olefin **160**. The stereospecific hydrogenation of olefin **160** afforded **161**, which underwent Birch reduction with Na/liq NH_3, to provide (+)-deoxybiotin **162** (Scheme 35).



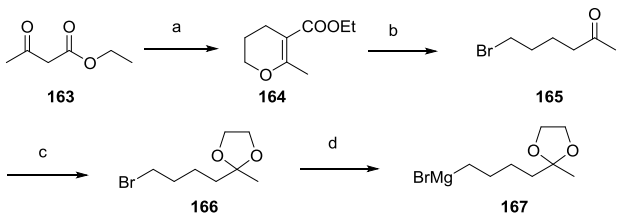
Scheme 35

Reagents and Conditions: *(a) $NaBH_4$ (4.0 eq), THF-H_2O (10:1), 71%; b) 2N H_2SO_4,1,4-dioxane (8:1), 0 ^oC, 92%; c) CH_3COSK, DMF, 150 ^oC, 87%; d) n-$C_5H_{11}MgBr$, THF,*

AcOH, reflux, 82%; e) Pd black, H_2, 40 ^oC, iPrOH-H_2O (6:1), 90%; (f) Na liq. NH_3, THF, 62%.

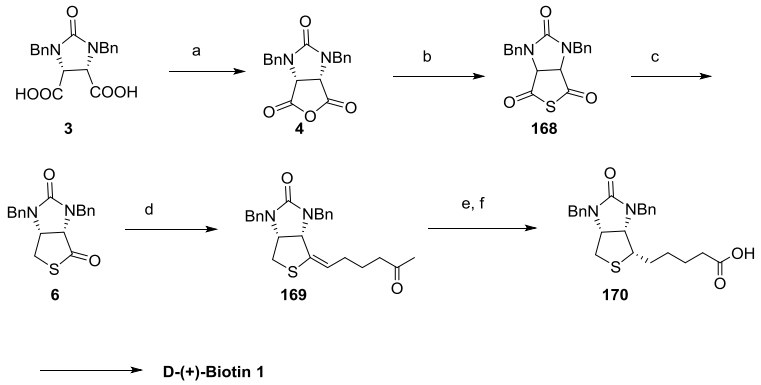
Chen's 1st approach (*Synthesis*, **2000**, 2004**)** [53]

Chen and co-workers in 2000 have reported an enantioselective synthesis of D-(+)-biotin using BINAL-H reduction of meso-thioanhydride **168** which is summarized in Scheme 36. The *cis*-1, 3-dibenzyl-2-imidazolidine-4, 5-dicarboxylic acid **3** was reacted with Ac_2O to give anhydride which on Na_2S treatement provided thioahdyride **168**. The thioanhydride **168** was subjected for the crucial enantioselective reduction that led to thiolactone **6**. The side chain was introduced on to thiolactone **6** by reaction with modified Grignard reagents **167** prepared from 163 as shown in Scheme 36.



Scheme 36

Reagents and conditions: (*a) 1-Bromo-3-chloropropane, K_2CO_3, toluene, 80 ^oC, 94%; (b) 47% HBr, NaBr, H_2SO_4, 50 ^oC, 86%; (c) $(CHOH)_2$, TsOH, toluene, reflux, 92%; (d) Mg, THF, rt.*



Scheme 37

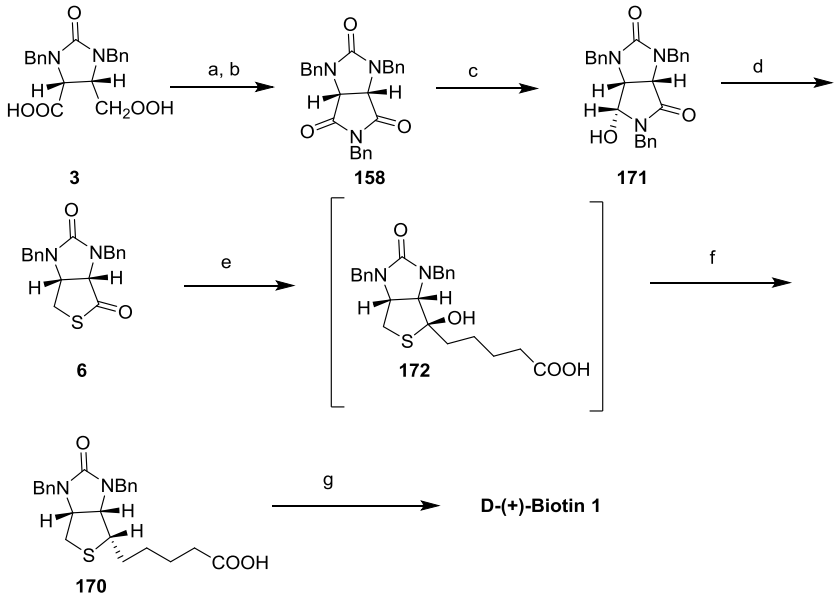
Reagents and conditions: *(a) Ac_2O, 83% H_3PO_4 (cat.), reflux, 98%; (b) $Na_2S.9H_2O$, THF, H_2O, rt, 49%; (c) (R)-BINAL-H, THF, -78 ^oC to rt, 83%; (d)* ***167****, THF, reflux, then*

30% H_2SO_4, 60 ^oC, 82%; (e) I_2, KI, 10% NaOH, dioxane, 60 ^oC, 75%; (f) 75% HCOOH, CH_3SO_3H, 10% Pd/C, reflux, 85%.

Acid **170** was obtained from ketone **169** by iodoform reaction followed by catalytic reduction in triflic acid to afford D-(+)-biotin **1**. The important feature of the strategy involves six steps and 21% overall yield starting from the diacid **3** (Scheme 37).

Chen's 2nd approach (*Tetrahedron Asymmetry* **2003**, *14*, 3667-3672) [54]

Chen and co-workers reported another approach shown in the Scheme 38 based on the enantioselective reduction of meso-cyclic imide **158** described earlier. Synthesis started with commercially available diacid **3**, which on benzyl amine treatment in presence of catalytic pyridine furnished meso-cyclic imide **158**. The enantioselective reduction of meso-imide **158** by the use of (1*S*, 2*S*)-(+)-*threo*-1- (4-nitrophenyl)-2-amino-1, 3-propanediol, LiH and $BF_3.Et_2O$ and reduced with $KBH_4/CaCl_2$ followed by acidic treatment afforded **171**. The **171** was converted to thiolactone **6** using reported procedure followed by introduction of side chain with modified Grignard reaction and Pd catalysed reduction in presence of $ZnCl_2$ resulted into acid **170**, which debenzylated to D-(+)-biotin **1**.



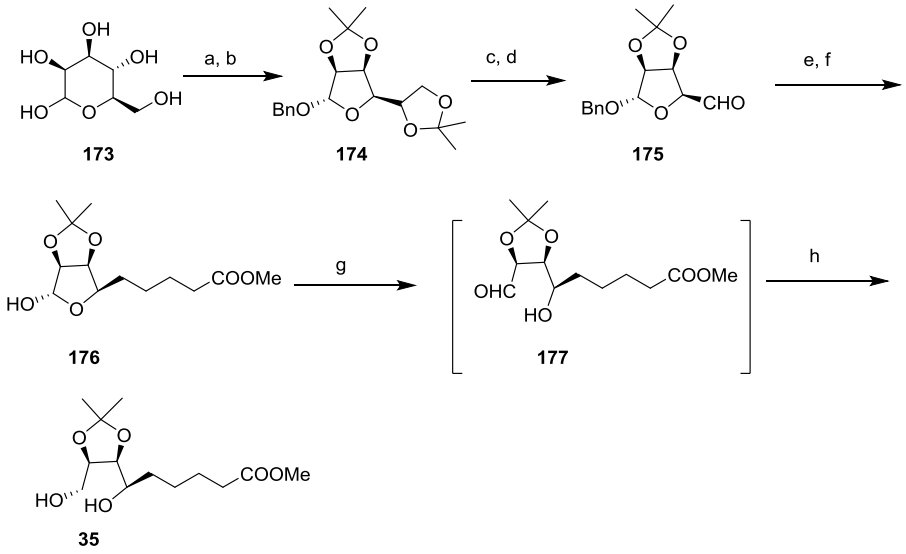
Scheme 38

Reagent and conditions: *(a) $BnNH_2$, pyridine, xylene, reflux, 8 h 90%; (b) (1S, 2S)-(+)-threo-1- (4-nitrophenyl)-2-amino-1, 3-propanediol, LiH, $BF_3{\cdot}Et_2O$, THF, reflux, 8 h; (c)*

KBH_4, $CaCl_2$, EtOH, rt 4 h, then 1 M aq HCl, rt, 92%; (d) $CH_3SC(S)SK$, DMA, 120 ^oC 6 h, 88%; (e) (i) $BrMg(CH_2)_4MgBr$, THF, -30 to -25 ^oC, 3 h; (ii) CO_2, -30 to -25 ^oC, 3 h; (iii) 1 M aq NH_4Cl; (f) H_2, 5% Pd/C, $ZnCl_2$, toluene, 40 atm, 110 ^oC, 6 h, 75%; (g) $H_2SO_4/HOAc/H_2O$ (1.5:1.5:1), reflux, 12 h, 75%.

Chen's 3rd approach (*Carbohydrate Research*, **2007**, *342*, 2461-2464**)** [55]

In 2007 Chen and co-workers have reported an efficient and reproducible process for the synthesis of key intermediate **35** starting from D-mannose **173** which is summarized in Scheme 39. The D-mannose **173** was converted to aldehyde **175** *via* acetonide protection, hydroxy protection with BnBr followed by selective terminal acetonide deprotection and oxidative diol cleavage which led to aldehyde **175**. The aldehyde **175** on Horner-Emmons olefination afforded unsaturated ester which was subjected to catalytic reduction to give hydroxy ester **176**. The alcohol **176** was reacted with NaOMe followed by reduction of of resultant aldehyde **177** to provide dihydroxy ester **35** the crucial intermediate for the D-(+)-biotin **1**.

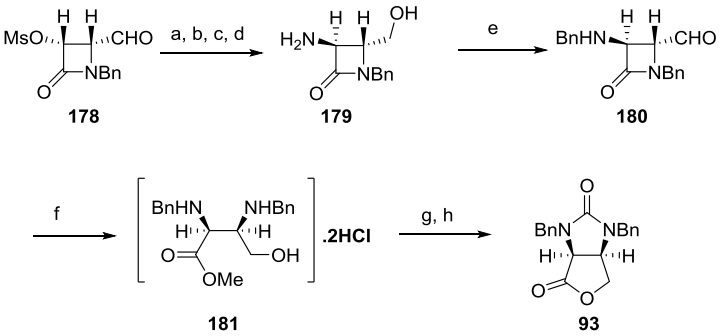


Scheme 39

Reagents and conditions*: (a) Acetone, $FeCl_3$, rt, 4 h, 88%; (b) KOH, BnBr, PEG-600, THF, rt, overnight, 90%; (c) 70%HOAc, rt, 18 h, 97.5%; (d) Silica gel supported $NaIO_4$, DCM, 0 ^oC, 1.5 h, 99.5%; (e) $(EtO)_2POCHCH=CHCOOMe$, MS 4Å, $LiOH.H_2O$, THF,*

reflux, 12 h, 80%; (f) 5% Pd/C, EtOH/HOAc, 1 atm H_2, rt, 18 h, 90%; (g) NaOMe, MeOH, 0 ^oC, 15 min; (h) $NaBH_4$, MeOH, rt, 2 h, 96.4%.

Deshmukh's approach (*Synthesis* **2007**, *8*, 1159-1164**)** [56]



Scheme 40

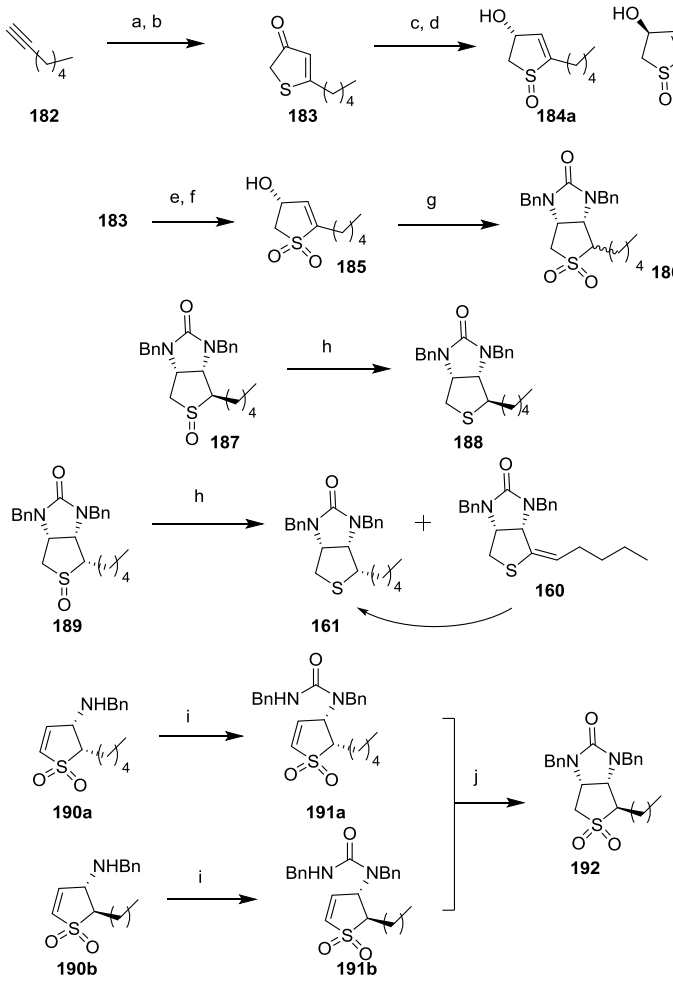
Reagents and conditions: *a) $NaBH_4$, MeOH, rt, 3 h; (b) HCl-MeOH (20%), reflux, 8 h. (c) NaN_3, DMF, 80 ^oC, 36 h; (d) HCO_2NH_4, Pd/C (10%), MeOH, reflux, 45 min; (e) (i) PhCHO, $MgSO_4$, DCM, rt, 12 h, (ii) $NaBH_4$, MeOH, 0 ^oC to rt, 2.5 h; (f) HCl-MeOH (20%), rt, 14 h; (g) Et_3N, triphosgene, -20 ^oC, 2 h; (h) aq KOH (2.5%), THF, 0 ^oC to rt, 5 h.*

Deshmukh and co-workers have reported the synthesis of key intermediate **93** which is summarized in Scheme 40. The synthesis started from starting β-lactam **178**, which was converted to amine **179** *via* reduction of aldehyde to corresponding alcohol, S_N2 displacement of mesyl with NaN_3 followed by transfer hydrogenation with ammonium formate/Pd. Amine **179** was reacted with benzyldehyde to give Schiff's base, which was reduced with $NaBH_4$ to provide sec-amine **180**. The amine **180** on acidic treatement led to dihydrochloride salt **181** and it was directly treated with phosgene/TEA in order to achieve one pot cyclic urea formation and chloromethylation. Finally treatment with KOH afforded the key intermediate lactone **93** for biotin synthesis.

Oh's approach (*Org. Lett.* **2007,** *9*, 2973-2975**)** [57]

In 2007 Oh has reported synthesis of a biotin core which was assembled in short and efficient sequence *via* Michael reaction/fragmentation/Michael reaction from vinyl sulfoxides and sulfone alcohol which is outlined in Scheme 41. The synthesis started with the 1-heptyne **182**, which was converted into **183** *via* Fridel-Crafts acylation and grinding

with NaSH. The compound **183** was subjected to oxidation with *m*-CPBA followed by reduction of the carbonyl functionality led to formation of sulfoxide **184a** as major product and **184b** as minor product. The **183** gave hydroxy sulfone **185** as single product on oxidation with oxone and reduction. The sulfone **185** was reacted with benzyl isocyanate and potassium *tert*-butoxide in one pot to afford urea **186** *via* Michael addition/fragmentation/Michael addition sequence in one pot, while hydroxy sulfoxide **184a** on similar reaction conditions led to sulfoxides **187** and **189**. The urea sulfoxides **187** and **189** on PCl_3 treatment converted to deoxy-biotin derivatives **188** and **161** respectively.



Scheme 41

Reagents and conditions: *(a) $AlCl_3$, DCM, $ClCOCH_2Cl$, 0-25 ^oC, 2 h, 80-90%, trans/cis= 5:1; (b) $NaSH:XH_2O$, neat, 25 ^oC, 1 h, 60-65%; (c) mCPBA, DCM, -78 ^oC, 1 h, 78=82%; (d) $NaBH_4$, MeOH, -10 ^oC,* ***184a****= 90-95%,* ***184b****= 2-5%; (e) Oxone, $MeOH/H_2O$, 0-25 ^oC, 5 h, 78-82 ^oC; (f) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -10 ^oC, 1 h, 90-95%; (g) BnNCO, TEA, DCM, then KOtBu /THF; (h) PCl_3, DCM, 0 ^oC, 1 h, 100 ^oC; (i) BnNCO, TEA, DCM, 25 ^oC, >95%; (j) KO^tBu, t-BuOH/THF or NaH, THF or DBU, THF.*

3.1.3 References

1) Kogl, F.; Tonnis, B.; Sey, H. Z. *Physiol. Chem.* **1936**, *242*, 443.

2) Du Vigneoud, V.; Hofmann, K.; Melville, D. B.; Gyorgy, P. *J. Biol. Chem.* **1941**, *140*, 643.

3) Melville, D. B.; Hofmann, K.; Hague, E. R.; Du Vigneaud, V. *J. Biol. Chem.* **1942**, *142*, 615.

4) Du Vigneoud, V.; Hofmann, K.; Melville, D. B.; Rachete, J. R. *J. Biol. Chem.* **1941**, *140*, 763.

5) (a) Du Vigneaud, V.; Melville, D. B.; Folkers, K.; Wolf, D. E.; Mozingo, R. Keresztesy, J. C; Harris, S. A. *J. Biol. Chem.* **1942**, *146*, 475. (b) Melville, D. B.; Moyer, A. W.; Hofmann, K.; Du Vigneaud, V. *J. Biol. Chem.* **1942**, *146*, 487.

6) (a) Harris, S. A.; Wolf, D. E.; Mozingo, R.; Anderson, R. C.; Arth, G. E.; Easton, N. R. *J. Am. Chem. Soc.* **1944**, *66*, 1756; (b) Heyl, D.; Wilson, A. N.; Folkers, K. *J. Am. Chem. Soc.* **1945**, *67*, 2098.

7) Traub, W. *Nature* **1956**, *178*, 647.

8) (a) Trotter, J.; Hamilton, Y. A. *Biochemistry* **1966**, *5*, 713, (b) De Titta, G. T.; Emond, J. W.; Stallings, W.; Donohue, J. *J. Am. Chem. Soc.* **1976**, *98*, 1920.

9) Glassel, J. A. *Biochemistry* **1966**, *5*, 1951.

10) Eisentberg, M. A. *Adv. Enzymol.* **1973**, *38*, 317.

11) Knappe, J. *Ann. Rev. Biochemistry* **1970**, *39*, 757.

12) Moss, J.; Lone, D. *Adv. Enzymol.* **1978**, *35*, 321.

13) Alberts, A. W.; Vagelse, P. R.; Boyer, P. D. *Academic Press, N. Y.*, **1972**, 37.

14) Bonjuir, J. P. *World Rev. Nutr. Diet* **1981**, *38*, 1.

15) (a) Wilcheck, M.; Bayer, E. A. *Anal. Biochem.* **1988**, *171*, 1; (b) Buenger, J.; Driller, H.; Wohlrab, W.; Motitschke, L.; Huschka, C.; Neubert, R. *PCT Int. Appl. WO 2000044342 A1* 3rd Aug **2000**, 39, *Chem. Abstr.* **2000**, *133*, 13994.

16) Wilcheck, M.; Bayer, E. A. *Trends Biochem. Sci.* **1989**, *14*, 408.

17) Crisp, G. T.; Gore, J. *Syn. Commun.* **1997**, *27*, 2203.

18) Han, Q.; Lafontaine, J.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Erickson, V S.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1371.

19) (a) Tejwani, R. B. *Ph.D. Thesis*, **1992** Pune University, INDIA; (b) Gopal, Ch. A. *Ph.D.Thesis*, **2001** Pune University, INDIA; (c) Ramakrishna, G. *Ph.D. Thesis*, **2005**

Pune University, INDIA (d) Ms. Soni, P. *Ph.D. Thesis*, **2003** Pune University, INDIA.

20) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.

21) Goldberg, M. W.; Strenbach, L. H. *US Pat. 2, 489232*, 22nd Nov **1949**; *Chem. Abstr.* **1951**, *45*, 184.

22) Goldberg, M. W.; Strenbach, L. H. *US Pat. 2, 489235*, 22nd Nov **1949**; *Chem. Abstr.* **1951**, *45*, 186a.

23) Goldberg, M. W.; Strenbach, L. H. *US Pat. 2, 489235*, 22nd Nov **1949**; *Chem. Abstr.* **1951**, *45*, 186g.

24) Harris, S. A.; Wolf, D. E.; Mozinco, R.; Anderson, R. C.; Arth, G. E.; Easton, N. R.; Hely, D.; Wilson, A. N.; Folkers, K. *J. Am. Chem. Soc.* **1944**, *60*, 1756.

25) (a) Bory, S.; Luche, M. J.; Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Letters* **1975**, 827; (b) Lavielle, S.; Bory, S.; Moreau, B.; Luche, J.; Marquet, A. *J. Am. Chem. Soc*. **1978**, *100*, 1558.

26) Confalone, P.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1975**, *97*, 5936.

27) Ohrui, H.; Emoto, S. *Tetrahedron Letters* **1975**, 2765.

28) Ogawa, T.; Kawano, T.; Matsui, M. *Carbohydr. Res.* **1977**, *57*, C31.

29) White, E. H.; Perks, H. M.; Roswell, D. F. *J. Am. Chem. Soc.* **1978**, *100*, 7423.

30) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6291.

31) Vogel, F. G. M.; Paust, J.; Nurrenbach, A. *Liebigs Ann. Chem*. **1980**, 1972.

32) Schmidt, R. R.; Maier, M. *Synthesis* **1982**, 747.

33) Ravindranathan, T.; Hiremath, S. V.; Reddy, D. R.; Rama Rao, A. V. *Carbohydr. Res.* **1984**, *134*, 332.

34) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148.

35) (a) Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391; (b). Casutt, M.; Poetsch, E.; Speckamp, W.N. *Ger.Offen. DE 3 926 690*, 14th Feb **1991**; *Chem. Abstr.* **1991**, *115*, 8429.

36) Turos, E.; Parvez, M.; Garigipati, R. S.; Weinreb, S. M.; *J. Org. Chem.* **1988**, *53*, 1116.

37) Mc Garrity, J.; Tenud, L.; Meul, T. *Eur. Pat. Appl. EP 0 270 076*, 8th June **1988**; *Chem. Abstr*. **1988**, *109*, 128718.

38) Bihovsky, R.; Bodepudi, V. *Tetrahedron* **1990**, *46*, 7667.

39) Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Letters* **1993**, *34*, 1167.

40) Senuma, M.; Fujii, T.; Seto, M.; Okamura, K.; Date, T.; Kinumake, A. *Chem. Pharm. Bull.* **1990**, *38*, 882.

41) Eyer, M.; Merrill, R. *PCT Int. Appl. WO 94/24137*, 27th Oct **1994**; *Chem. Abstr*. **1995**, *122*, 56043.

42) (a)Ravindranathan, T.; Chavan, S. P.; Tejwani, R. B. *Eur. Pat. Appl. EP* 564, *723*, 13th Oct **1993**; *Chem. Abstr*. **1994**, *120*, 217097t; *US patent* 5-274-107; *J. Org. Chem*. **2001**, *66*, 6197; (b) Bevezovski, V. M.; Mikhno, S. D.; Kulachkina, N. S.; Zhuk, V. B.; Preobrazhenskii, N. A. *Zh. Obshch. Khim.* **1963**, *33*, 2888.

43) Chavan S. P.; Chittiboyina A. G.; Ramakrishna, G.; Tejwani R. B.; Ravindranathan, T.; Kamat, S. K.; Sivadasan, L.; Deshpande, V. H. *J. Org. Chem*. **2005**, 70, 1901.

44) Chavan, S. P.; Chittiboyina, A. G.; Ravindranathan, T.; Kamat, S. K.; Kalkote, U. R. *Tetrahedron* **2005**, 61, 9273.

45) Seki, M.; Mori, Y.; Kimura, M. *Synthesis* **2003,** 15, 2311-2316.

46) Seki, M.; Shimizu, T. *Tetrahedron Letters* **2000**, *41*, 5099.

47) (a) Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S. C. *Tetrahedron Letters* **2002,** *43*, 3269; (b) Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S. C. *J. Org. Chem.* **2002**, *67*, 5527.

48) Seki, M.; Shimizu T.; Inubushi, K. *Synthesis* **2002,** *3*, 361.

49) Deroose, F. D.; De Clercq, P. J. *Tetrahedron Letters* **1993**, *34*, 4365.

50) Deroose, F. D.; De Clercq, P. J. *Tetrahedron Letters* **1994**, *35*, 2615.

51) Kurimoto, I.; Mizuno, M.; Hirata, N.; Minami, M. Jpn. Kokai Tokkyo Koho JP 06 263752, 20th Sept **1994**; *Chem. Abstr.* **1995**, *122*, 81011s.

52) Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Letters* **1999**, *40*, 8873.

53) Chen, F. E.; Huang, Y. D.; Fu, H.; Cheng, Y.; Zhang, D. M.; Li, Y. Y.; Peng, Z. Z. *Synthesis*, **2000**, 2004.

54) Chen, F. E.; Huang, Y. D.; Kuang, Y. Y.; Jia, H. Q. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3667.

55) Chen, F. E.; Zhao, J. F.; Xiong, F. J.; Xie, B.; Zhang, P.; *Carbohydrate Research* **2007**, 3*42*, 2461.

56) Kale, A. S.; Puranik, V. G.; Deshmukh, A. R. A. S. *Synthesis* **2007**, *8*, 1159-1164.

57) Oh, K. *Org. Lett.* **2007**, *9*, 2973.

Section 2

C-Alkylation strategy towards Biotin

3.2.1 Present work

3.2.1.1 Objective

D-(+)-Biotin (Vitamin H)[1] is a biocatalyst of reversible metabolic reactions involving carbon dioxide transport in organisms. It is used as an additive and as an avidin complex in the area of drug delivery, immunoassay, isolation and localization. In pharmaceutical industry, biotin has massive commercial importance especially in the tonic prescribed for the young children. Use of biotin is very popular particularly in US and European countries and mostly it is used in the poultry industry and animal husbandry. Recent study shows that biotin is also effective for the diabetes management in patients. Due to high price of biotin, in India its use is limited. Lack of efficient fermentation methods for biotin have drawn the attention of organic chemists towards its synthesis.

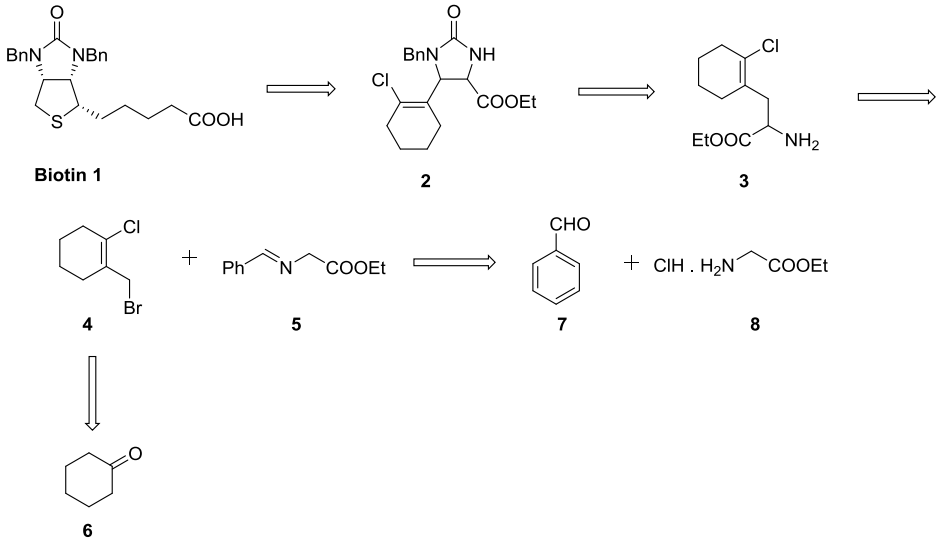
Although number of synthetic approaches for biotin are known (Chapter 3 Section 1),[2] such as diastereoisomeric or enzymatic resolutions,[3] chiral pool methods involving carbohydrates,[4] cysteine,[5] L-aspartic acid,[6] as well as asymmetric syntheses[7], yet there is a need for synthetic route for biotin that serves the industrial purpose. Increasing demand for biotin in the field of medicine and nutrition along with lack of efficient chiral synthetic route has prompted many synthetic chemists to pursue research towards the synthesis of biotin as evidenced by the number of publications in this area over last few years leading to the innovation of new synthetic strategies.

This group has been engaged in the synthesis of the biologically active molecule. In search of the development of practical, efficient and economically viable protocol, this group has reported some synthetic strategies for important bioactive molecules like camphothecin, venlafaxine, stemoamide, 3-hydroxy pipecolic acid and D-(+)-biotin starting from inexpensive and abundant starting material.[8]

Although a number of syntheses for biotin are known, no practical synthesis is available. Thus, there is a need to design a novel and more practical synthesis of biotin. The synthesis should start from materials which are very cheap and commercially easily available. In the present section, an alternative approach towards (±)-biotin was undertaken, which involved ethyl glycinate hydrochloride salt and cyclohexanone as abundant and inexpensive starting materials.

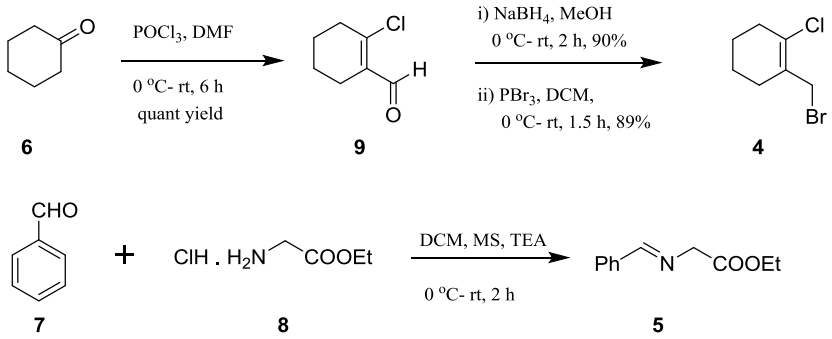
3.2.1.2 Retrosynthetic analysis

The retrosynthetic plan for the biotin **1** is shown in scheme 1. Accordingly the target compound **1** could be accessed from the urea intermediate **2**, which can be derived from the amine **3**. The amine **3** could be simply obtained from the cyclohexanone **6** and ethyl glycinate hydrochloride salt **8** as starting materials.



Scheme 1 Retrosynthetic analysis for Biotin **1**

3.2.1.3 Results and discussion

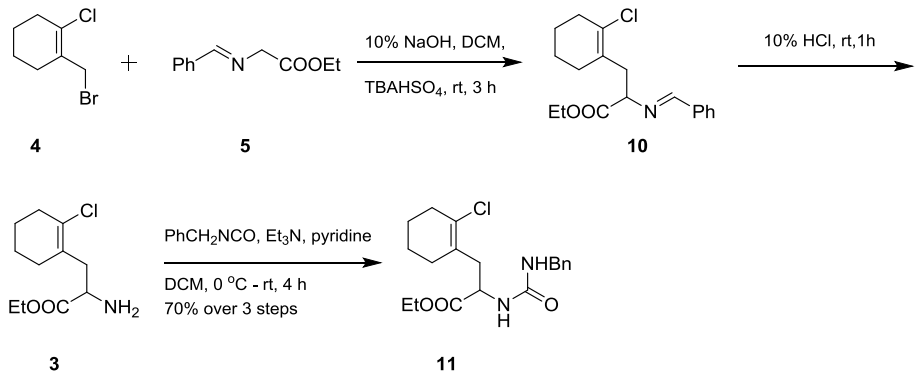


Scheme 2 Synthesis of bromide **4** and imine **5**

The synthesis started from the simple starting materials *viz* cyclohexanone **6** and ethyl glycinate hydrochloride salt **8** as starting materials. The synthesis of the bromide **4**[9] and imine **5** is described in the Scheme 2.

The next step was *C*-alkylation of the imine **5**, which was carried out using bromide **4** and 10% NaOH in DCM at rt to afford the compound **10**. The crude compound **10**

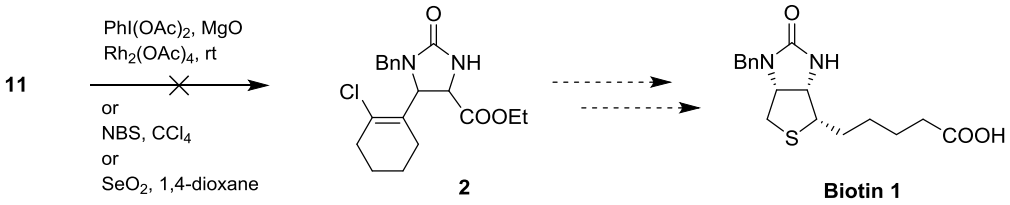
without purification was subjected to hydrolysis using 10% HCl at room temperature to furnish the amine **3**.[10] The crude amine **3** was directly treated with the benzyl isocyanate, pyridine and TEA as the base in DCM to afford the urea **11** in 70% yield over three steps (Scheme 3).



Scheme 3 Synthesis of acyclic urea **11**

The IR spectrum of urea **11** showed the bands at 1738 and 1669 cm^{-1} indicating presence of ester and urea functionality respectively. The ^{1}H NMR spectrum revealed the peaks at δ 7.33 - 7.07 (m, 5H) ppm for the aromatic protons and peaks at 4.05 (q, J = 7.1 Hz, 2H) and 1.22 (t, J = 7.1 Hz, 3H) ppm corresponding to ethyl ester protons. The peaks in ^{13}C NMR spectrum at δ 173.6 and 157.5 ppm were attributed to ester carbonyl and amide carbonyl carbon respectively while peaks at δ 128.8, 128.3, 127.28 and 126 ppm were assigned to aromatic carbons and ^{13}C DEPT spectrum showed the peaks at δ 61.25 and 14.0 ppm for methylene and methyl carbon of ethyl ester respectively while peaks at δ 37.3, 33.8, 29.8, 23.8 and 22.3 ppm were due to four cyclohexene $–CH_2$ carbons. The peak at 387.05 $(M+Na)^+$ in mass spectrum confirmed the molecular formula $C_{19}H_{25}ClN_2O_3$ of urea **11**.

Further urea **11** was subjected for intramolecular cyclisation under different reaction conditions like $PhI(OAc)_2/MgO/Rh_2(OAc)_4$,[11] NBS/CCl_4/AIBN and SeO_2/1,4-dioxane. These attempts led to complex reaction mass instead of getting desired cyclic urea **2** (Scheme 4).



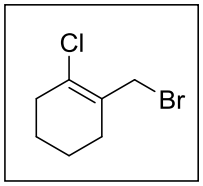
Scheme 4 Attempts towards biotin **1** synthesis from **11**

3.2.2 Conclusion

In conclusion, the synthesis of biotin started from cyclohexanone and ethyl glycinate hydrochloride salt as cheap and inexpensive materials. In a very short and efficient manner the urea was synthesized as the important intermediate, which could be explored further for the biotin synthesis with the proper choice of chemical tools.

3.2.3 Experimental Section

1-(Bromomethyl)-2-chlorocyclohex-1-ene (4)



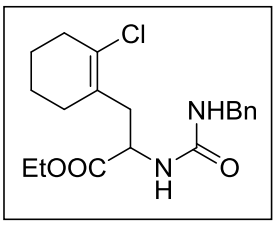
To the stirred solution of the aldehyde **9** (5 gm, 34.77 mmol) (which was prepared from the cyclohexanone **6** using reported procedure[9]) in methanol (50 mL) was added $NaBH_4$ (1.31 gm, 34.77 mmol) portion wise at 0 ^oC. The reaction mixture was stirred additionally at room temperature for 2 h and progress of reaction was monitored by TLC. The reaction mass was quenched with saturated aq. solution of NH_4Cl and solvent was evaporated under reduced pressure. The compound was extracted in DCM (3 X 30 mL) and combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford alcohol in sufficiently pure form, which was directly subjected to next reaction.

To the stirred solution of alcohol (4.5 gm, 30.82 mol) in dry DCM (50 mL) was added PBr_3 (1.85 mL, 12.32 mmol) dropwise at 0 ^oC. The reaction mixture was stirred at room temperature for 1.5 h and quenched with solid $NaHCO_3$. Water (70 mL) was added to the reaction mass and the compound was extracted in DCM (3 X 50 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford bromide **4** (5.73 gm, 89%).

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 4.11 (s, 2H), 2.38 - 2.29 (m, 4H), 1.81 - 1.63 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 132.1, 129.7, 34.1, 33.2, 28.7, 23.7, 22.2.

Ethyl 2-(3-benzylureido)-3-(2-chlorocyclohex-1-en-1-yl)propanoate (11)



To a solution of ethyl glycinate ester hydrochloride salt **8** (3 gm, 21.58 mmol) in DCM (30 mL) were added 4 Å MS (1.5 gm) and TEA (9 mL, 64.74 mmol) at 0 ^oC and the reaction mixture was stirred for 2 h min at same temperature. To the reaction mass was added benzaldehyde **7** (2.28 mL, 21.58 mmol) dropwise at same temperature and kept stirring for 1 h. The reaction mixture was filtered through the

simple filter paper and thoroughly washed with DCM (3 X 30 mL). Water (50 mL) was added to filtrate and the compound was extracted in DCM (3 X 40 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude imine **5**.

The crude imine **5** (4 gm, 20.94 mmol) was directly subjected for the next reaction. Imine **5** was dissolved in DCM (50 mL) and to it was added the bromo compound **4** (4.33 gm, 20.94 mmol), $TBAHSO_4$ (625 mg, 2.09 mmol) and aq. solution of 10% NaOH (837 mg, 20.94 mmol) at 0 ^oC. The reaction mixture was stirred vigorously at room temperature for 3 h. Water was added to the reaction mixture and compound was extracted in DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude imine **10**.

Further the crude imine **10** (4.1 gm, 12.85 mmol) was subjected to hydrolysis using aq. solution of the 10% HCl (0.703 gm, 19.27 mmol) and the reaction mixture was stirred vigorously at room temperature for 1 h. Water (30 mL) was added to the reaction mixture and organic impurities were removed by extraction with ethyl acetate (3 X 30 mL). The aq. layer was basified with solid $NaHCO_3$ and the compound was extracted in DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford amine **3**.

To a stirred solution of amine **3** (2.8 gm, 12.12 mmol) in dry DCM (30 mL) was added TEA (2.52 mL, 18.18 mmol) and pyridine (1.44 mL, 18.18 mmol) at 0 ^oC and stirred for 15 min at same temperature. To the reaction mixture was added benzylisocyanate (1.77 mL, 13.33 mmol) and the reaction mixture was stirred at room temperature for 4 h at rt. After completion of reaction, water (30 mL) was added and the compound was extracted with DCM (3 X 50 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet ether (2:8) as an eluent to provide urea **11** (3.84 gm, 70% over three steps) as a colorless syrup.

R_f: 0.5 (Pet.ether-ethyl acetate, 7:3).

Yield: 70% (over 3 steps).

MF: $C_{19}H_{25}ClN_2O_3$, **MW:** 364.87.

IR ($CHCl_3$, cm^{-1}): νmax 2924, 1738, 1669, 1450, 1170.

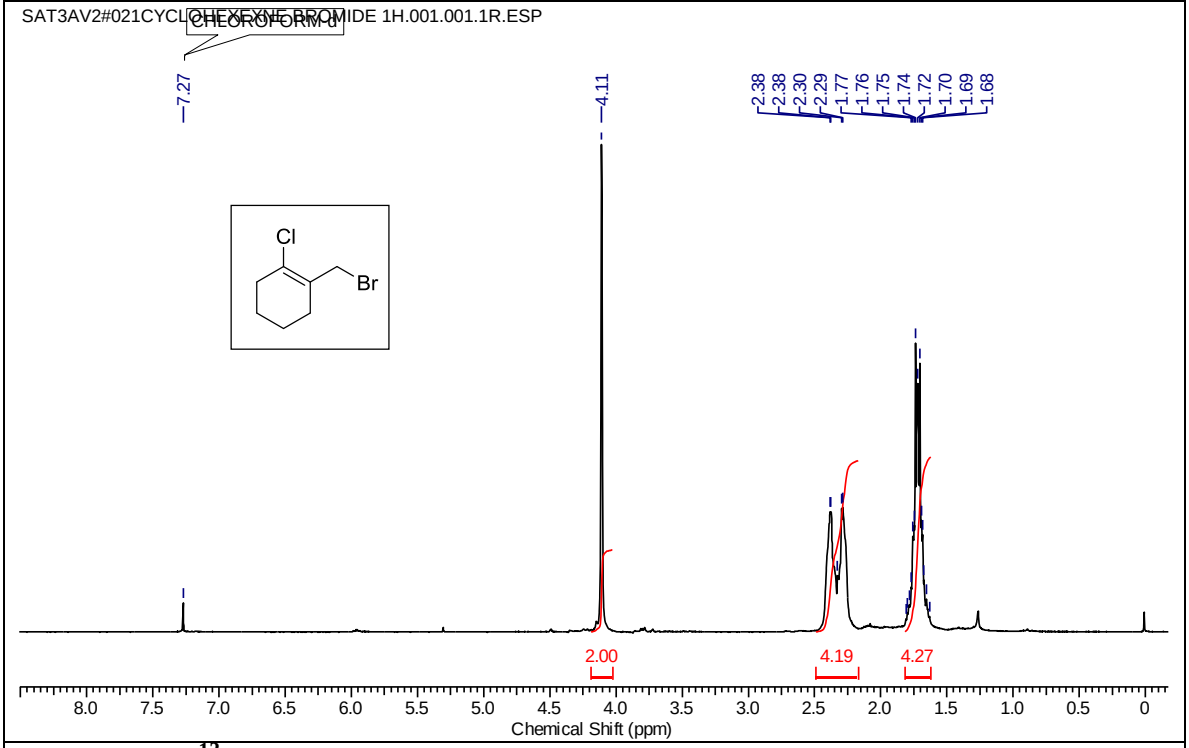
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.33 - 7.17 (m, 5H), 5.69 (bs, 2H), 4.62 (q, *J* = 8 Hz, 1H), 4.46 - 4.18 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.74 - 2.49 (m, 2H), 2.30-2.04 (m, 4H), 1.76 - 1.50 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 173.6, 157.5, 139.3, 129.4, 128.8, 128.3, 127.2, 126.93, 61.25, 51.2, 44.1, 37.3, 33.8, 29.8, 23.8, 22.3, 14.0.

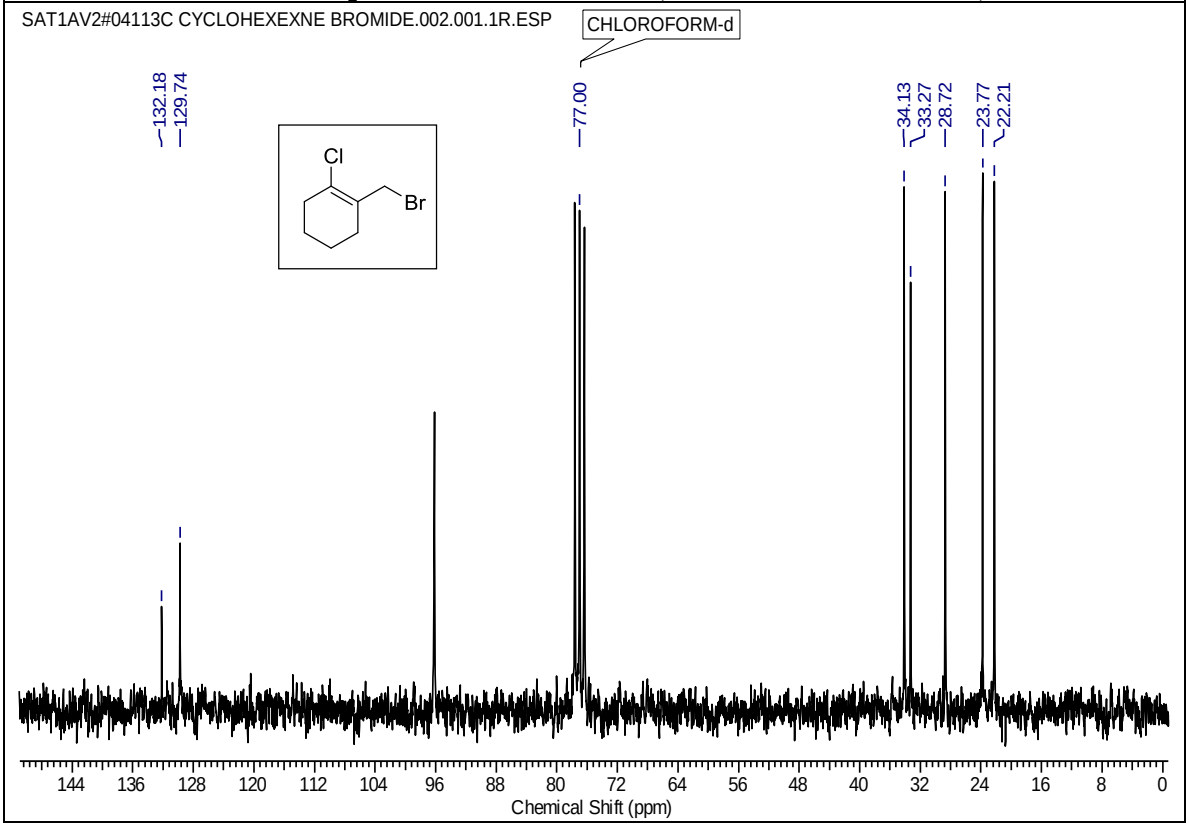
HRMS (ESI) : Observed-387.0524, caculated-387.0531.

3.2.4 Spectra

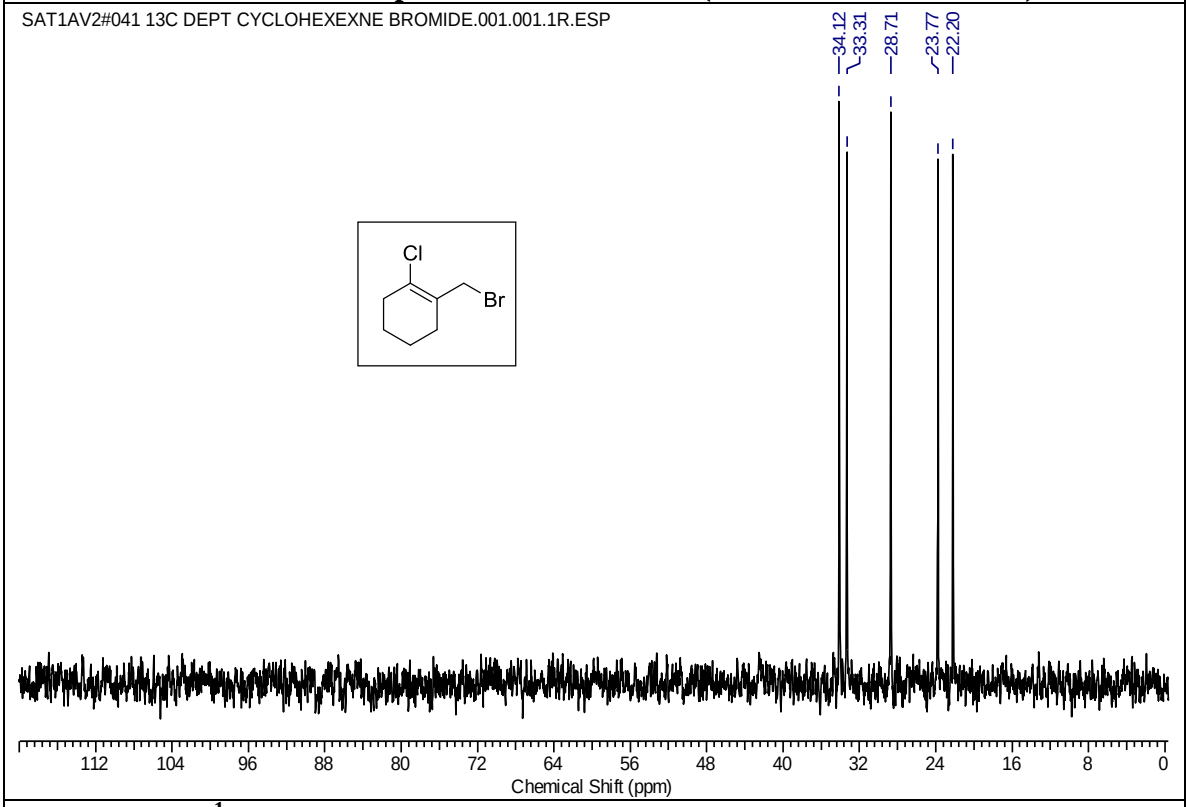
^{1}H NMR spectrum of bromide 4 (200 MHz, $CDCl_3$ + CCl_4)



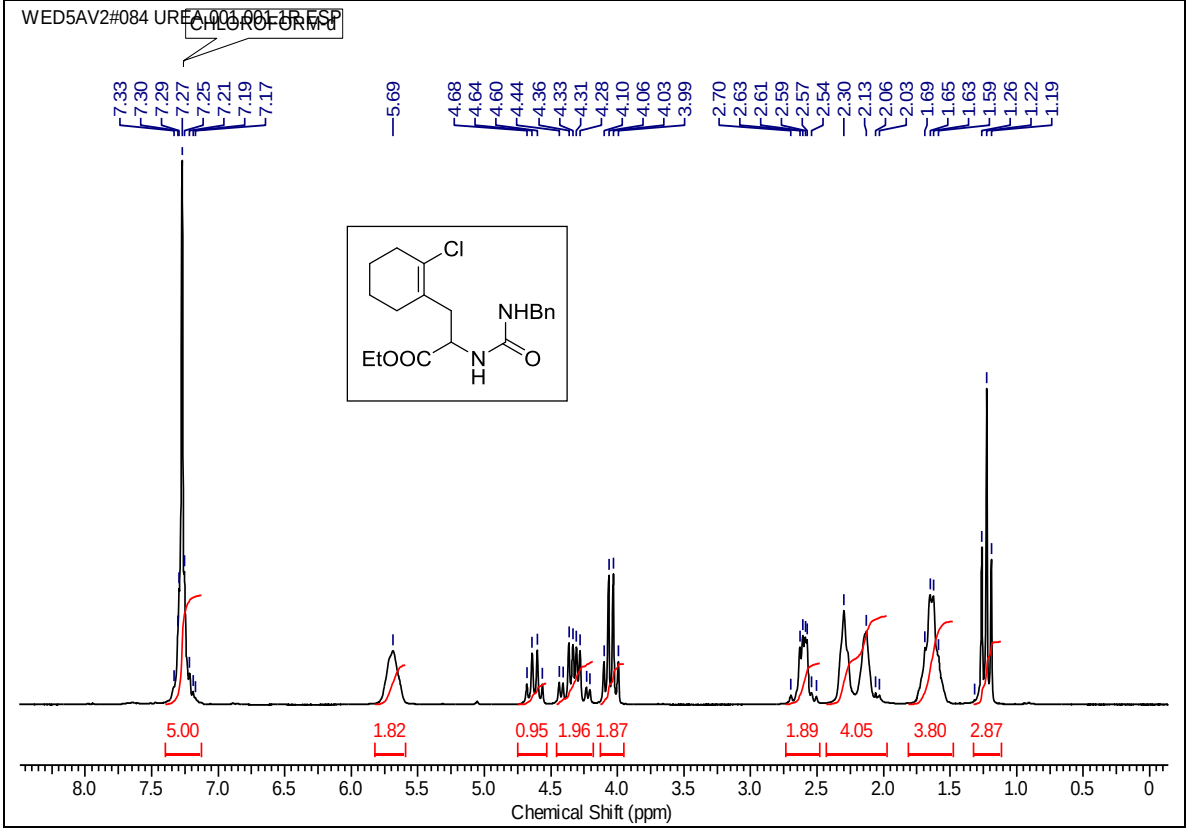
^{13}C NMR spectrum of bromide 4 (50 MHz, $CDCl_3$ + CCl_4)



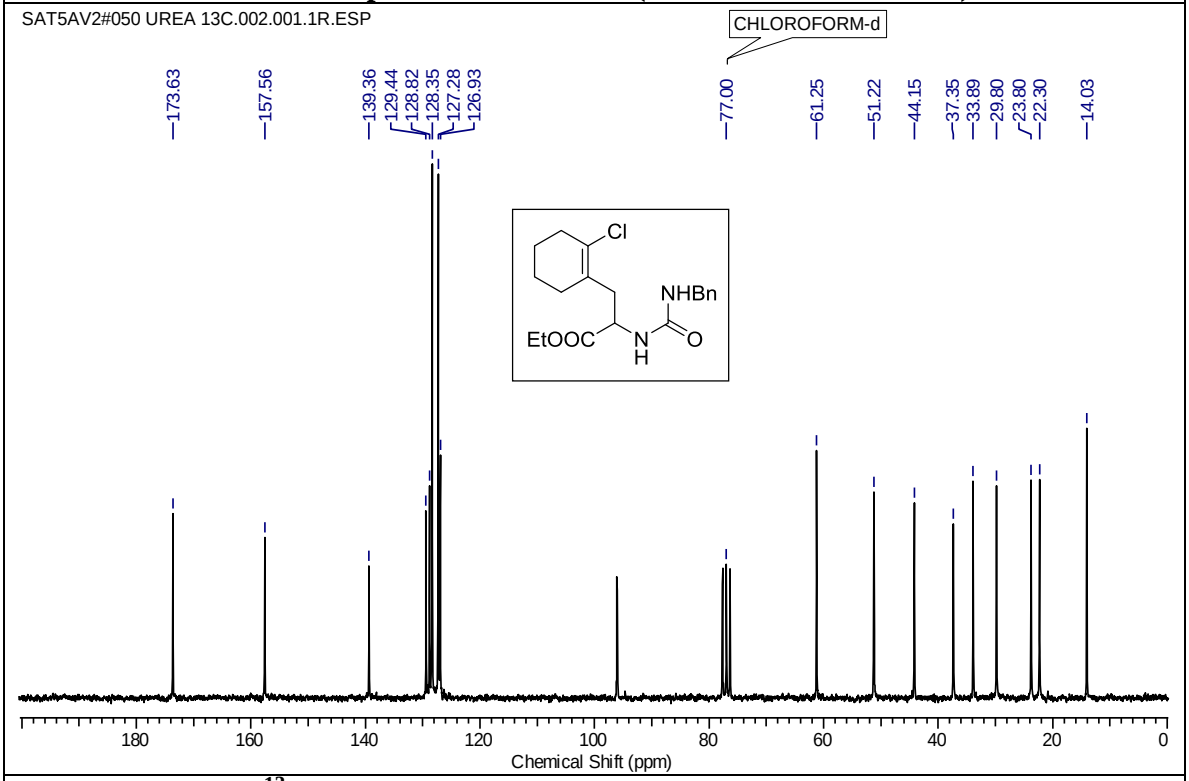
DEPT ^{13}C NMR spectrum of bromide 4 (50 MHz, $CDCl_3$ + CCl_4)



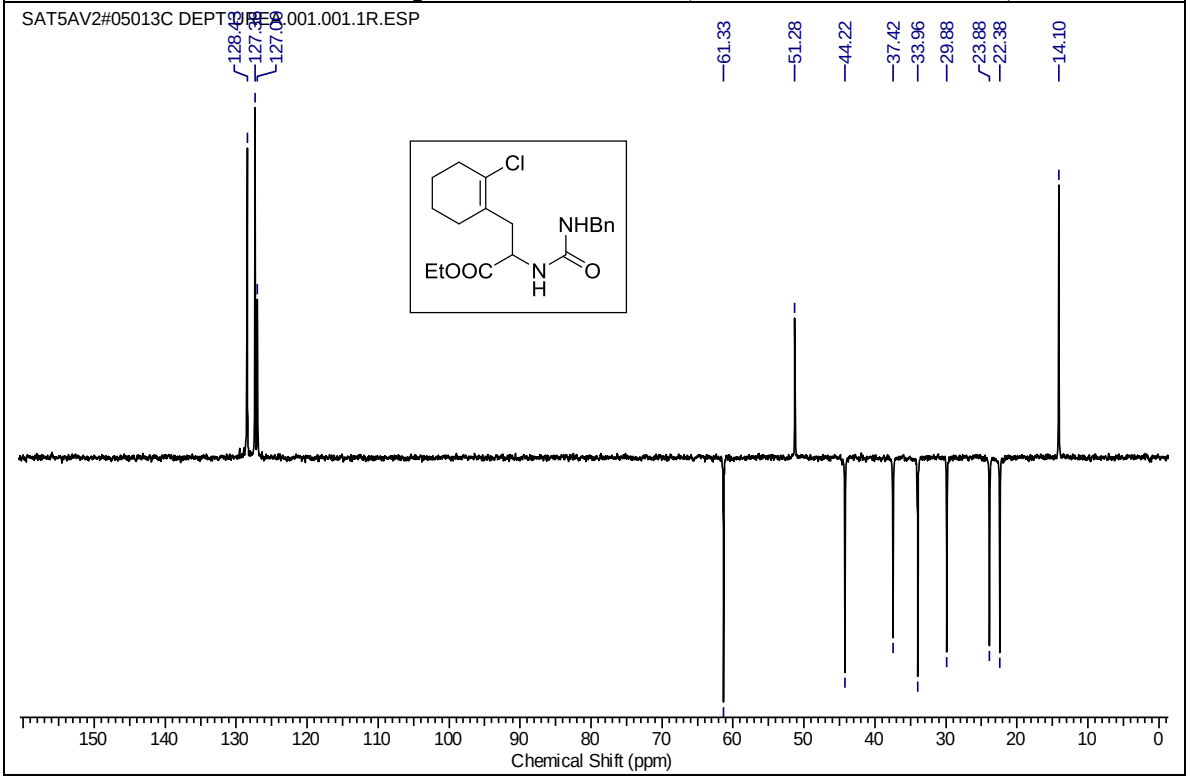
^{1}H NMR spectrum of urea 11 (200 MHz, $CDCl_3$ + CCl_4)



^{13}C NMR spectrum of urea 11 (50 MHz, $CDCl_3$ + CCl_4)



DEPT ^{13}C NMR spectrum of urea 11 (50 MHz, $CDCl_3$ + CCl_4)



3.2.5 References

1) Kogl, F.; Tonnis, B.; Sey, H. Z. *Physiol. Chem.* **1936**, *242*, 443.
2) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.
3) (a) Senum, M.; Fujii, T.; Okamu, K.; Date, T.; Kinumaki, K. *Chem. Pharm. Bull.* **1990**, *38*, 882; (b) Iriuchijuma, S.; Hasegawa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1982**, *46*, 1907.
4) (a) Ravindranathan, T.; Hiremath, S. V.; Reddy, D. R.; Rama Rao, A. V. *Carbohydr. Res.* **1984**, *134*, 332; (b) Ohuri, H.; Emoto, S. *Tetrahedron Lett.* **1975**, *16*, 2765; (c) Ogawa, T.; Kawano, T.; Matsui, M. *Carbohydr. Res.* **1997**, *57*, C31; (d) Ohuri, H.; Sueda, N.; Emoto, S. *Agric. Biol. Chem.* **1978**, *42*, 865; (e) Vogel, F. G. M.; Paust, J.; Nurrenbach, A. *Liebigs Ann. Chem.* **1980**, 1972.
5) (a) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148; (b) Fusijawa, T.; Nagai, M.; Kaike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865; (c) De Roose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321; (d) Moolenaer, M. J.; Speckamp, W. N.; Hiemstra, H.; Poestsch, E.; Casutt, M. *Angew. Chem.; Int. Ed. Engl.* **1995**, *34*, 2392; (e) Chavan, S. P.; Tejwani, B; Ravindranathan, T. *J. Org. Chem.* **2001**, *66*, 6197; (f) Chavan, S. P.; Chittiboyina, A, G.; Ravindranathan, T.; Kamat, S. K.; Kalkote, U. R. *J. Org. Chem.* **2005**, *70*, 1901.
6) Seki, M.; Simizu, T.; Inubushi, K. *Synthesis* **2002**, 361.
7) Chavan, S. P.; Lasonkar, P. B.; Chavan, P. N. *Tetrahedron: Asymmetry* **2013**, *24*, 1473.
8) (a) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879; (b) Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Tetrahedron Lett.* **2007**, *48*, 965; (c) Chavan, S. P.; Garai, S.; Pawar. K. P. *Tetrahedron Lett.* **2013**, *54*, 2137*;* (d) Chavan, S. P.; Harale, K. R.; Puranik, V. G.; Gawade. R. L. *Tetrahedron Lett.* **2012**, *53*, 2647*;* (e) Chavan, S. P.; Dumare, N. B.; Harale, K. R.; Kalkote, U. R. *Tetrahedron Lett.* **2011**, *52*, 404.
9) (a) Vilsmeier, A.; Haack, A. *B.* **1927**, *60*, 119; (b) Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789.
10) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *40*, 3847.
11) Espino, C. C.; Bois, J. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 598.

Section 3

Formal synthesis of Biotin: $MgCl_2/Et_3N$ mediated coupling and Mitsunobu reaction

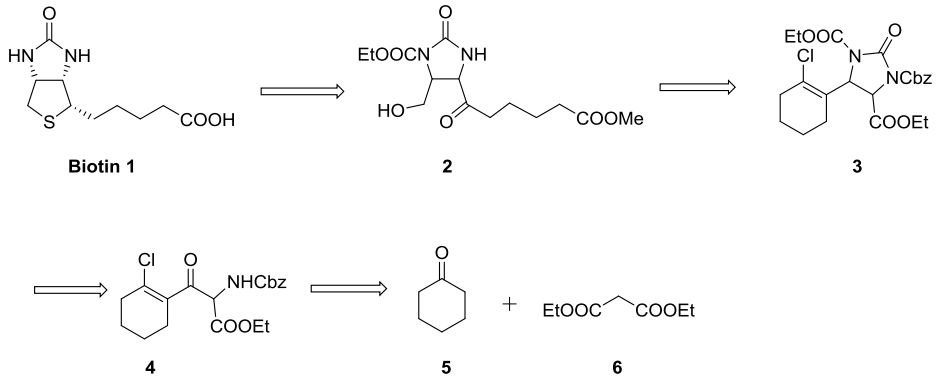
3.3.1 Present Work

3.3.1.1 Objective

This section describes the formal synthesis of (±)-biotin starting from inexpensive and abundant cyclohexanone and diethyl malonate as starting materials. The synthetic strategy involves $MgCl_2/Et_3N$ mediated coupling, Mitsunobu reaction, Staudinger reduction, enzymatic hydrolysis and ozonolysis as key reactions.

3.3.1.2 Retrosynthetic analysis

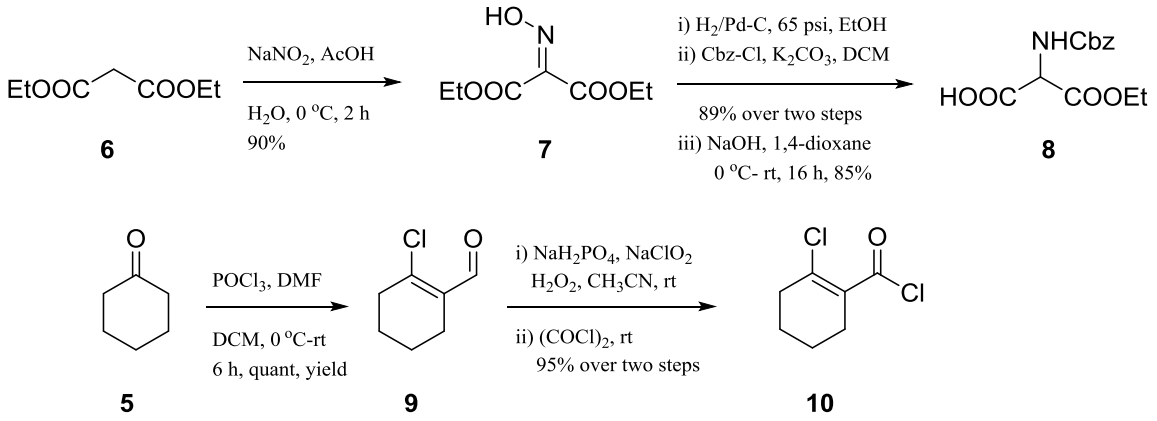
It is envisioned that biotin **1** can be accessed from keto alcohol **2** which could be derived from the urea **3** using proper chemical transformations. The urea **3** can be obtained from the β-ketone ester **4**. The β-keto ester **4** can be easily prepared from cyclohexanone **5** and diethyl malonate **6** (Scheme 1).



Scheme 1 Retrosynthetic analysis for biotin **1**

3.3.1.3 Results and discussion

Synthesis of biotin began with coupling of the acid **8** and acyl choride **10** (which were prepared from diethyl malonate and cyclohexanone shown in Scheme 2) in the presence of $MgCl_2$ and TEA in THF to furnish β-ketone ester **4** in 65% yield.[1] The IR spectrum showed the bands at δ 1728 and 1716 cm^{-1} indicating the presence of ester and ketone functionality respectively. The ^1H NMR spectrum showed the peaks at δ 2.59 - 2.21 (m, 4H) and 1.83 - 1.52 (m, 4H) ppm corresponding to cyclohexene $–CH_2$ protons and peaks at δ 4.23 (q, *J* = 7.0 Hz, 2H) and 1.28 (t, *J* = 7.1 Hz, 3H) for ethyl ester group. ^{13}C NMR spectrum showed peaks at δ 195.2 and 165.9 ppm for ketone and ester carbonyl carbon



Scheme 2 Synthesis of acid **8** and acyl chloride **10**

respectively and peaks at δ 34.0, 28.2, 23.0 and 21.2 ppm corresponding to cyclohexene methylene carbons. The HRMS spectrum showed the peak at 402.1074 which confirmed molecular formula $C_{19}H_{22}ClNO_5$ of the β-keto ester **4**.

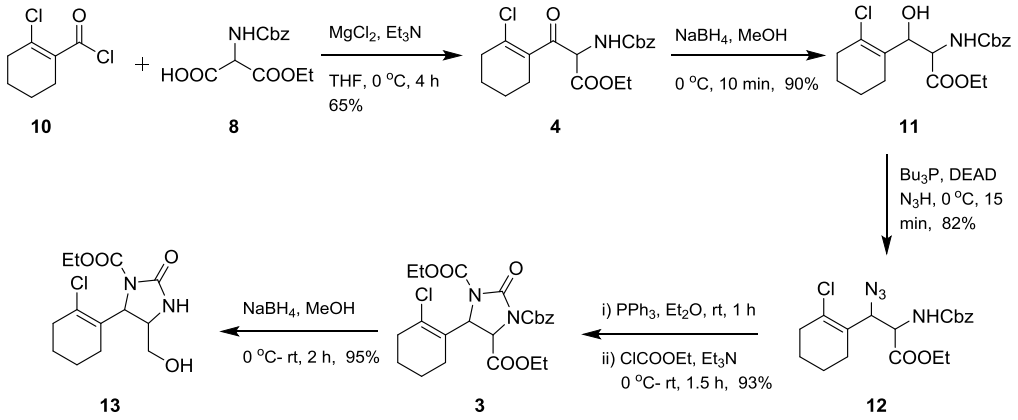
The chemoselective reduction of β-keto ester **4** was carried out using $NaBH_4$ in MeOH at 0 ^oC to furnish β-hydroxy ester **11** in 90% yield. The band at 3409 cm^{-1} in IR spectrum indicated chemoselective reduction of β-keto ester **11** and band at 1718 cm^{-1} confirmed the presence of ester functionality. The peak at δ 5.41 (d, *J* = 9.3 Hz, 1H) ppm in ^1H NMR spectrum for one proton showed presence of -NHCO group and peaks at δ 4.24 (q, *J* = 7.0, 2H) and 1.32 (t, *J* = 7.0 Hz, 3H) corresponding to five protons indicated the presence of ethyl ester. The ^{13}C NMR spectrums showed the peak at δ 171.1 ppm for ester carbonyl carbon and in 13C DEPT NMR spectrum peaks at δ 34.1, 24.7, 23.6 and 21.8 ppm were assigned for four methylene carbons of cyclohexene and peak at 67.1 for ester methylene carbon. The peak in HRMS at 404.1232 confirmed molecular formula $C_{19}H_{24}ClNO_5$ of the β-hydroxy ester **11**.

Next task was introduction of second nitrogen, which was done by treating **11** in optimized condition, Bu_3P, N_3H in toluene and DEAD at 0 ^oC to afford azide **12** in 82% yield.[2] The strong band at 2105 cm^{-1} in IR spectrum was assigned to azide functionality. The ^1H spectrum showed the peak at δ 4.67-4.60 (m, 1H) ppm corresponding to proton attached to azide group. The ^{13}C NMR spectrum showed peaks at δ 169.2 and 155.7 corresponding to carbons of ester and carbamate groups respectively. The peaks at δ 64.4

and 56.2 ppm in ^{13}C DEPT NMR spectrum indicated presence of two –CH carbons. The peak observed at 429.1295 in HRMS confirmed molecular formula $C_{19}H_{23}ClN_4O_4$ of azide **12**.

The azide **12** was subjected to Staudinger reaction[3] condition using PPh_3 in Et_2O at room temperature to afford amine, which without further purification was subjected to chemical masking with ethyl chloroformate and TEA as base to afford cyclic urea **3** as sole product in excellent yield. The strong bands at 1817, 1750 and 1728 cm^{-1} in IR spectrum indicated both nitrogens of urea were masked as *N*-Cbz and *N*-COOEt. The ^1H NMR spectrum showed the peaks at δ 1.34 (t, *J* = 7.2 Hz, 3H) and 1.25 (t, *J* = 7.2 Hz, 3H) which were related to methyl protons of two ethyl ester groups. The ^{13}C DEPT NMR spectrum showed the peaks at δ 57.9 and 55.4 ppm for two methyl carbons present in urea **3**. The HRMS spectrum showed peak at 501.1400 which confirmed molecular formula $C_{23}H_{27}ClN_2O_7$ of urea **3** (Scheme 3).

The urea **3** was reduced with $NaBH_4$ in MeOH wherein *N*-Cbz deprotection and ester reduction occurred to furnish alcohol **13** in 95% yield (Scheme 3). The strong bands at 3366 and 1742 cm^{-1} in IR spectrum indicated presence of hydroxy and ester functionality respectively. The disappearance of aromatic protons at δ 7.43 - 7.28 (m, 5H) in ^1H NMR spectrum strongly supported *N*-Cbz deprotection and ester reduction to afford alcohol **13**. The ^{13}C NMR spectrum showed peaks at δ 154.6 and 150.8 ppm corresponding to ester and urea carbonyl carbon respectively while ^{13}C DEPT NMR spectrum showed the peak.

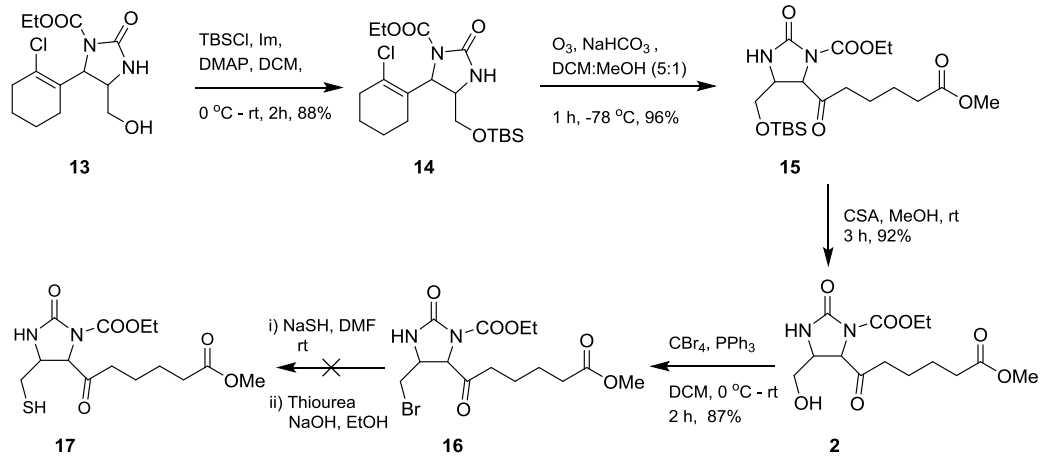


Scheme 3 Synthesis of alcohol **13**

at δ 55.6 ppm for methylene carbon of $–CH_2OH$ group. The peak observed at 325.0924 in HRMS spectrum confirmed molecular formula $C_{13}H_{19}ClN_2O_4$ of alcohol **13.**

Alcohol **13** was subjected to TBS ether protection using TBSCl, imidazole and cat. DMAP at 0 ^oC to room temperature in dry DCM to give TBS derivative **14** in 88% yield. The IR spectrum showed bands at 1783 and 1751 cm^{-1} for ester and urea carbonyl respectively. The peaks in ^1H NMR at δ 0.88 (s, 9H) and 0.07 (s, 6H) ppm revealed for presence of TBS protons which confirmed TBS protection of alcohol **13**. The ^{13}C DEPT NMR spectrum showed peaks at δ -5.4 and -5.5 ppm for two methyl carbons and peak at 25.7 ppm for *t*-butyl of TBS functionality. The HRMS spectrum showed peak at 439.1790 which confirmed molecular formula $C_{19}H_{33}ClN_2O_4Si$ of the TBS derivative **14**.

The TBS derivative **14** was subjected to ozonolysis using O_3 and $NaHCO_3$ in DCM: MeOH to furnish ester **15** in 96% yield. The IR spectrum showed band at 1735 cm^{-1} which indicated the presence of ester functionality. ^1H NMR spectrum showed the peak at δ 3.67 (s, 3H) ppm for methyl ester and peaks at δ 0.91 (s, 9H) and 0.10 (s, 6H) ppm for TBS group protons. The ^{13}C NMR spectrum showed peaks at δ 204.8 and 173.4 ppm for ketone and ester carbonyl carbon respectively. The peak at δ 51.5 ppm in ^{13}C DEPT NMR spectrum corresponded to methyl carbon of ester while peaks at δ 65.3, 62.9, 37.9, 33.6, 24.2 and 22.5 ppm were observed for six methyl carbons of **15**. The HRMS spectrum showed peak at 467.2180 corresponding to molecular formula $C_{20}H_{36}N_2O_7Si$ of ketone **15** (Scheme 4).



Scheme 4 Synthetic attempt towards thiol **17**

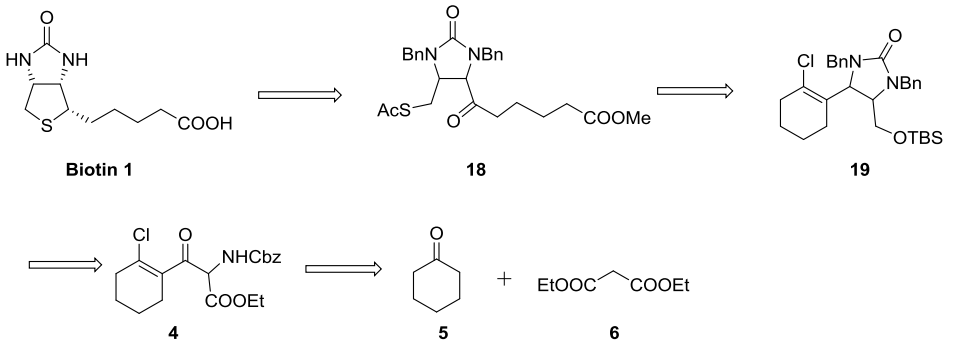
The TBS deprotection of keto ester **15** was carried out with CSA in MeOH at room temperature to afford ester **2** in 92% yield.[4] The strong band at 3422 cm^{-1} in IR spectrum confirmed the presence of hydroxy functionality in **2**. Disappearance of peaks at δ 0.91 (s, 9H) and 0.10 (s, 6H) ppm in ^{1}H NMR spectrum supported to TBS deprotection. The ^{13}C NMR spectrum showed peaks at δ 205.1, 173.7 ppm assigned for ketone and ester carbonyl carbon and ^{13}C DEPT NMR spectrum showed peak at δ 14.2 ppm corresponding to methyl carbon of ethyl ester. The HRMS spectrum showed the peak at 353.1312 which confirmed molecular formula $C_{14}H_{22}N_2O_7$ of alcohol **2**.

Alcohol **2** was subjected to Apple reaction condition using PPh_3 and CBr_4 in dry DCM to afford bromide **16** in 87% yield.[5] The IR spectrum showed bands at 1723 and 1708 cm^{-1} indicating presence of ester and ketone functionality. The ^{1}H NMR showed peaks at δ 3.53 - 3.26 (m, 2H) and 3.66 (s, 3H) ppm corresponding to two protons of $–CH_2Br$ group and methyl ester respectively. The HRMS spectrum showed the peak at 415.0470 which confirmed the molecular formula $C_{14}H_{21}BrN_2O_6$ of the bromide **16**.

For the preparation of thiol **17**, the bromide **16** was treated under different reaction conditions as shown in the Scheme 4. However, the attempts led to failure to obtain thiol **17**.

3.3.1.4 Revised retrosynthetic analysis

The alternative strategy was planned wherein it was envisioned that biotin **1** could be obtained from crucial intermediate thioacetate **18**. The thioacetate **18** can be easily



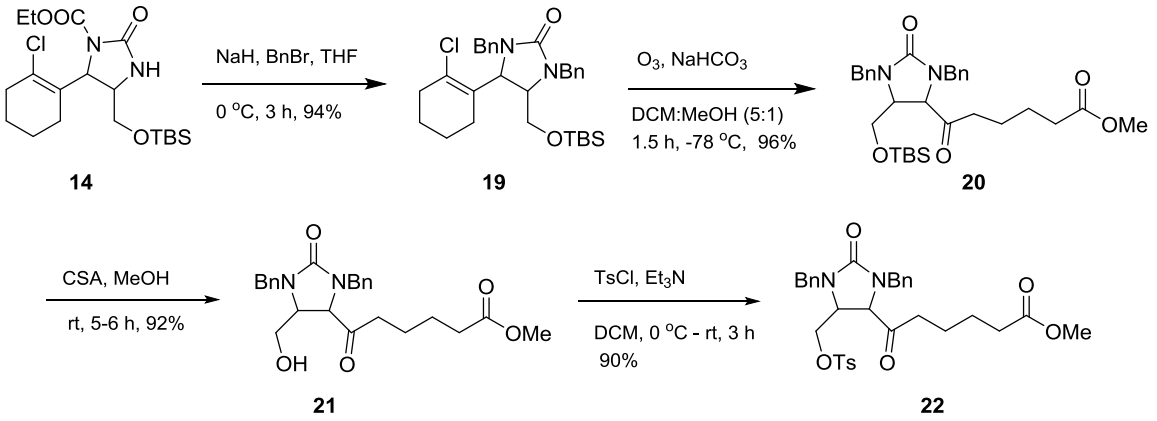
Scheme 5 Revised retrosynthetic analysis for biotin **1**

accessed from the urea **19** by ozonolysis and thiol introduction. The urea **19** can be

obtained from β-keto ester **4** using proper choice of reactions. The β-keto ester **4** can be derived from the cheap and inexpensive starting materials cyclohexanone and diethyl malonate (Scheme 5).

The synthesis of urea **14** is described in Chapter 3.3.1.4. The urea **14** was treated with benzyl bromide and NaH as base in dry THF at 0 ^{o}C to room temperature for decaboxylation followed by benzyl protection to give dibenzyl urea **19** in 94% yield. The band at 1698 cm^{-1} in IR spectrum corresponded to the urea functionality. The ^{1}H NMR spectrum showed the peaks at δ 7.34 - 7.21 (m, 10H) ppm for aromatic protons which supported to dibenzyl urea formation. The peaks at δ 131.1, 130.1, 128.8, 128.4, 128.3, 127.3 and 127.2 ppm in ^{13}C NMR indicated the aromatic carbons and ^{13}C DEPT NMR spectrum showed the peaks at δ 46.8 and 46.1 ppm related with benzyl methylene carbons. The HRMS spectrum showed the peak at 547.2523 which confirmed molecular formula $C_{30}H_{41}ClN_2O_2Si$ of the dibenzyl urea **19**.

The dibenzyl urea **19** was subjected to ozonolysis to afford ester **20** in good yield. The strong bands present in IR spectrum at 1733, 1706 and 1690 cm^{-1} indicated the presence of ester, ketone and urea functionality respectively. The ^{1}H NMR spectrum showed the peak at δ 3.68 (s, 3H) related to methyl ester protons. The ^{13}C NMR spectrum showed the peaks at δ 207, 173.4 and 159.5 ppm assigned for ketone, ester and urea carbonyl carbons respectively and its ^{13}C DEPT NMR spectrum exhibited peak at δ 51.4 ppm for carbon of methyl ester. The peak observed in HRMS at 575.2915 confirmed molecular formula



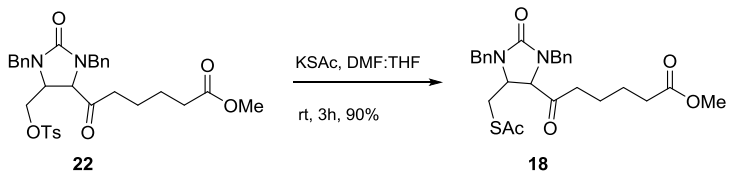
14 **19** **20** **21** **22**

Scheme 6 Synthesis of tosylate **22**

$C_{31}H_{44}N_2O_5Si$ of ester **20** (Scheme 6).

The TBS deprotection of ester **20** was carried out in MeOH using CSA at room temperature to give alcohol **21** in 92% yield. The IR spectrum showed strong band at 3436 cm^{-1} indicating the hydroxy functionality. The disappearance of the protons at δ 0.87 - 0.79 (m, 9H) and -0.02 (s, 6H) ppm in ^1H NMR supported the deprotection of TBS. The peaks at δ 207.5 and 173.5 ppm in ^{13}C NMR spectrum corresponded to ketone and ester carbonyl carbon respectively and its ^{13}C DEPT NMR spectrum showed the peaks at δ 61.5 and 51.5 corresponding with methyl carbon of ester and methylene carbon of $–CH_2OH$ group respectively. The peak observed at 461.2045 in HRMS clearly confirmed molecular formula $C_{25}H_{30}N_2O_5$ of alcohol **21**.

Next task was to introduce thiol group. Accordingly, alcohol **21** was converted into tosylate **22** using tosyl choride, TEA and cat. DMAP to furnish tosylate **22**. The disappearance of band at 3436 cm^{-1} in IR spectrum of **22** confirmed formation of tosyl derivative. The ^1H NMR spectrum showed the peak at δ 2.48 (s, 3H) for methyl protons of tosyl group. The ^{13}C DEPT NMR spectrum showed peaks at δ 21.7 and 51.5 for methyl carbon of tosyl and ester functionality respectively. The HRMS spectrum showed

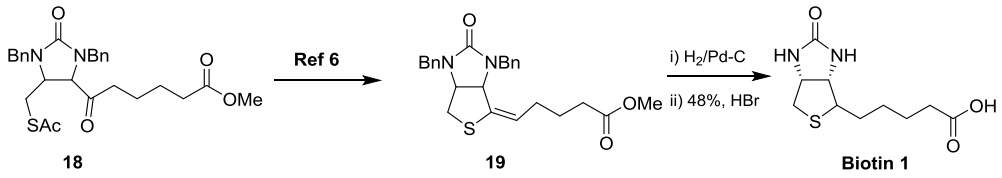


Scheme 7 Synthesis of thioacetate **18**

the peak at δ 615.2130 corresponding to molecular formula $C_{32}H_{36}N_2O_7S$ of tosylate **22**. Tosylate **22** was subjected to nucleophilic displacement using potassium thioacetate in DMF: THF at room temperature to afford thioacetate **18** in 90% yield. The bands at 1728 and 1710 cm^{-1} in IR spectrum related to ester and ketone functionality respectively. The ^1H NMR spectrum showed peak at δ 2.23 (s, 3H) ppm corresponding to methyl protons of thioacetate group. The ^{13}C NMR showed peak at δ 194.1 ppm for thioacetate carbon while ^{13}C DEPT NMR spectrum showed peaks at δ 51.4 and 30.5 ppm for methyl carbon

of ester and thioacetate group respectively. The peak observed at 519.1918 in HRMS spectrum confirmed molecular formula $C_{27}H_{32}N_2O_5S$ of thioacetate **18** (Scheme 7).

Conversion of thioacetate **18** to olefin **19** is well reported in literature.[6]



Scheme 8 Synthesis of biotin **1**

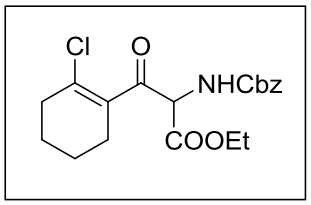
3.3.3 Conclusion

In conclusion, the synthesis of alcohol **2** as a key intermediate has been achieved, which could be explored for the preparation of biotin using appropriate chemical tools. The synthesis was started from the very cheap, abundant and readily available starting materials, diethyl malonate and cyclohexanone. The key features of the synthesis involved Mitsunobu reaction, ozonolysis and Apple reaction.

Formal synthesis of biotin has been achieved from economical and abundant starting materials diethyl malonate and cyclohexanone. This synthesis involved Mitsunobu reaction, ozonolysis and Apple reaction as key steps.

3.3.4 Experimental section

Ethyl 2-(((benzyloxy)-carbonyl)-amino)-3-(2-chlorocyclohex-1-en-1-yl)-3-oxopropan oate (4)



To the solution of the mono acid **8** (20 gm, 71.17 mmol) in dry THF (200 mL) was added $MgCl_2$ (3.58 gm, 37.72 mmol) and TEA (79 mL, 569 mmol) at 0 ^oC. The slurry was stirred at same temperature for 2 h and to the reaction mixture was added acid chloride **10** (6.37 mL, 35.58 mmol) dropwise in dry THF (50 mL). The reaction mixture was stirred additionally for 2 h and reaction was monitored by TLC. After completion of reaction, saturated aq. solution of NH_4Cl was added and compound was extracted in DCM (3 X 150 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using pet ether and ethyl acetate (1:9) as an eluent to provide β-keto ester **4** (17.53 gm, 65%) as colorless syrup.

***R_f*:** 0.6 (Pet. ether: ethyl acetate, 70:30).

MF: $C_{19}H_{22}ClNO_5$, **MW:** 379.84.

Yield: 65%.

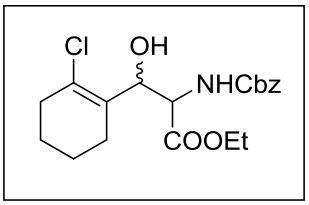
IR ($CHCl_3$, cm^{-1}): ν_{max} 2937, 2866, 1728, 1716, 1699, 1653, 1502, 1330.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.40 - 7.26 (m, 5H), 5.99 (d, *J* = 7.7 Hz, 1H), 5.66 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.59 - 2.21 (m, 4H), 1.83 - 1.52 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 195.2, 165.9, 155.3, 134.5, 133.2, 128.5, 128.0, 127.8, 67.1, 62.6, 62.3, 34.0, 28.2, 23.0, 21.2, 14.0.

HRMS (ESI) : Observed- 402.1074, calculated- 402.1079 $(M+Na)^+$.

Ethyl 2-(((benzyloxy)carbonyl)amino)-3-(2-chlorocyclohex-1-en-1-yl)-3-hydroxy pro panoa te (11)



To a solution of keto ester **4** (15 gm, 39.57 mmol) in methanol (150 mL) was added $NaBH_4$ (0.902 gm, 23.74 mmol) at 0 ^oC in small portion. The reaction mixture was allowed to stir for 10 min at same temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The aq. solution of NH_4Cl was added to the semisolid mass and allowed to stir for 30 min and the reaction mixture was extracted with DCM (3 X 150 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether (2:8) as an eluent to provide alcohol **11** (13.57 gm, 90%) as colorless syrup.

***R_f*:** 0.5 (Pet. ether-ethyl acetate, 70:30).

MF: $C_{19}H_{24}ClNO_5$, **MW:** 381.85.

Yield: 90%.

IR ($CHCl_3$, cm^{-1}): ν_{max} 3409, 2928, 1718, 1708, 1527, 1217, 1048.

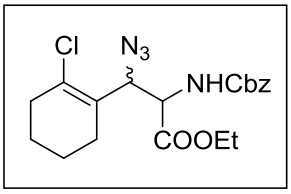
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.45 - 7.28 (m, 10H), 5.41 (d, *J* = 9.3 Hz, 1H), 5.21 - 4.99 (m, 3H), 4.52 (s, 1H), 4.24 (q, *J* = 7.0, 2H), 2.92 (bs, 1H), 2.40 - 1.93 (m, 4H), 1.71 - 1.46 (m, 4H), 1.32 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 171.1, 155.8, 136.2, 131.2, 130.6, 128.5, 128.2, 128.1, 72.0, 67.1, 61.9, 56.6, 34.1, 24.7, 23.6, 21.8, 14.1.

HRMS (ESI): Observed- 404.1232, calculated- 404.1235 $(M+Na)^+$.

Ethyl 3-azido-2-(((benzyloxy) carbonyl) amino)-3-(2-chlorocyclohex-1-en-1-yl)propanoate (12)

To alcohol **11** (6 g, 15.74 mmol) were added PBu_3 (6.32 mL, 25.44 mmol) and N_3H solution in toluene (47 mL, 47.24 mmol) at -20 ^oC and stirred for 15 min, followed by addition of DEAD (7 mL, 34.64 mmol) and then reaction mixture was allowed to stir at same temperature for 15 min. The reaction mixture was quenched by adding water and



extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether (2:8) as an eluent to afford azide **12** (5.24 gm, 82%) as colorless syrup.

***R_f*:** 0.6 (Pet. ether: ethyl acetate, 75:25).

MF: $C_{19}H_{23}ClN_4O_4$, **MW:** 406.87.

Yield: 82%.

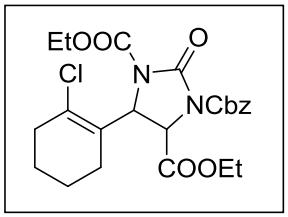
IR ($CHCl_3$, cm^{-1}): ν_{max} 3038, 2938, 2105, 1730, 1654, 1513, 1257.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.51 - 7.28 (m, 10H), 5.37 (d, *J* = 9.2 Hz, 1H), 5.22 (d, *J* = 5.1 Hz, 1H), 5.13 (d, *J* = 3.9 Hz, 2H), 4.67-4.60 (m, 1H), 4.32 - 4.18 (m, 2H), 2.50 - 2.11 (m, 4H), 1.80 - 1.49 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 169.2, 155.7, 136.1, 132.2, 128.5, 128.2, 128.1, 67.2, 64.4, 62.0, 56.2, 34.0, 26.3, 23.4, 21.9, 14.2.

HRMS (ESI): Observed- 429.1295, calculated- 429.1300 $(M+Na)^+$.

3-Benzyl 1, 4-diethyl 5-(2-chlorocyclohex-1-en-1-yl)-2-oxoimidazolidine-1,3,4-tri-car boxylate (3)



The azide **12** (3 gm, 7.38 mmol) was dissolved in the diethyl ether (30 mL) and triphenyl phosphine (2.90 gm, 11.08 mmol) was added at room temperature portion wise (bubbling was seen). The reaction mixture was stirred till bubbling ceased and it was further kept stirring for 1 h min and solvent was evaporated under reduced pressure. The crude amine residue was subjected for the next reaction.

To a solution of crude amine obtained above (4 gm, 10.5 mmol) in dry DCM (40 mL) was added triethylamine (4.4 mL, 31.57 mmol) followed by ethylchoroformate (3 mL, 31.49 mmol) and cat. DMAP at 0 ^{o}C. The reaction mixture was allowed to stir for 1.5 h under nitrogen atmosphere. After completion of reaction, reaction mixture was poured in cold ice water and then the product was extracted with DCM (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether as an eluent to provide ureide **3** in 93% yield as colorless syrup.

***R_f*:** 0.7 (Pet. ether: ethyl acetate, 75:25).

MF: $C_{23}H_{27}ClN_2O_7$, **MW:** 478.93.

Yield: 93%.

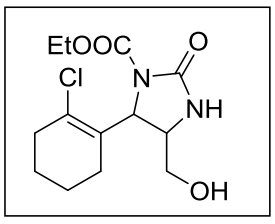
IR ($CHCl_3$, cm^{-1}): ν_{max} 2983, 2938, 1817, 1750, 1728, 1661, 1370, 1024..

^{1}H NMR (400MHz, $CDCl_3$ + CCl_4): δ 7.43 - 7.28 (m, 5H), 5.39 - 5.23 (m, 3H), 4.40 - 4.14 (m, 5H), 2.48 - 2.36 (m, 2H), 1.98 (bs, 2H), 2.06 - 1.91 (m, 2H), 1.79 - 1.60 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 168.5, 150.9, 150.5, 147.3, 134.7, 131.6, 129.4, 128.5, 128.4, 127.9, 68.8, 63.2, 62.4, 57.9, 55.4, 33.9, 24.1, 23.3, 21.7, 14.2, 14.0.

HRMS (ESI): Observed- 501.1400, calculated- 510.1399 $(M+Na)^+$.

Ethyl 5-(2-chlorocyclohex-1-en-1-yl)-4-(hydroxymethyl)-2-oxoimidazolidine-1-carboxylate (13)



To a solution of ureide **3** (1.8 gm, 3.76 mmol) in methanol (20 mL) was added $NaBH_4$ (0.290 gm, 7.53 mmol) portion wise at 0 ^{o}C. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The aq. solution of NH_4Cl (10 mL) was added to the semisolid mass and allowed to stir for 30 min. The

reaction mixture was extracted with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether as an eluent to give alcohol **13** as colorless syrup in 95% yield.

***R_f*:** 0.3 (Pet. ether: ethyl acetate, 30:70).

MF: $C_{13}H_{19}ClN_2O_4$, **MW:** 302.76.

Yield: 95%.

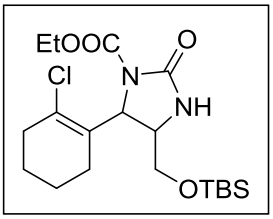
IR ($CHCl_3$, cm^{-1}): ν_{max} 3366, 3018, 2928, 2856, 1773, 1742, 1661, 1216, 757.

^{1}H (400 MHz, DMSO-d_6): δ 6.44 - 6.27 (m, 1H), 4.05 (d, *J* = 2.8 Hz, 1H), 3.26 - 2.99 (m, 2H), 2.20 (d, *J* = 3.3 Hz, 2H), 1.53 (bs, 1H), 1.30 (bs, 1H), 1.12 - 0.87 (m, 2H), 0.77 - 0.45 (m, 4H), 0.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 154.6, 150.8, 131.4, 131.3, 63.3, 61.1, 57.1, 55.6, 33.5, 24.0, 23.1, 21.4, 13.9.

HRMS (ESI): Observed- 325.0924, calculated- 325.0926 $(M+Na)^+$.

Ethyl 4-(((tert-butyldimethylsilyl) oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl)-2-oxo imid-azolidine-1-carboxylate (14)



To a stirred solution of hydroxyl ureide **13** (1 gm, 3.31 mmol) in DCM (10 mL) was added imidazole (0.423 gm, 6.62 mmol), DMAP (40 mg, 0.331 mmol) and TBSCl (1 gm, 6.62 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 3 h. Water was added to the reaction mixture and the compound was extracted with DCM (3 X 30 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether as an eluent to afford TBS derivative **14** as colorless syrup in 88% yield.

***R_f*:** 0.6 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{19}H_{33}ClN_2O_4Si$, **MW:** 417.02.

Yield: 88%.

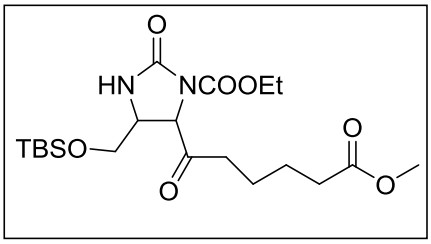
IR ($CHCl_3$, cm^{-1}): ν_{max} 2930, 2858, 1783, 1751, 1661, 1463, 1326, 1118.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 5.70 (bs, 1H), 5.13 (d, *J* = 3.0 Hz, 1H), 4.35 - 4.17 (m, 2H), 3.76 - 3.58 (m, 2H), 3.36 (td, *J* = 3.3, 6.5 Hz, 1H), 2.41 - 2.31 (m, 2H), 2.14 - 1.97 (m, 2H), 1.77 - 1.60 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 155.3**,** 151.4, 131.6, 129.0, 65.4, 62.3, 57.8, 56.2, 33.9, 25.7 24.5, 23.5, 21.8, 18.1, -5.4, -5.5.

HRMS (ESI): Observed- 439.1790, calculated- 439.1790 $(M+Na)^+$.

Ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(6-methoxy-6-oxohexanoyl)-2-oxo imidazoli dine-1-carboxylate (15)



To a stirred solution of urea **14** (400 mg, 0.96 mmol)) in MeOH:DCM (2:10, 10 mL) was added pinch of $NaHCO_3$ and the reaction mixture was cooled at -78 ^oC. Ozone was passed through the reaction mixture blue colour was observed and the ozone bubbling was continued for the additional 1 h. The ozone flow was stopped and reaction mass was quenched with dimethyl sulfide (0.4 mL, excess) at same temperature and reaction mixture was allowed to warm to room temperature. The reaction mixture was evaporated under reduced pressure and water was added to the residue. The compound was extracted with ethyl acetate (3 X 10 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether (4:6) as an eluent to furnish ketone **15** (408 mg, 96%) as colorless syrup.

***R_f*:** 0.3 (Pet. ether: ethyl acetate, 40:60).

MF: $C_{20}H_{36}N_2O_7Si$, **MW:** 444.60

Yield: 96%.

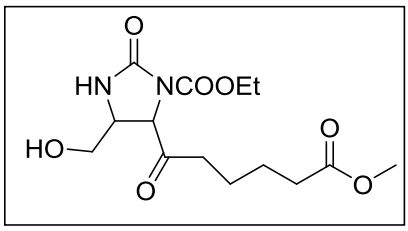
IR ($CHCl_3$, cm^{-1}): ν_{max} 3292, 2930, 1785, 1735, 1464, 1329, 1116, 839.

^{1}H NMR (400MHz, $CDCl_3$ + CCl_4): δ 6.16 (bs, 1H), 4.51 (d, *J* = 2.5 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 3.64 - 3.57 (m, 1H), 3.47 (bs, 1H), 2.60 - 2.52 (m, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 1.65 (d, *J* = 3.0 Hz, 4H), 1.33 (t, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 6H).

^{13}C (100 MHz, $CDCl_3$ + CCl_4): 204.8, 173.4, 154.5, 151.7, 65.3, 63.8, 63.0, 52.6, 51.5, 38.0, 33.7, 25.8, 24.8, 22.5, 18.2, 14.4, -5.3.

HRMS (ESI): Observed- 467.2180, calculated- 467.2184 $(M+Na)^+$.

Ethyl 4-(hydroxymethyl)-5-(6-methoxy-6-oxohexanoyl)-2-oxoimidazolidine-1-carboxylate (2)



To a stirred solution of **15** (300 mg, 0.675 mmol) in MeOH (5 mL) was added camphor sulfonic acid (156 mg, 0.675 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 3 h and the completion of reaction was moinitored by TLC. The reaction mixture was neutralised with TEA (0.2 mL) and solvent was evaporated under reduced pressure to obatin a residue. Water was added to the residue and the compound was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using methanol and pet. ether as an eluent to provide alcohol **2** (205 mg, 92%) as colorless syrup.

***R_f*:** 0.2 (Methanol: pet. ether, 5:95).

MF: $C_{14}H_{22}N_2O_7$, **MW:** 330.34.

Yield: 92%.

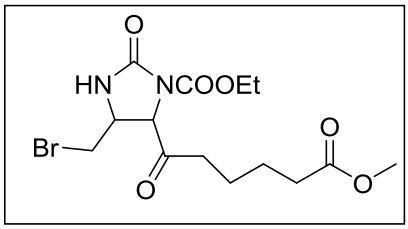
IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 2962, 1778, 1735, 1714, 1638, 1466, 1381, 1235.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 6.85 (bs, 1H), 4.62 (d, *J* = 3.4 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.76 - 3.62 (m, 4H), 3.53 (d, *J* = 3.7 Hz, 1H), 2.64 - 2.47 (m, 2H), 2.37 - 2.30 (m, 2H), 1.69 - 1.58 (m, 4H), 1.26 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 205.1, 173.7, 155.5, 151.3, 64.3, 63.6, 62.8, 52.8, 51.5, 38.2, 33.7, 24.2, 22.6, 14.2.

HRMS (ESI): Observed- 353.1312, calculated- 353.1319 $(M+Na)^+$.

Ethyl 4-(bromomethyl)-5-(6-methoxy-6-oxohexanoyl)-2-oxoimidazolidine-1-carboxylate (16)



To a stirred solution of alcohol **2** (0.100 gm, 0.303 mmol) in dry DCM (3 mL) was added PPh_3 (120 mg, 0.454 mmol) at 0 ^oC and stirred the reaction mixture for 15 mint at same temperature. To the reaction mixture was added CBr_4 (120 gm, 0.363 mmol) and stirred the reaction mass for additional 2 h at room temperature. After completion of reaction saturated aq. solution of $NaHCO_3$ (5 mL) was added and compound was mixture was extracted with DCM (3 X 5 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet ether (4:6) as an eluent to provide bromide **16** (103 mg, 87%) as colorless syrup.

***R_f*:** 0.3 (Pet ether-ethyl acetate, 40:60).

Yield:87%.

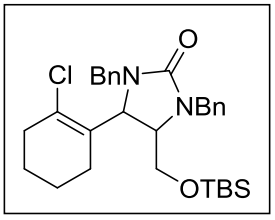
MF: $C_{14}H_{21}BrN_2O_6$, **MW:** 392.23

IR ($CHCl_3$, cm^{-1}): ν_{max} 2954, 1771, 1723, 1708, 1638, 1438, 1175, 1035.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.14 (bs, 1H), 4.57 (s, 1H), 4.39 - 4.20 (m, 2H), 3.66 (s, 4H), 3.53 - 3.26 (m, 2H), 2.67-2.56 (m, 2H), 2.39 - 2.23 (m, 2H), 1.73 - 1.53 (m, 4H), 1.33 (t, J= 8 Hz, 3H).

HRMS (ESI): Observed- 415.0470, calculated- 415.0475 $(M+Na)^+$.

(1,3-Dibenzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-chlorocyclohex-1-en-1-yl) -imid azolidin-2-one (19)



To a stirred solution of ureide **14** (1 gm, 2.39 mmol) in dry THF (5 mL) was added sodium hydride (115 mg, 4.79 mmol) at 0 ^oC and the reaction mixture was stirred for 30 min. To the reaction mixture at 0 ^oC was added benzyl bromide (0.58 mL, 4.79 mmol) and stirred additionally at room temperature for 2.5 h. After completion of reaction, saturated aq. solution of NH_4Cl (10 mL) was added and compound was extracted in DCM (3 X 15 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether as an eluent to provide dibenzyl urea **19** (1.18 gm, 94%) as a white solid.

***R_f*:** 0.5 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{30}H_{41}ClN_2O_2Si$, **MW:** 525.20.

Yield: 94%.

Mp: 87-89 ^oC.

IR ($CHCl_3$, cm^{-1}): ν_{max} 3030, 2930, 1698, 1657, 1448, 1357, 1119.

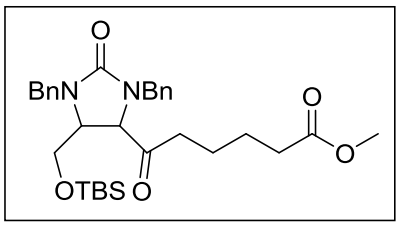
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.34 - 7.21 (m, 10H), 4.59 (d, *J* = 6.0 Hz, 1H), 4.52 (d, *J* = 14.7 Hz, 1H), 4.12 - 3.97 (m, 1H), 4.10-4.00 (m, 2H), 3.52 - 3.45 (m, 1H), 3.14 - 3.07 (m, 1H), 2.22 (t, *J* = 6.2 Hz, 2H), 1.77 - 1.68 (m, 1H), 1.58 - 1.49 (m, 3H),

1.42 - 1.33 (m, 1H), 1.20 (dd, *J* = 6.4, 13.3 Hz, 1H), 0.84 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 160.3, 137.3, 131.1, 130.1, 128.8, 128.4, 128.3, 127.3, 127.2, 62.5, 57.6, 56.5, 46.8, 46.1, 34.2, 25.8, 23.6, 21.6, 18.2., -5.4, -5.5.

HRMS (ESI): Observed- 547.2523, calculated- 547.2518 $(M+Na)^+$.

Methyl 6-(1, 3-dibenzyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate (20)



To a stirred solution of dibenzyl ureide **19** (600 mg, 1.14 mmol) in MeOH:DCM (1:5, 10 mL) was added a pinch of $NaHCO_3$ and cooled the reaction mixture to -78 ^oC. Ozone was passed through the reaction mixture the blue coloure was observed and continued the ozone bubbling for the additional 1.5 h. The ozone flow was stopped and reaction mass was quenched with dimethyl sulfide (0.84 mL, 11.4 mmol) at same temperature and brought the reaction mixture to room temperature. The reaction mixture was evaporated under reduced pressure and water (10 mL) was added to the residue. The compound was extracted with ethyl acetate (3 X 15 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet. ether as an eluent to afford ester **20** (605 mg, 96%) as a white solid.

***R_f*:** 0.5 (Pet. ether: ethyl acetate, 60:40).

MF: $C_{31}H_{44}N_2O_5Si$, **MW:** 552.79.

Yield: 96%.

Mp: 62-64 ^oC.

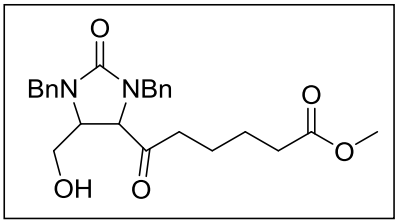
IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 2853, 1733, 1706, 1690, 1463, 1361, 1215.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.27 (bs, 10H), 4.99 - 4.74 (m, 2H), 4.07 (d, *J* = 14.8 Hz, 2H), 3.73 (d, *J* = 4.3 Hz, 1H), 3.68 (s, 3H), 3.58 - 3.40 (m, 2H), 3.19 (d, *J* = 5.3 Hz, 1H), 2.27 - 2.13 (m, 3H), 1.45 - 1.33 (m, 5H), 0.87 - 0.79 (m, 9H), -0.02 (d, *J* = 3.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 207.3, 173.4, 159.5, 136.9, 136.4, 128.0, 127.7, 127.6, 63.5, 62.7, 56.3, 51.4, 47.2, 46.2, 37.4, 33.6, 25.8, 24.1, 22.4, 18.2, -5.5.

HRMS (ESI): Observed- 575.2915, calculated- 575.2912 $(M+Na)^+$.

Methyl 6-(1, 3-dibenzyl-5-(hydroxymethyl)-2-oxoimidazolidin-4-yl)-6-oxohexanoate (21)



To a stirred solution of ureide **20** (500 mg, 0.904 mmol) in MeOH (5 mL) was added camphor sulfonic acid (315 mg, 1.35 mmol) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 5-6 h and the completion of reaction was moinitored by TLC. The reaction mixture was neutralised with the TEA (0.3 mL) and solvent was evaporated under reduced pressure to obatin residue. Water was added to the residue and the compound was extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using methanol and pet. ether as an eluent to provide alcohol 2**1** (365mg, 92%) as a white solid.

***R_f*:** 0.3 (Methanol: pet. ether, 5:95).
MF: $C_{25}H_{30}N_2O_5$, **MW:** 438.52.

Yield: 92%.

Mp: 84-86 ^{o}C.

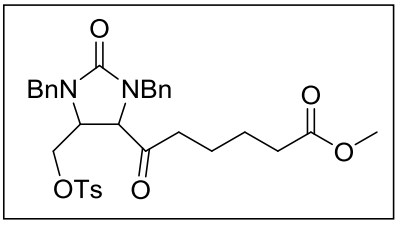
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 2928, 1726, 1704, 1682, 1451, 1238, 702.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.39 - 7.21 (m, 10H), 4.85 (d, *J* = 15.3 Hz, 2H), 4.21 - 4.09 (m, 2H), 3.89 (d, *J* = 5.3 Hz, 1H), 3.75 - 3.62 (m, 4H), 3.56 - 3.48 (m, 1H), 3.23 (q, *J* = 4.3 Hz, 1H), 2.26 - 2.07 (m, 4H), 1.47 - 1.29 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 207.5, 173.5, 160.0, 136.8, 136.1, 128.8, 128.7, 128.5, 128.0, 127.8, 63.4, 61.5, 56.7, 53.3, 51.5, 47.4, 46.2, 33.5, 22.4.

HRMS (ESI): Observed- 461.2045, calculated- 461.2047 $(M+Na)^+$.

Methyl 6-(1,3-dibenzyl-2-oxo-5-((tosyloxy)methyl)imidazolidin-4-yl)-6-oxohexanoate (22)



To a stirred solution of alcohol **21** (200 mg, 0.457 mmol) in dry DCM (5 mL) was added TEA (0.38 mL, 1.37 mmol) at 0 ^oC and stirred for 15 min at the same temperature. To the reaction mixture was added tosyl chloride (175 mg, 0.91 mmol) and cat. DMAP (6 mg, 0.046 mmol) and the reaction mass was stirred for additional 3 h at room temperature. After completion of reaction water (5 mL) was added and compound was extracted in DCM (3 X 10 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet ether (4:6) as an eluent to give tosylate **22** (242 mg, 90%) as a white solid.

***R_f*:** 0.3 (Pet ether-ethyl acetate, 40:60).

MF: $C_{32}H_{36}N_2O_7S$, **MW:** 592.71.

Yield: 90%.

Mp: 79-81 ^oC.

IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 1704, 1602, 1450, 1170.

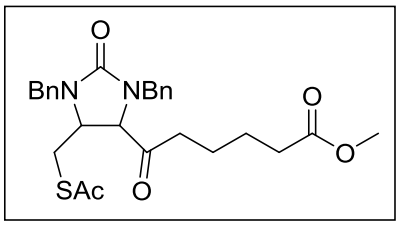
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.35 - 7.28 (m, 8H), 7.20 - 7.15 (m, 4H), 4.87 (dd, *J* = 2.6, 15.1 Hz, 2H), 4.01 - 3.89 (m, 3H), 3.83 (dd, *J* =

2.6, 15.1 Hz, 1H), 3.67 (s, 3H), 3.59 (d, *J* = 4.6 Hz, 1H), 3.30 (q, *J* = 4.8 Hz, 1H), 2.48 (s, 3H), 2.21 - 2.16 (m, 2H), 2.15 - 1.96 (m, 2H), 1.39 - 1.31 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 206.3, 173.3, 159.0, 145.2, 136.2, 135.8, 130.0, 128.9, 128.4, 128.2, 128.0, 127.9, 67.7, 62.8, 53.6, 51.5, 47.2, 46.2, 37.7, 33.6, 24.0, 22.3, 21.7.

HRMS (ESI): Observed- 615.2130, calculated- 615.2135 $(M+Na)^+$.

Methyl 6-(5-((acetylthio)methyl)-1, 3-dibenzyl-2-oxoimidazolidin-4-yl)-6-oxohexano ate (18)



To a solution of tosyl **22** (100 mg, 0.17 mmol) in dry DMF (2 mL) and THF (1 mL) was added sodium thioacetate and the reaction mixture was stirred at 80 ^oC for 3 h under nitrogen atmosphere. Progress of reaction was monitored by TLC. Water was added to reaction mixture and compound was extracted with ethyl acetate (3 X 5 mL). The combined organic layer washed with brine (5 mL) and concentrated under reduced pressure to obtained crude residue. The crude residue was purified by flash chromatography in pet. ether and ethyl acetate as eluent to afford thioacetate **18** (75 mg, 90%) in 90% yield.

***R_f*:** 0.4 (Pet. ether: ethyl acetate, 30:70).

MF: $C_{27}H_{32}N_2O_5S$, **MW:** 496.62.

Yield: 90%.

IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 1704, 1602, 1450, 1170.

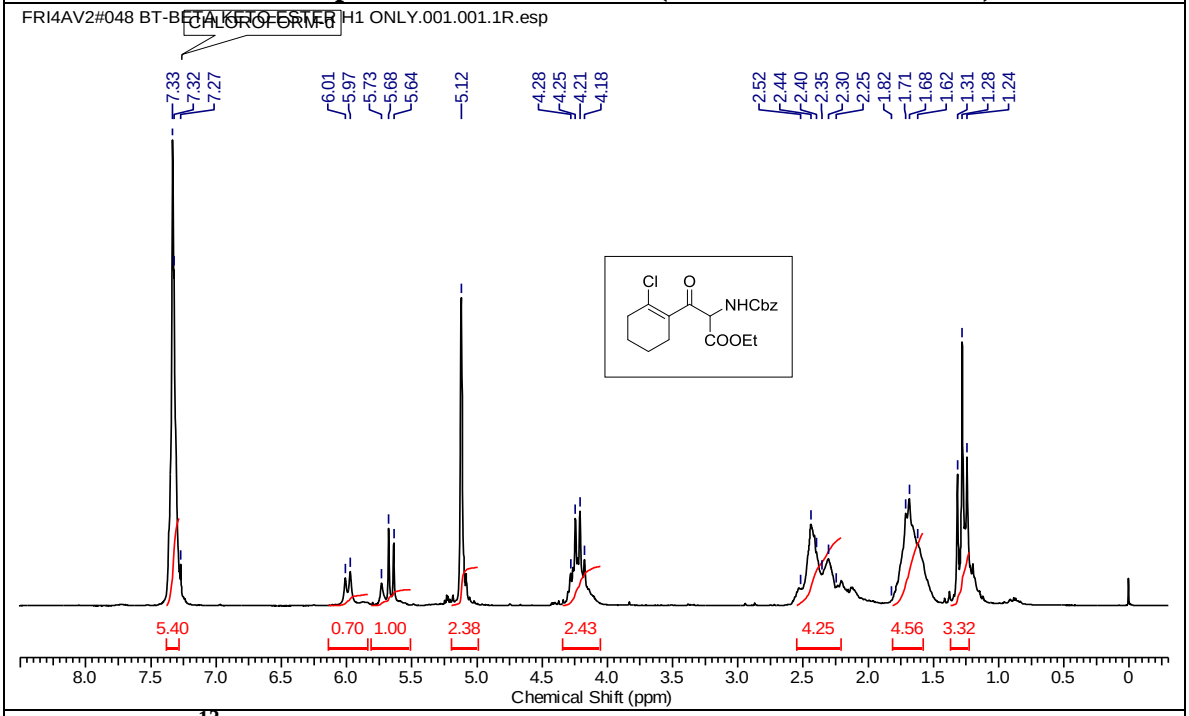
^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 7.35 - 7.18 (m, 10H), 4.87 (d, *J* = 15.0 Hz, 2H), 4.08 - 3.90 (m, 2H), 3.64 (s, 3H), 3.46 (d, *J* = 4.6 Hz, 1H), 3.33 - 3.28 (m, 1H), 3.14 (dd, *J* = 2.7, 14.3 Hz, 1H), 2.84 (dd, *J* = 6.3, 14.2 Hz, 1H), 2.23 (s, 3H), 2.19 - 2.12 (m, 3H), 2.07 - 1.96 (m, 1H), 1.41 - 1.29 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 206.5, 194.1, 173.4, 159.0, 136.5, 136.2, 128.8, 128.7, 128.3, 127.8, 64.8, 54.2, 51.4, 47.0, 45.8, 37.7, 33.6, 31.4, 30.5, 24.1, 22.4.

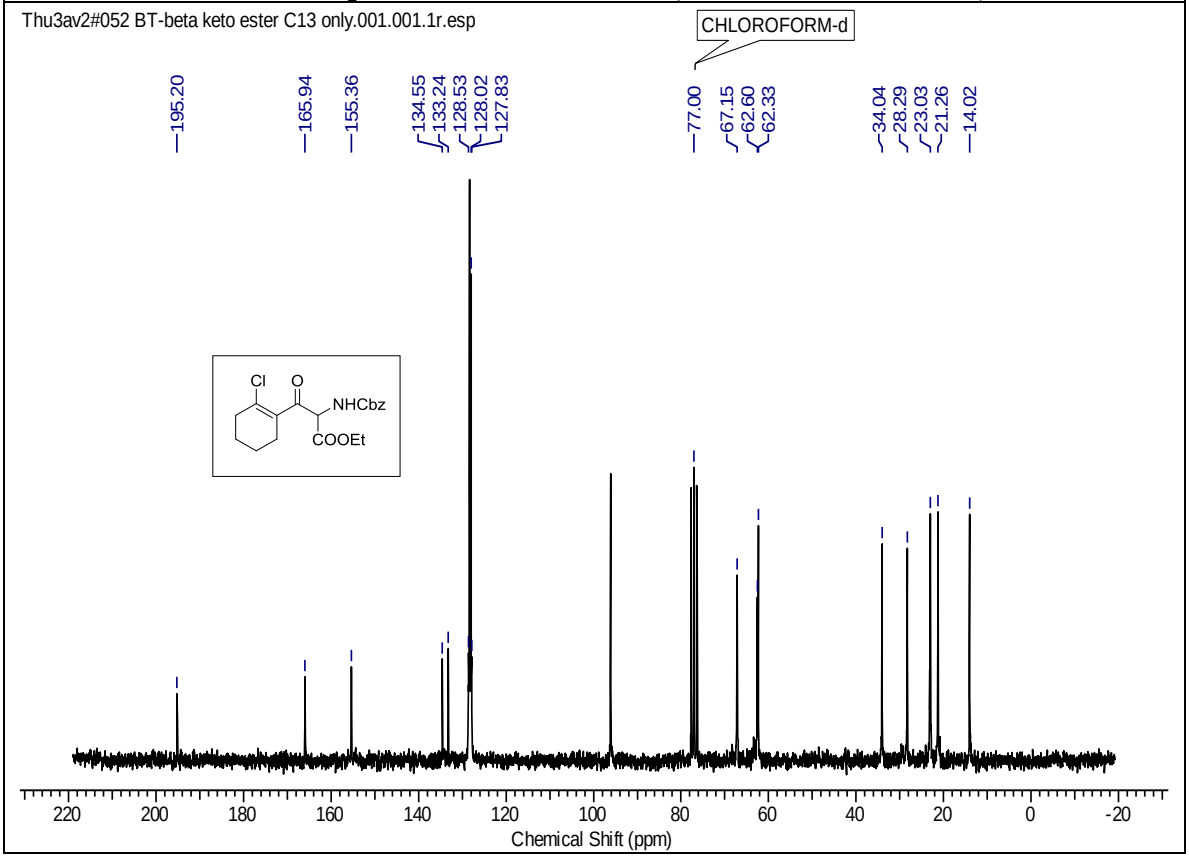
HRMS (ESI): Observed- 519.1918, calculated- 519.1924 $(M+Na)^+$.

3.3.5 Spectral data

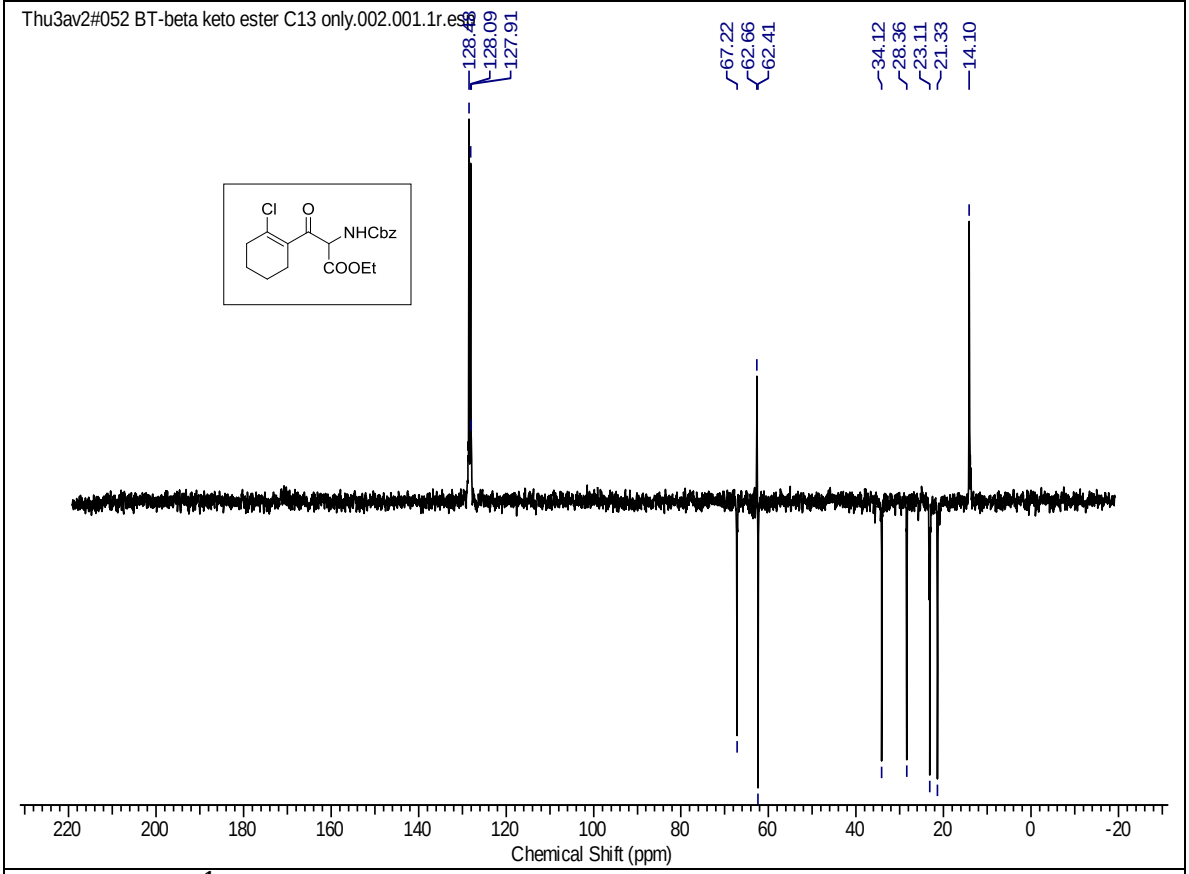
^{1}H NMR spectrum of keto ester 4 ($CDCl_3$+CCl_4, 200 MHz)



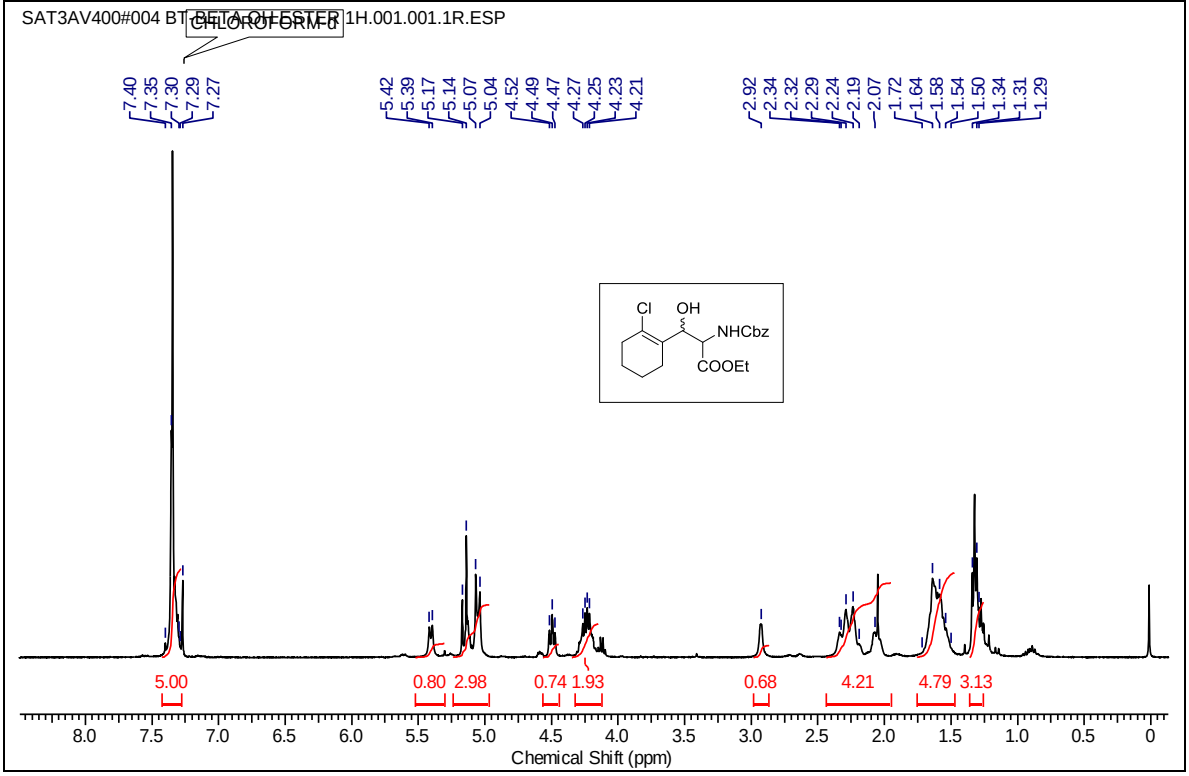
^{13}C NMR spectrum of keto ester 4 ($CDCl_3$+CCl_4, 50 MHz)



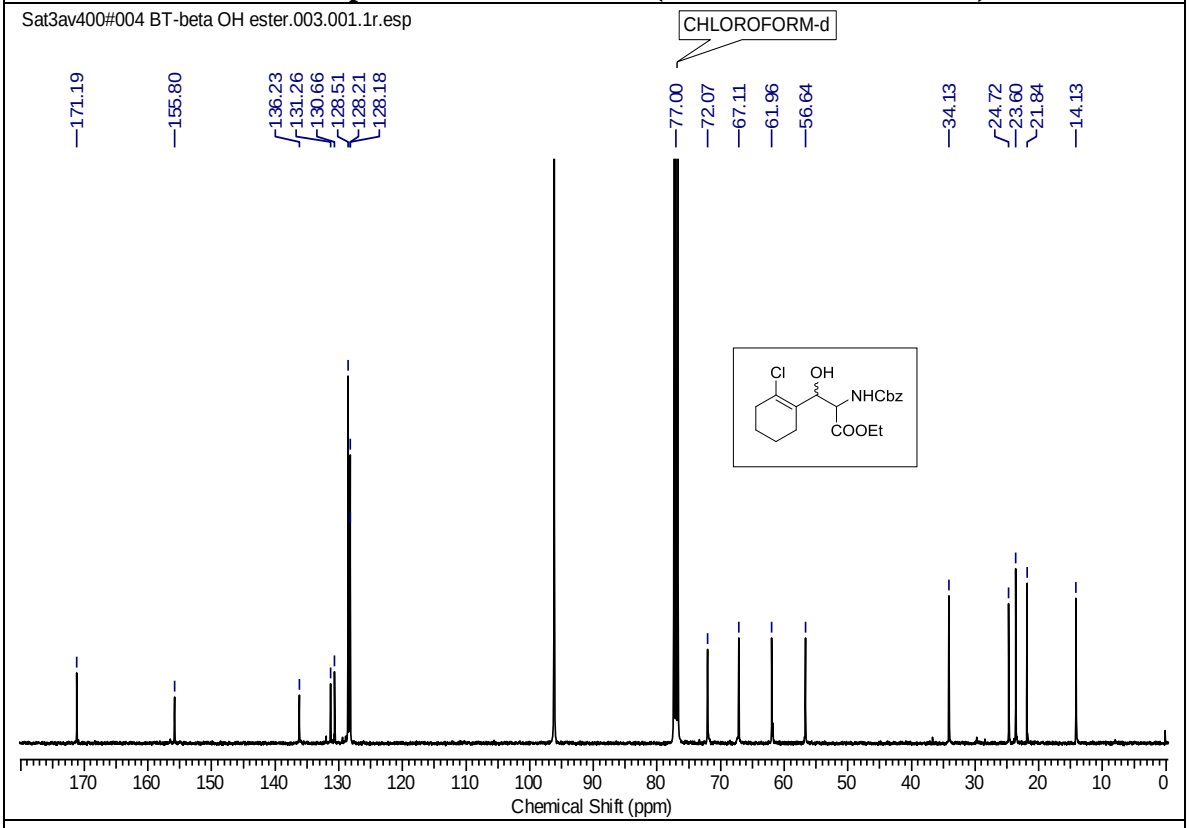
DEPT spectrum of keto ester 4 ($CDCl_3$+CCl_4, 50 MHz)



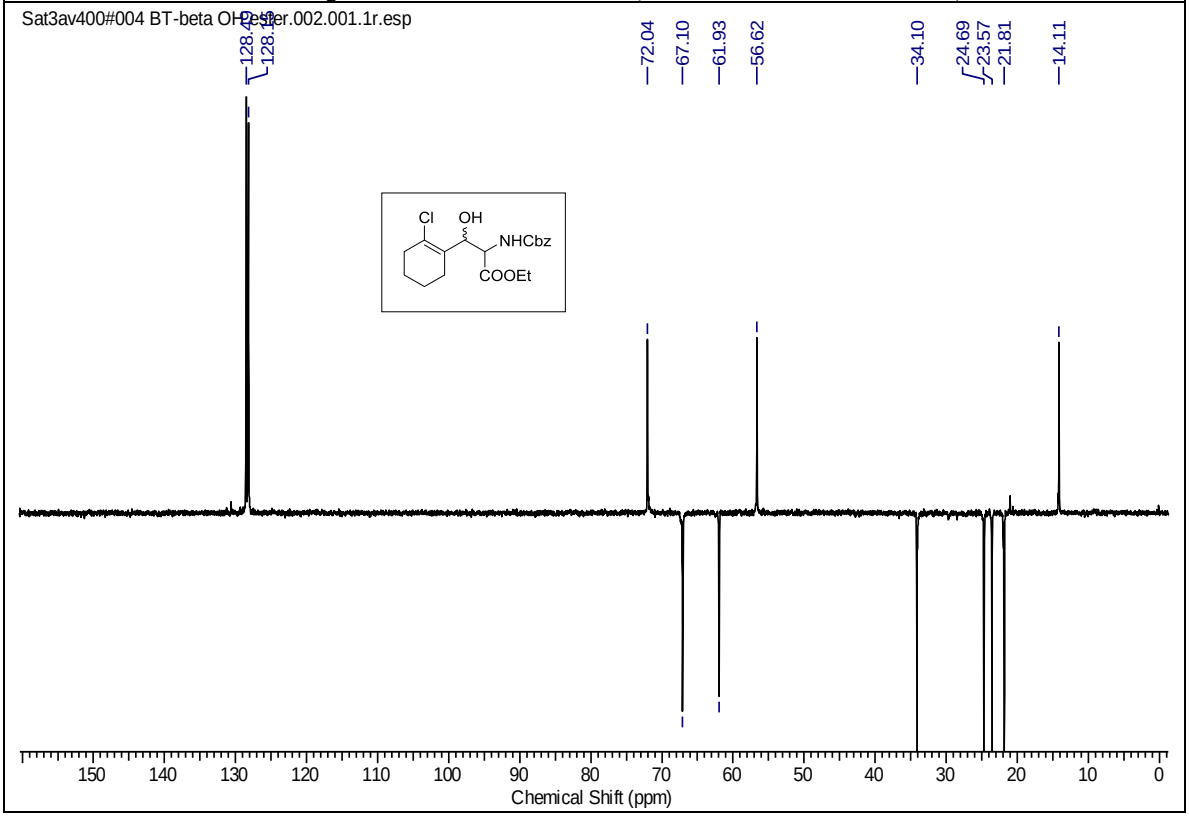
^{1}H NMR spectrum of alcohol 11 ($CDCl_3$+CCl_4, 400 MHz)



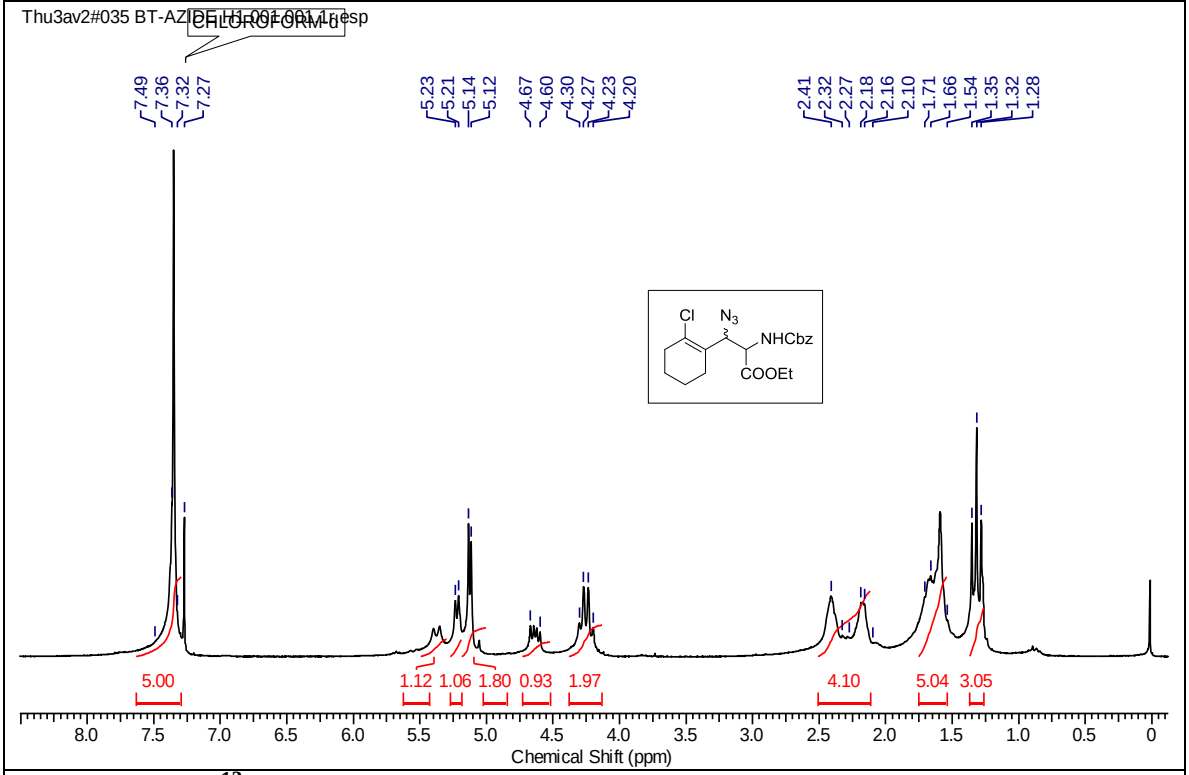
^{13}C NMR spectrum of alcohol 11 ($CDCl_3$+CCl_4, 100 MHz)



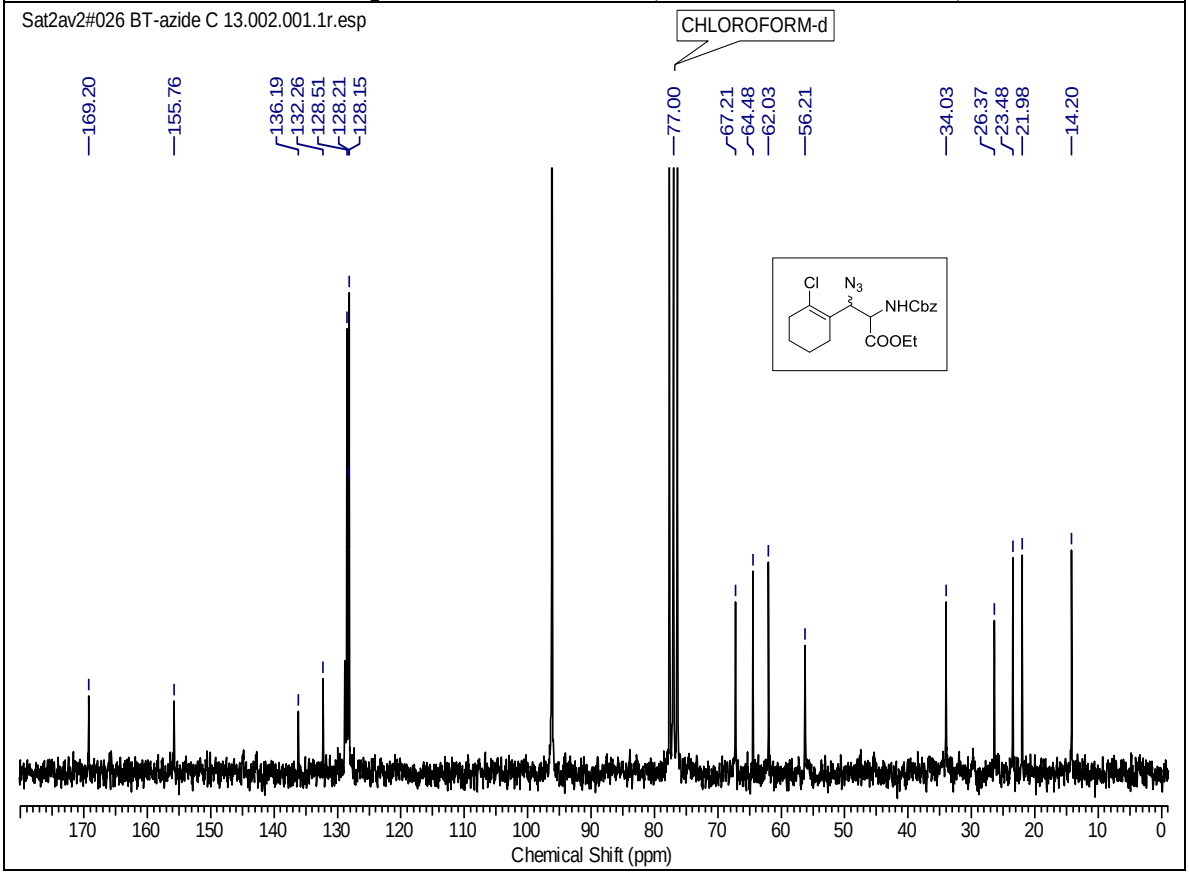
DEPT spectrum of alcohol 11 ($CDCl_3$+CCl_4, 100 MHz)



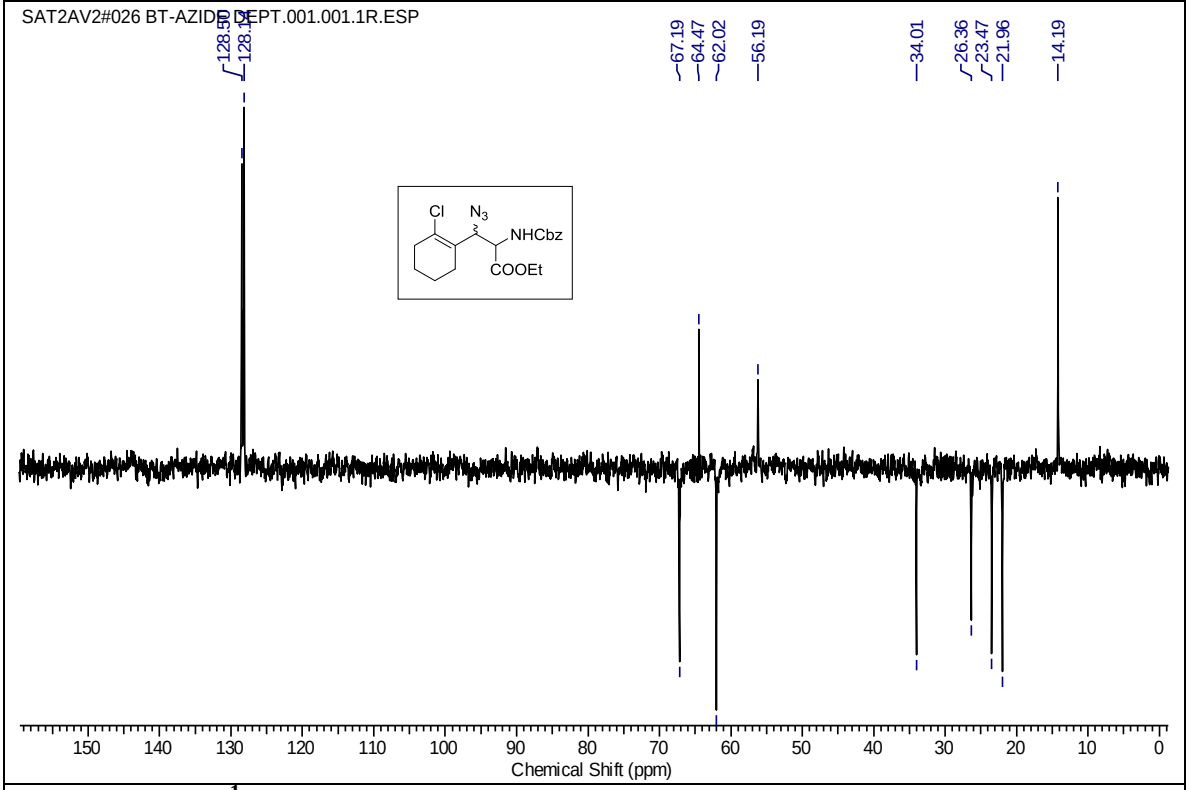
^{1}H NMR spectrum of azide 12 ($CDCl_3$+CCl_4, 200 MHz)



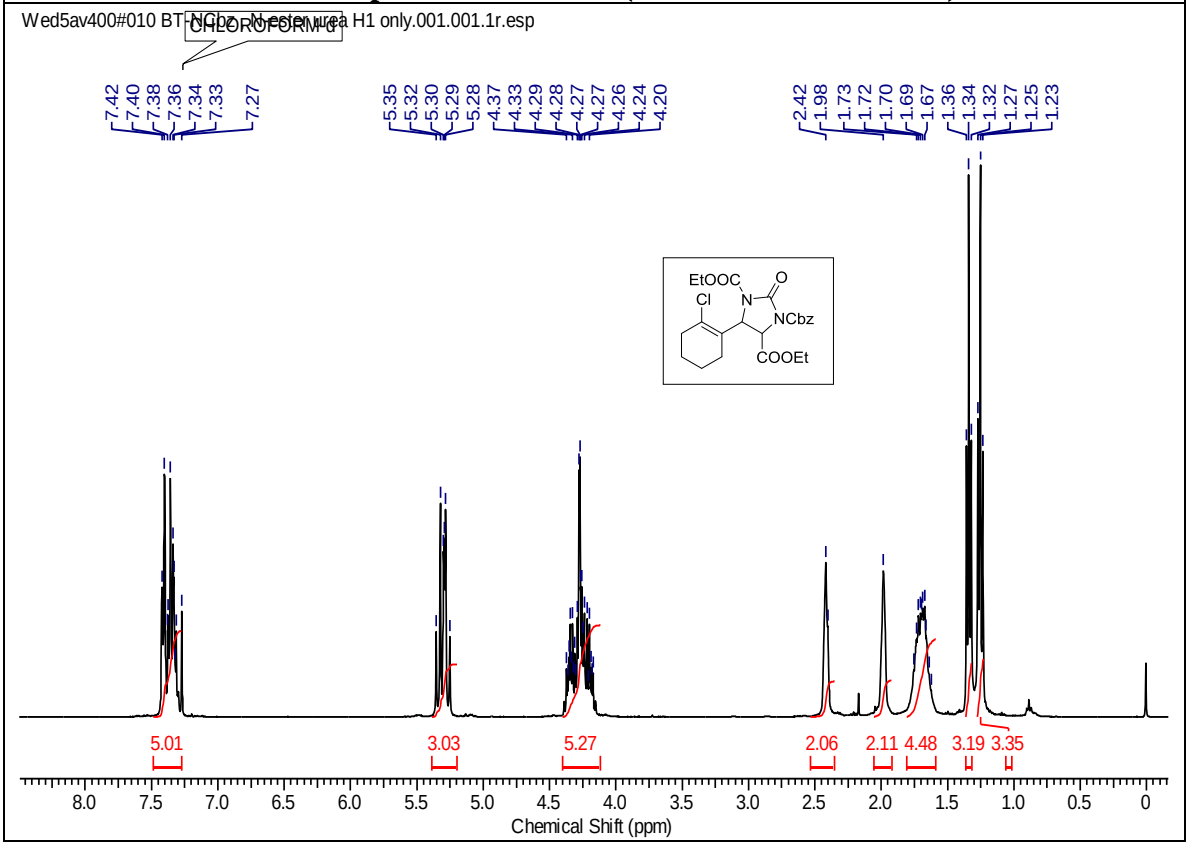
^{13}C NMR spectrum of azide 12 ($CDCl_3$+CCl_4, 50 MHz)



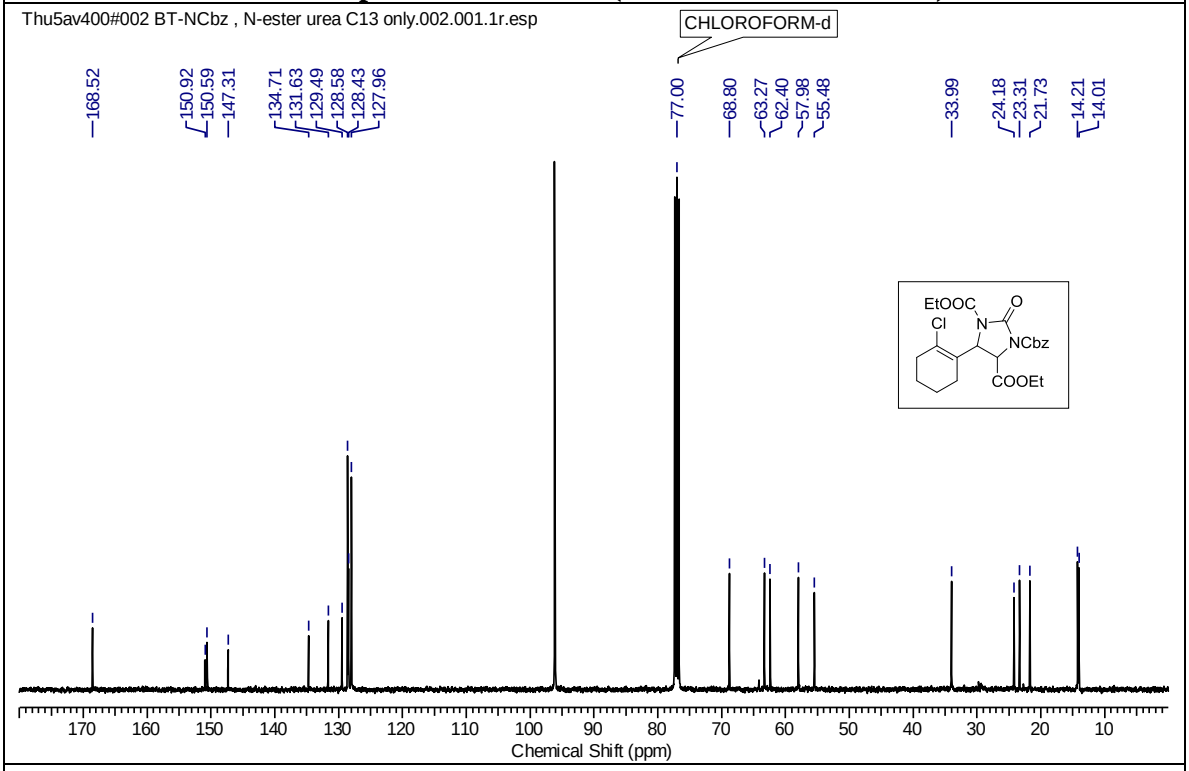
DEPT spectrum of azide 12 ($CDCl_3$+CCl_4, 50 MHz)



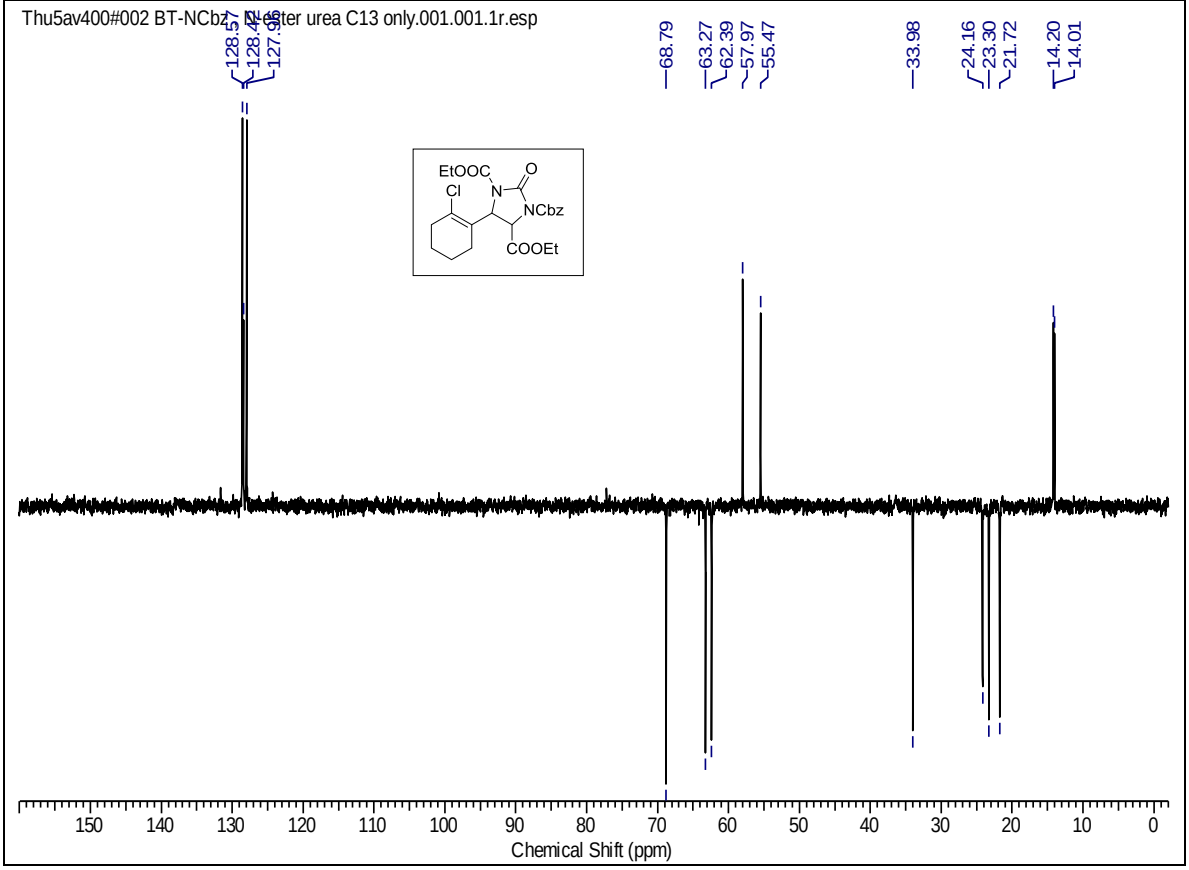
^{1}H NMR spectrum of urea 3 ($CDCl_3$+CCl_4, 400 MHz)



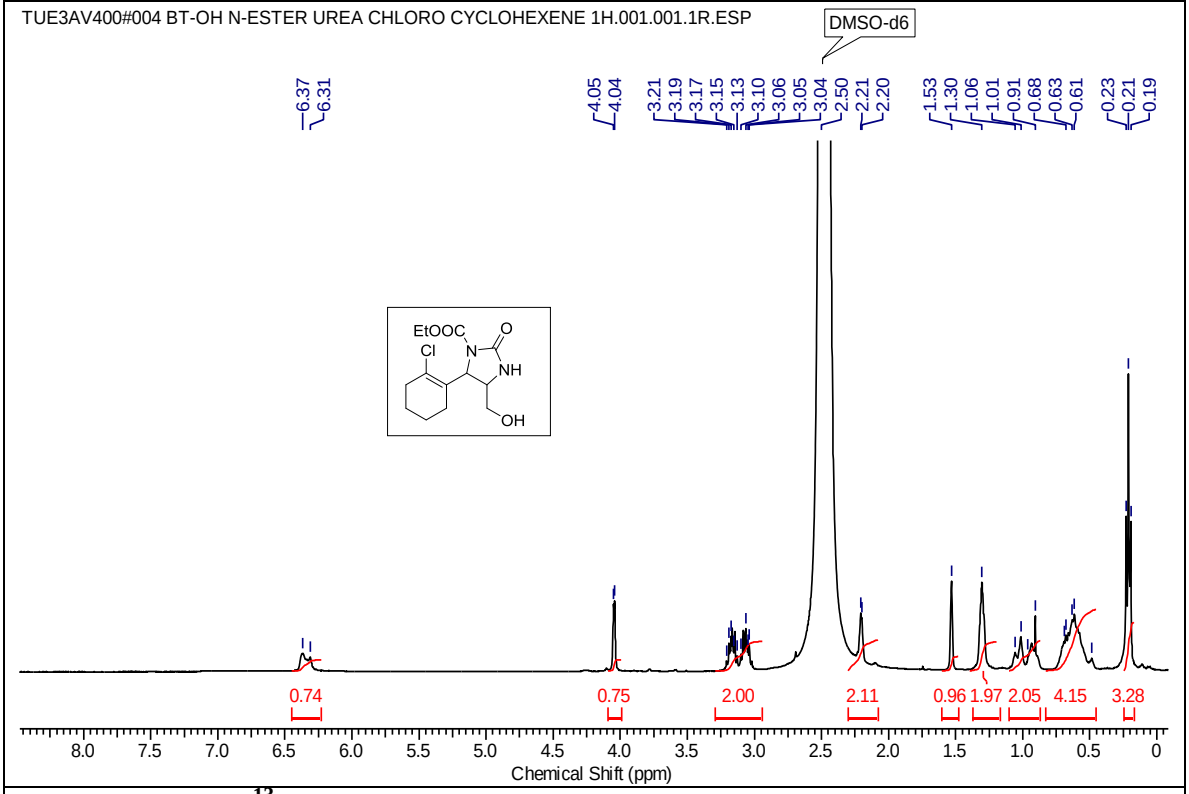
^{13}CMR spectrum of urea 3 ($CDCl_3$+CCl_4, 100 MHz)



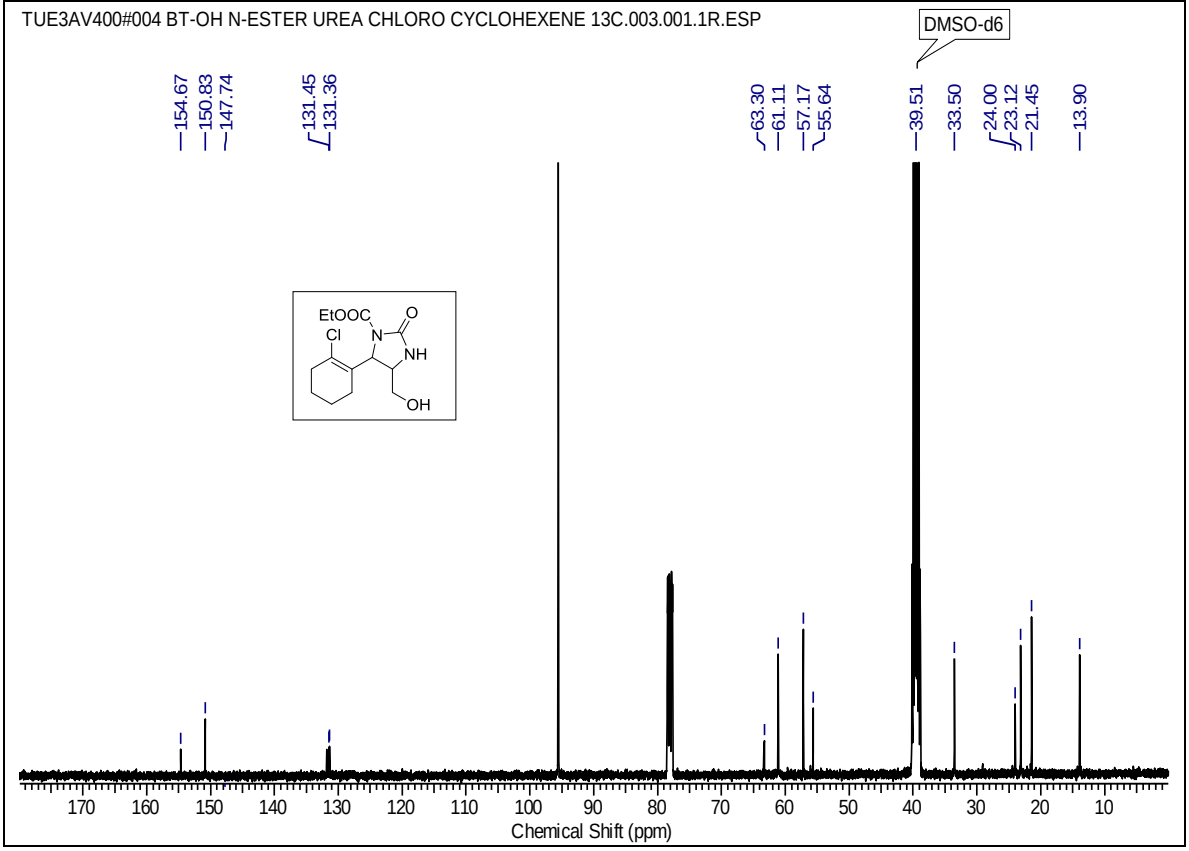
DEPT spectrum of urea 3 ($CDCl_3$+CCl_4, 100 MHz)



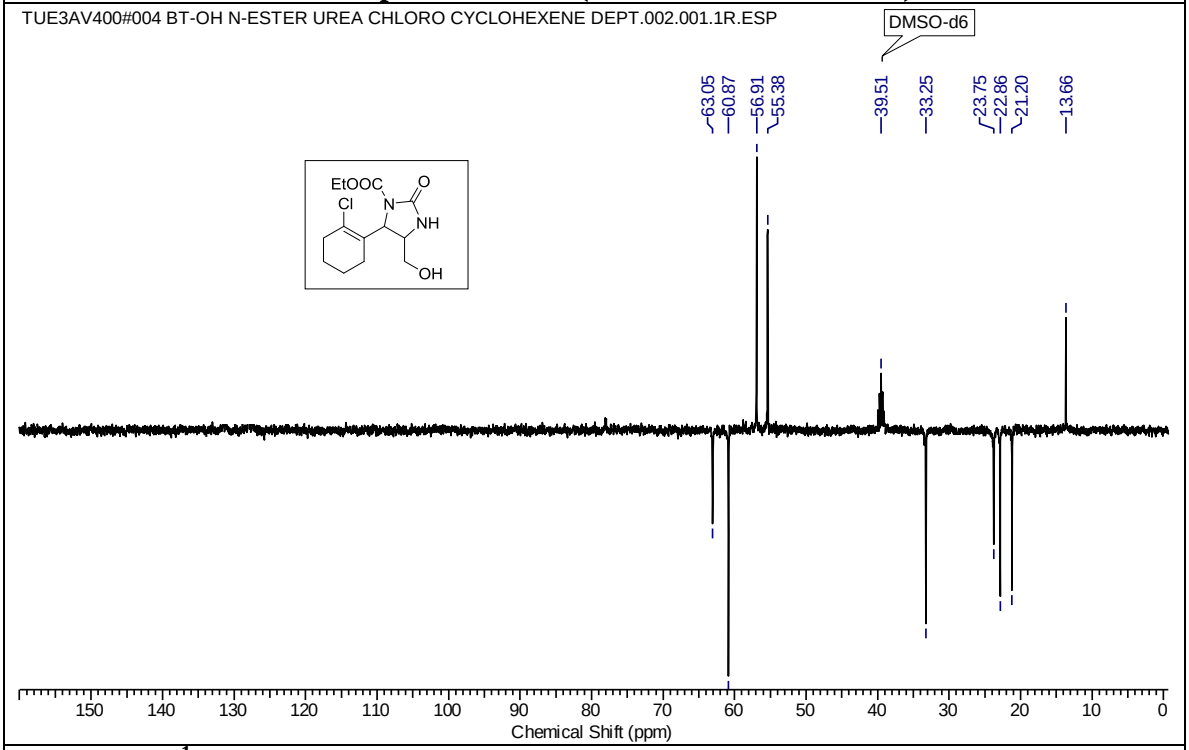
^{1}H NMR spectrum of 13 ($CDCl_3$+CCl_4, 400 MHz)



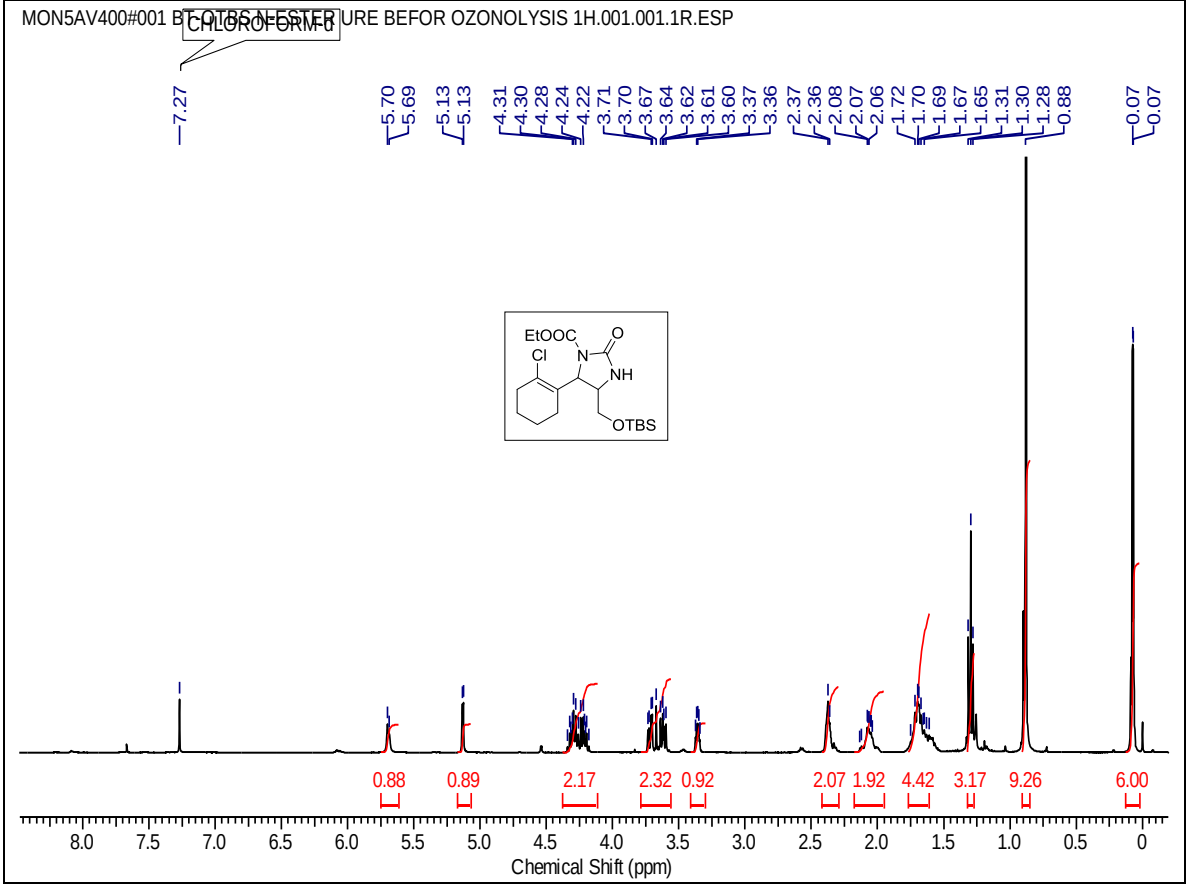
^{13}C NMR spectrum of 13 ($CDCl_3$+CCl_4, 100 MHz)



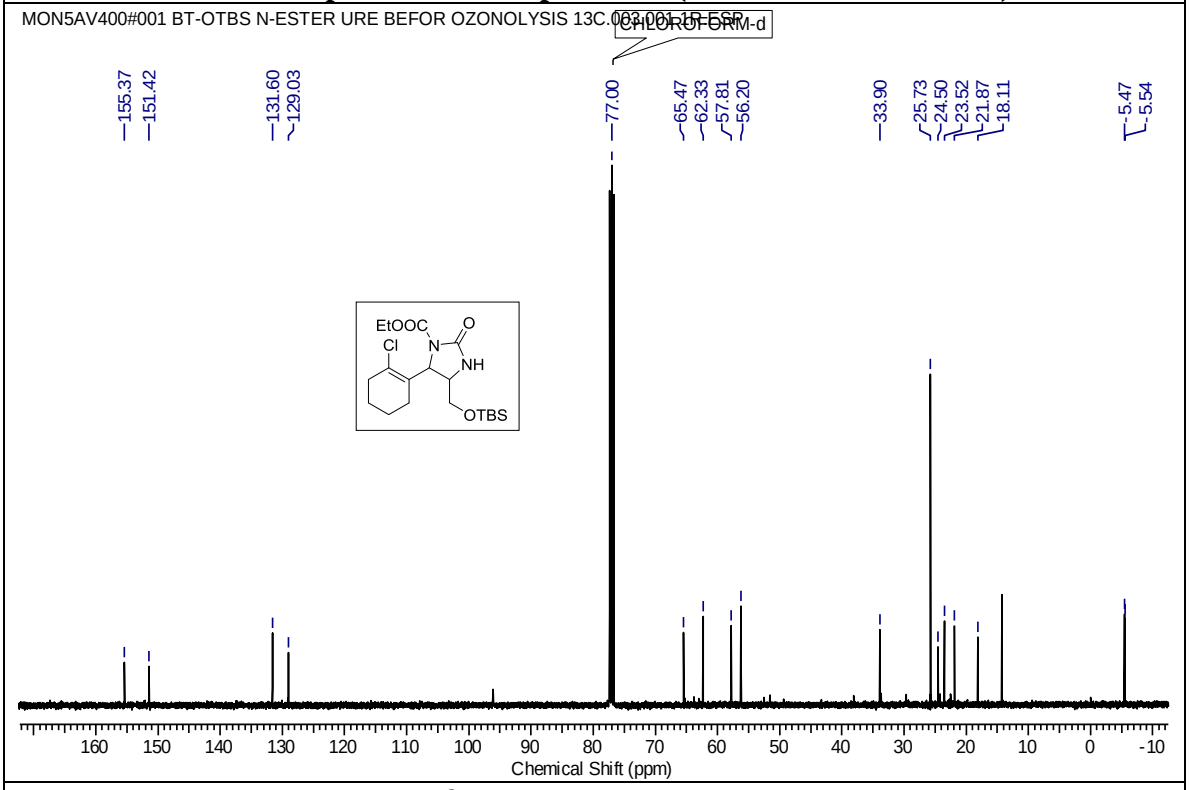
DEPT spectrum of 13 ($CDCl_3$+CCl_4, 100 MHz)



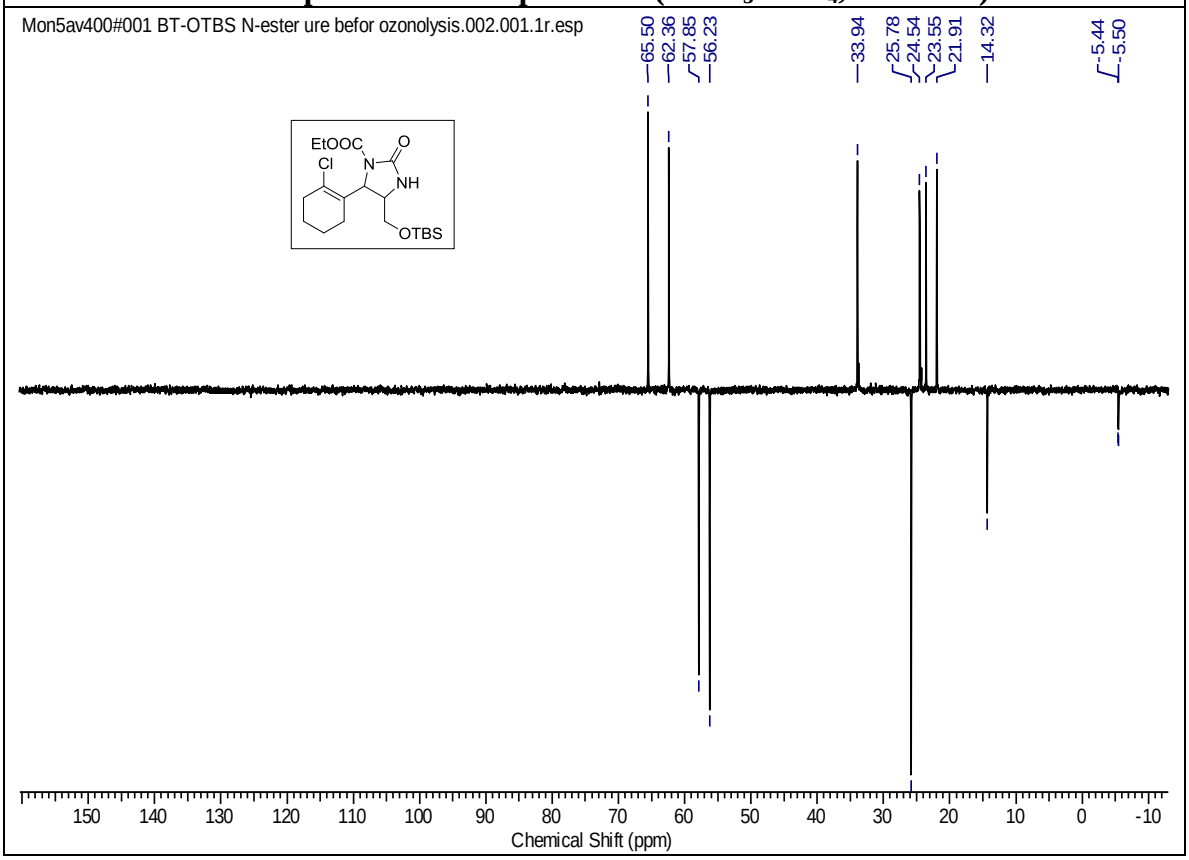
^{1}H NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 400 MHz)



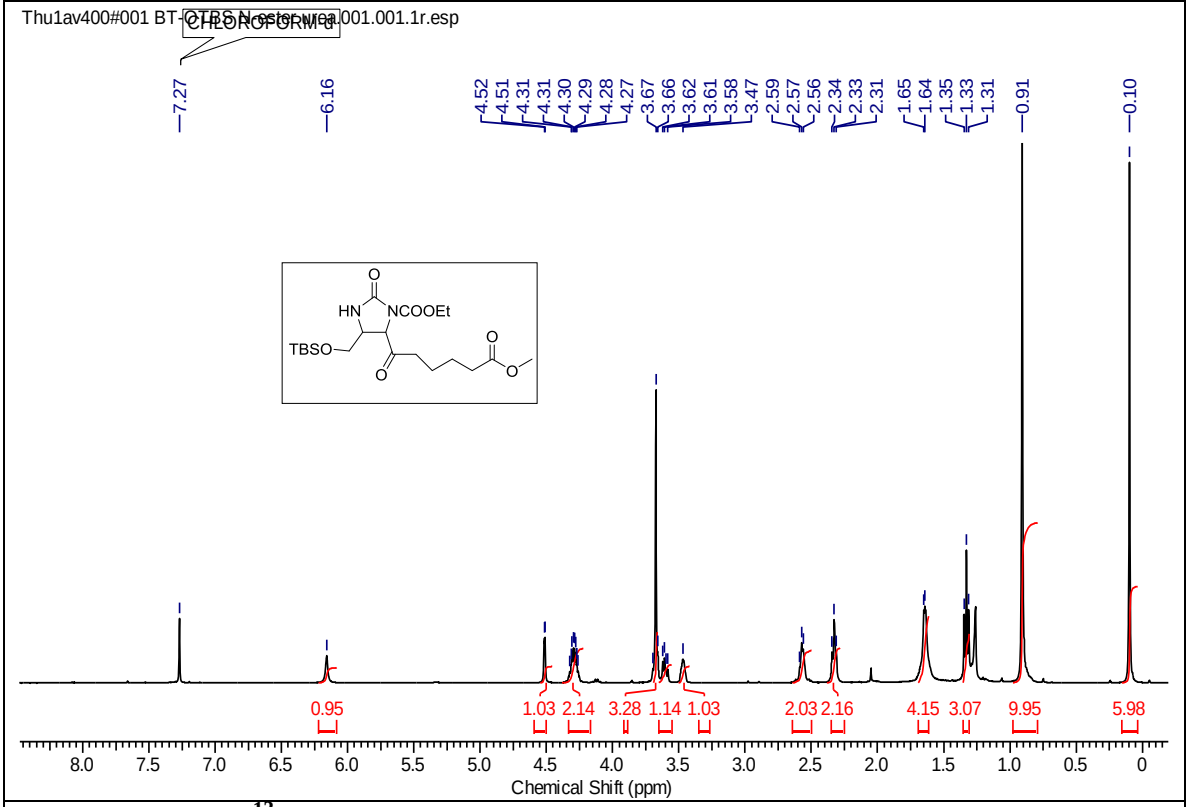
^{13}C NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 100 MHz)



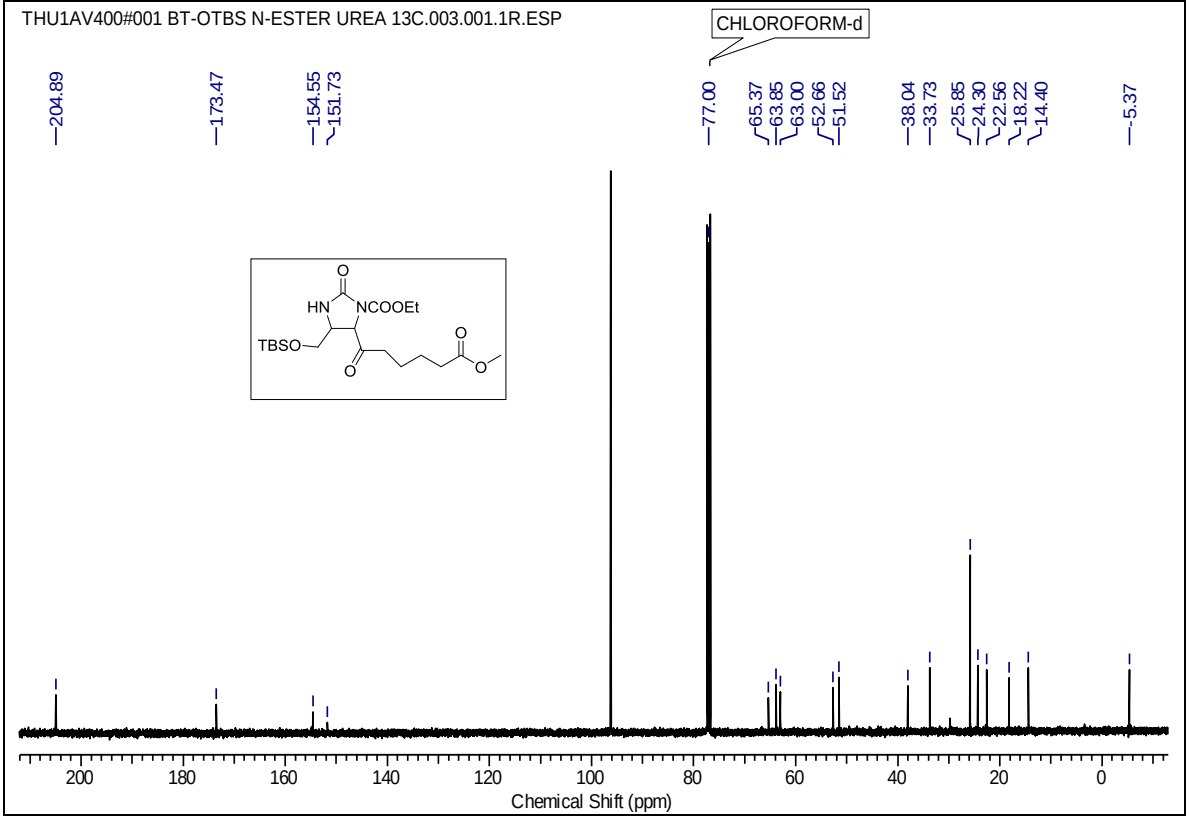
DEPT spectrum of compound 14 ($CDCl_3$+CCl_4, 100 MHz)



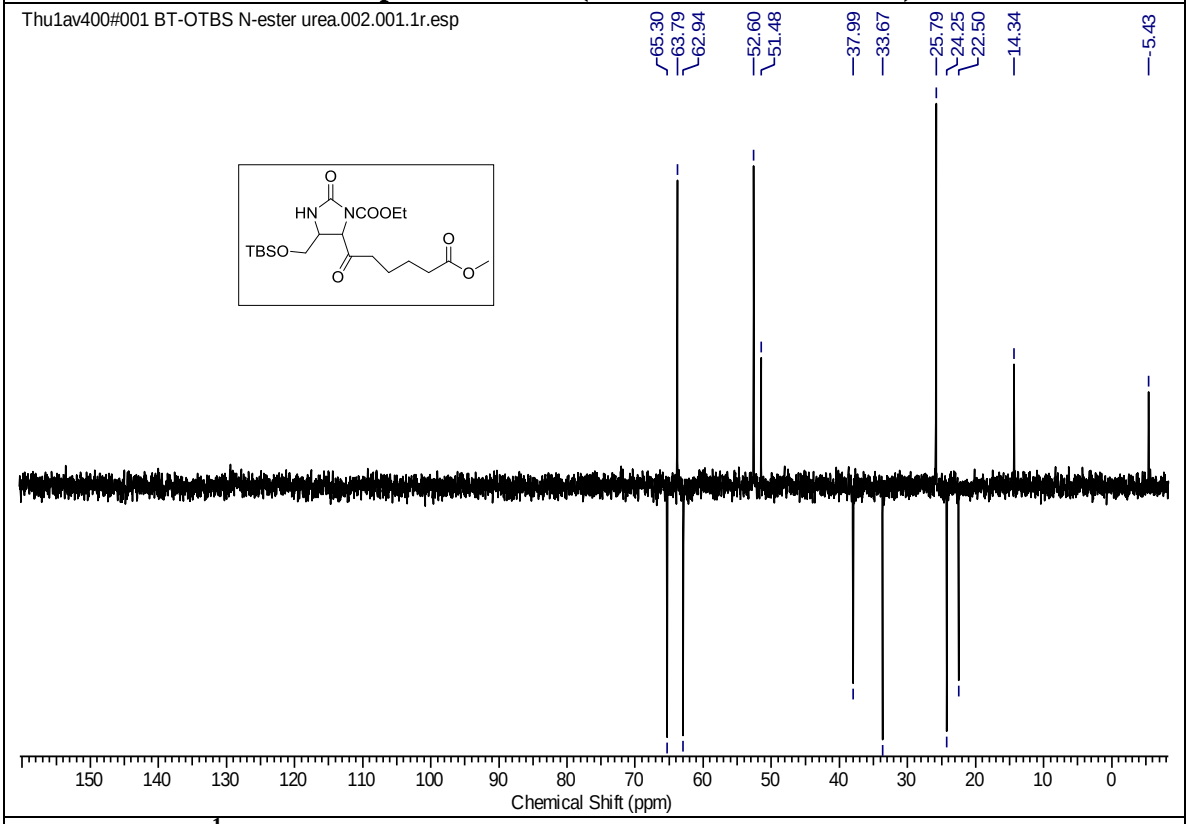
^{1}H NMR spectrum of 15 ($CDCl_3$+CCl_4, 400 MHz)



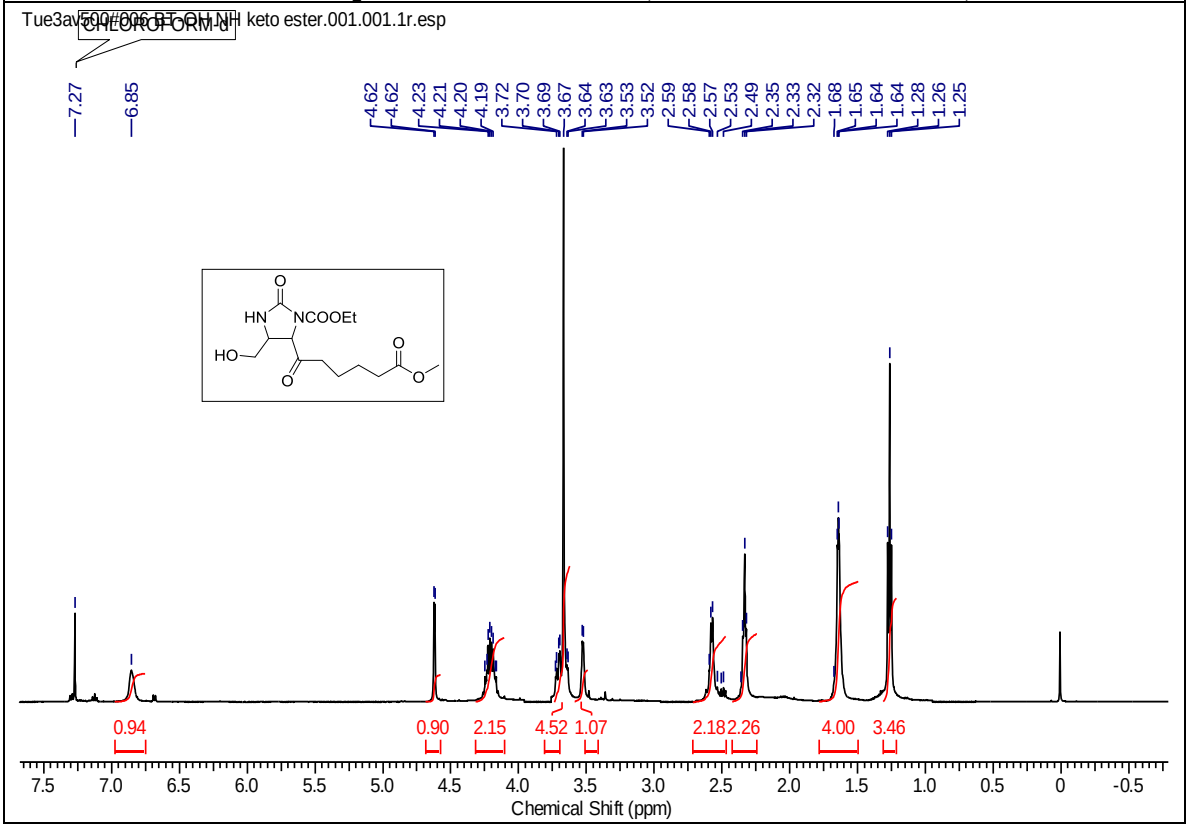
^{13}C NMR spectrum of 15 ($CDCl_3$+CCl_4, 100 MHz)



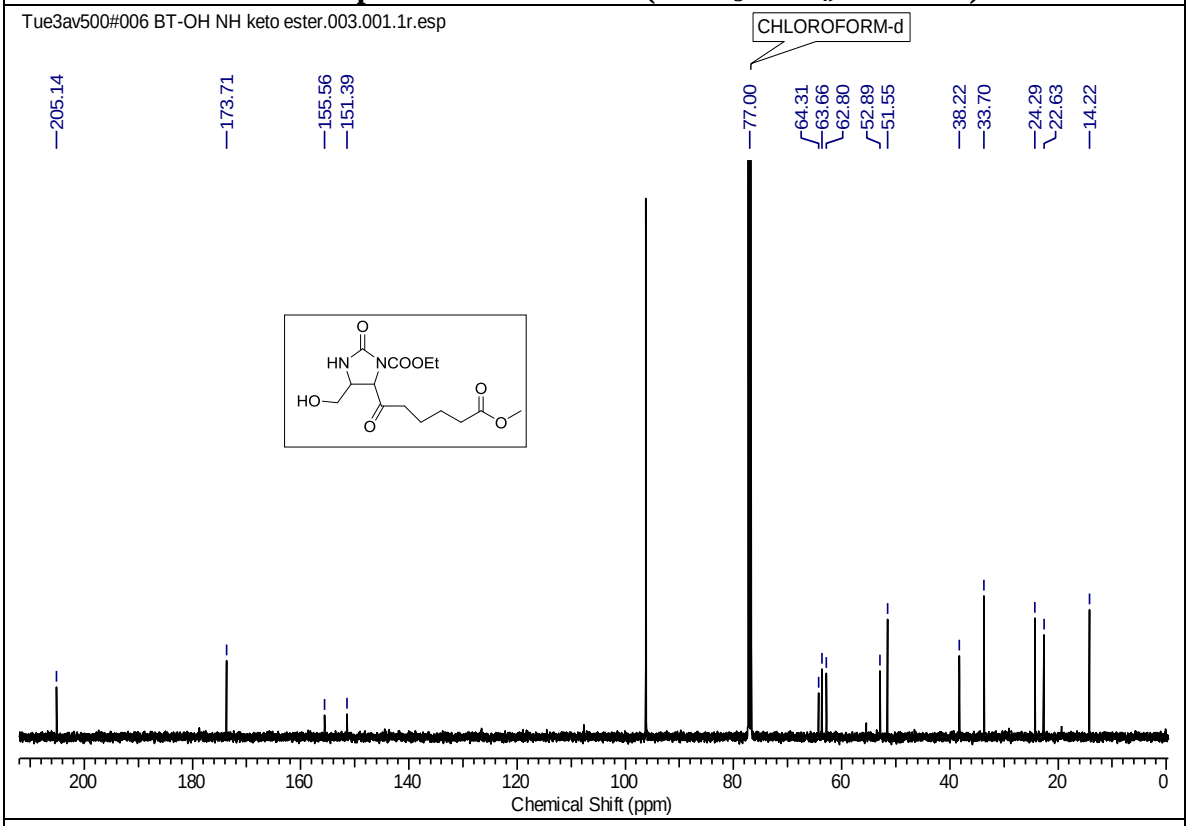
DEPT spectrum of 15 ($CDCl_3$+CCl_4, 100 MHz)



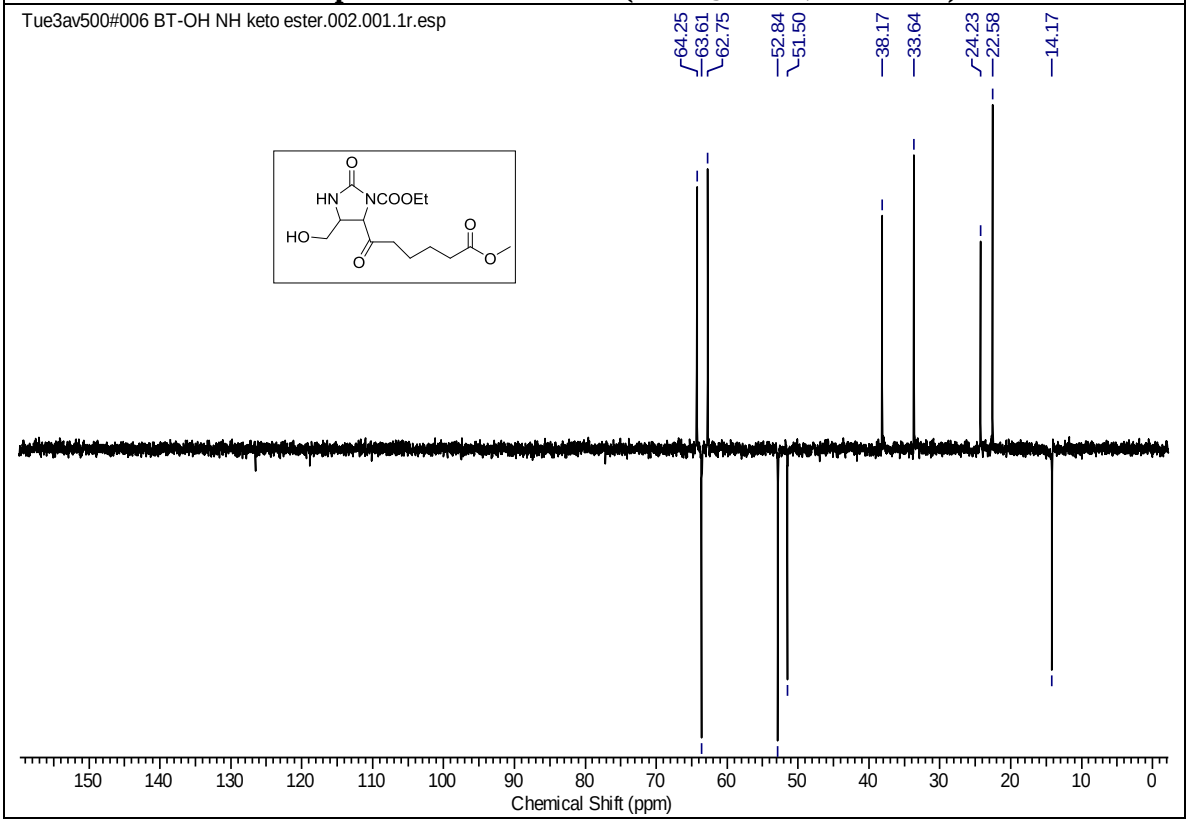
^{1}H NMR spectrum of alcohol 2 ($CDCl_3$+CCl_4, 500 MHz)



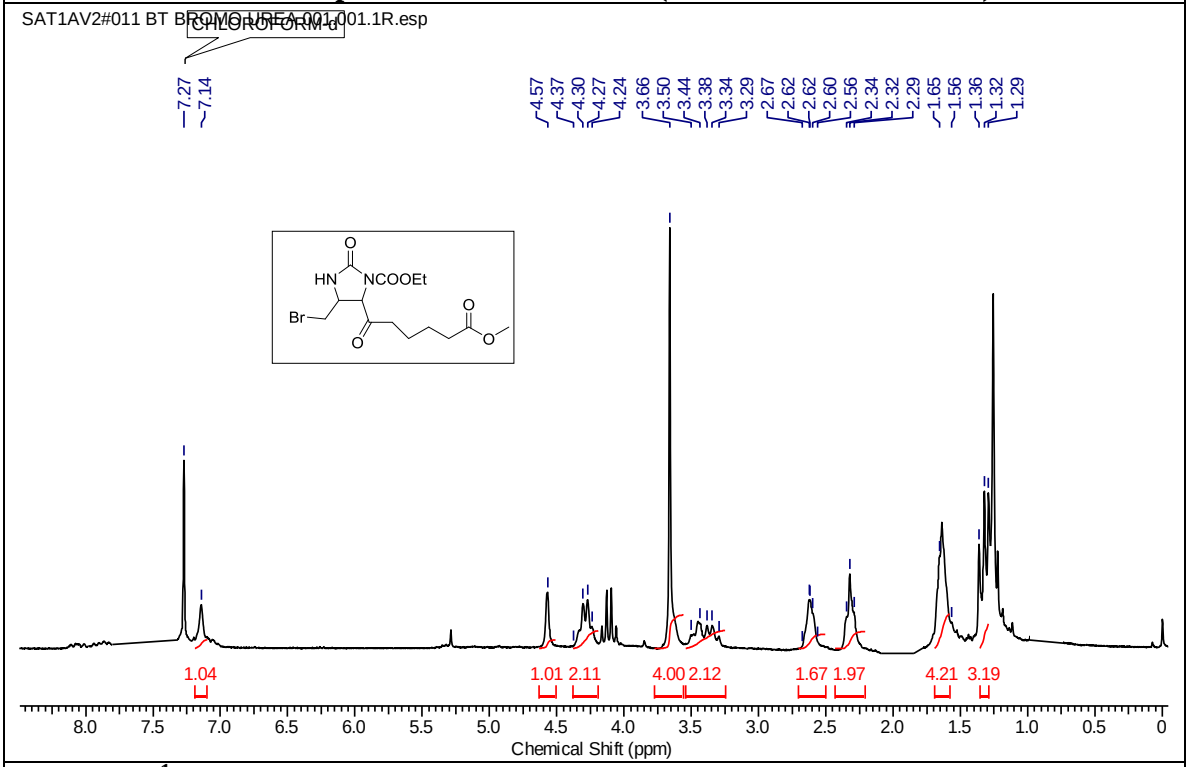
^{13}C NMR spectrum of alcohol 2 ($CDCl_3$+CCl_4, 125 MHz)



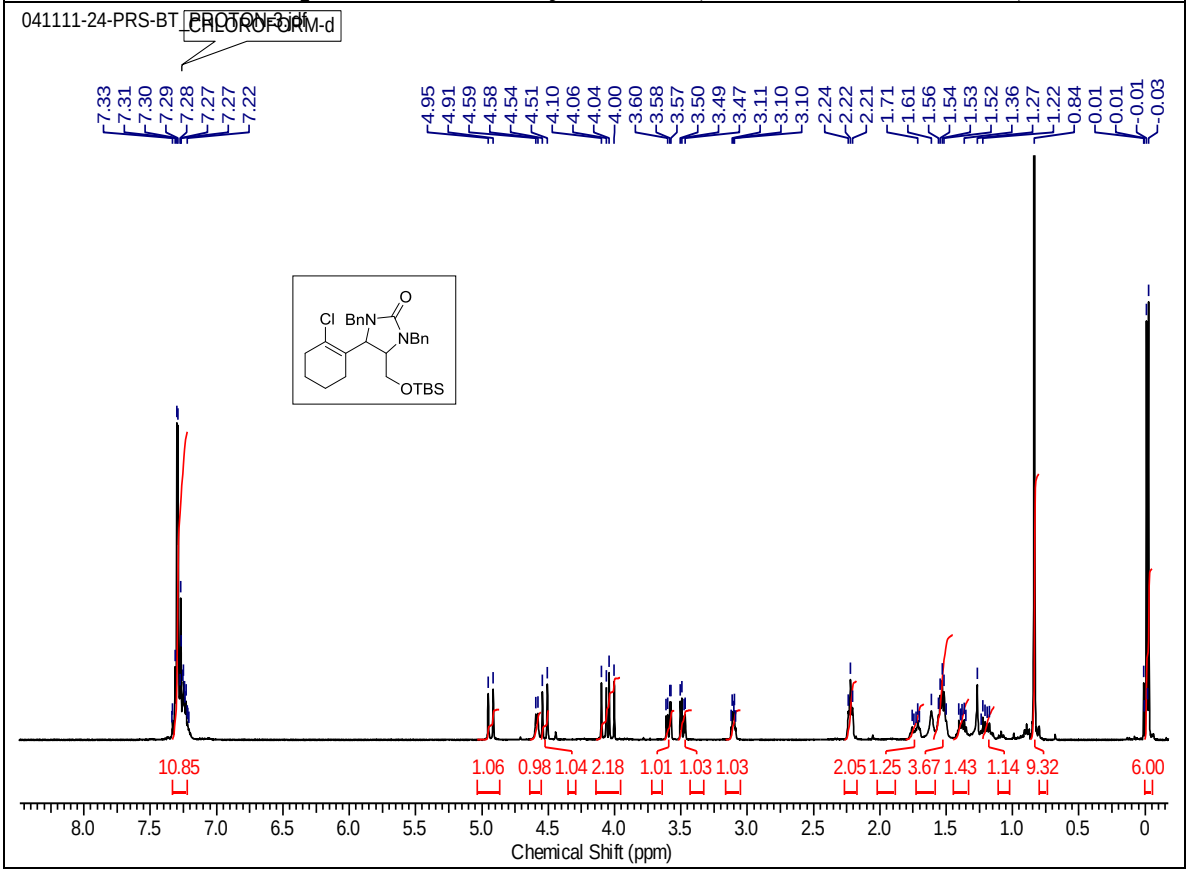
DEPT spectrum of alcohol 2 ($CDCl_3$+CCl_4, 125 MHz)



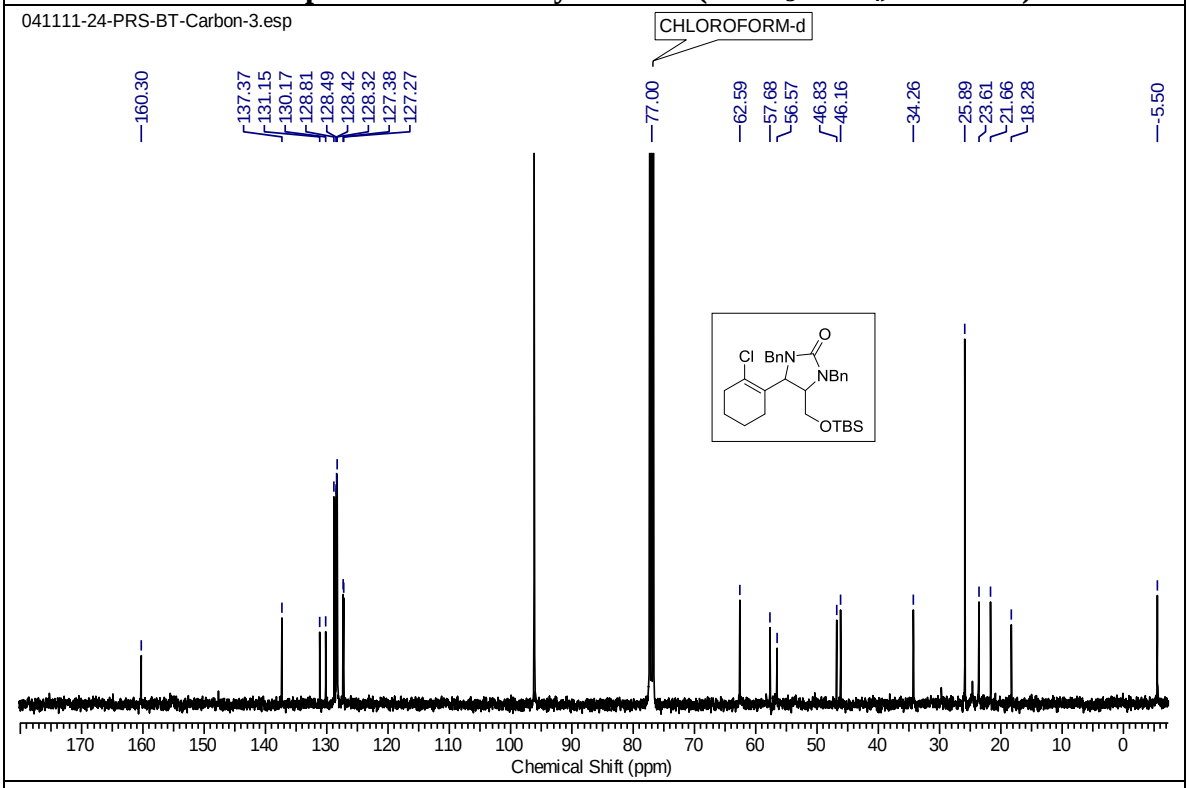
^{1}H NMR spectrum of bromide 16 ($CDCl_3$+CCl_4, 400 MHz)



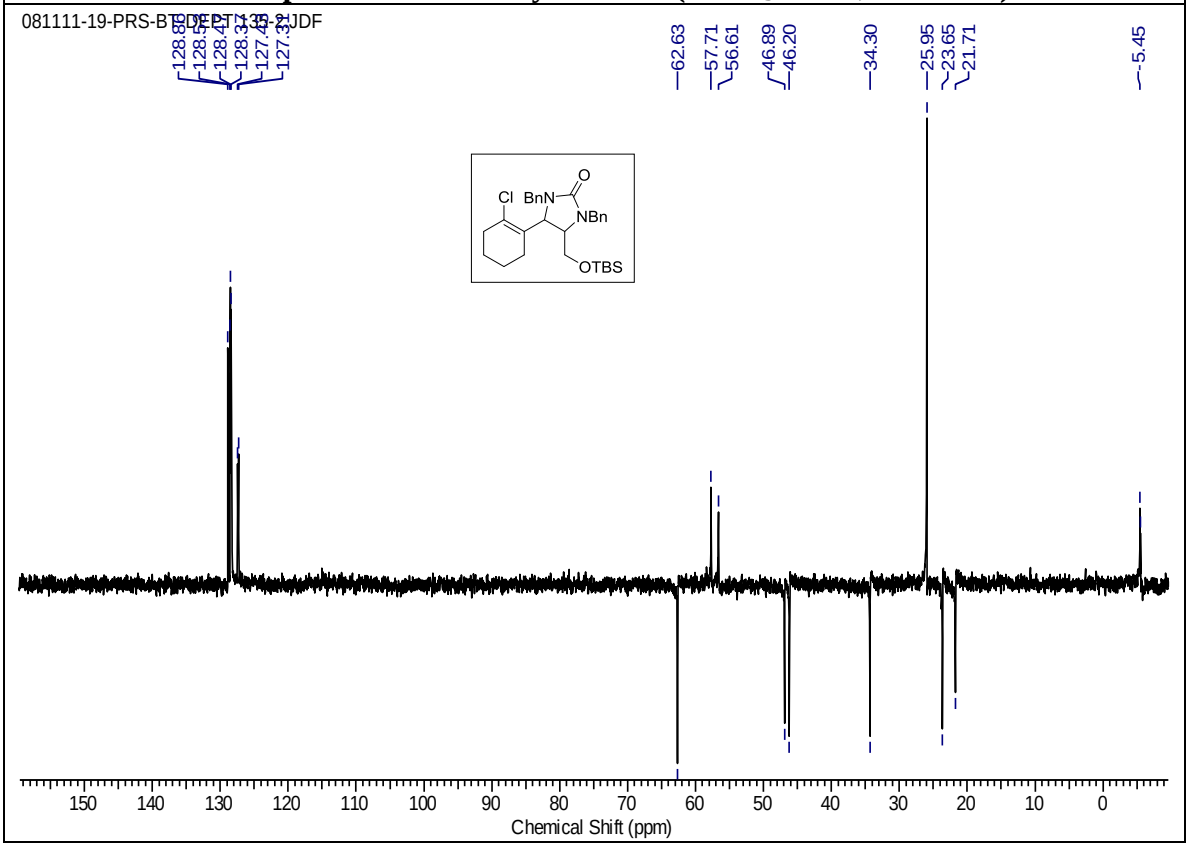
^{1}H NMR spectrum of dibenzyl urea 19 ($CDCl_3$+CCl_4, 400 MHz)



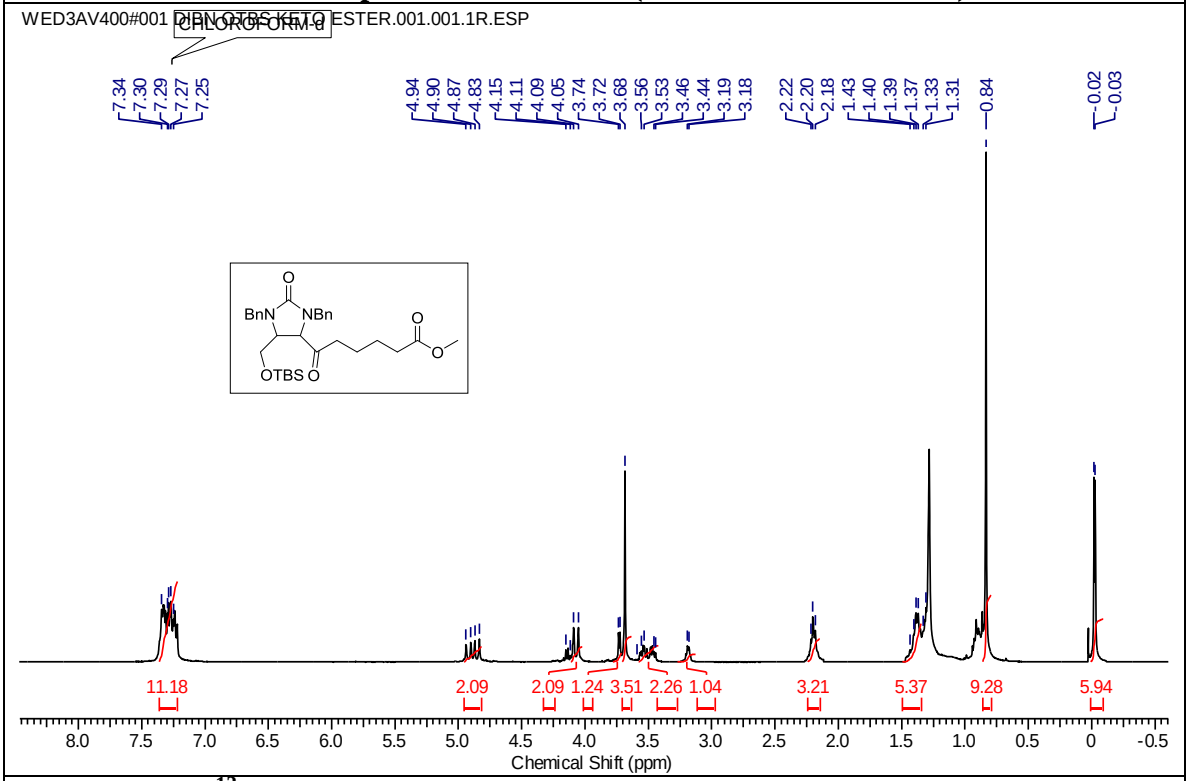
^{13}C NMR spectrum of dibenzyl urea 19 ($CDCl_3$+CCl_4, 100 MHz)



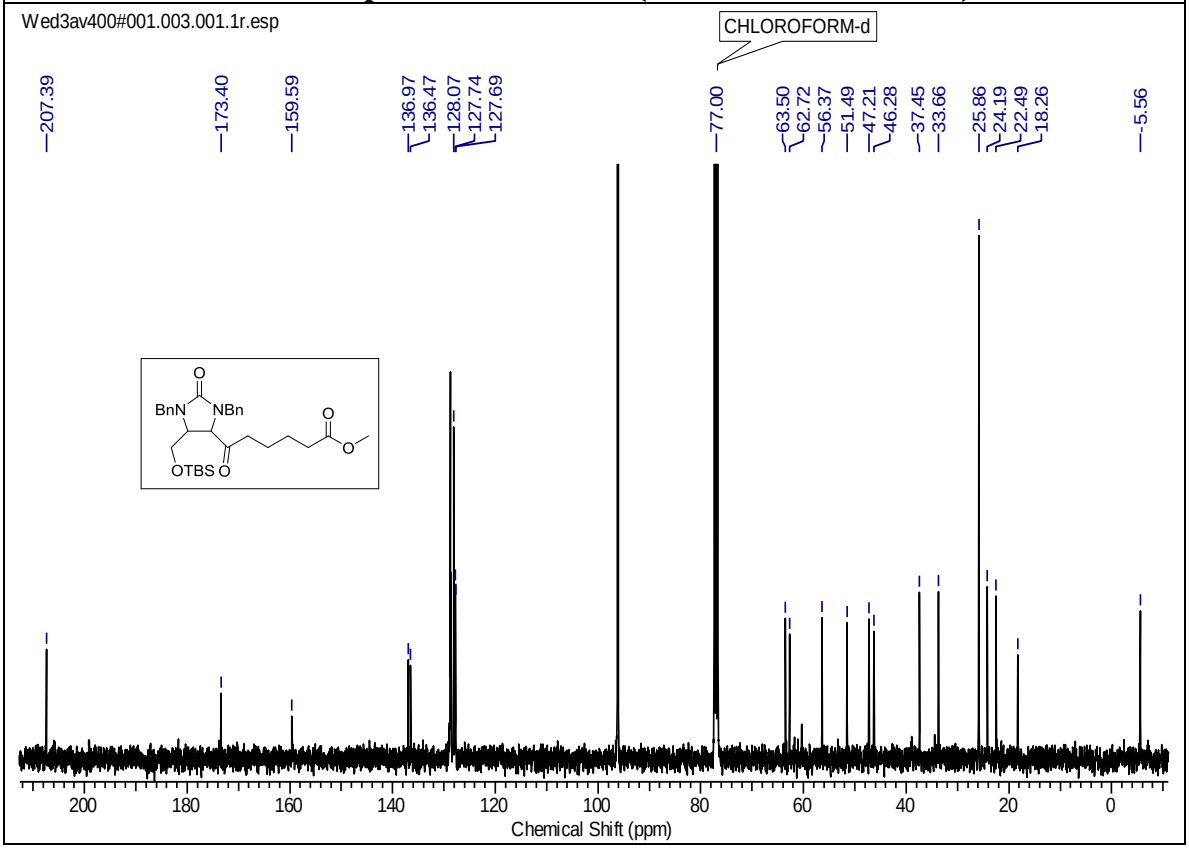
DEPT spectrum of dibenzyl urea 19 ($CDCl_3$+CCl_4, 100 MHz)



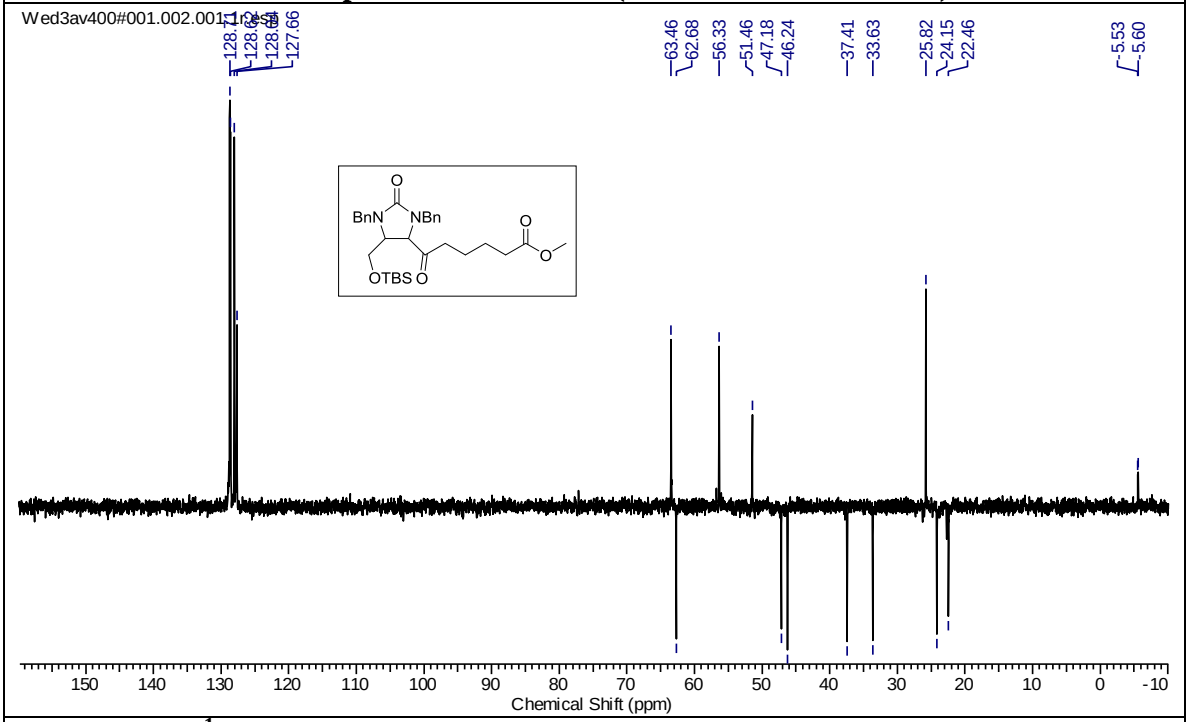
^{1}H NMR spectrum of ester 20 ($CDCl_3$+CCl_4, 400 MHz)



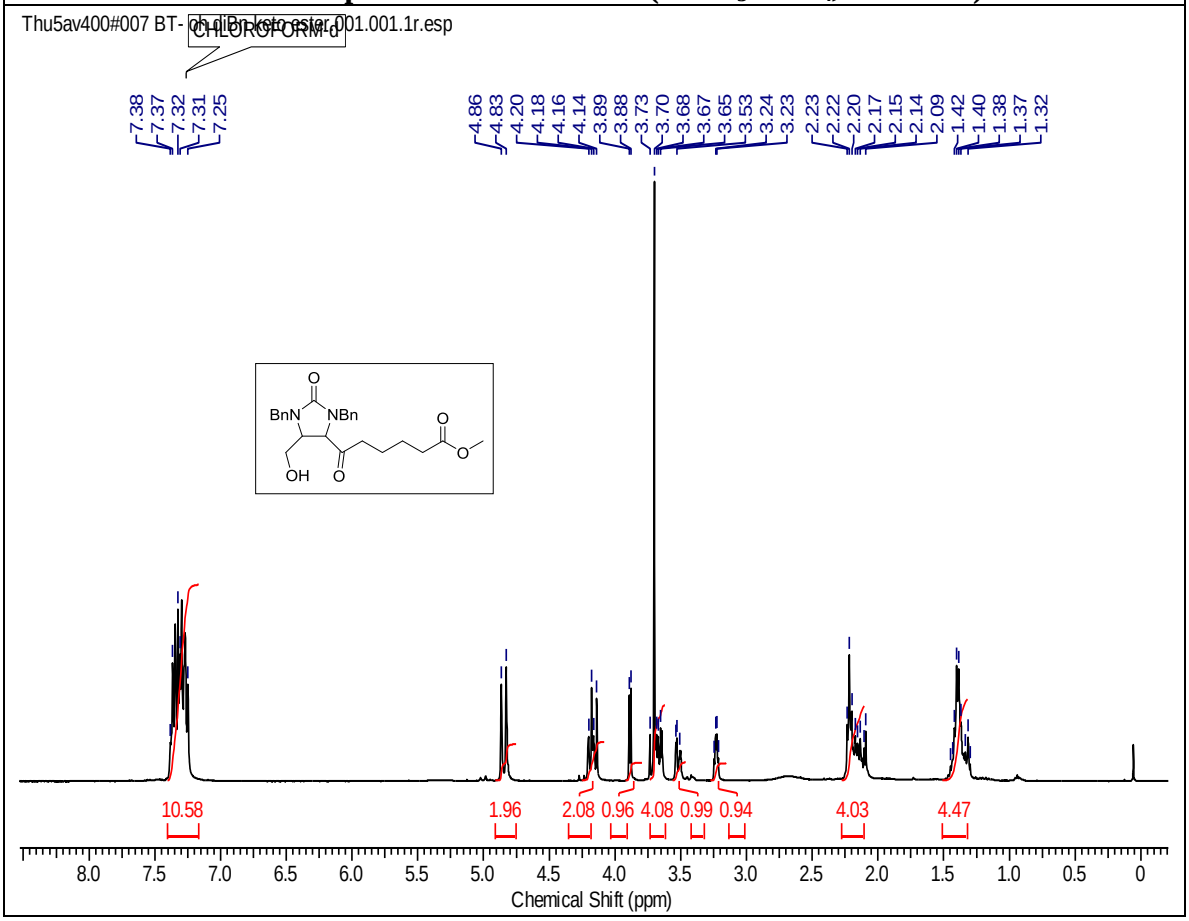
^{13}C NMR spectrum of ester 20 ($CDCl_3$+CCl_4, 100 MHz)



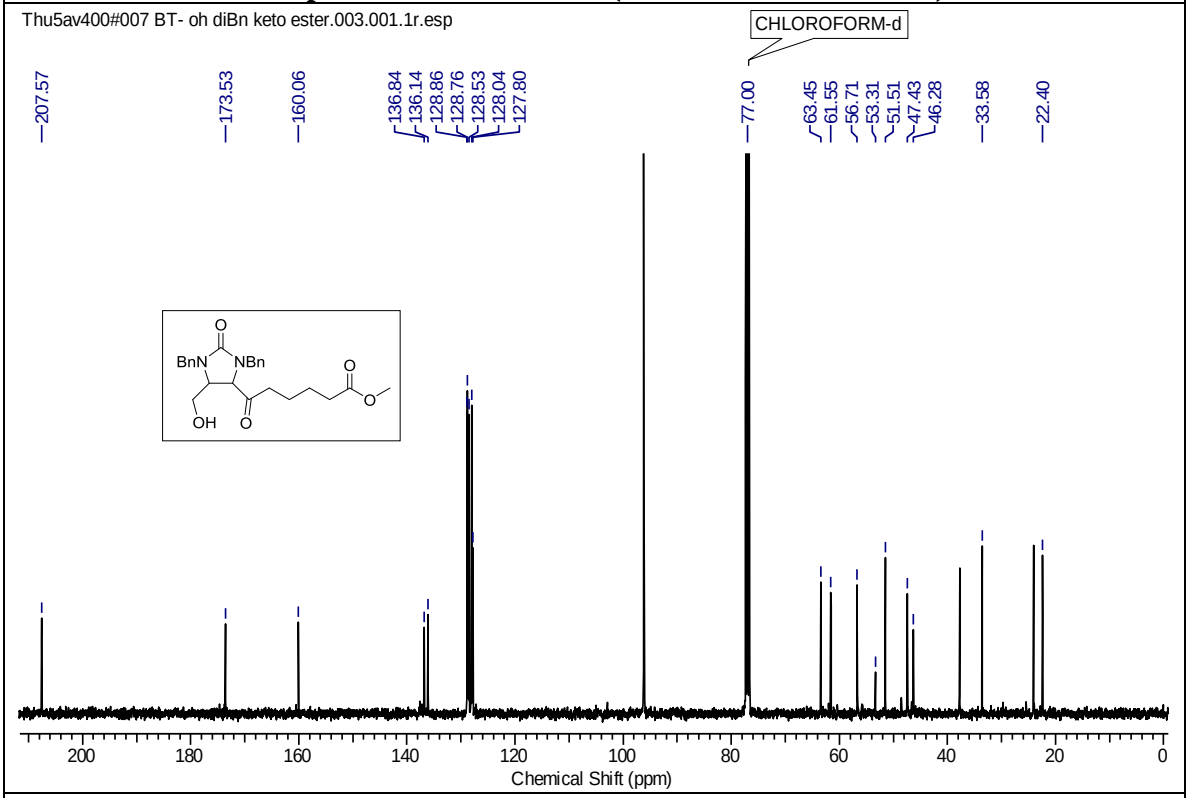
DEPT spectrum of ester 20 ($CDCl_3$+CCl_4, 100 MHz)



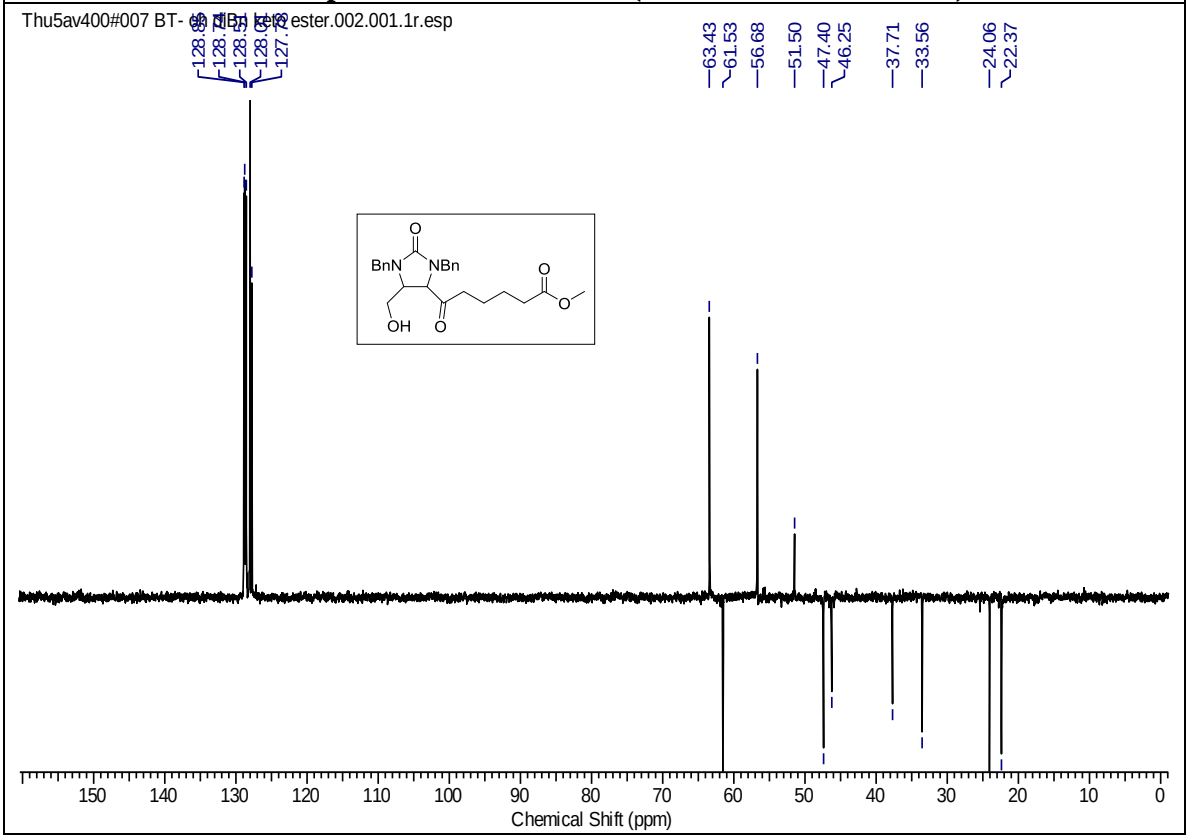
^{1}H NMR spectrum of alcohol 21 ($CDCl_3$+CCl_4, 400 MHz)



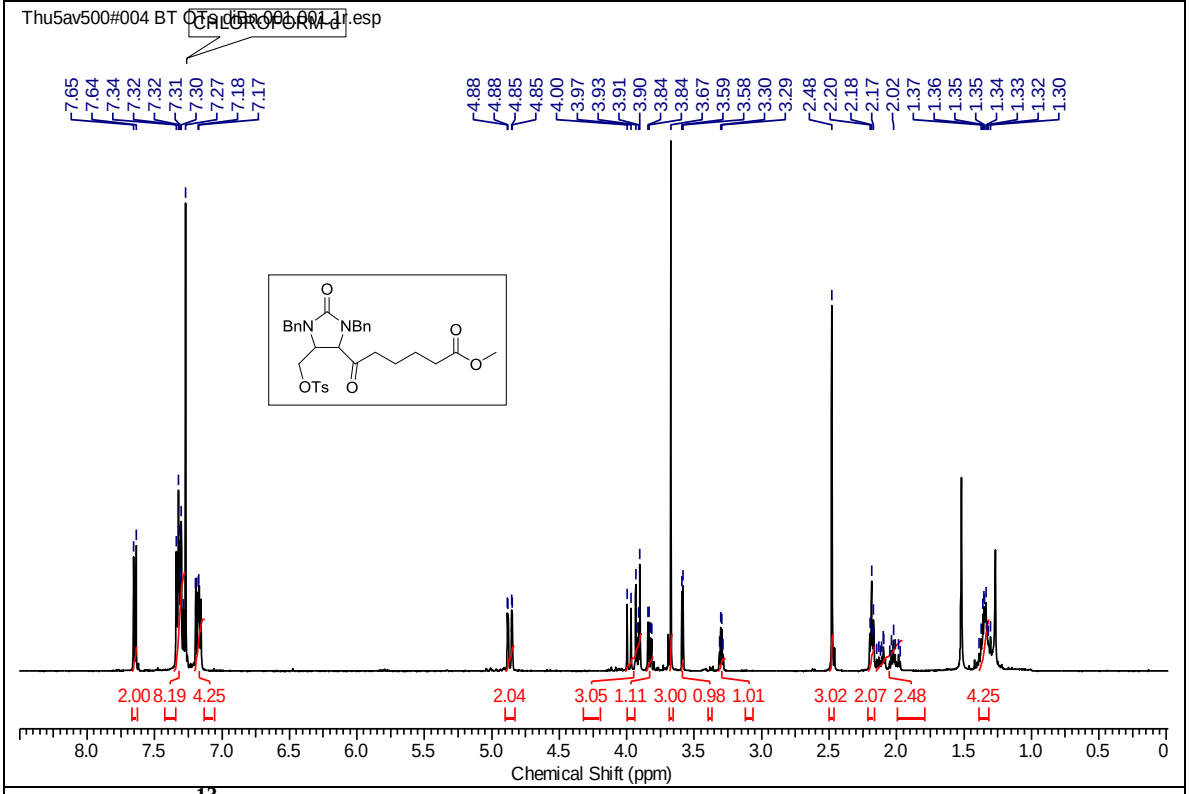
^{13}C spectrum of alcohol 21 ($CDCl_3$+CCl_4, 100 MHz)



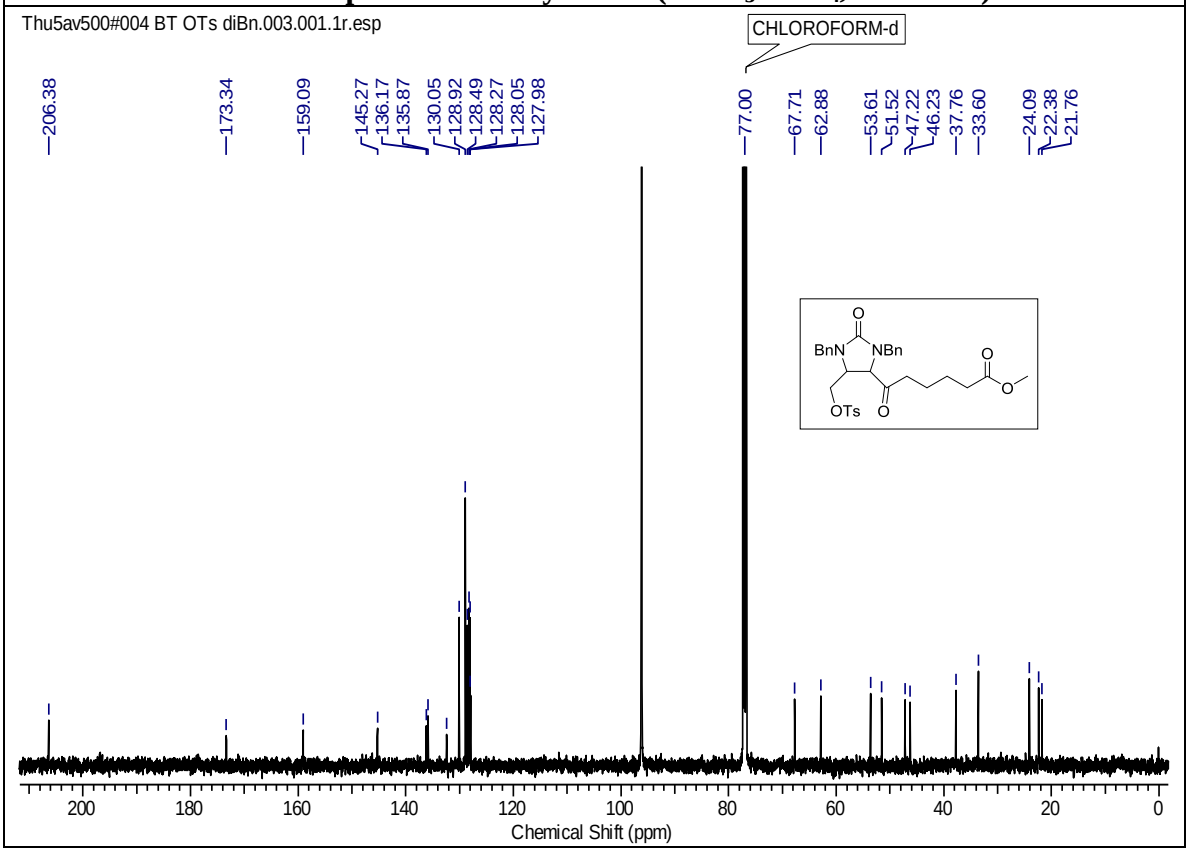
DEPT spectrum of alcohol 21 ($CDCl_3$+CCl_4, 100 MHz)



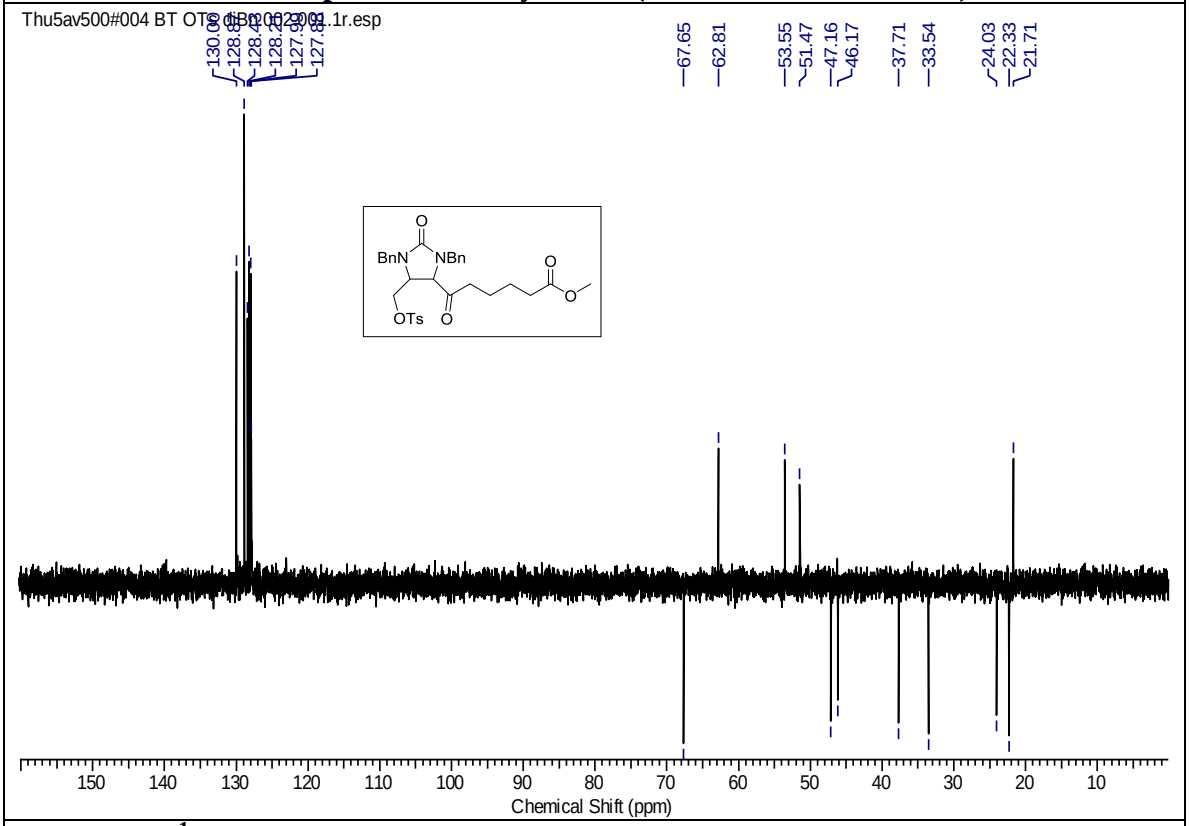
^{1}H NMR spectrum of tosylate 22 ($CDCl_3$+CCl_4, 500 MHz)



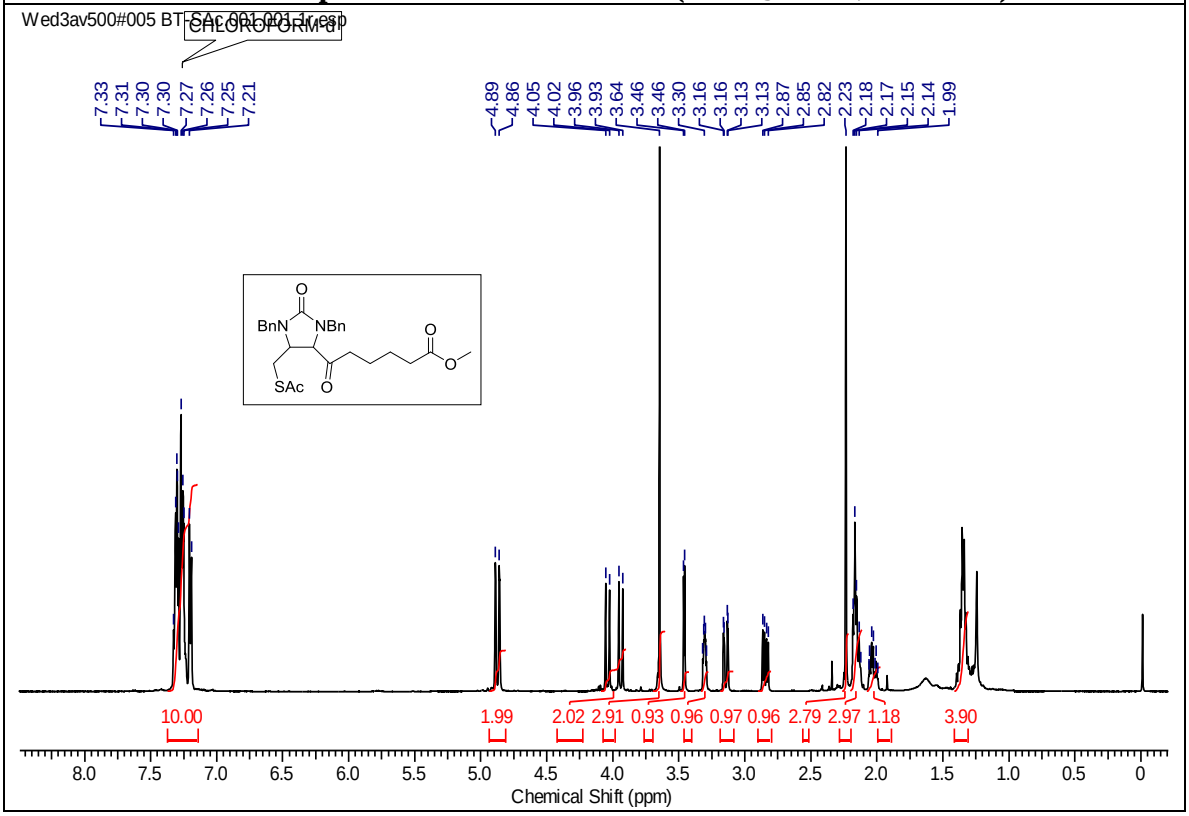
^{13}C NMR spectrum of tosylate 22 ($CDCl_3$+CCl_4, 125 MHz)



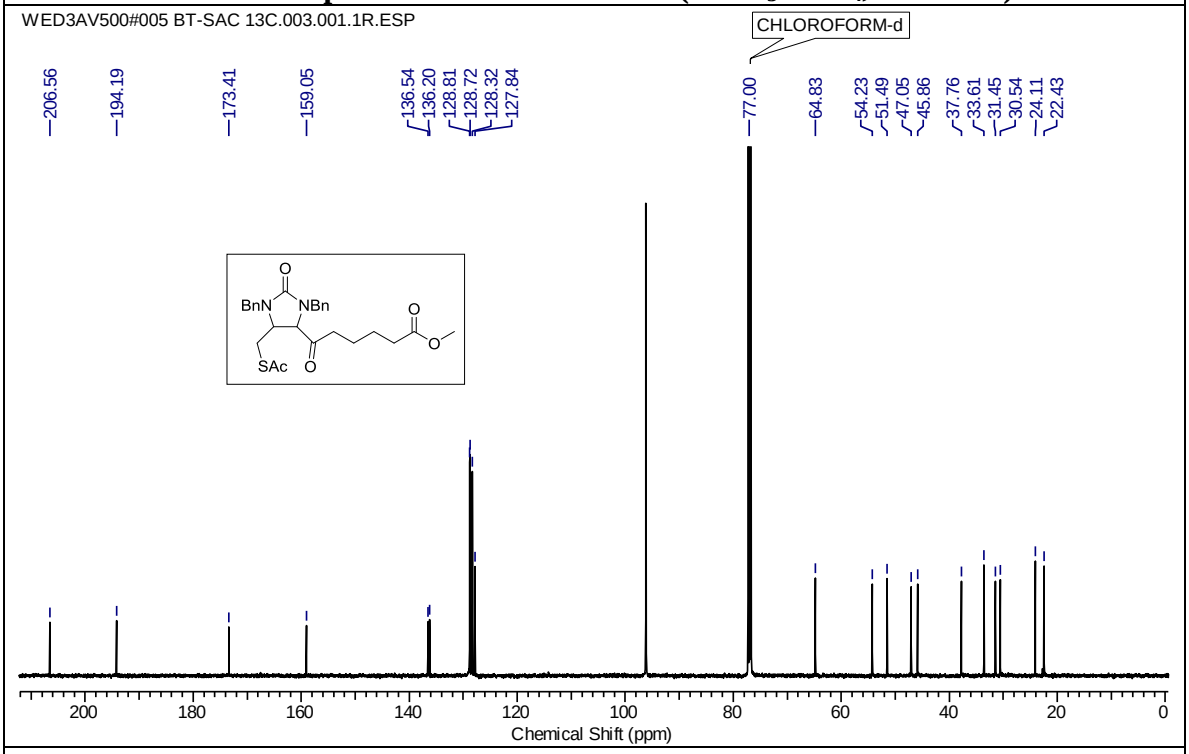
DEPT spectrum of tosylate 22 ($CDCl_3$+CCl_4, 125 MHz)



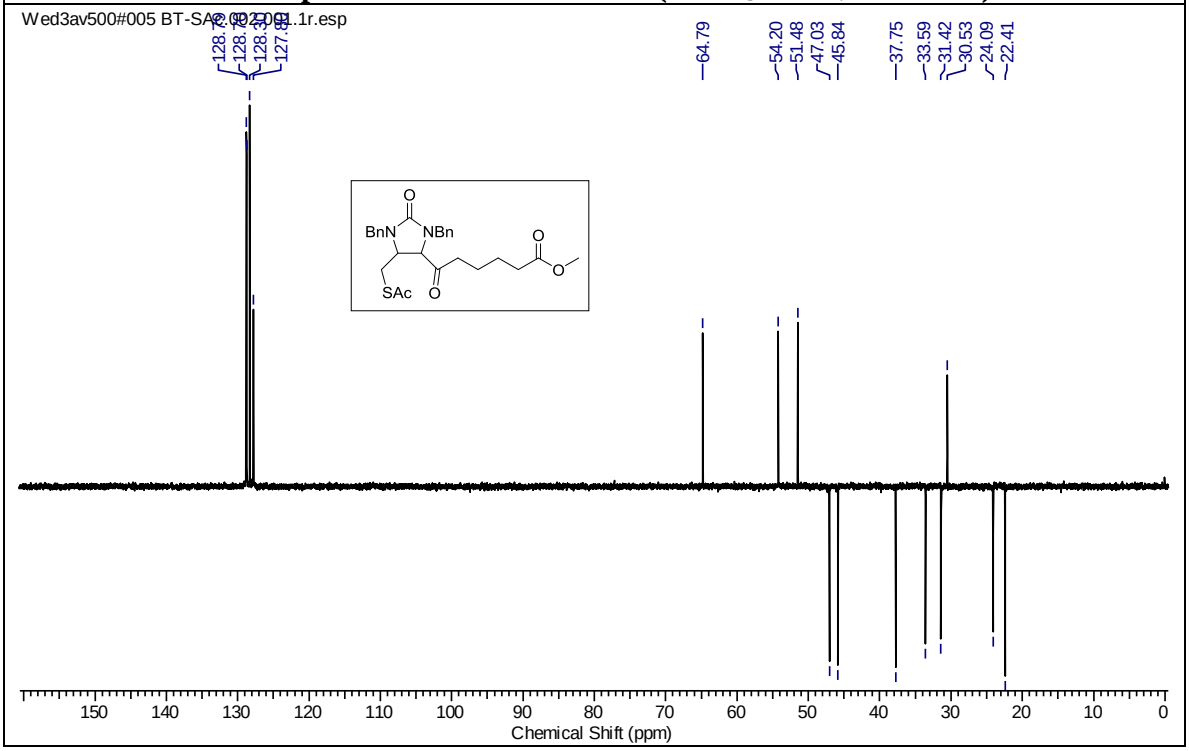
^{1}H NMR spectrum of thioacetate 18 ($CDCl_3$+CCl_4, 500 MHz)



^{13}C NMR spectrum of thioacetate 18 ($CDCl_3$+CCl_4, 125 MHz)



DEPT spectrum of thioacetate 18 ($CDCl_3$+CCl_4, 125 MHz)



3.3.6 References

1) Krysan, D. J. *Tetrahedron Letters* **1996**, *37*, 3303.
2) Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. R. *Org. Lett*. **2009**, *11*, 807.
3) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
4) Narina, S. V.; Kumar, T. V.; Gorge, S.; Sudalai, A. *Tetrahedron Letters* **2007**, *48*, 65.
5) Appel, R. *Angewandte Chemie International Edition in English* **1975**, 14, 801.
6) (a) Chavan, S. P.; Lasonkar, P. B.; Chavan, P. N. *Tetrahedron: Asymmetry* **2013**, 24, 1473, (b) Chavan, S. P.; Chittiboyina, A. G.; Ravindranathan, T.; Kamat, S. K.; Kalkote, U. R. *J. Org. Chem.* **2005**, *70*, 1901; (c) Chavan, S. P.; Chittiboyina, A. G.; Ramakrishna, G.; Tejwani, R. B.; Ravindranathan, T.; Kamat, S. K.; Rai, B.; Sivadasan, L.; Balakrishnan, K.; Ramalingam, S.; Deshpande, V. H. *Tetrahedron* **2005**, *61*, 9273.