

**STUDIES IN SYNTHESIS AND  
TRANSFORMATIONS OF  $\beta$ - LACTAMS**

**BY**

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**DOCTOR OF PHILOSOPHY**

**(IN CHEMISTRY)**

**RESEARCH GUIDE**

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**DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)**

**NATIONAL CHEMICAL LABORATORY**

**PUNE - 411 008**

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**STUDIES IN SYNTHESIS AND TRANSFORMATIONS  
OF  $\beta$ - LACTAMS**

**A THESIS**

*Submitted to the*

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*For the degree of*

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*in*

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*BY*

**AJAYKUMAR S. KALE**

**DIVISION OF ORGANIC CHEMISTRY: SYNTHESIS**

**NATIONAL CHEMICAL LABORATORY**

**PUNE 411 008, INDIA**



**Dedicated to my  
Parents, Brothers and Sister in law**

## CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Studies in Synthesis and Transformations of  $\beta$ -Lactams**" which is being submitted to the University of Pune for the award of **Doctor of Philosophy in Chemistry** by **Mr. Ajaykumar S. Kale** was carried out by him under my supervision at the **National Chemical Laboratory, Pune**. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date:

(Dr. A. R. A. S. Deshmukh)

National Chemical Laboratory

Research Supervisor

Pune 411 008

## National Chemical Laboratory



### Candidate's Declaration

---

I hereby declare that the thesis entitled “**Studies in Synthesis and Transformations of  $\beta$ -Lactams**” submitted for the degree of **Doctor of Philosophy** in Chemistry to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. A. R. A. S. Deshmukh. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other university.

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Research Student

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*(Ajay Kale.)*



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## GENERAL REMARKS

1. All melting points (recorded on a Büchi melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or in chloroform, or neat on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FTIR and Shimadzu FTIR, using sodium chloride optics. IR bands are expressed in frequency ( $\text{cm}^{-1}$ ).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, AV 200, MSL-300, AV400 and DRX-500 spectrometer. Chemical shifts were recorded in parts per million ( $\delta$ , ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, bs = broad singlet and m = multiplet have been used to describe the spectral data.  $\text{CDCl}_3$  was used as the solvent unless otherwise mentioned.
4.  $^{13}\text{C}$  NMR spectra were recorded on Bruker AC-200, AV 200, MSL-300, AV400 and DRX-500 instrument operating at 50.3 MHz, 75 MHz and 125.8 MHz respectively.
5. Elemental analyses (C, H, N, S) were obtained on a Carlo-Erba, 1100 automatic analyzer.
6. Optical rotations were measured on a JASCO-181 digital Polarimeter, JASCO P-1020 Polarimeter and ADP-220 Polarimeter using sodium D line (5893 Å). Concentration is expressed in g/ 100 ml.
7. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system or electron spray ionization method (EI).
8. Petroleum ether refers to the fraction boiling between 60-80 °C.
9. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F<sub>254</sub> (Merck) and glass plates coated with silica gel F<sub>254</sub>.

10. Silica Gel used for column chromatography was 60-120 mesh, 100-200 mesh or 230-400 mesh size.
11.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of the representative compounds are attached at the end of the corresponding chapter. For all the samples containing methylene and quaternary carbons, DEPT spectrum was scanned after scanning  $^{13}\text{C}$  NMR spectra and then the assignment of the peaks in  $^{13}\text{C}$  NMR was done.
12. Solvents for column chromatography were distilled at their respective constant boiling points.
13. All the dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents.
14. Dichloromethane was dried over anhydrous  $\text{P}_2\text{O}_5$  and stored over  $4\text{\AA}$  molecular sieves. THF was freshly distilled over sodium benzophenone ketyl. Triethyl amine was dried over potassium hydroxide.
15. All other solvents were dried following the procedures given in the book 'Purification of Laboratory Chemicals' by Armarego and Perrin (third edition).
16. Compounds have been named based on nomenclature provided by CS-ChemDraw software.

## Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile $[(\text{CH}_3)_2\text{C}(\text{CN})\text{N}=\text{NC}(\text{CH}_3)_2\text{CN}]$
Ar	Aryl
Bn	Benzyl
Boc	<i>t</i> -Butoxy carbonyl
CAN	Ceric ammonium nitrate
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	<i>N,N'</i> -Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	Dichloroethane or ethylene dichloride
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
h	Hour(s)
Hz	Hertz
Me	Methyl
Ms	Methanesulfonyl

min	Minute
MP	Melting point
ORTEP	Oak Ridge Thermal Ellipsoid Plot Programme
Pet ether	Petroleum ether
Pd/C	Palladium carbon
PMP	<i>p</i> -Methoxyphenyl
PTSA or TSOH	<i>p</i> -Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
TBDMS	<i>t</i> -Butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	<i>p</i> -Toluenesulfonyl

## **Abstract of thesis**

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Compound numbers in the abstract are different from those in the thesis

Name of candidate: **Ajaykumar Sadashiv Kale**

Name of research guide: Dr. A. R. A. S. Deshmukh

Abstract of thesis entitled: **Studies in Synthesis and Transformations of  $\beta$ -Lactams.**

## **Chapter 1**

### **An efficient synthesis of 2,3-aziridino- $\gamma$ -lactones from azetidin-2-ones**

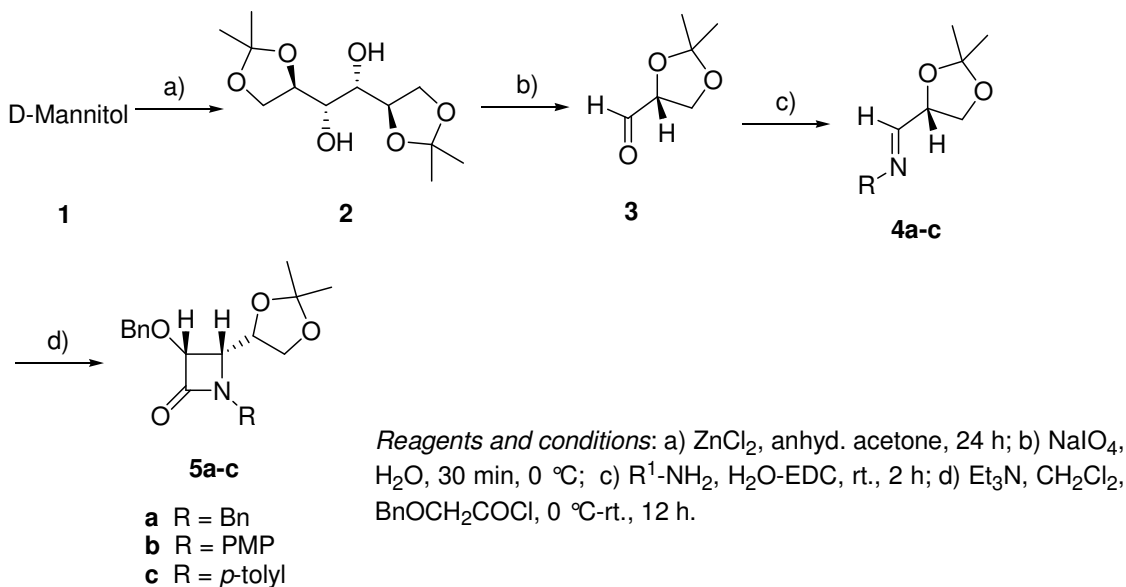
$\beta$ -Lactams, apart from their prominent role in medicinal chemistry as the most widely used antibiotics; continue to exhibit utility in newer applications. Over the last few decades the scope and applications of the  $\beta$ -lactams has widened appreciably opening new avenues for research. Amongst these applications the single and the most important one, which has shown a staggering growth, has been their use as synthons for other biologically important products. The ease of cleavage of the lactam bond; ascribable largely to the ring strain, makes it amenable to various transformations. The selective bond cleavage of the strained ring coupled with further interesting transformations render this fascinating molecule a powerful building block. Efforts have been made in exploring such new aspects of  $\beta$ -lactam chemistry using enantiomerically pure  $\beta$ -lactams as versatile intermediates for the synthesis of heterocyclic non  $\beta$ -lactam structures, aromatic  $\beta$ -amino acids and their derivatives, oligopeptides, labelled peptides and azetidines, which are further converted to polyamines, polyamino alcohols, amino sugars and polyamino ethers.

We have also exploited these  $\beta$ -lactams for the synthesis of biologically useful compounds. This chapter deals with the synthesis of biologically useful 2,3-aziridino- $\gamma$ -lactones. These bicyclic lactones are very important intermediates in the synthesis of biologically useful 3,4-dihydroxy glutamic acids, especially L-glutamic acid, an important excitatory neurotransmitter of the central nervous system. The regioselective nucleophilic opening of the aziridine ring also gives variety of useful products including  $\alpha$ -amino acids, such as polyoxamic acid and  $\beta$ -amino acids. The regioselectivity of the ring cleavage is mainly controlled by the hardness and softness of the nucleophile.

We have developed a short and efficient method for the synthesis of 2,3-aziridino- $\gamma$ -lactones from optically pure 3-benzyloxy- $\beta$ -lactams. The 3-benzyloxy- $\beta$ -lactams are readily prepared in enantiomerically pure form by using asymmetric Staudinger reaction

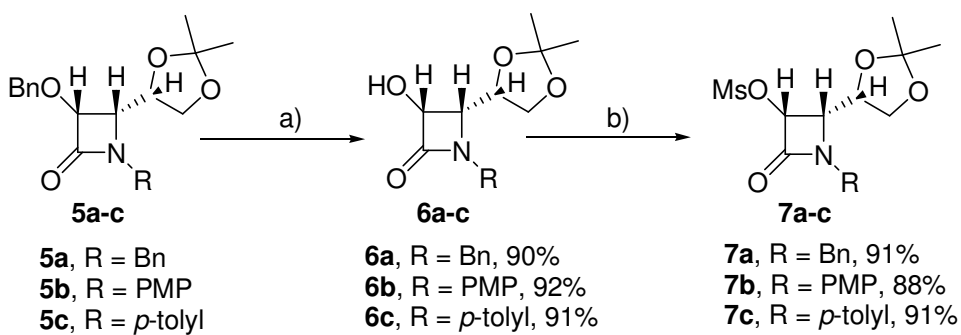


of chiral imines derived from glyceraldehyde acetonide by reaction with various amines and ketene generated *in situ* from benzyloxy acetyl chloride (Scheme 1).

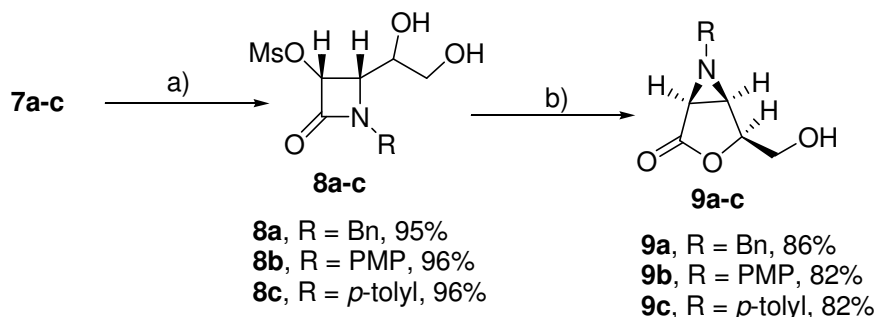


**Scheme 1**

The key step in this synthesis is the selective intramolecular nucleophilic β-lactam ring opening followed by aziridine ring formation *via* elimination of the mesylate group (Scheme 2).



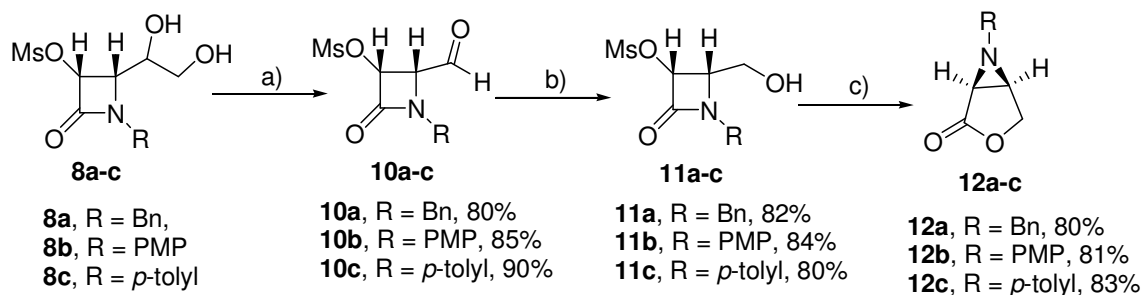
*Reagents and conditions:* a) 10%Pd/C, HCOONH<sub>4</sub>, MeOH, reflux, 0.5 h; b) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -10°C-rt, 2 h.



*Reagents and conditions:* a) PTSA, THF-H<sub>2</sub>O, reflux, 12-24 h;  
 b) HCl-MeOH (20%), reflux, 18-24 h.

### Scheme 2

The formation of 2,3-aziridino- $\gamma$ -lactone was further confirmed by the synthesis of aziridino- $\gamma$ -lactone **12a** and comparing its spectral data with the reported racemic compound. The IR and NMR data for the compound **12a** was found to be exactly similar with that of the reported racemic compound.



*Reagents and conditions:* a) NaIO<sub>4</sub> supported on silica gel, MeOH, rt, 3.5 h;  
 b) NaBH<sub>4</sub>, MeOH or THF, rt, 3 h; c) HCl-MeOH (20%), reflux, 18-24 h.

### Scheme 3

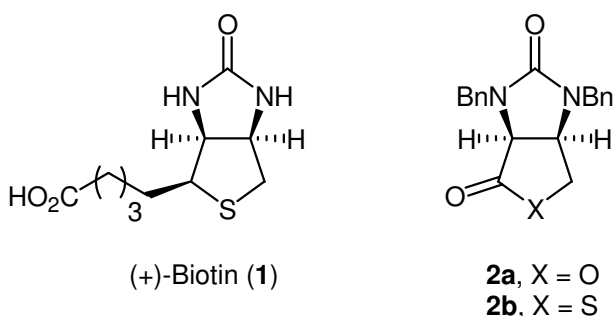
This confirms the formation of aziridino- $\gamma$ -lactones *via* tandem nucleophilic azetidinone ring opening and aziridine ring formation. Other aziridino- $\gamma$ -lactones **9b-c** (Scheme 2) and **12b-c** (Scheme 3) were also prepared in good yields showing the generality of the reaction.

In conclusion, we have demonstrated an efficient synthetic method for the synthesis of 2,3-aziridino- $\gamma$ -lactones using azetidin-2-ones as synthons. One-pot nucleophilic azetidinone ring opening followed by the formation of aziridine ring is the key step in this synthesis.

## Chapter 2

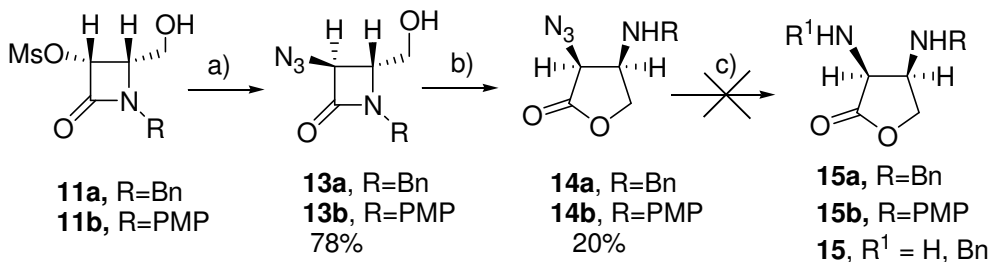
### A Practical formal synthesis of D-(+)-biotin from 4-formylazetididin-2-one

(+)-Biotin **1** (Figure 1) is one of the water-soluble B-complex vitamins. It plays an important role as coenzyme in carboxylation reaction related to biochemical process, such as glyconeogenesis and fatty acid biosynthesis. It is also widely used in poultry feeds for growth of chicks and healthy hatching of eggs. The main sources of biotin are liver, kidney, pancreas, yeast, egg yolk and milk. Biotin deficiency in poultry and swine causes series of severe symptoms. These deficiencies are corrected by using biotin as a feed additive. Hence it is commercially very important molecule.



**Figure 1**

Although numerous synthetic approaches have been reported to date, the first synthesis of biotin described by Goldberg and Sternbach, and subsequent modifications is still one of the best syntheses. The potential of this approach depends upon the efficient method available for making optically active lactone **2a** or thiolactone **2b**.



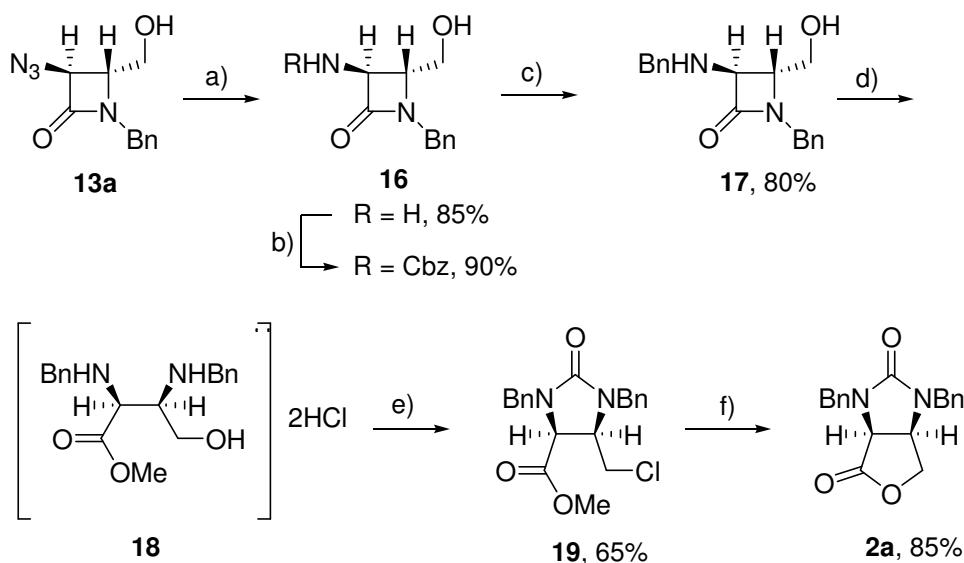
*Reagents and Conditions:* a) NaN<sub>3</sub>, DMF, 80 °C, 36 h; b) HCl-MeOH (20%), rt, 34 h; c) HCOONH<sub>4</sub>, Pd/C (10%), MeOH, reflux, 40 mi.; or H<sub>2</sub>, Pd/C (10%), EtOH, 60 psi, 5 h, or Bu<sub>3</sub>P, THF, Et<sub>3</sub>N, BnBr, 5 h.

**Scheme 4**

We have developed a new synthetic method for (+)-biotin from optically pure *N*-benzyl-4-formyl-3-mesyloxyazetid-2-one **10a**. 4-Formyl- $\beta$ -lactam **10a** was reduced to the corresponding alcohol **11a**, which was further converted to azide **13a**.

The azetid-2-one ring expansion reaction of **13a-b** with methanolic-HCl at room temperature resulted in very poor yield (20%) of the azidolactone **14a-b** (Scheme 4). All our efforts to improve the yield of **14a-b** were unsuccessful. Moreover, the reduction of azido group by catalytic hydrogenation or transfer hydrogenation gave a complex mixture of products.

Therefore, we decided to reduce azido- $\beta$ -lactam **13a** to the corresponding amino- $\beta$ -lactam **16** (R = H).

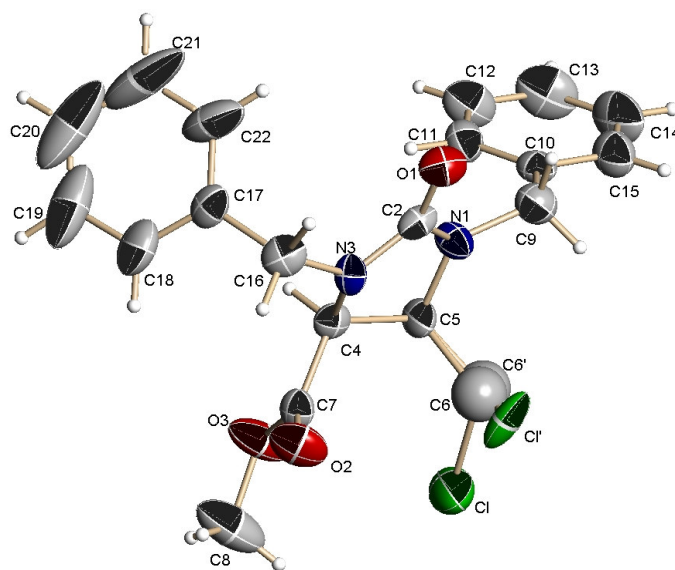


*Reagents and conditions:* a) HCOONH<sub>4</sub>, Pd/C (10%), MeOH, reflux, 45 min; b) CbzCl, NaHCO<sub>3</sub>, acetone-water (2:1), 1.5 h; c) i) PhCHO, MgSO<sub>4</sub>, DCM, rt, 12 h, ii) NaBH<sub>4</sub>, MeOH, 0° C to rt, 2.5 h; d) HCl-MeOH (20%), rt, 14 h e) Et<sub>3</sub>N, triphosgene, -20 °C-0 °C, 2 h; f) aq. KOH (2.5%), THF, 0° C to rt, 5 h.

### Scheme 5

The reduction of azido- $\beta$ -lactam **13a** was successfully achieved by transfer hydrogenation using Pd/C and ammonium formate in methanol to get amino- $\beta$ -lactam **16** (R = H) in very good yield. The amino- $\beta$ -lactam **16** (R = H) was further converted to the corresponding *N*-Cbz-derivative for the purpose of characterization. The amino- $\beta$ -lactam **16** (R = H) was then transformed to *N*-benzyl derivative **17** in good yield by reacting with benzaldehyde followed by *in situ* reduction of the corresponding Schiff base with sodium

borohydride. *N*-Benzylamino- $\beta$ -lactam **17** was treated with methanolic-HCl (20%) at room temperature to get highly polar ring cleavage product, dihydrochloride **18**. Our efforts to isolate the free base from the dihydrochloride **18** in pure form were unsuccessful. Therefore, the dihydrochloride **18** was directly reacted with triphosgene in the presence of triethylamine. Interestingly, a one-pot conversion of diamine to cyclic urea and hydroxymethylene to the corresponding chloromethylene took place simultaneously to afford chloroester **19** (Scheme 5). The structure of **19** was established by spectral data and further confirmed by single crystal X-ray analyses (Fig. 2).



**Figure 2** ORTEP diagram of **19**

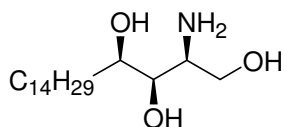
The conversion of the chloroester **19** to the desired (3*S*,6*R*)-1,3-dibenzyl-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (**2a**), was achieved by stirring with aqueous KOH (2.5%) in THF at room temperature. The optical purity (ee > 99%) was determined by chiral HPLC. The spectral data and the specific rotation were found to be identical with the reported values. The synthesis of D-(+)-biotin **1** from the lactone **2a** can be achieved by using a reported synthetic protocol.

In conclusion we have demonstrated the utility of azetidin-2-one as a synthon for the synthesis of the bicyclic lactone **2a**, an important intermediate in biotin synthesis.

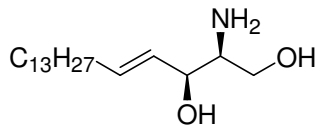
## Chapter 3

### 4-Formyl azetidin-2-one an useful building block for the formal synthesis of *xylo-(2S,3R,4R)*-phytosphingosine and *threo-(2S,3S)*-sphingosine

Sphingolipids are membrane components of all eukaryotic cells, plasma membranes and some intramolecular cell organelles. It is known that sphingosines and ceramides play a vital role in intracellular signaling along with secondary messenger molecules. Sphingosines (Figure 3) are lipophilic components of glycosphingolipids and ceramides. Phytosphingosines constitute the major base component of higher plants, protozoa, yeast and fungi. They have also been found in human kidney cerebroside and in some cancer cell types. *D-erythro*-Sphingosine shows promising protein kinase inhibitory activity. Moreover it has been shown that diastereomers of ceramides, sphingosines and dihydrosphingosines exhibit different activities and metabolisms. The subtle variations in biological activities over a range of diastereomers have inevitably led to synthesis of all diastereomers of sphingosines. This fact is reflected in steep rise in the number of publications dealing with the synthesis of sphingosines.



*xylo-(2S,3R,4R)*-phytosphingosine (**3**)

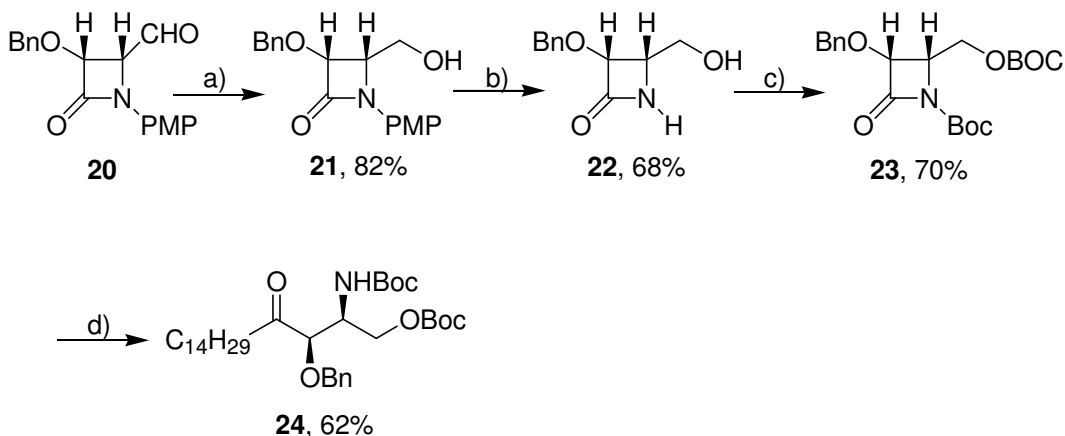


*threo-(2S,3S)*-sphingosine (**4**)

**Figure 3**

We have used  $\beta$ -lactam as a synthon for the synthesis of *xylo-(2S,3R,4R)*-phytosphingosine and *threo-(2S,3S)*-sphingosine. The starting 4-formyl  $\beta$ -lactam **20** was reduced to 4-hydroxymethyl azetidin-2-one using  $\text{NaBH}_4$  to get compound **21**, which was then treated with CAN which brought about oxidative cleavage of N-PMP group to yield **22** (Scheme 6). The *N*-unsubstituted  $\beta$ -lactam **22** was then treated with excess of  $(\text{Boc})_2\text{O}$  to get *N*-Boc and *O*-Boc protected derivative **23**.

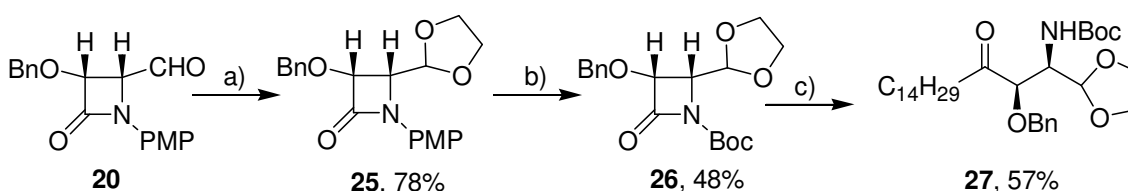
The compound **23** on nucleophilic azetidinone ring opening using appropriate Grignard reagent gave core structure of sphingosine **24**. Various reactions were carried out on compound **24** for Boc deprotection. However, all our attempts yielded complex reaction mixture. Efforts to reduce the keto group using various conditions also failed.



*Reagents and conditions:* a)  $\text{NaBH}_4$ , MeOH, 8 h; b) CAN,  $\text{CH}_3\text{CN-H}_2\text{O}$ , 45 min; c)  $(\text{Boc})_2\text{O}$ , DMAP, DCM, 12 h; d)  $\text{C}_{14}\text{H}_{29}\text{MgBr}$ , THF,  $-78^\circ\text{C}$ - $40^\circ\text{C}$ , 1 h;

### Scheme 6

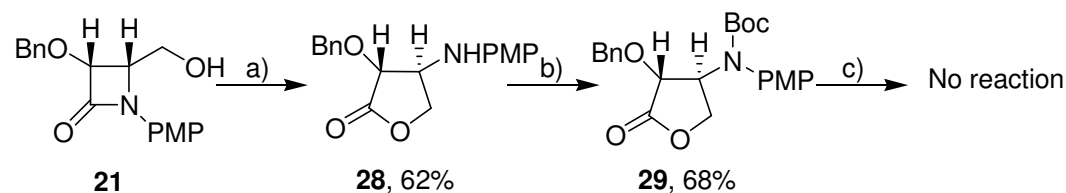
Therefore, the aldehyde group was protected as an acetal and compound **25** so obtained was subjected CAN oxidation to remove PMP and subsequently protected as a Boc derivative to yield compound **26** (Scheme 7).



*Reagents and conditions:* a) Ethylene glycol, PTSA, benzene, reflux, 8 h; b) (i) CAN,  $\text{CH}_3\text{CN-H}_2\text{O}$ ,  $0^\circ\text{C}$ , 45 min (ii)  $(\text{Boc})_2\text{O}$ , DMAP, DCM, rt, 12 h; c)  $\text{C}_{14}\text{H}_{29}\text{MgBr}$ , THF,  $-78^\circ\text{C}$ - $40^\circ\text{C}$ , 1 h

### Scheme 7

Compound **26** on reacting with Grignard reagent afforded compound **27** in good yield. Unfortunately our attempts to selectively deprotect the acetal were unsuccessful.



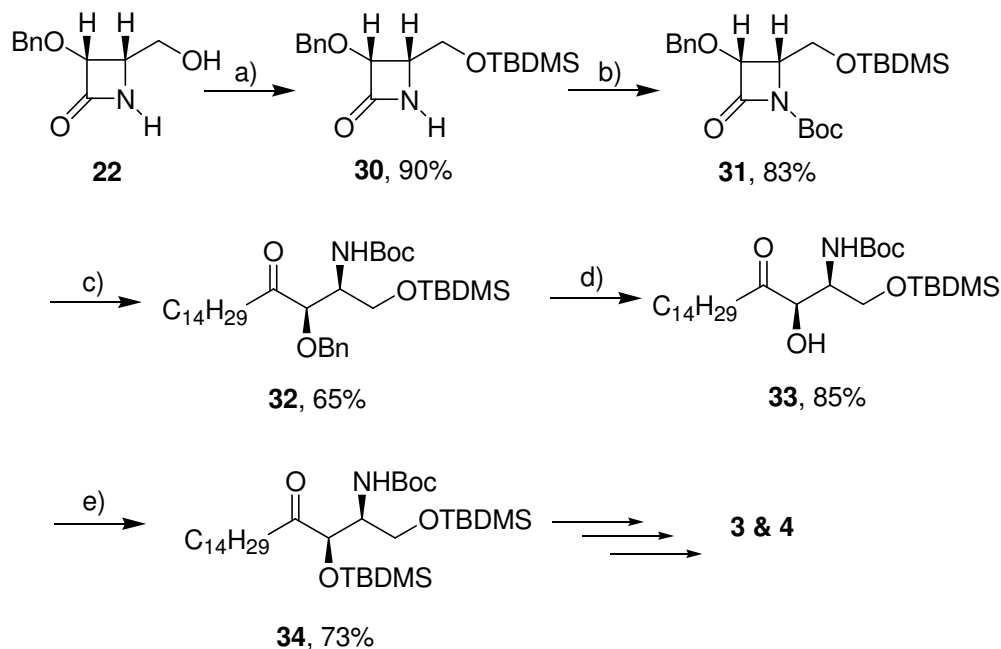
a)  $\text{H}^+/\text{MeOH}$ , rt, 12 h; b)  $(\text{Boc})_2\text{O}$ , DMAP, DCM, 12 h; c)  $\text{C}_{14}\text{H}_{29}\text{MgBr}$ , THF,  $-78^\circ\text{C}$ - $40^\circ\text{C}$ , 1 h.

### Scheme 8

The 4-hydroxymethylene azetidion-2-one (**21**) was lactonized using methanolic HCl to obtain compound **28** (Scheme 8).

The secondary amino group of **28** was protected as a carbamate **29** and Grignard reaction with tetradecylmagnesium bromide did not give the desired product.

The *N*-unsubstituted 4-hydroxymethylene  $\beta$ -lactam **22** was protected as TBDMS derivative **30**. The lactam nitrogen was then protected as a carbamate **31** (Scheme 9).



*Reagents and conditions:* a) TBDMS-Cl, imidazole, DMF, 3 h; b) (Boc)<sub>2</sub>O, DMAP, DCM, 5 h; c) C<sub>14</sub>H<sub>29</sub>MgBr, THF, -78°-40°C, 1 h; d) HCOONH<sub>4</sub>, Pd/C, MeOH, reflux, 1h; e) TBDMS-Cl, imidazole, DMF, 35°C, 12 h.

### Scheme 9

Compound **31** on reaction with tetradecyl magnesium bromide yielded compound **32**. The benzyloxy group was deprotected by transfer hydrogenation using ammonium formate and Pd/C and subsequently protected as TBDMS derivative to obtain compound **34** which is a precursor for *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**3**) and *threo*-(2*S*,3*S*)-sphingosine (**4**). Further conversion of **34** into *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine is a well established synthetic protocol.

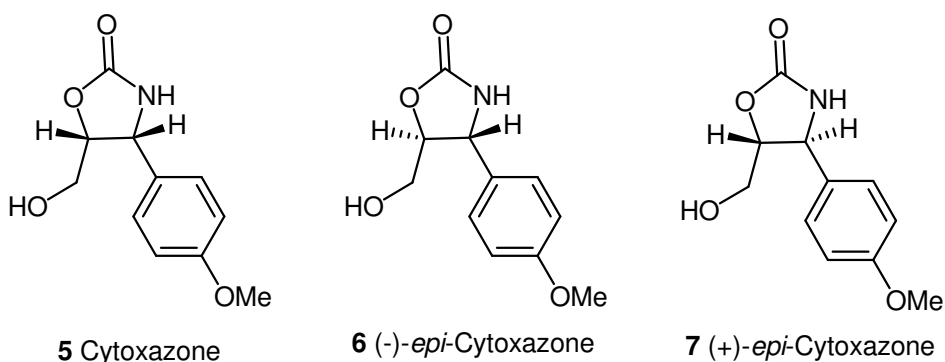
In conclusion a stereoselective formal synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine was achieved starting from enantiopure 4-formyl  $\beta$ -lactam.



## Chapter 4

### An Efficient Synthesis of (4*R*,5*S*) and (4*S*,5*R*)-*epi*-Cytoxazone from 3-Hydroxyazetidin-2-one

Cytoxazone **5**, (Figure 4) a novel cytokine modulator was isolated in 1998 from fermentation broth of *Streptomyces sp.*, and its absolute configuration was unambiguously established by total synthesis. It interferes with cytokine IL4, IL10, and IgG production *via* selective inhibition of the signaling pathway in Th2 cells. Cytoxazone **5**, a potent chemotherapeutic agent in the field of immunotherapy is different from other known immunomodulators, such as FK 506 and rapamycin in respect of structure and biological activity. Therefore, cytoxazone and its analogs have become interesting synthetic targets.



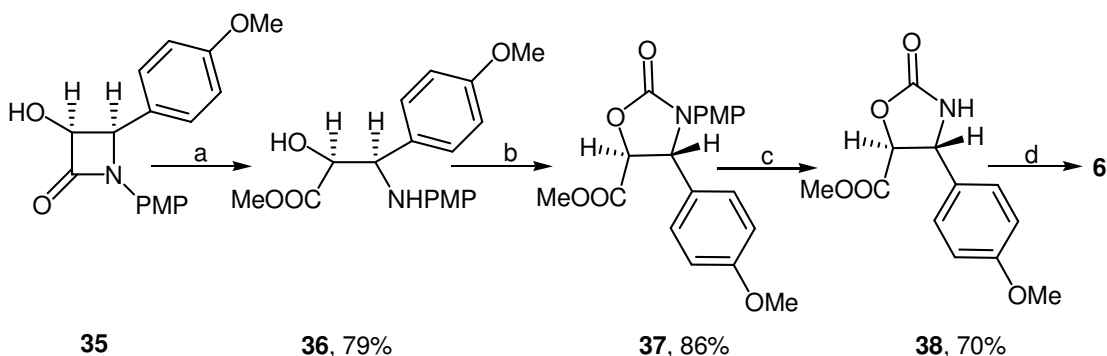
**Figure 3**

During the course of our research work in the area of asymmetric synthesis of  $\beta$ -lactams we developed very good method for asymmetric synthesis of 3-hydroxyazetidin-2-ones using ephedrine derived recyclable chiral auxiliary. Having 3-hydroxyazetidin-2-one **35** in hand we envisaged that the enantiopure compound **35** would be a very good starting material for the synthesis of *epi*-cytoxazone.

We envisaged that an acid catalysed ring opening **35** followed by cyclization with triphosgene would provide cyclic carbamate ester **37**. Subsequent PMP removal (**38**) followed by reduction would give the target molecule.

Initially we established the reaction conditions with racemic 3-hydroxyazetidin-2-one **35**, which was easily obtained by the hydrolysis of the corresponding 3-acetoxy-

azetidin-2-one in very good yield. 3-Acetoxy-azetidin-2-one was prepared by well-established Staudinger's ketene-imine cycloaddition reaction.



*Reagents and conditions:* a) H<sup>+</sup>/ MeOH (20%), rt, 48 h; b) triphosgene, Et<sub>3</sub>N, THF, 0° C to rt, 8 h; c) CAN, CH<sub>3</sub>CN - H<sub>2</sub>O, 0° C, 45 min; d) NaBH<sub>4</sub>, CaCl<sub>2</sub>, EtOH, 0° C to rt, 4 h.

### Scheme 10

3-Hydroxy- $\beta$ -lactam **35** on treatment with methanolic HCl (20%) at room temperature furnished  $\beta$ -amino methyl ester **36** (Scheme 10). The structure was established by IR and NMR spectra.  $\beta$ -Amino methyl ester **36** on treatment with triphosgene in the presence of triethyl amine gave the oxazolidinone **37** in excellent yield. The selective removal of the *N*-PMP group was successfully achieved using ceric ammonium nitrate (CAN) in CH<sub>3</sub>CN-H<sub>2</sub>O to get compound **38** in good yield. The spectral and physical data was in agreement with that of the reported compound. The reduction of ester group was achieved by the known procedure using CaCl<sub>2</sub> and NaBH<sub>4</sub> to get *epi*-cytoxazone. The structure was established by comparing the spectral data with that of the reported *epi*-cytoxazone.

After establishing the reaction conditions for the synthesis of racemic *epi*-cytoxazone, the same synthetic protocol was used for the synthesis of enantiomerically pure *epi*-cytoxazone starting from enantiomerically pure (3*S*,4*R*)-3-hydroxy azetidin-2-one. The specific rotation of the (-)- *epi*-cytoxazone was in agreement with the reported value. The other enantiomer of *epi*-cytoxazone was also synthesized following same protocol using enantiomeric (3*R*,4*S*)-3-hydroxy azetidin-2-one.

In conclusion, synthesis of racemic as well as (4*R*,5*S*) and (4*S*,5*R*)-*epi*-cytoxazone has been achieved in four synthetic high yielding steps from the corresponding azetidin-2-ones.

**CHAPTER 1**

**AN EFFICIENT SYNTHESIS OF  
2,3-AZIRIDINO- $\gamma$ -LACTONES  
FROM AZETIDIN-2-ONES.**

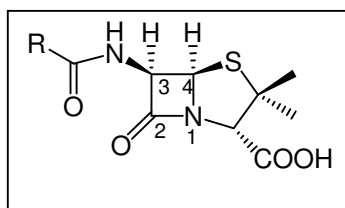
*Imagination is more important than knowledge...*

-Albert Einstein

This work has been published in *Synlett* **2005**, *15*, 2370-2372.

## 1.1: Introduction

Azetidin-2-one ( $\beta$ -lactam), a four membered cyclic amide, is a part structure of many biologically important antibiotics. The unique structural feature and chemotherapeutic properties of  $\beta$ -lactam antibiotics continue to attract the attention of synthetic chemists, as much for their pharmaceutical value as for the variety they provide in terms of synthetic challenges. Although the first synthesis of  $\beta$ -lactam ring was reported way back in 1907 by Staudinger,<sup>1</sup>  $\beta$ -lactam as a class acquired immense importance only after the discovery of penicillin by Fleming in 1928.<sup>2</sup> It was actually Prof. R. B Woodward who first proposed the structure of penicillin based on a  $\beta$ -lactam ring, which was indeed later confirmed and unambiguously proved the presence of 4-membered amide ring by X-ray crystallography.<sup>3</sup> The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.

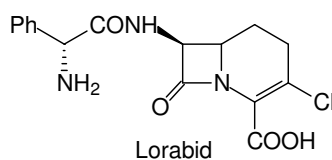


Azetidin-2-one  
( $\beta$ -Lactam ring)

**Figure 1**

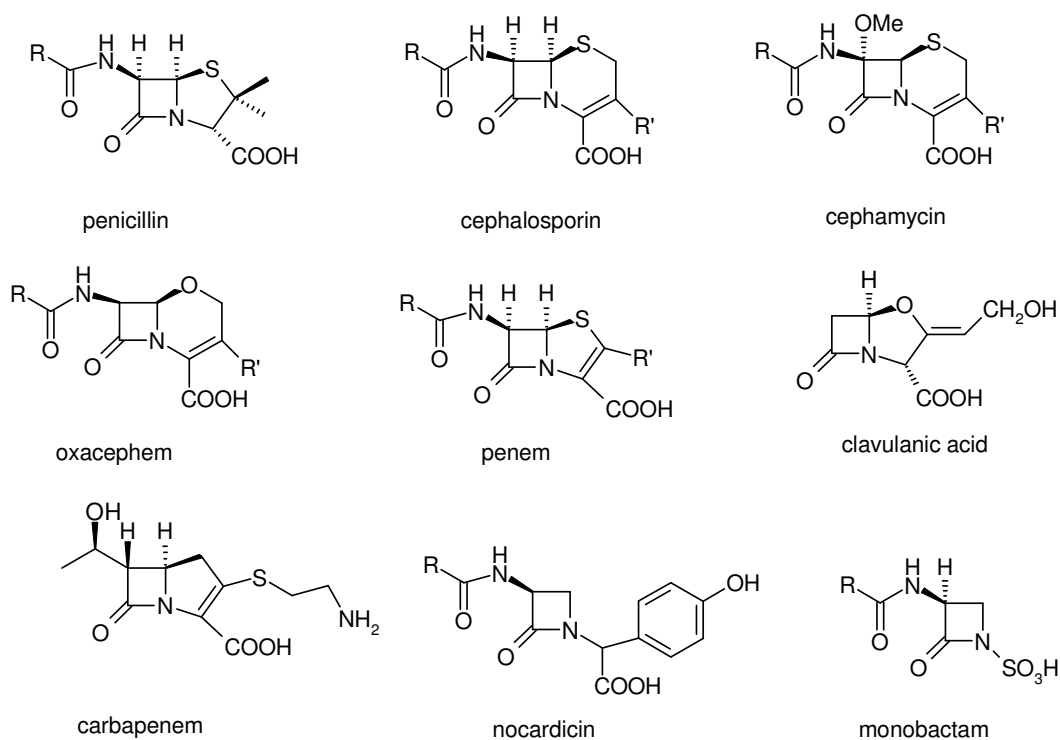
Until 1970, penicillin and cephalosporins<sup>4</sup> were the only examples of naturally occurring  $\beta$ -lactam antibiotics. The discovery of 7- $\alpha$ -methoxycephalosporins<sup>5</sup> from “*Streptomyces*” in 1971 stimulated the search for novel antibiotics. The  $\beta$ -lactam antibiotics can be classified into several groups based on their structures (Figure 3).

Carbacephems,<sup>6</sup> which are carbon analogues of cephalosporins are also being used as antibiotics. They have superior stability over cephalosporin. Loracarbef (lorabid) is the first carbacephem approved for clinical use (Figure 2).



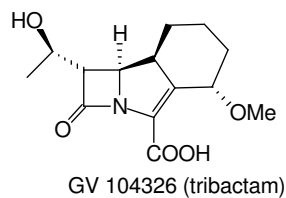
**Figure 2**

- Penicillin
- Cephalosporin (penams)
- Cephamycin (Cephems)
- Oxacephems
- Penems
- Oxapenams like clavulanic acid
- Carbapenems like thienamycin
- Nocardicins
- Monobactams



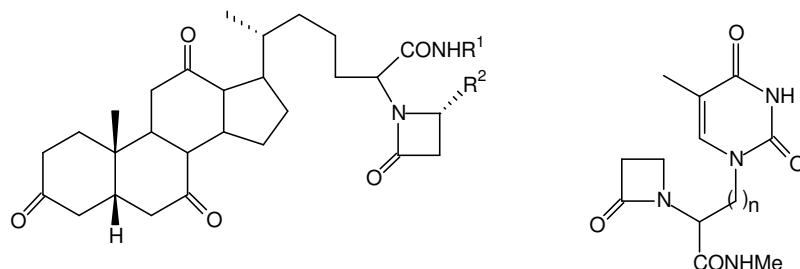
**Figure 3.** Classification of  $\beta$ -lactam antibiotics based on core structure

Tricyclic  $\beta$ -lactam antibiotics called trinems<sup>7</sup> (Figure 4) belong to a new class of tricyclic carbapenems. GV 104326, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria, is an example of tribactam antibiotic.



**Figure 4**

In 1995, a new class of compounds was reported<sup>8</sup> in which the antibiotic property of  $\beta$ -lactams and the antiviral property of nucleosides were incorporated together to afford dual properties of the drug. Kehagia et al.<sup>9</sup> reported another member of this class of  $\beta$ -lactams in which a steroidal and  $\beta$ -lactam units were coupled together *via* Ugi reaction in a one step process (Figure 5).



**Figure 5**

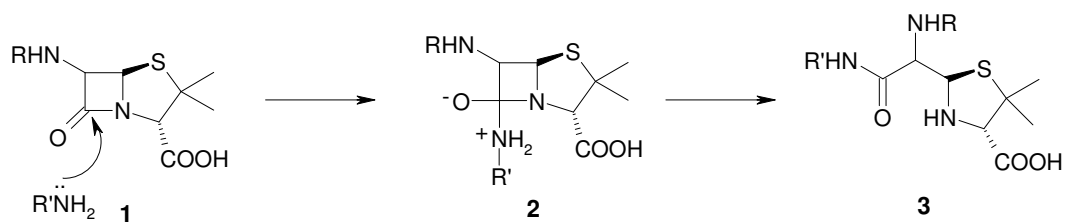
Apart from their antibacterial activities,  $\beta$ -lactams also show other biological activities that include cholesterol absorption inhibition<sup>10</sup> and human leukocyte elastase (HLE).<sup>11</sup>

#### **Mode of action of penicillin:**

The biological activity of these antibiotics is mainly due to the presence of  $\beta$ -lactam ring. The SAR (structure activity relationship) studies<sup>12</sup> have shown that the essential requirement for an antibiotic activity is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in an active form to the target site. Penicillin binds to the so-called ‘penicillin-binding proteins (PCBs), which are specific molecules on the inner membrane of the cell wall. The binding of penicillin to the PCBs causes termination of the peptide chain cross-linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.<sup>13</sup>

#### **Biological activity of penicillin:<sup>14</sup>**

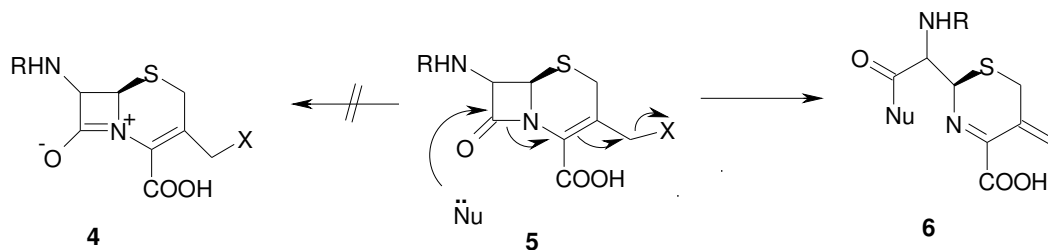
**Scheme 1.1**



The schematic representation of this phenomenon in the case of penicillin **1** and cephalosporin **2** is shown in Scheme 1.01, 1.02. Penicillin and cephalosporin enter into human body and bind with transpeptidases, which are responsible for cell wall growth synthesis. This disturbs the peptidoglycan structure and acylation of active site of enzyme weaken the cell wall synthesis and destroys the bacteria.

**Biological activity of cephalosporin:**<sup>15</sup>

**Scheme 1.2**

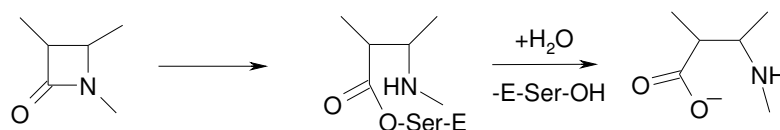


**$\beta$ -lactamases and  $\beta$ -lactamase inhibitors:**

$\beta$ -lactamases<sup>16</sup> are bacterial enzymes mainly responsible for the resistance against  $\beta$ -lactam antibiotics. They present a serious and growing threat to the efficacy of antibacterial chemotherapy and thus pose a major challenge to human health. These defensive enzymes, prevalent in nearly every pathogenic bacterial strain, hydrolyze the  $\beta$ -lactam ring and release the cleaved, inactive antibiotics as amino acids.

There are four different classes of  $\beta$ -lactamase enzymes and they have been divided into two categories according to their catalytic active site. Class A, class C and class D enzymes, named as serine enzyme lactamases, possess serine in their active site and act by covalent acyl enzyme mechanism as shown below.<sup>16</sup> Class B enzymes on the other hand, called as Zinc enzyme lactamases, possess Zn metal ion in their active site and act *via* a non ionic intermediate mechanism.

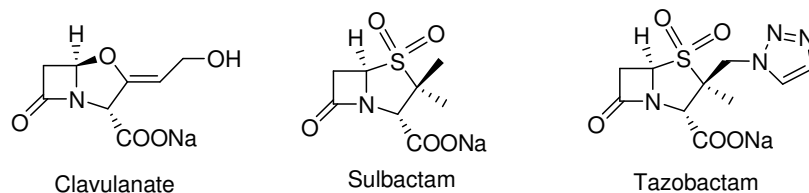
**Scheme 1.3**



The problem of bacterial resistance to commercial antibiotics has opened a gateway to develop novel  $\beta$ -lactam antibiotics as  $\beta$ -lactamase inhibitors.<sup>17-18</sup> These  $\beta$ -lactamase inhibitors are compounds which are structural variants of natural antibiotics with a modified  $\beta$ -lactam skeleton. These compounds may not themselves possess

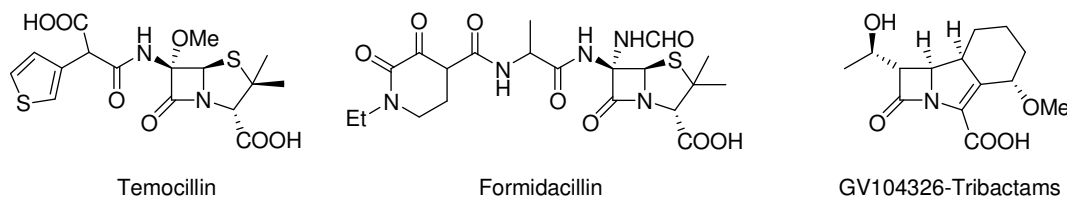
antibiotic activity and hence would have to be used in combination with biologically active antibiotics. More specifically, they associate themselves with the lactamases, preventing prior interaction of  $\beta$ -lactamase with the  $\beta$ -lactam antibiotics and thereby safeguarding the antibiotic activity of the  $\beta$ -lactams.

Clavulanic acid in combination with amoxicillin or ticarcillin, sulbactam in combination with ampicillin and tazobactam in combination with piperacillin are a few examples of clinically used  $\beta$ -lactamase inhibitors.



**Figure 6**

Temocillin, Formidacillin<sup>18</sup> and tricyclic tribactams<sup>19</sup> are other examples of effective  $\beta$ -lactamase inhibitors.



**Figure 7**

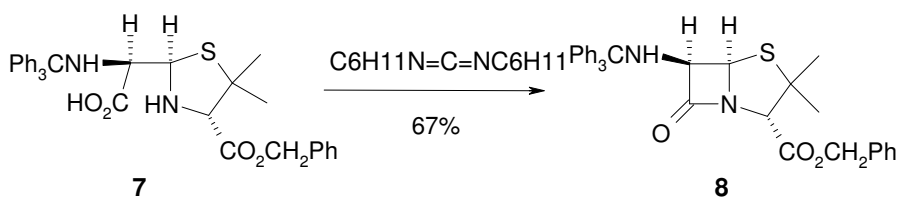
### Methods for constructing $\beta$ -lactam ring:

There are several approaches available to construct these  $\beta$ -lactam building blocks and a few important methods will be discussed here.

#### Formation of the amide N1-C2 bond:

The simplest approach to the synthesis of azetidinone structures is *via* dehydration of  $\beta$ -amino acids. This method has been used in the landmark synthesis of penicillin by Sheehan et al. using dicyclohexylcarbodiimide as a condensing agent.<sup>20</sup>

**Scheme 1.4**



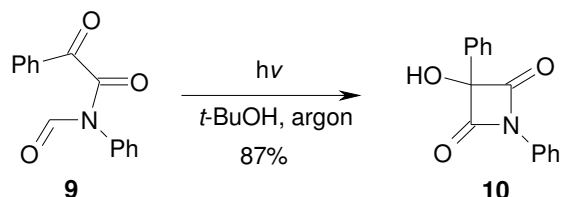


Triphenylphosphine-pyridine disulfide, methanesulfonyl chloride in combination with base and Grignard reagent (RMgX) can also be used instead of DCC to form the amide bond from  $\beta$ -amino acids (Scheme 1.4).

#### Formation of C2-C3 bond:

The formation of carbon-carbon bond at C2-C3 position is inherently more difficult compared to the N1-C2 amide bond formation. Maruyama et al. have achieved it *via* a photochemical approach to synthesize 4-keto- $\beta$ -lactam<sup>21</sup> (Scheme 1.5).

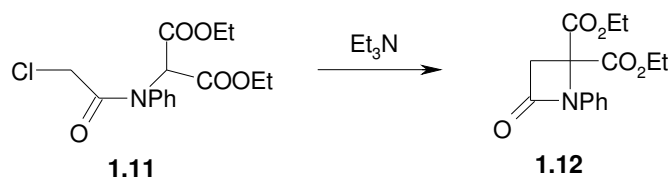
Scheme 1.5



#### Formation of C3-C4 bond:

The simplest method for the formation of C3-C4 bond is to generate a nucleophilic center at C3 and an electrophilic center at C4, or vice versa. Sheehan and Bose have first reported azetidinone formation via an intramolecular nucleophilic displacement reaction using malonate anions and halides as the nucleophilic and electrophilic components respectively<sup>22</sup> (Scheme 1.6).

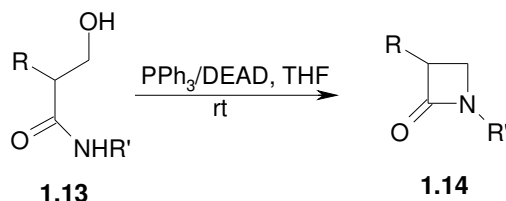
Scheme 1.6



#### Formation of C4-N1 bond:

This methodology involves an S<sub>N</sub>2 displacement of a good leaving group attached at  $\beta$ -carbon amide by an intramolecular amide nitrogen under basic conditions. Miller has reported the synthesis of  $\beta$ -lactams by the cyclization of  $\beta$ -hydroxy amides under Mitsunobu reaction conditions<sup>23</sup> (Scheme 1.7).

### Scheme-1.7

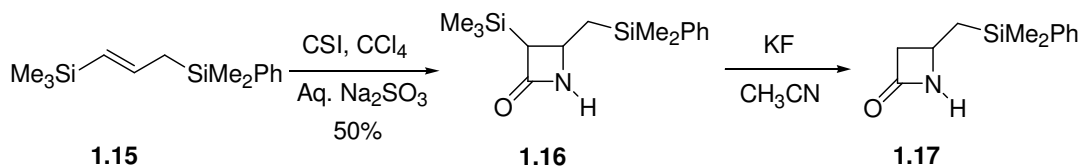


### Multiple bond forming reactions:

#### Olefin-isocyanate cycloaddition reaction:

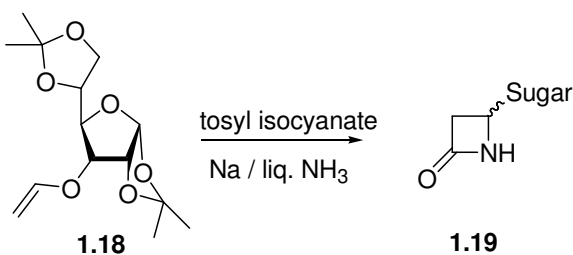
The addition of chlorosulfonyl isocyanate to olefins is a well-known method for the construction of  $\beta$ -lactams.<sup>24</sup> Colvin et al.<sup>25</sup> have reported the addition of chlorosulfonyl isocyanate to various allyl and allenyl silanes to give functionalized  $\beta$ -lactams, which were then converted into synthetically important 3-unsubstituted *NH*- $\beta$ -lactams by removal of the chlorosulfonyl group followed by silyl deprotection (Scheme 1.8).

### Scheme 1.8



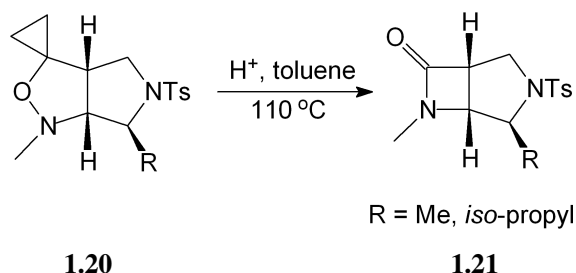
Chmielewski and co-workers have used this cycloaddition reaction between tosyl isocyanate and sugar derived vinyl ethers to obtain good diastereoselectivities in  $\beta$ -lactam formation (Scheme 1.9).<sup>26</sup>

### Scheme 1.9



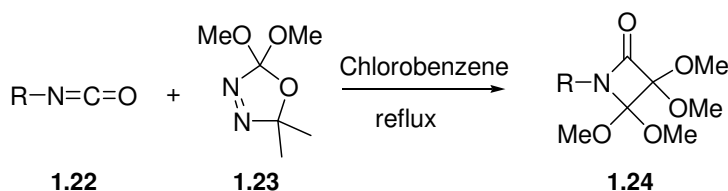
Cordero *et al.*<sup>27</sup> have reported that spirocyclopropane isoxazolidines undergo ring contraction to yield  $\beta$ -lactams on heating in the presence of protic acid (Scheme 1.10).

**Scheme 1.10**



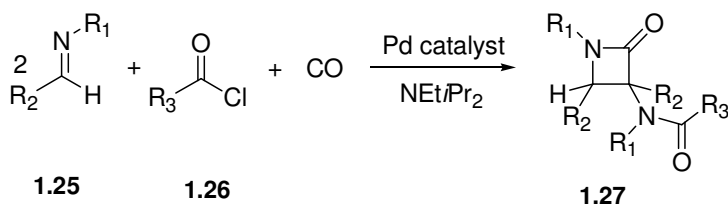
Rigby *et al.*<sup>28b</sup> have reported a highly substituted  $\beta$ -lactam ring formation *via* a reaction between dimethoxycarbene with selected isocyanates. This reaction offers a new entry into  $\beta$ -lactams and the potential for rapid access into variety of highly functionalized species (Scheme 1.11).

**Scheme 1.11**



Recently, Arndtsen *et al.*<sup>28c</sup> have developed a new palladium-catalyzed synthesis of 3-amido-substituted  $\beta$ -lactams. This is multicomponent approach, which involved the one-pot coupling of four components, imines, carbon monoxide and acid chloride (Scheme 1.12).

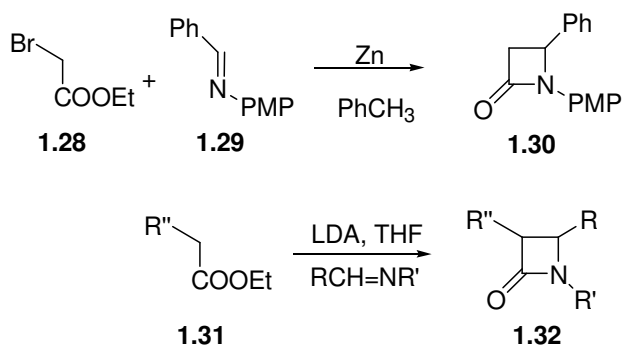
**Scheme 1.12**



### Enolate-imine condensation:

The first example of this type of reaction has been reported by Gilman and Speeter by the condensation of zinc enolate (Reformatsky reagent) with imines to give  $\beta$ -lactams. Other metal enolates have also been used in enolate-imine cycloaddition to achieve diastereoselective synthesis of  $\beta$ -lactams (Scheme 1.13).<sup>29</sup>

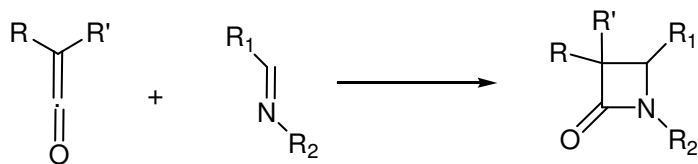
Scheme 1.13



### Staudinger reaction:

The first synthesis of a  $\beta$ -lactam was achieved by Staudinger<sup>1</sup> in 1907 by the [2+2] cycloaddition of ketene and imine. This reaction is called as Staudinger or ketene-imine cycloaddition reaction. In the modified Staudinger reaction, acid chlorides or activated carboxylic acids were used in the presence of a base as a ketene precursor. It is an excellent and well adopted method in the literature for the construction of  $\beta$ -lactam rings (Scheme 1.14).

Scheme 1.14



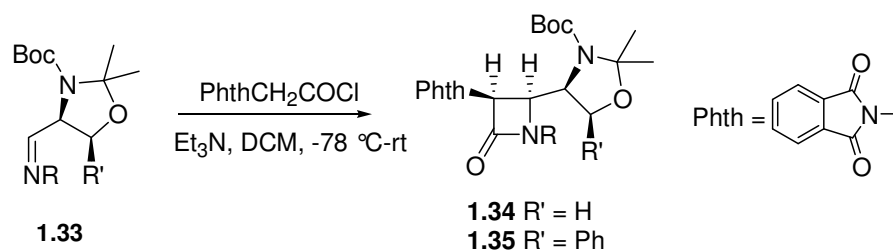
### Asymmetric synthesis of $\beta$ -lactams using Staudinger reaction:

Better understanding of the mechanistic aspects of the  $\beta$ -lactam's biological activity, their inhibition and the chemical exploitation of  $\beta$ -lactams as synthetic intermediates in organic chemistry have led to profound development in this field. In this regard, the accessibility of enantiopure  $\beta$ -lactams is an important requirement considering their pharmaceutical importance. The asymmetric Staudinger reaction is

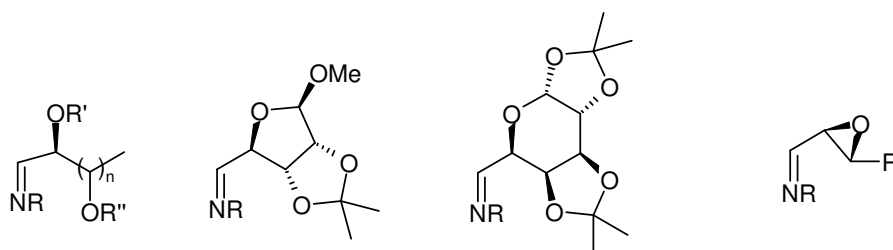
the most attractive and widely used method for this purpose because of its simplicity and predictability of stereo chemical outcome of the reaction. Asymmetry can be induced by using either chiral ketenes derived from acid precursors or chiral imines (derived from either chiral aldehydes or amines).

Chiral imines, derived from chiral aldehydes and achiral amines are the most effective for introducing asymmetry in the asymmetric Staudinger reaction. Generally, these imines give a very high level of diastereoselectivity in the cycloaddition reaction. Among the useful chiral imines, the *N*, *O*-protected aldimines are the most efficient ones (Scheme 1.15).<sup>30</sup>

**Scheme 1.15**



The most common approaches in the Staudinger reaction involve the use of  $\alpha$ -oxyaldehyde derived imines, sugar derived imines and  $\alpha$ ,  $\beta$ -epoxyimines.<sup>31</sup>

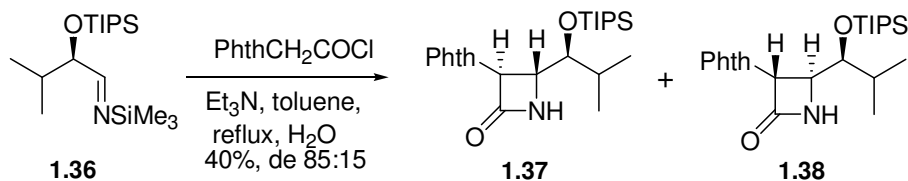


**Figure 8**

Formation of *cis* isomer is generally favoured in all these cases with the observed ratios being as high as 90:10 in favour of the *cis* diastereomer.

Recently, Panunzio and co-workers have reported a case of *trans*-selectivity preference in cycloaddition reaction. The method involves the reaction of phthalimidoacetyl chloride with *N*-trimethylsilyl imines and triethylamine in refluxing toluene (Scheme 1.16).<sup>32</sup>

### Scheme 1.16

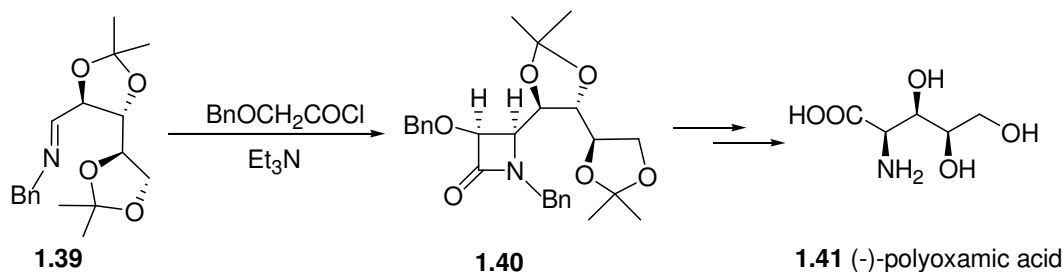


### Carbohydrate derived chiral imines:

Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.<sup>33</sup> The use of carbohydrates in the asymmetric synthesis of  $\beta$ -lactams has become well established and considerable amount of work has been done on sugar derived imines for  $\beta$ -lactam ring construction.

Bose and Manhas<sup>34</sup> have reported successful utilization of chiral imines derived from carbohydrates in the asymmetric Staudinger reaction. They synthesized different chiral auxiliaries derived from sugars and employed them as chiral imine components. These chiral imines proved to be very efficient, providing a high level of diastereoselectivity (de >90%) in all cases. They have mainly used these  $\beta$ -lactams as chiral synthons rather than as a chiral pool and have utilized the carbohydrate skeleton for the synthesis of important natural products.

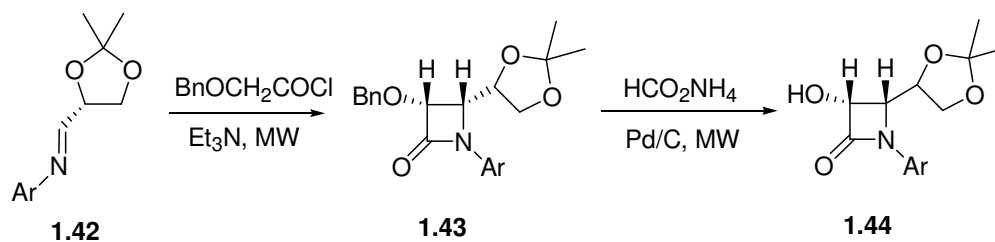
### Scheme 1.17



The cycloaddition reaction of benzyloxyketene with the imine provided *cis*- $\beta$ -lactams with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, an antipode of natural (+)-polyoxamic acid (Scheme 1.17).<sup>34</sup>

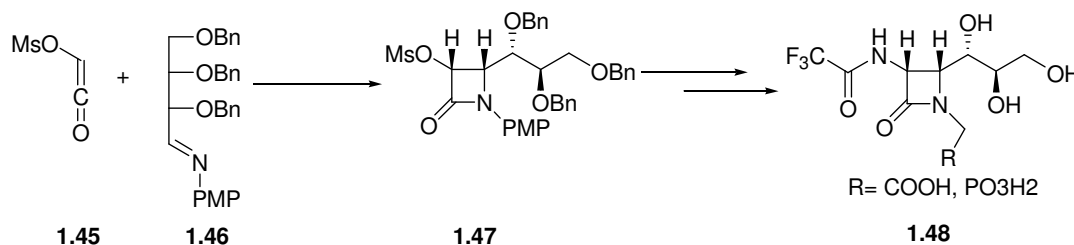
Bose and Manhas have recently reported the enantiospecific synthesis of  $\alpha$ -hydroxy- $\beta$ -lactams using Schiff's bases derived from D-glyceraldehyde under microwave irradiation (Scheme 1.18).<sup>35</sup>

**Scheme 1.18**



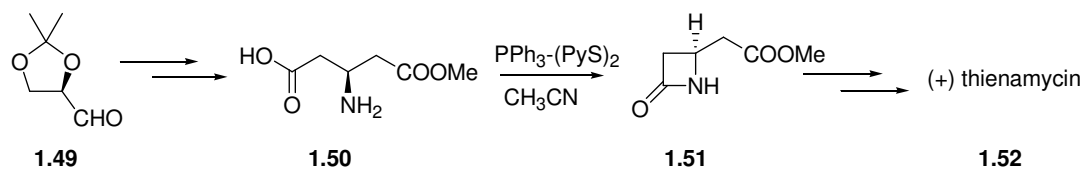
Recently, Stortz et al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-mannonic acid derivatives (Scheme 1.19).<sup>36</sup>

**Scheme 1.19**

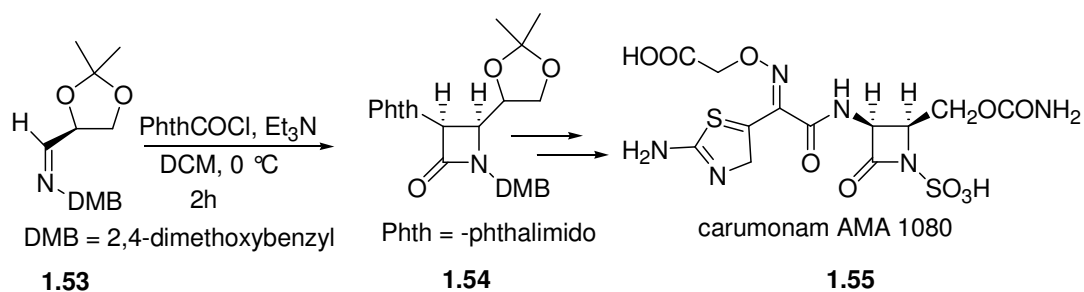


The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into a  $\beta$ -amino ester, which on cyclization with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubstituted  $\beta$ -lactam. This  $\beta$ -lactam has been converted into (+)-thienamycin antibiotic in several steps (Scheme 1.20).<sup>37</sup>

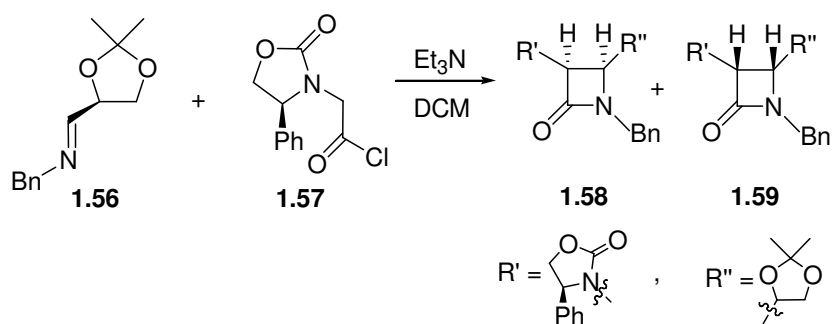
**Scheme 1.20**



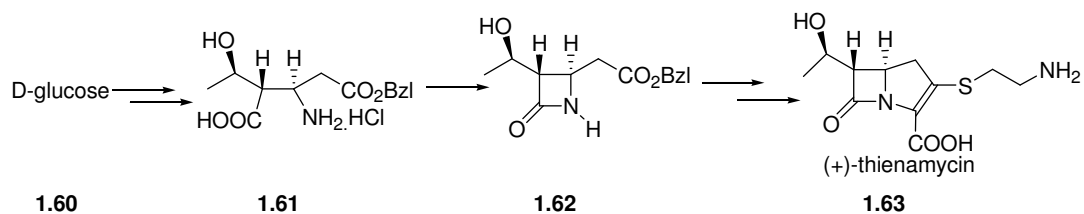
The imine derived from L-(-)-glyceraldehyde and 2,4-dimethoxybenzylamine underwent Staudinger reaction with phthalimidoacetyl chloride to afford the corresponding 3-Phth substituted  $\beta$ -lactam, which is a key intermediate in the synthesis of carumonam antibiotics (Scheme 1.21).<sup>38</sup>

**Scheme 1.21**

Palomo et al. have treated the imine derived from L(-)-glyceraldehyde and benzylamine with oxazolidinone derived acid chloride to give *cis*- $\beta$ -lactams in good yield with 40:60 diastereomeric ratio (Scheme 1.22).<sup>39</sup>

**Scheme 1.22**

The  $\beta$ -amino acid derived from D-glucose, on cyclization in the presence of DCC gave  $\beta$ -lactam, which was further converted into (+)-thienamycin antibiotic in several steps (Scheme 1.23).<sup>40</sup>

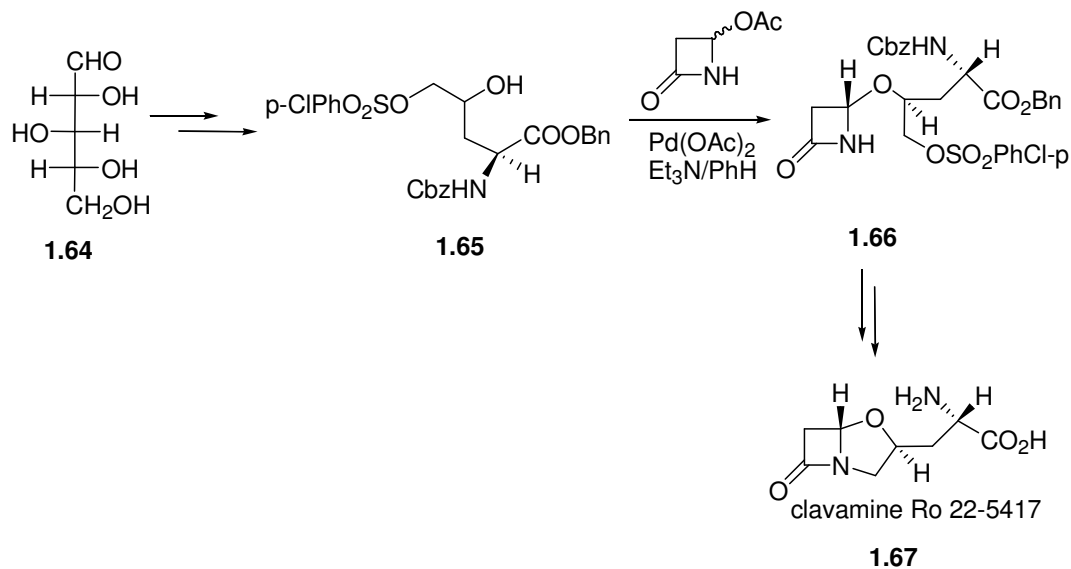
**Scheme 1.23**

A chiral amino alcohol derived from D-xylose was coupled with racemic 4-acetyloxy- $\beta$ -lactam in the presence of palladium acetate/ Et<sub>3</sub>N to give



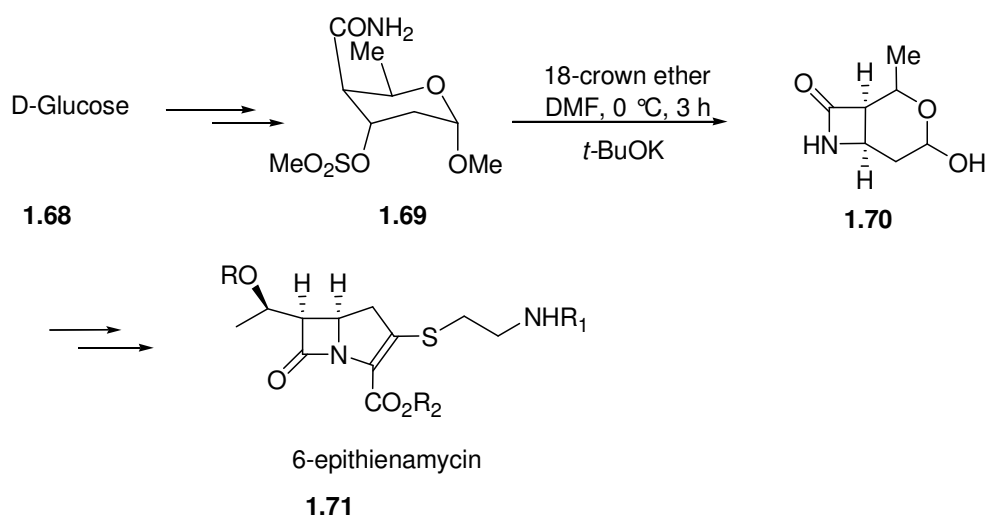
a 70:30 diastereomeric mixture of  $\beta$ -lactams in 65% yield. The major isomer has been converted to the antibiotic clavamine Ro 22-5417 (Scheme 1.24).<sup>41</sup>

**Scheme 1.24**



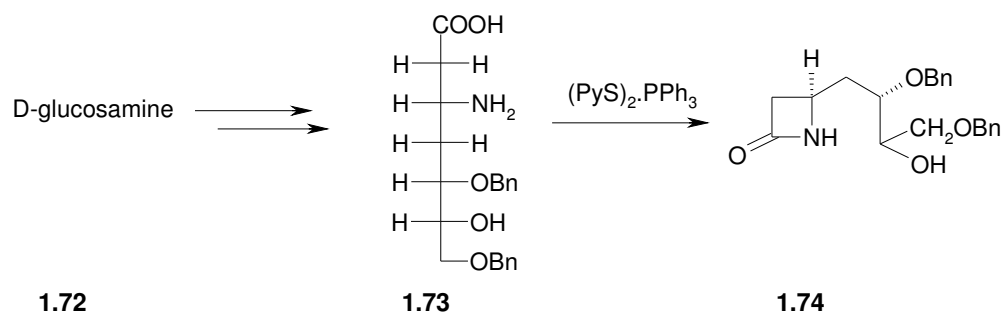
The amide derived from D-glucose has been cyclized in the presence of potassium *tert*-butoxide, to give bicyclic  $\beta$ -lactams in 45% yield. This bicyclic  $\beta$ -lactam has been transformed into 6-*epithienamycin* in a multi-step process (Scheme 1.25).<sup>42</sup>

**Scheme 1.25**



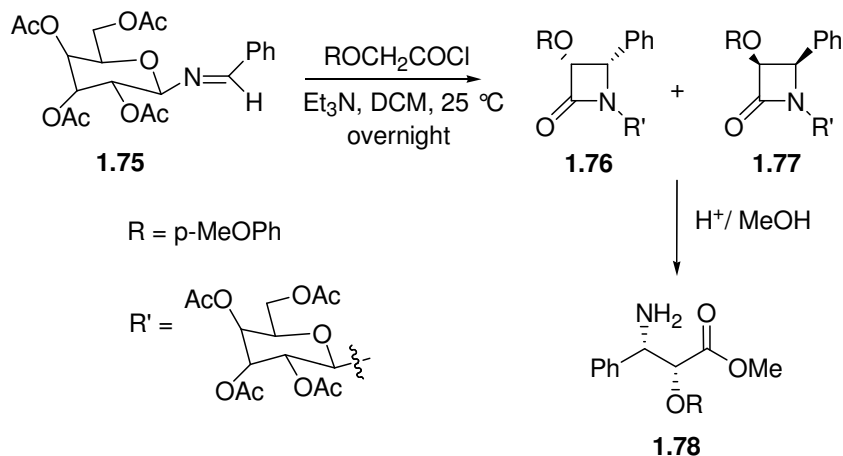
The  $\beta$ -amino acid derived from D-glucosamine has been cyclized to *N*-unsubstituted  $\beta$ -lactam in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. This *N*-unsubstituted  $\beta$ -lactam serves as an intermediate for the synthesis of (+)-thienamycin antibiotic (Scheme 1.26).<sup>43</sup>

**Scheme 1.26**



Georg et al. have used the chiral imine derived from 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-galactose amine for diastereoselective synthesis of  $\beta$ -lactams. They obtained a 60:40 diastereomeric mixture of  $\beta$ -lactams in 90% yield.

**Scheme 1.27**



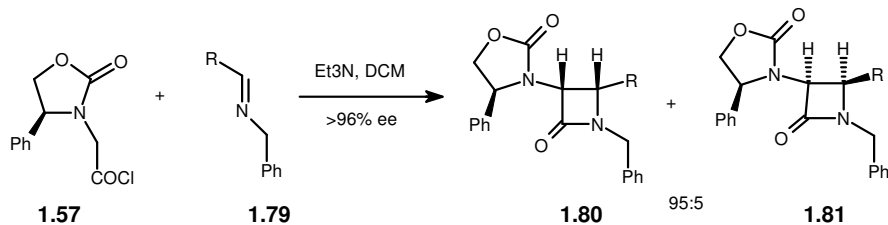
The  $\alpha$ -isomer is transformed to  $\beta$ -amino ester, which is used as a building block for the synthesis of side chain of anticancer agent taxol (Scheme 1.27).<sup>44</sup>

### Chiral Ketenes:

Chiral ketenes have also been used in the Staudinger reaction. However, in most of the cases poor diastereoselectivity has been observed. The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides and

triethylamine, with achiral imines afforded optically active  $\beta$ -lactams with high levels of asymmetric induction, typically greater than 96% de (Scheme 1.28).<sup>45</sup>

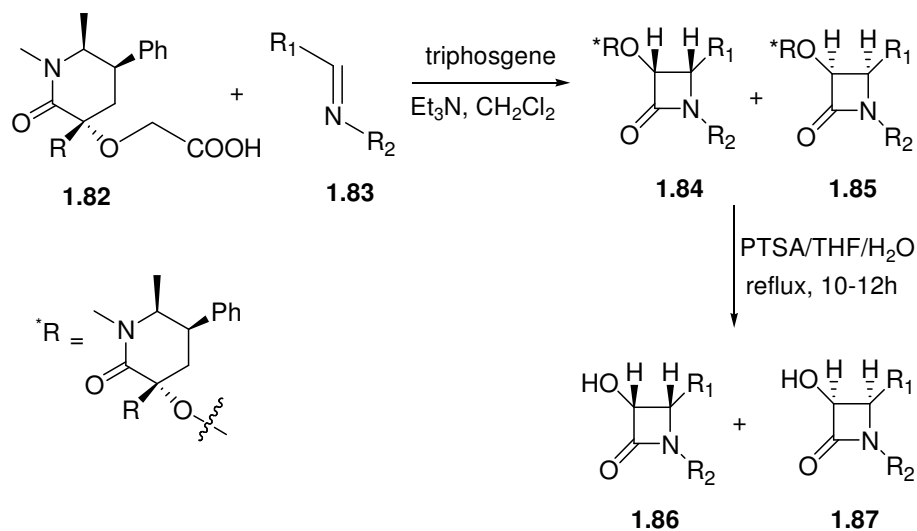
**Scheme 1.28**



Shinkre *et al.* have reported an ephedrine derived chiral acid for the asymmetric Staudinger reaction with various imines in the presence of triphosgene as an acid activator to afford a diastereomeric mixture of *cis*  $\beta$ -lactams in good yields.

The ephedrine derived chiral auxiliary, was removed under acidic hydrolysis and furnished both the enantiomers of 3-hydroxy-4-aryl  $\beta$ -lactams. One of these hydroxy  $\beta$ -lactams ( $\beta$  isomer) is an advanced intermediate for the synthesis of taxol side chain (Scheme 1.29).<sup>46d</sup>

**Scheme 1.29**

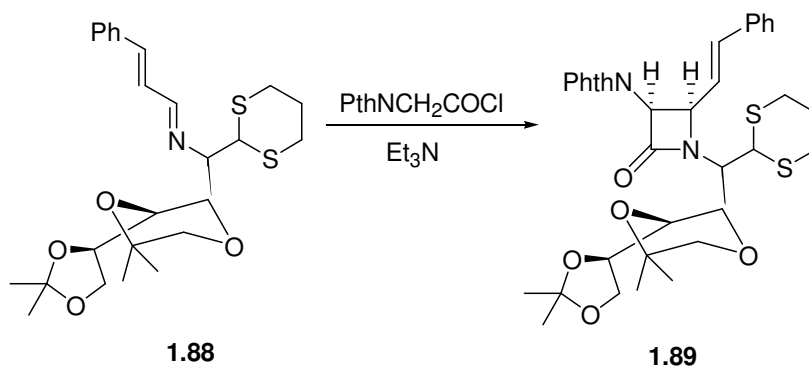


### Chiral Amines:

Asymmetric Staudinger reaction using imines derived from achiral aldehydes and chiral amines often result in poor diastereoselectivity in  $\beta$ -lactam formation. This

is because the stereo directing group in the chiral amine is far away from the newly formed chiral center. However there are few reports on efficient use of chiral amines in the asymmetric Staudinger reaction, which will be discussed here.

**Scheme 1.30**

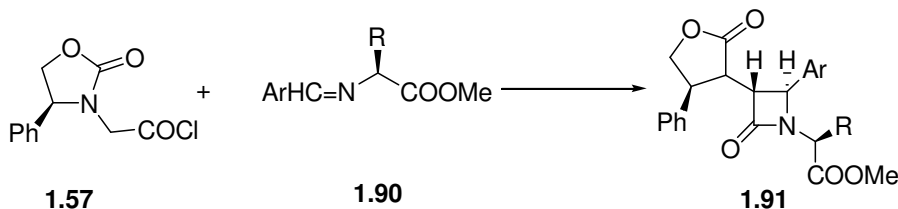


Asymmetric Staudinger reaction using imines derived from D-Glucosamine<sup>47</sup> and cinnamaldehyde have resulted in diastereospecific formation of single *cis*  $\beta$ -lactam (Scheme 1.30).

#### Double Stereodifferentiation:

The concept of double asymmetric induction has been applied to Staudinger reaction with variable success. High levels of asymmetric induction have been achieved in Staudinger reaction between the Evans-Sjogrens ketene and imines derived from (*R*) and (*S*)- $\alpha$ -amino acid esters<sup>48</sup> (Scheme 1.31).

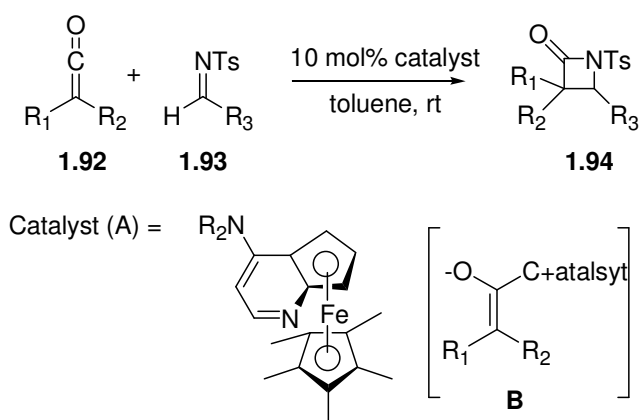
**Scheme 1.31**



#### Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu<sup>49</sup> have reported a highly enantioselective synthesis of  $\beta$ -lactams catalyzed by a chiral catalyst (**A**). This chiral catalyst (**A**) was found to be very effective in promoting the [2+2] cycloaddition reaction of symmetrical and unsymmetrical ketenes with variety of imines (Scheme 1.32).

**Scheme 1.32**



The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka<sup>50</sup> has observed.

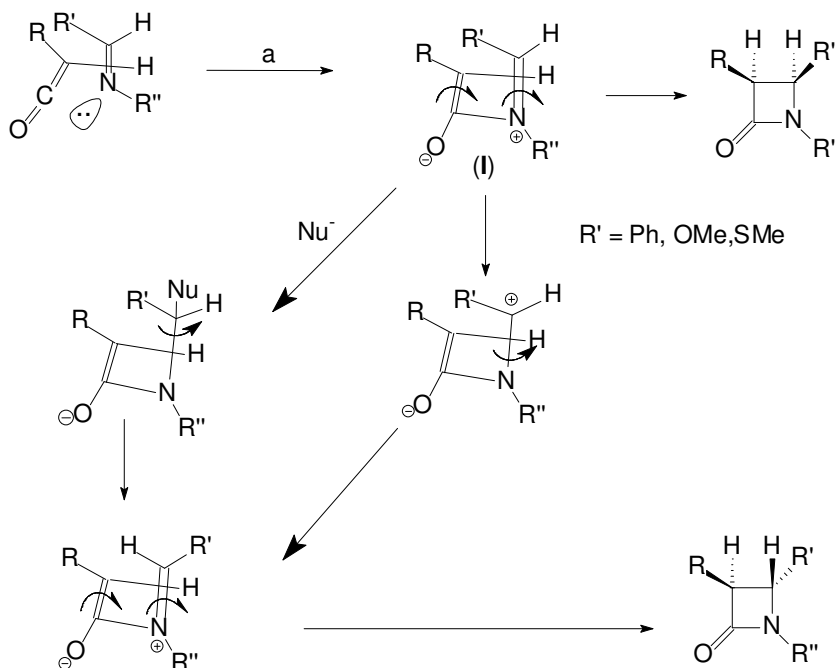
#### **Mechanism of Staudinger reaction:**

Although the ketene-imine cycloaddition (Staudinger reaction) has been known for over nine decades, the mechanism and the stereochemical course of this reaction are still obscure. Recent efforts in this aspect have resulted in a series of papers by various groups.<sup>51</sup> Based on these results; a two-step zwitterionic mechanism has been preferred to a concerted [2+2] cycloaddition.

The involvement of a zwitterionic intermediate has been proved by various spectroscopic methods and zwitterion trapping experiments.<sup>52</sup> That the zwitterion intermediate was indeed formed from a ketene precursor was proved by results from Lynch's group<sup>53</sup> wherein, treatment of the acid chloride with diisopropylamine in an FT-IR cell displayed a strong band at 2120 cm<sup>-1</sup>, which was assigned to the ketene.

It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, that is, in a plane perpendicular to the substituents of the ketene, resulting in the formation of the zwitterionic intermediate (**I**).<sup>54</sup> This hypothesis was supported by semi empirical molecular orbital calculations (MNDO) of a transition intermediate in the reaction between methyl ketene and *N*-methyl-2-methylimine.<sup>55</sup>

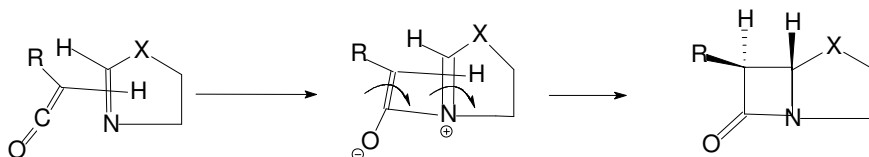
Scheme 1.33



It is further believed that the attack of the imine occurs from the less hindered side of the ketene while forming the zwitterionic intermediate (I). Rotation of the imine into the plane of the ketene followed by a *con*-rotatory ring closure produces the thermodynamically less stable  $\beta$ -lactam in which the smaller group on the imine (hydrogen) and the smaller substituent on the ketene are *cis* to each other. The *con*-rotatory ring closure can occur only in a clockwise direction since ring closure in other direction (anticlockwise) would necessitate the imine and ketene substituent to pass through each other. These stereochemical explanations are in good agreement with the results obtained from many acyclic imines and ketenes.

When the substituent R' on the  $sp^2$  carbon can stabilize a positive charge (e.g. Ph, OMe, or SMe), the zwitterionic intermediate may undergo isomerization from the more stable imine geometry to the *syn* imine geometry, before cyclization, producing the thermodynamically more stable *trans*  $\beta$ -lactam. This is the case with imidates, thioimidates and in some cases with benzaldimines. If the amino substituent R' is large, this isomerization can be suppressed.

### Scheme 1.34



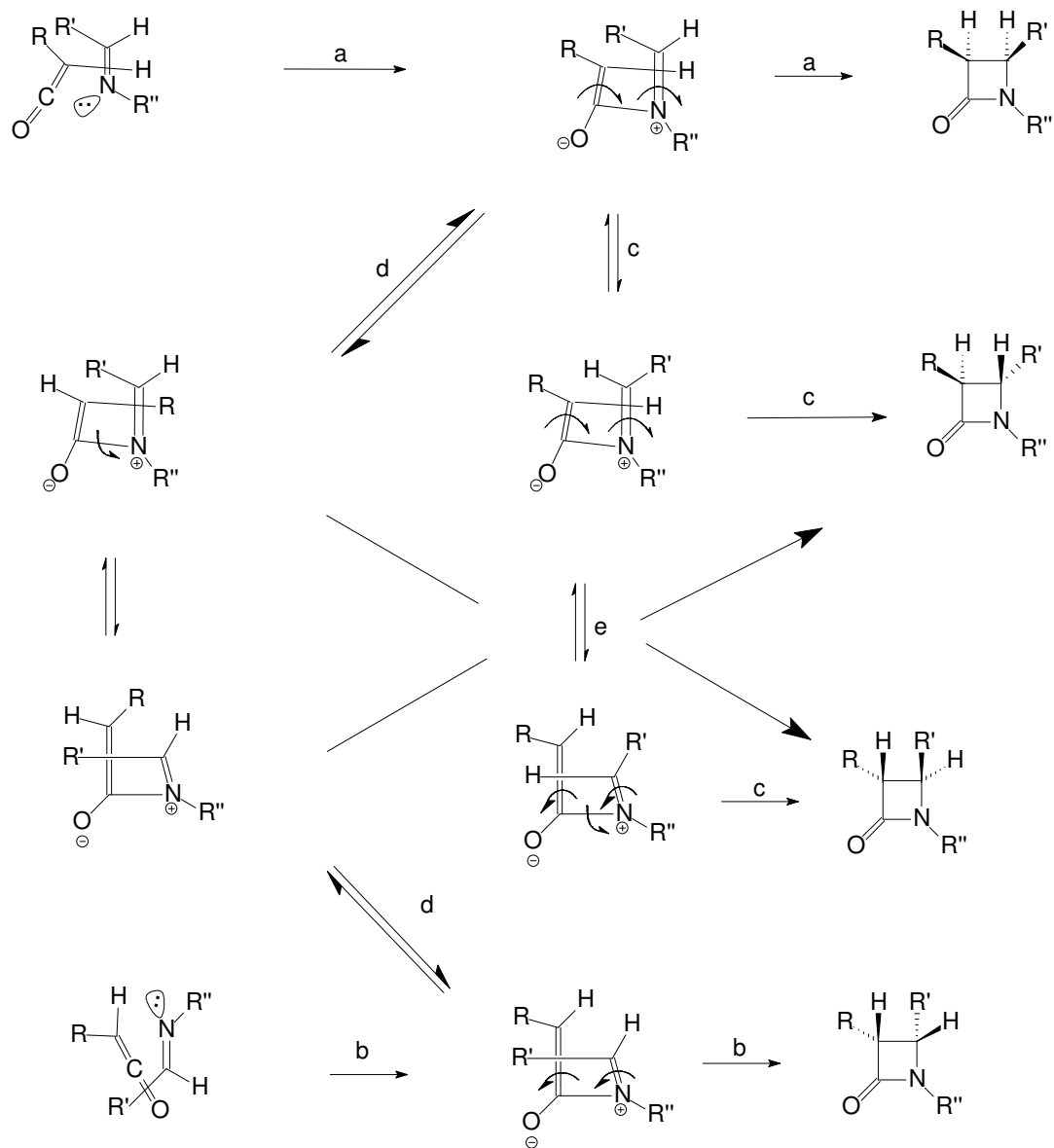
Isomerization of the zwitterionic intermediate can also occur by addition of nucleophiles to the zwitterion followed by rotation and elimination. The relative rate of each of these processes determines the stereochemical outcome of the reaction. In the case of cyclic imines one should always get a *trans*  $\beta$ -lactam since the imine substituents are held in *syn* geometry and the same has been observed in most cases (Scheme 1.34).

#### Asymmetric Induction:

Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene; attack of the imine over the top face of the ketene followed by *con*-rotatory ring closure will produce one enantiomer, while the attack of the imine from the bottom face followed by *con*-rotatory ring closure will produce the other enantiomer. Since two new chiral centers are formed during  $\beta$ -lactam ring formation, four isomers are possible, i.e. a pair each of *cis* and *trans* isomers. Depending upon the reaction conditions and the different paths followed the formation of a single or all four isomers are possible. The chart below explains the formation of all four isomers depending on the stereochemical course of the reaction.

The attack of the imine from the less hindered side of the ketene can occur with two different perpendicular orientations; as in *path a* or as in *path b*. For reactions exhibiting high diastereoselectivity in *cis* manifold, differentiation between these two must be high and cyclization of the zwitterions must be faster than any of the possible isomerizations. If reaction conditions or structural features in the ketene or imine slow down the cyclization step or accelerate the isomerization or both, stereoselectivity may be drastically altered, even if the initial selectivity between *path a* and *b* is high.

Scheme 1.35



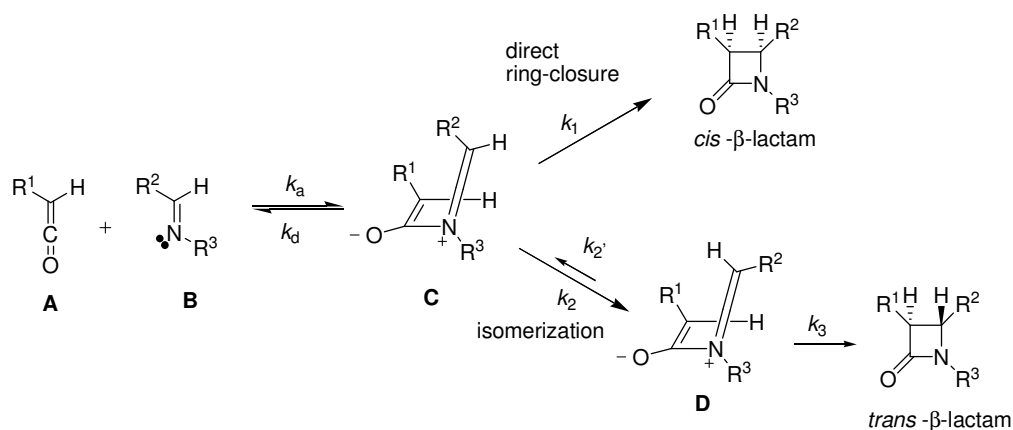
The formation of the thermodynamically more stable *trans*  $\beta$ -lactam from a *trans* imine can only result from isomerization of either the iminium portion (*path c*) or the enolate portion (*path d*) of the zwitterions prior to cyclization. Isomerization should be promoted by substituents that stabilize positive charge on the iminium carbon and / or by substituents that stabilize the enolate, slowing cyclization relative to isomerization. If the cyclization of the initially formed zwitterions is very slow, all



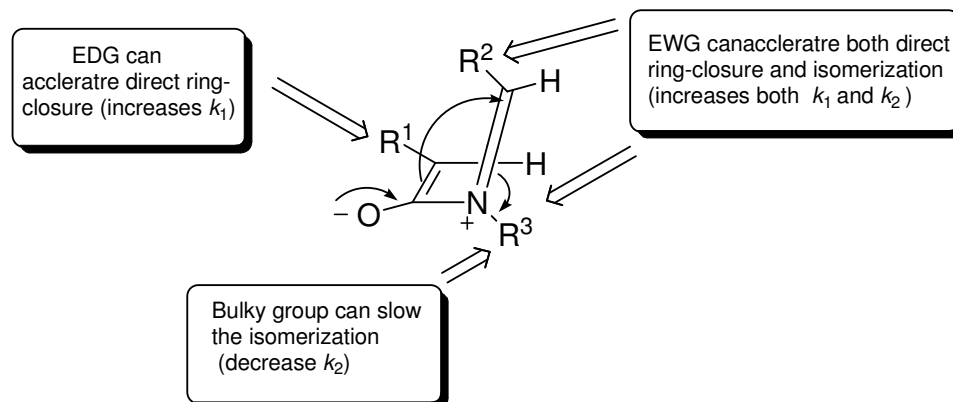
four diastereomeric  $\beta$ -lactams are then accessible from any single zwitterion by isomerization followed by rotation about the C-N single bond (*path e*).

Recently, Xu et al.<sup>56</sup> have proposed a model for the relative stereoselectivity in the Staudinger reaction and clearly pointed out the kinetic origin of the *cis/trans* ratio of  $\beta$ -lactam products. The results indicated that the ring closure step as an intramolecular nucleophilic addition process rather than an electrocyclic process (Figure 9). The electronic effect of the substituents is the key factor in the stereoselectivity. The electron-donating ketenes substituents and the electron-withdrawing imine substituents accelerate the ring closure (increase  $k_1$ ), leading to a preference for *cis*- $\beta$ -lactam formation while reverse substituents lower the ring closure (decrease  $k_1$ ), leading to a preference for *trans*- $\beta$ -lactam (Scheme 1.35).

**Scheme 1.36**



Competition between the direct ring-closure and the isomerization controls the relative stereoselectivity



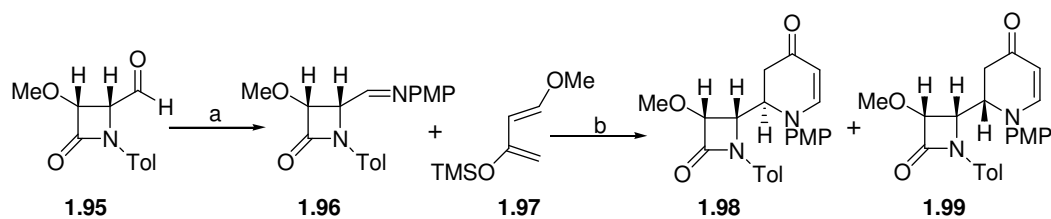
**Figure 9**

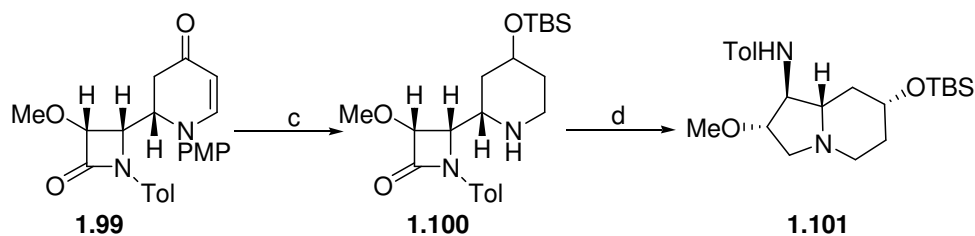
The relative stereoselectivity is determined by the competition between direct ring closure ( $k_1$ ) and the isomerization of the imine moiety ( $k_2$ ) in the zwitterionic intermediates. The *cis/trans* ratio of  $\beta$ -lactam products depends upon  $k_1/k_2$  ratio and the electronic effect of the substituents is a key factor in deciding the stereoselectivity.

**Azetidin-2-ones, synthon for alkaloids, aminosugars, polyhydroxy amino compounds and other heterocyclic compounds:**

Besides their biological activity, the importance of  $\beta$ -lactams as synthetic intermediates has been widely recognized in organic synthesis because ring cleavage of any of the four single bonds of the  $\beta$ -lactam system is enhanced by ring strain. Selective bond cleavage of the 2-azetidinone ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks. Opening of the  $\beta$ -lactam ring can occur through cleavage of any of the single bonds of the four-membered ring. However, the sequential or simultaneous fragmentation of two bonds of the 2-azetidinone ring has been seldom reported. The present account is a survey of the recent salient synthetic achievements exploiting selective bond cleavage of the  $\beta$ -lactam nucleus, with particular emphasis to diastereoselective processes. The usefulness of these substrates for the preparation of substances of biological interest, including  $\alpha$ -amino acids,  $\beta$ -amino acids, indolizidines, pyrrolizidines, eight-membered lactams, and complex natural products is presented. In fact, the development of a methodology based on the 2-azetidinone nucleus has reached such a level of importance as to merit its own:  $\beta$ -lactam synthon method. In this context, selective bond cleavage of the strained  $\beta$ -lactam ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks.

**Scheme 1.37**



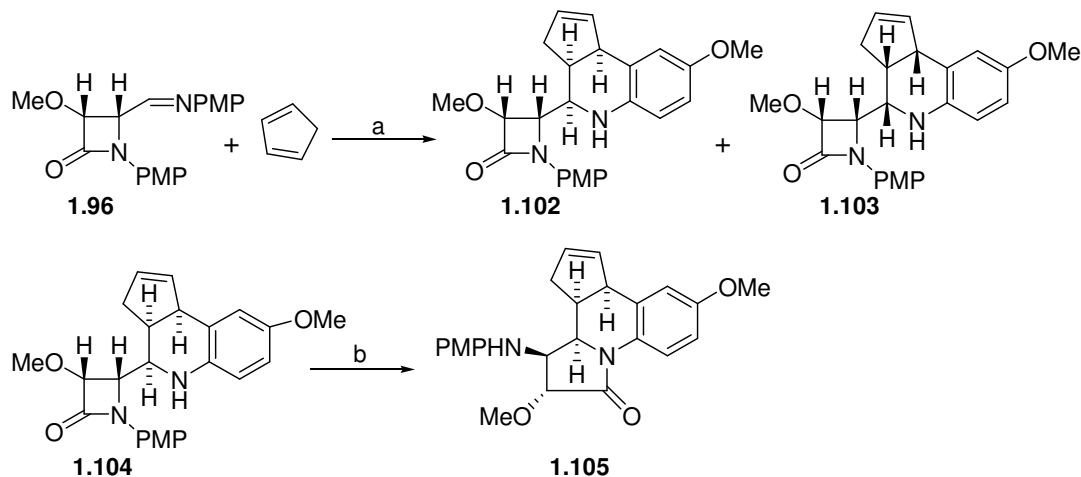


*Reagents and conditions:* a) *P*-anisidine, MgSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; b) ZnCl<sub>2</sub>, CH<sub>3</sub>CN, -20 °C; c) i) L-Selectride, ii) NaBH<sub>4</sub>, iii) TBSCl, iv) CAN; d) NaOMe, MeOH, rt, 16 h.

In the past decade azetidin-2-ones have been used as building blocks for a number of alkaloids, amines, polyhydroxy amines and various other heterocyclic compounds. Indolizidine alkaloids are wide spread in nature and show antiviral, antitumor activity. The 1,6,7,8-tetrahydroindolizidine, castanospermine is a potent competitive and reversible inhibitor of several glucosidases.<sup>57</sup>

It has the potential for the treatment of diabetes, obesity, cancer, and viral infections. In addition, the functionalized bicyclic lactams, structurally related to indolizidine have been discovered as conformationally restricted peptide mimetics.<sup>58</sup> The indolizidine systems can be directly prepared from  $\beta$ -lactams. The process involves the amide bond cleavage of the  $\beta$ -lactam ring in the aza-Diels-Alder cycloadducts with concomitant cyclization (Schemes 1.37 and 1.38).<sup>59</sup>

**Scheme-1.38**



*Reagents and conditions:* a) InCl<sub>3</sub>, CH<sub>3</sub>CN, rt, 1 h; b) NaOMe, MeOH, rt, 16 h.

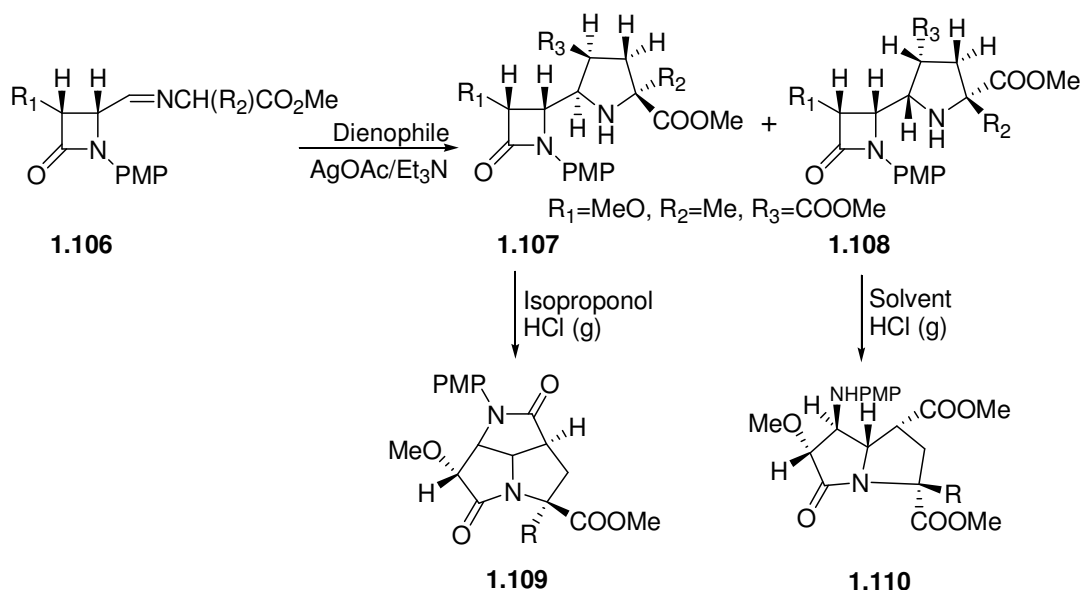
Azetidin-2-one tethered aryl imines function both as heterodienes and dienophiles in the [4+2] aza-Diels-Alder reaction to afford different types of

cycloadducts, which after rearrangement serve as valuable chiral intermediates for different indolizidinones.

Pyrrolizidine alkaloids having 1-aza bicycle (3.3.0) octane skeleton are wide spread in nature. They occur in various plant species as well as in insects. These compounds show biological activities like hepatotoxicity, antiviral, carcinogenic activity and many of them act as DNA cross linkers. Their structural and stereochemical complexity, coupled with their diverse and potent biological activities<sup>60</sup> make pyrrolizidine alkaloids as well as structurally related unnatural compounds very attractive synthetic targets.<sup>61</sup> These angular fused tricycles represent structurally intriguing unit present in many natural products and among prominent targets of this class of compounds are triquinanes.<sup>62</sup> Functionalized bicyclic lactams structurally related to pyrrolizidine have been discovered as conformationally restricted peptide mimetics<sup>63</sup> and some of the chiral pyrrolizidines have been used as catalyst in the asymmetric Baylis-Hillman reaction.<sup>64</sup>

The combination of 1,3-dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides with rearrangement reactions on the 2-azetidinone ring was used by Alcaide et al.<sup>65</sup>

**Scheme 1.39**

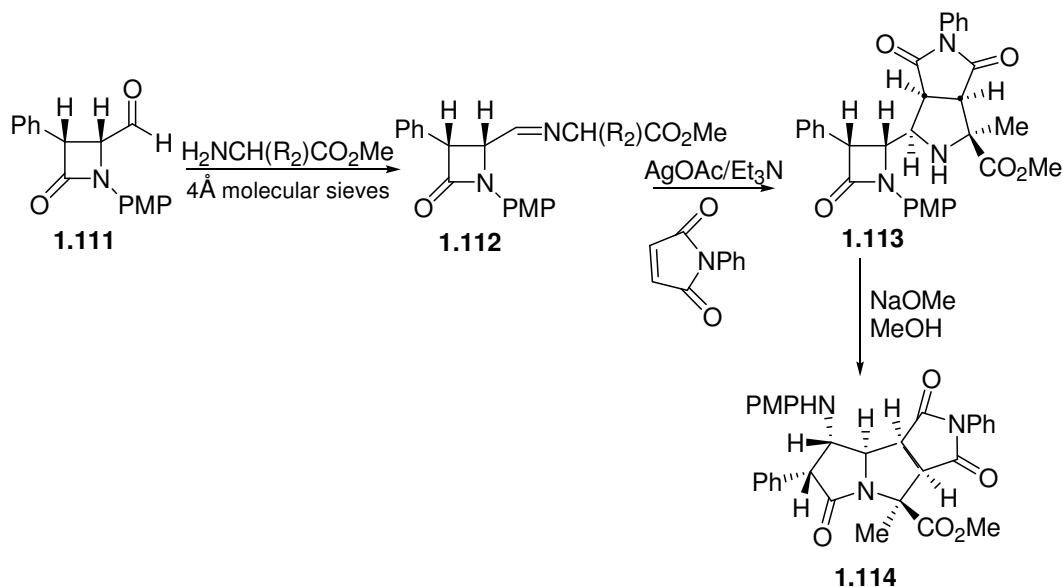


as a powerful hitherto unknown strategy for the asymmetric synthesis of different highly functionalized enantiopure pyrrolizidine (Scheme 1.39) diazatriquinane systems (Scheme 1.40).

The formation of pyrrolizidine lactam involves a selective O=C-N bond cleavage in the four member ring, followed by rearrangement under the reaction conditions.

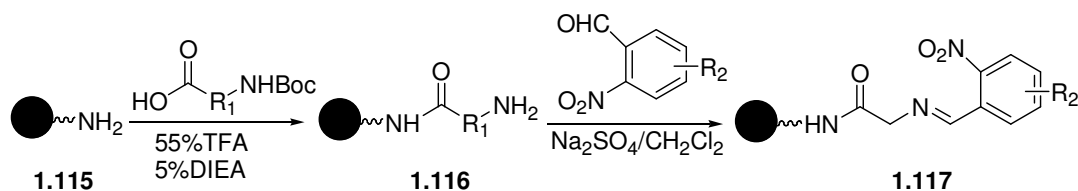
The relief of the strain associated with the four member ring on forming more stable polycyclic systems must be the driving force for this transformation. This methodology is useful for the preparation of variously substituted pyrrolizidine derivatives.

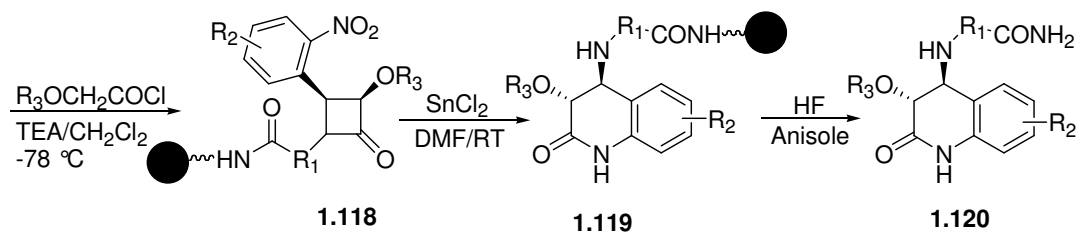
**Scheme 1.40**



The synthesis of 3,4-dihydro-2(*1H*)-quinolinones was achieved by Yazhong Pei and workers<sup>66</sup> through the rearrangement of  $\beta$ -lactam intermediates on solid-phase.

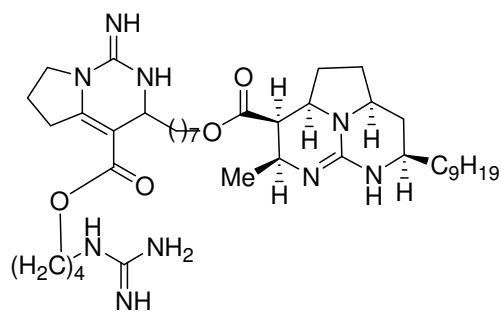
**Scheme 1.41**





The required  $\beta$ -lactam intermediates were constructed through [2+2] cycloaddition between ketenes and imines on the solid-phase (Scheme 1.41).

The Smith-Kline Beecham group reported<sup>67</sup> the isolation of novel polycyclic guanidine alkaloids batzelladines A-E from bright red Caribbean sponge of genus batzella. These natural products not only possess unusual cyclic guanidine skeletons but also show potent anti-HIV activity.

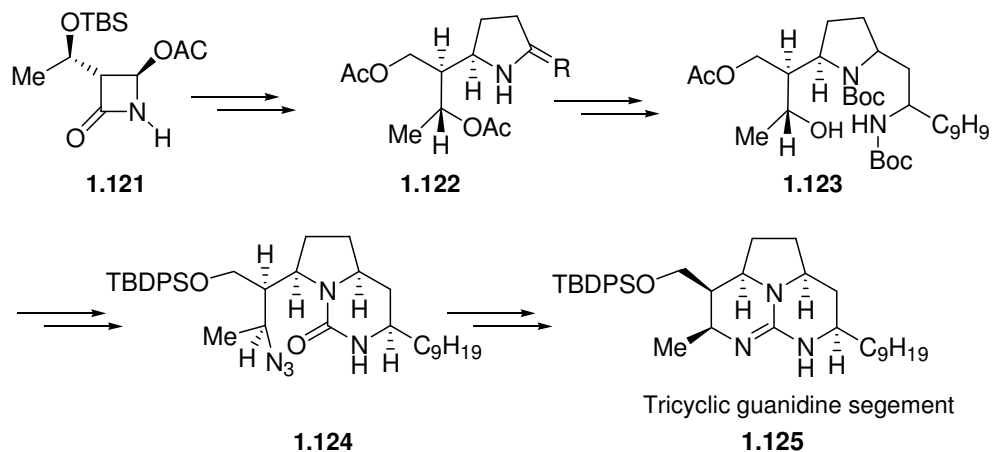


**Batzelladine A**

**Figure 10**

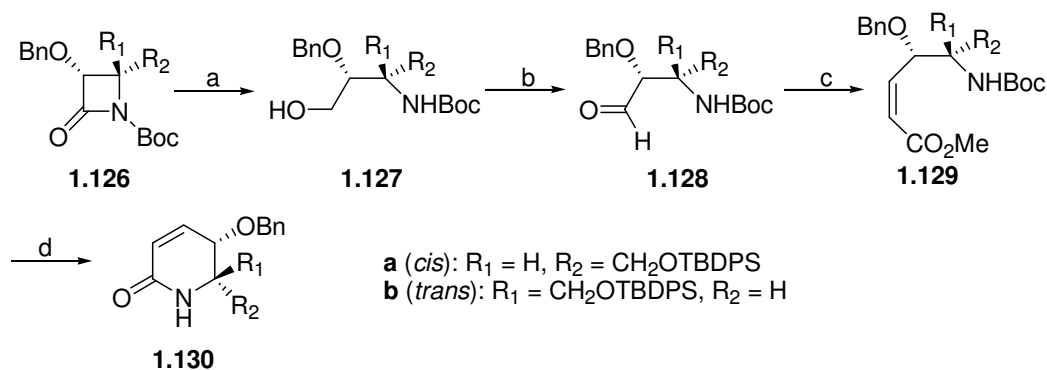
Gurjar *et al*<sup>68</sup> have reported a multi-step synthesis of tricyclic guanidine segment **I** of batzelladine A from commercially available azetidinone derivative (Scheme 1.42).

**Scheme 1.42**



H. K. Lee *et al.*<sup>69</sup> have developed an efficient method for the synthesis of chiral 5,6-dihydro-2-pyridones and 3,4,5,6-tetrahydro-2(1H)-pyridones from easily accessible 2-azetidiones<sup>58</sup> having desired substituents and stereochemistry. The reductive ring opening of azetidin-2-ones ring followed by oxidation to get amino aldehyde. The Wittig reaction of methyl(triphenylphosphoranylidene)acetate with the amino aldehyde followed by cyclization gave the desired 2-pyridones (Scheme 1.43). These 5,6-dihydro-2-pyridones can serve as valuable intermediates for aza-sugars and other piperidine alkaloids.

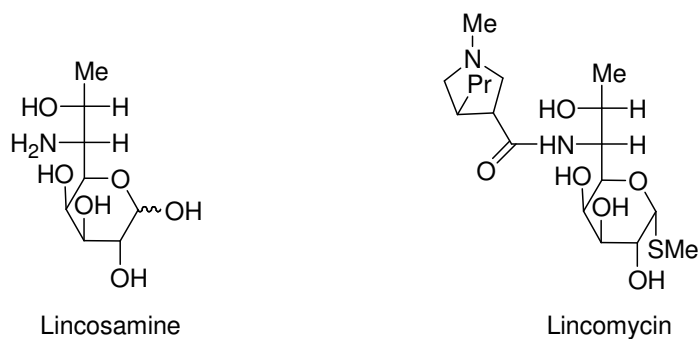
**Scheme 1.43**



*Reagents and conditions:* : a) LiAlH<sub>4</sub>, THF, 0 °C, 30 min; b) IBX, DMSO, rt, 3 h; c) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me, MeOH, rt, 12 h; d) TMSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, then cat. DMAP, toluene, reflux, 1 h.

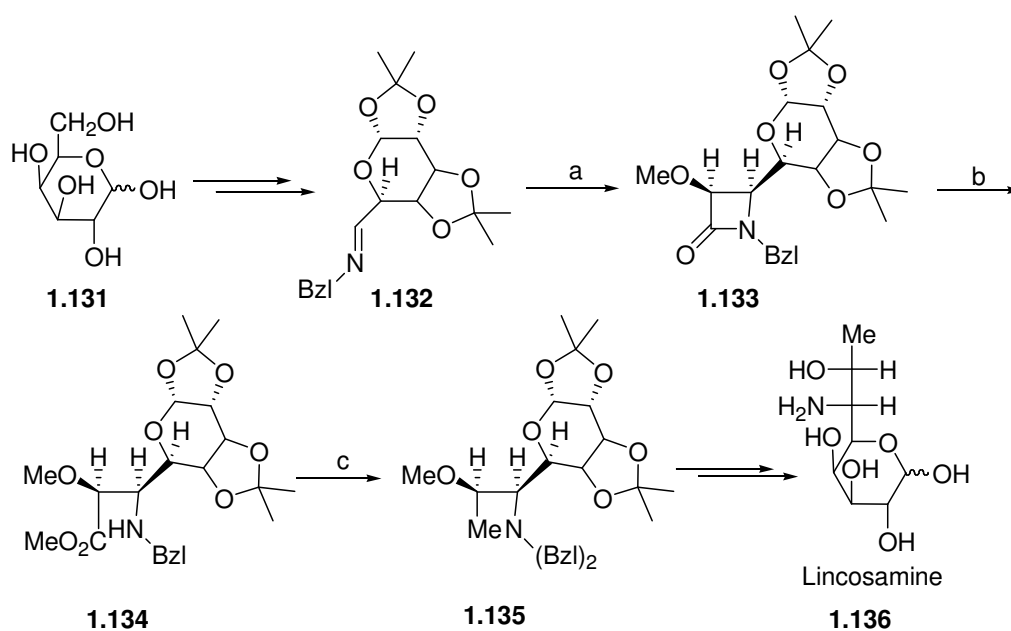
Apart from their applications in various biologically important heterocyclic compounds, the β-lactams are widely used in the synthesis of polyhydroxy amino alcohols, aminosugars and poly hydroxyl amino acids. Bose *et al.*<sup>70</sup> have used the four member heterocyclic β-lactam as synthon for the synthesis lincosamine an eight carbon amino sugar and its isomers. Lincosamine is a part structure of antibiotic lincomycin. The required β-lactam was obtained by enantiospecific cycloaddition reaction between methoxyacetyl chloride and optically active imine in the presence of triethylamine.

The chiral imine was obtained from benzyl amine and enantiopure aldehyde derived from D-galactopyranose. A 6-*epi*-lincosamine derivative, an eight carbon amino sugar that is a part structure of antibiotic lincomycin (Figure 11), has been prepared by a sequence of stereospecific reaction steps from optically pure *cis*-3-methoxy β-lactam. The 3-methoxy β-lactam synthesized from a D-galactose derivative provided access to an epimer of lincosamine (Scheme-1.44).



**Figure 11**

**Scheme 1.44**

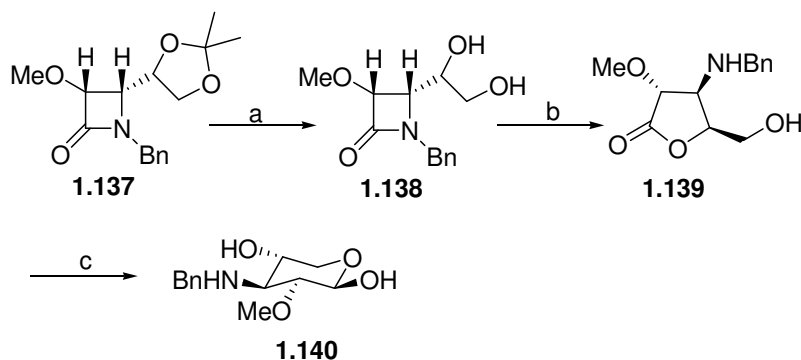


*Reagent and conditions:* a)  $\text{MeOCH}_2\text{COCl}$ ,  $\text{Et}_3\text{N}$ ; b)  $\text{NaOMe}$ ; c) i)  $\text{BnBr}$ ,  $\text{MeCN}$ , ii)  $\text{LAH}$ , ether,  $0\text{ }^\circ\text{C}$ , iii)  $\text{MsCl}$ ,  $0\text{ }^\circ\text{C}$  - rt, iv)  $\text{LAH}$ ,  $\text{THF}$ ,  $0\text{ }^\circ\text{C}$ .

The optically pure 3-methoxy  $\beta$ -lactam was converted into  $\gamma$ -lactone, which was then reduced by diisobutylaluminium hydride to get the amino pyranose derivative (Scheme 1.45). This pyranose derivative is the natural enantiomer of gentosamine, which is a 3-aminosugar present in the antibiotic gentamicin-A.



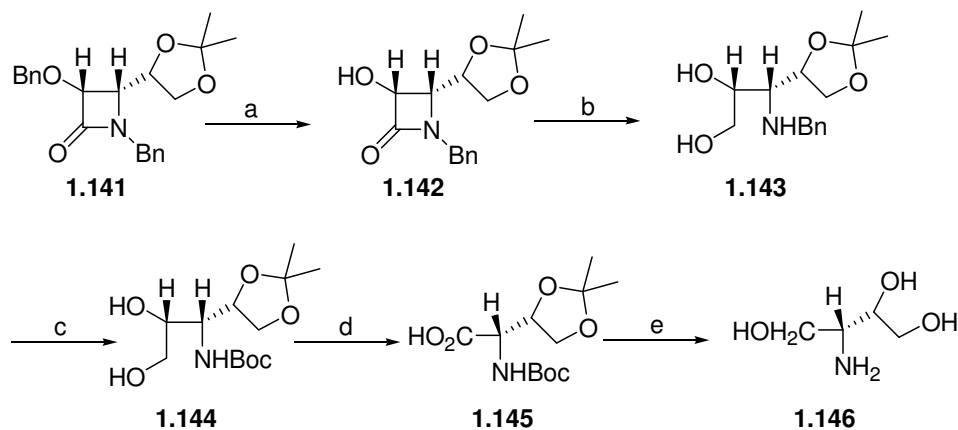
### Scheme 1.45



*Reagents and conditions:* a) PTSA, THF, Reflux, 24 h; b) CF<sub>3</sub>COOH, reflux, 8 h; c) DIBAL-H, THF.

The unusual amino acid L-α-hydroxythreonine was prepared from *cis*-β-lactam starting from D-glyceraldehyde acetonide derived imine and benzyloxyacetyl chloride. This lactam was converted to L-α-hydroxythreonine by various reaction steps (Scheme 1.46).

### Scheme 1.46



*Reagents and conditions:* a) HCOONH<sub>4</sub>, 10% Pd/C, MWI, EtOH; b) LAH, THF; c) i) HCOONH<sub>4</sub>, 10% Pd/C, MWI, EtOH, ii) (Boc)<sub>2</sub>O, NaOH; d) NaIO<sub>4</sub>, RuCl<sub>3</sub>, CCl<sub>4</sub>, H<sub>2</sub>O, CH<sub>3</sub>CN; e) TFA, MeOH.

## 1.2: Background for the present work

The β-lactam skeleton, apart from being a part structure of a variety of β-lactam antibiotics, has also been recognized as a useful building block in the synthesis of variety of pharmaceutically useful products. We were also interested in using β-lactam as a synthon for biologically important products and as a part of same we took up the synthesis of 2,3-Aziridino-γ-lactones from suitably substituted β-lactam. 2,3-Aziridino-γ-lactones are very important intermediates in the synthesis of biologically

useful 3,4-dihydroxy glutamic acids, especially L-glutamic acid, an important excitatory neurotransmitter of the central nervous system, acts through two major classes of receptors, the ionotropic or ion-gated ( $\text{Ca}^{2+}$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ) channel receptors and the metabotropic receptors which are coupled to second messenger systems *via* GTP-binding proteins. Each of these major classes is in turn subdivided into several distinct receptor subclasses.<sup>71</sup> In the case of the ionotropic receptors, these subclasses are defined by their selective interactions with N-methyl-D-aspartic acid (NMDA receptors), with kainic acid (KA receptors) or with  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA receptors) while the metabotropic receptors are grouped into three different subclasses based on their amino acid sequence homology and the nature of the coupling to the metabolic processes regulated by phospholipase C or adenylyl cyclase. The glutamic acid receptors are implicated in such important phenomenon as synaptic plasticity and memory processing.<sup>72</sup> Over-activation of these receptors has also been linked to ischemia, epilepsy and several long-term neurodegenerative syndromes such as Alzheimer's, Huntington's and Parkinson's diseases.<sup>73</sup> In order to discover possible treatments for the latter and, more fundamentally, to understand the physiological importance of each of the many subclasses of glutamic acid receptors, much effort has been made in recent years to design and synthesize subclass-selective ligands. Among these, substituted, optically pure derivatives of glutamic acid itself have received considerable attention.<sup>74</sup> Both the nature and the stereochemistry of these substituents have been shown to influence binding affinities and, therefore, selectivities for a particular glutamic acid receptor subclass.

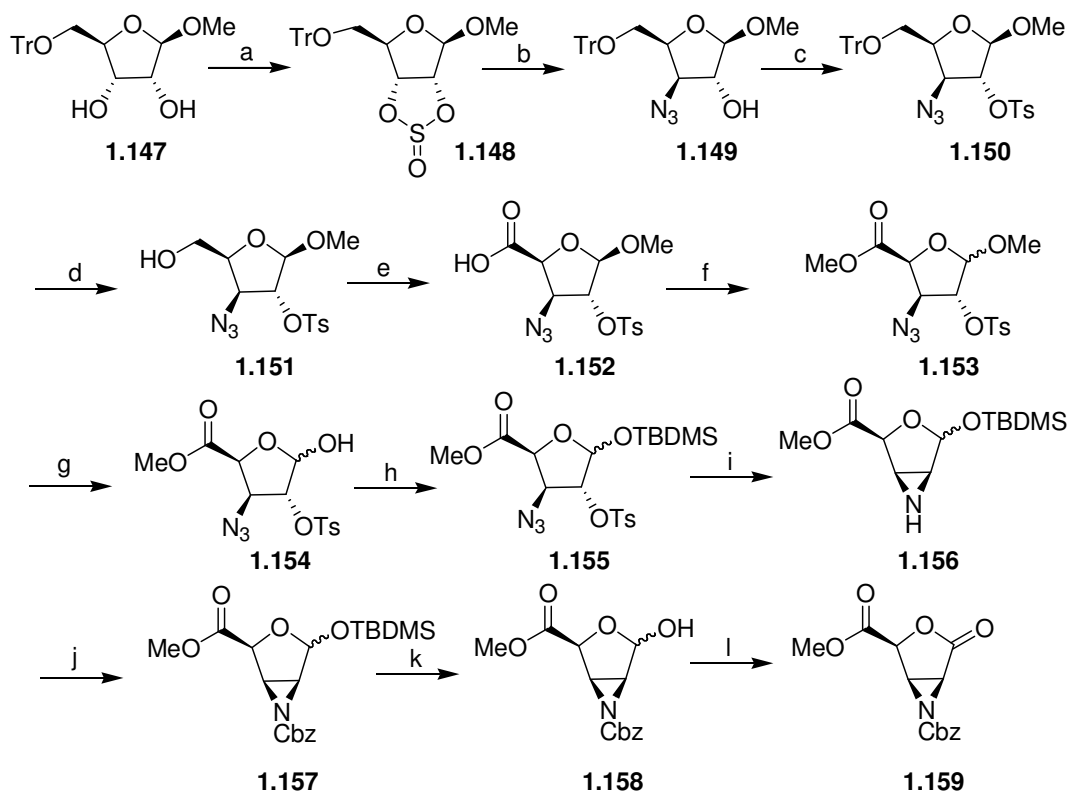
The regioselective nucleophilic opening of the aziridine ring also gives variety of useful products including  $\alpha$ -amino acids, such as polyoxamic acid and  $\beta$ -amino acids. The regioselectivity of the ring cleavage is mainly controlled by the hard nucleophile (alcohols and benzyl amine) and soft nucleophile (thiols, acetic acid, and bromide).

There are few reports on the synthesis 2,3-aziridino- $\gamma$ -lactone analogues.<sup>75-81</sup> The important approaches are described here. However, none of these methods start with  $\beta$ -lactam as a starting material.

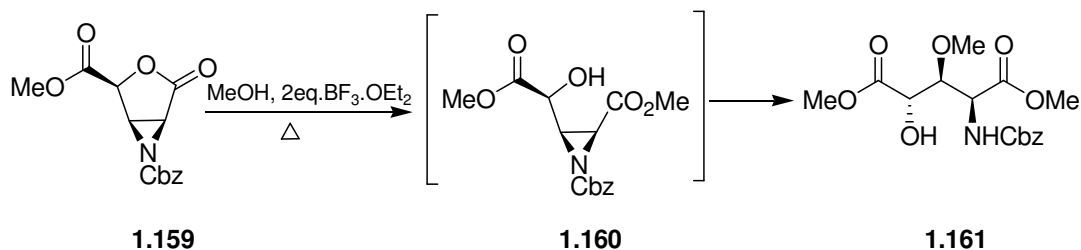
## 1) Synthesis of optically pure 3,4-Disubstituted L-Glutamates:

The synthesis of the *N*-Cbz derivatives of (1*S*,4*S*,5*R*)-4-(methoxycarbonyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**1.159**) from D-ribose is described. While compound **1.159** reacted with methanol in the presence of boron trifluoride etherate to give the novel 2,3-iminoglutamate derivative **1.160**, compound **1.159** afforded, under the same conditions, the 4(*S*)-hydroxy-3(*S*)-methoxy-L-glutamate **1.161** (Scheme 1.48).<sup>76a</sup>

Scheme 1.48



*Reagents and Conditions* a)  $\text{SOCl}_2$ ,  $\text{Et}_3\text{N}$ ; b)  $\text{NaN}_3$ , HMPA,  $100^\circ\text{C}$ ; c)  $\text{TsCl}$ ,  $\text{CH}_2\text{Cl}_2$ ; d) aq.  $\text{H}_2\text{SO}_4$ , doixane,  $100^\circ\text{C}$ ; e)  $\text{RuCl}_4$ ,  $\text{NaIO}_4$ ; f)  $\text{SOCl}_2$ ,  $\text{MeOH}$ ; g) aq.  $\text{CH}_3\text{CO}_2\text{H}$ , rt, 70 h; h)  $\text{TBDMS-Cl}$ , imidazole,  $\text{DMF}$ ; i) i)  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{AcOEt}$ , ii)  $\text{Et}_3\text{N}$ ,  $\text{CH}_3\text{CN}$ ,  $80^\circ\text{C}$ ; j)  $\text{CbzCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{DMF}$ ; k)  $n\text{Bu}_4\text{NF}$ ,  $\text{CH}_2\text{Cl}_2$ ; l)  $\text{TPAP}$ ,  $\text{NMO}$ , molecular sieves 4A°.

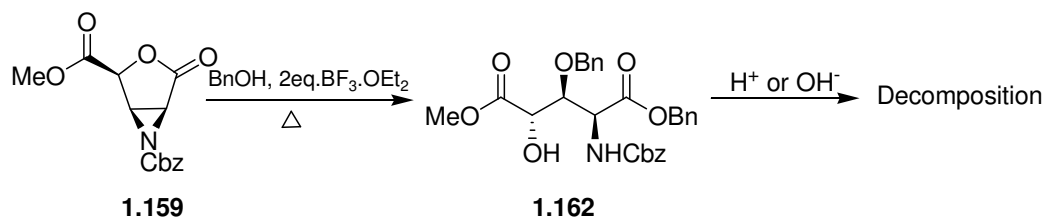


This represents the first example of the use of a carbohydrate for the preparation of L-glutamate derivatives as well as the first example of a stereocontrolled synthesis of glutamate analogues dissymmetrically substituted at the  $\beta$ ,  $\gamma$ -positions.

## 2) Enantiospecific Synthesis of the (3*S*,4*S*)-isomer of Dihydroxy-L-glutamic Acid:

For the synthesis of dihydroxy-L-glutamic acid when benzyl alcohol was used as a nucleophile and boron trifluoride etherate as a Lewis acid, both aziridine ring as well as lactone ring opened to give the protected 3-alkoxy-4-hydroxy L-glutamate **1.162**. Further, while the benzyl and benzyloxycarbonyl (Cbz) protecting groups could easily be removed by hydrogenolysis, hydrolysis of methyl ester under either acidic or basic conditions led to extensive decomposition (Scheme 1.49).<sup>76b</sup>

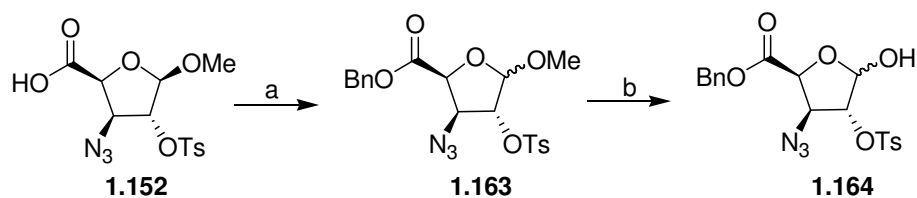
**Scheme 1.49**

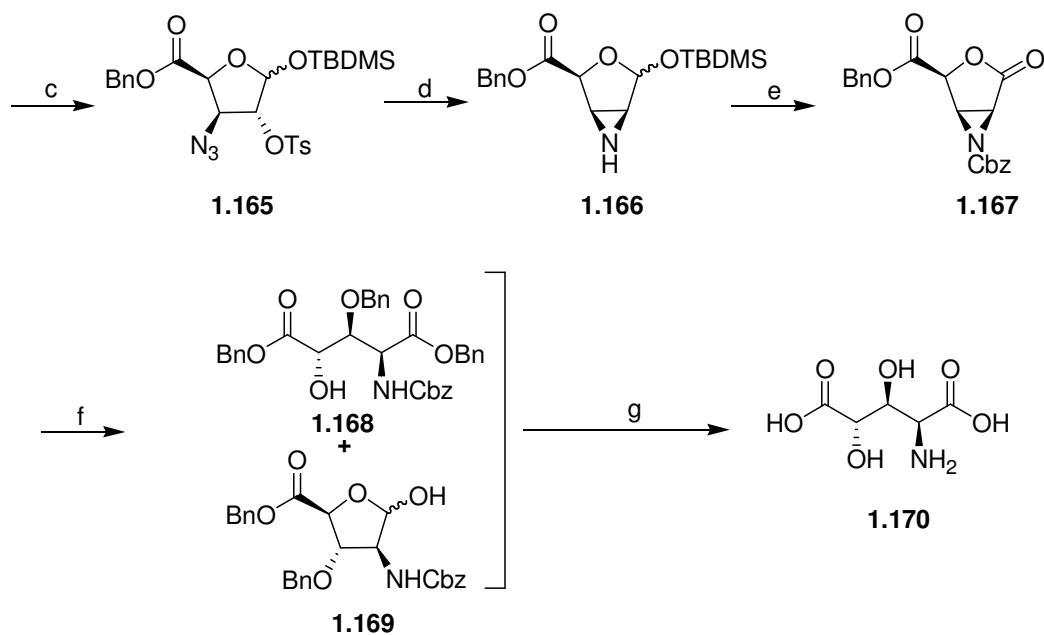


An obvious solution to this problem would be to prepare the benzyl ester analogue of methyl ester **1.159** which would allow the all the blocking groups to be removed by hydrogenolysis.

However, this would require a modification of reaction conditions previously used for preparation of aziridine ring which are incompatible with presence of benzyl ester functionality on substrate (Scheme 1.48). Starting from intermediate **1.152** by using same reaction conditions the synthesis of benzyl 2,3-aziridino-*N*-(benzyloxycarbonyl)-2,3-dideoxy- $\gamma$ -butyrolactone (**1.167**) was achieved. Reaction of **1.167** with excess benzyl alcohol in the presence of boron trifluoride etherate and hydrogenolysis of product gave (3*S*,4*S*)-dihydroxy-L-glutamic acid (**1.170**) (Scheme 1.50).

**Scheme 1.50**



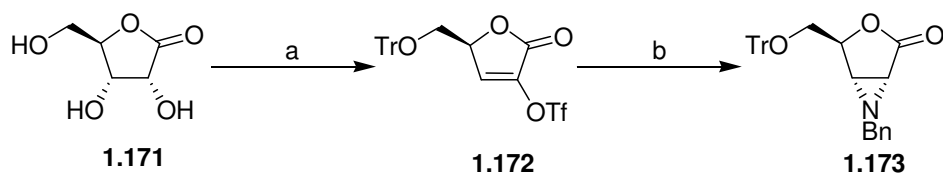


*Reagents and conditions:* a) BnOH, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; b) TFA/H<sub>2</sub>O; c) TBDMSCl, Imidazole, DMF; d) PPh<sub>3</sub>, H<sub>2</sub>O, pyridine, Et<sub>3</sub>N, 70 °C; e) i) CbzCl, aq. NaOH, CH<sub>2</sub>Cl<sub>2</sub>, ii) TPAP, NMO, CH<sub>3</sub>CN; f) BnOH, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>3</sub>CN, 0 °C; g) i) H<sub>2</sub>, Pd/C (10%), MeOH/H<sub>2</sub>O, ii) AG1-X4 (OH<sup>-</sup>) resin.

### 3) A Straightforward synthesis of 2,3-Aziridino- $\gamma$ -Lactone:

Dodd *et al.*<sup>79</sup> have reported a method for the concise synthesis of 2,3-aziridino- $\gamma$ -lactone from commercially available  $\alpha,\beta$ -dihydroxy- $\gamma$ -lactone (D-ribonolactone) **1.171**. The strategy involves a Michael-type addition of benzylamine to a key triflate derivative of 2-oxo-5-trityloxymethyl-2,5-dihydro-furan-3-yl ester **1.172**, followed by *in situ* cyclization to a aziridine without opening of lactone-ring (Scheme 1.51).<sup>79b</sup>

**Scheme 1.51**

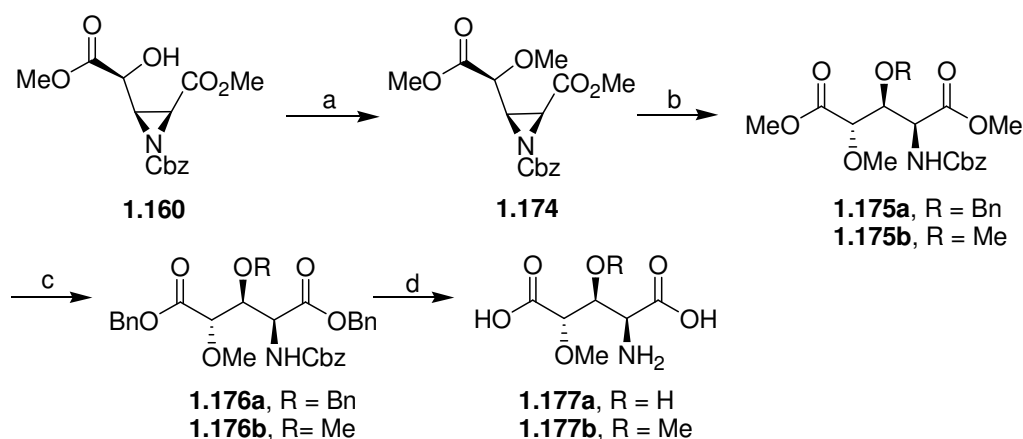


*Reagents and conditions:* a) i) Ph<sub>3</sub>Cl, pyridine, 65 °C, ii) Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C -> -25 °C; b) BnNH<sub>2</sub>, DMF, -20 °C.

#### 4) Synthesis of 3,4-disubstituted glutamic acid via controlled stepwise ring opening of 2,3-Aziridino- $\gamma$ -Lactone:

In this approach author has described synthesis of enantiomerically pure 3,4-disubstituted glutamic acids starting from D-ribose *via* controlled stepwise ring opening of 2,3-Aziridino- $\gamma$ -lactone, in which at lower temperature only the lactone ring was opened first selectively. This preparation involved the use of a 2,3-aziridino- $\gamma$ -lactone whose reactivity towards nucleophiles could be efficiently controlled to allow selective functionalization at the  $\beta$ -position. A key step of the strategy was a titanate-mediated transesterification of a dimethyl ester into a dibenzyl analogue **1.176a**, allowing efficient deprotection to the free amino acids **1.177a-b** by hydrogenolysis (Scheme 1.52).<sup>75a</sup>

Scheme 1.52



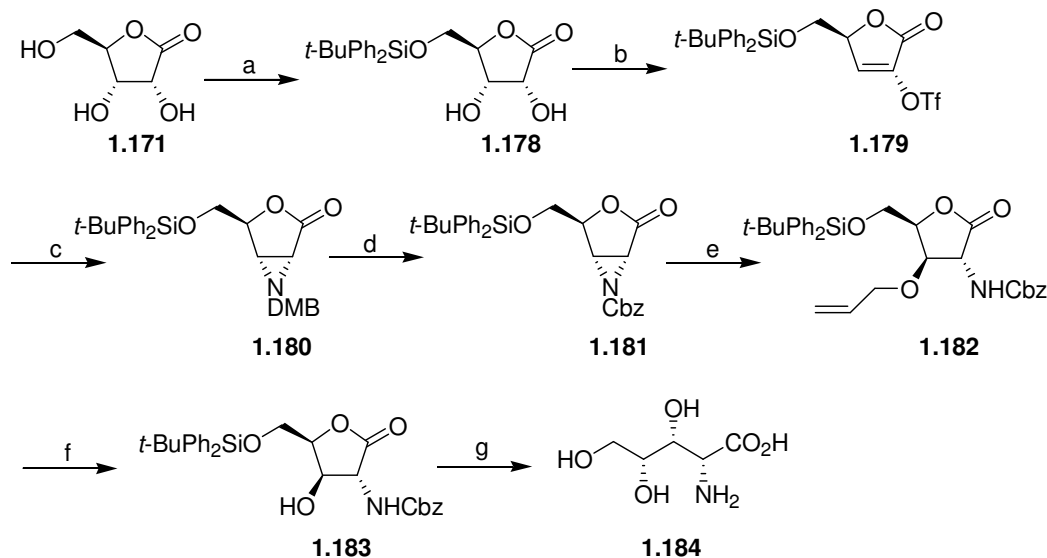
*Reagents and conditions:* a) MeI, Ag<sub>2</sub>O, CaSO<sub>4</sub>, THF, rt; b) BnOH, BF<sub>3</sub>·OEt<sub>2</sub>, rt - .60 °C; c) Ti(OBn)<sub>4</sub>, BnOH, 120 °C, toluene; d) H<sub>2</sub>, Pd/C, MeOH, rt.

#### 5) Synthesis of (-)- Polyoxamic Acid:

An enantiospecific synthesis of (-)- polyoxamic acid was accomplished from 2,3-aziridino- $\gamma$ - lactone **1.181** in six steps. The synthesis uses D-ribonolactone as a starting material for synthesis of 2,3-aziridino- $\gamma$  - lactone **1.181** which on further transformations yielded target the molecule. A notable feature of the strategy is a sequence of deprotection- protection reactions applied to compound **1.181** that occurred in good yield leaving the aziridine ring intact. *N*-dimethoxybenzyl was replaced with a more electron withdrawing group in form of carbobenzyloxy group. This methodology is now being applied to the preparation of unusual natural amino

acids and particularly of  $\alpha$ -substituted  $\beta$ -amino acids accessible from 2,3-aziridino- $\gamma$ -lactones by reaction with soft nucleophiles (Scheme 1.53).<sup>77a</sup>

**Scheme 1.53**



*Reagents and conditions:* a)  $t\text{-BuPh}_2\text{SiCl}$ , Imidazole, DMF; b)  $\text{Tf}_2\text{O}$ , Pyridine,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{DMBNH}_2$ , DMF; d) i) DDQ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , ii)  $\text{CbzCl}$ , Pyridine, DMAP; e) allyl alcohol,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{CHCl}_3$ ; f)  $\text{SeO}_2$ , AcOH, Dioxane; g) i)  $n\text{-Bu}_4\text{NF}$ , AcOH, THF, ii)  $\text{H}_2$ , Pd-C,  $\text{MeOH}/\text{H}_2\text{O}$ , iii) AG1-X4 ( $\text{AcO}^-$ )resin.

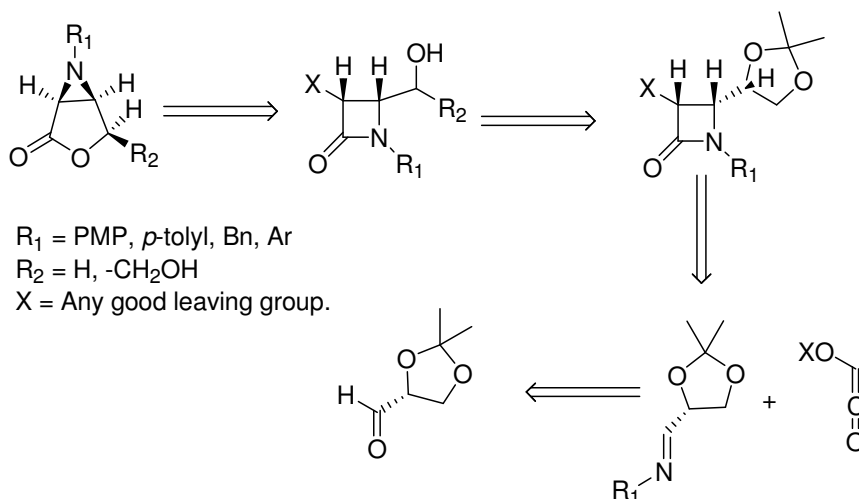
### 1.3: Present work

Aziridino- $\gamma$ -lactones can now be considered important synthons for enantiospecific synthesis of a wide variety of substituted  $\alpha$ - and  $\beta$ -amino acids. The objective of this investigation was to develop an efficient method for the synthesis of enantiopure 2,3-aziridino- $\gamma$ -lactones from azetidin-2-ones. Acid catalyzed tandem intramolecular azetidinone ring opening followed by aziridine ring formation *via* elimination of mesylate group is the key step in this synthesis.

### 1.4: Result and discussion

The knowledge of the fact that  $\beta$ -lactams having a hydroxy methylene group at C-4 position, on acid catalyzed opening of the lactam ring spontaneously lactonize prompted us to think that, such a lactonization could well be followed by another cyclization wherein the free amino group displaces the already present good leaving group at C-3 position of the precursor  $\beta$ -lactam as shown in the retrosynthetic strategy (Scheme 1.54).

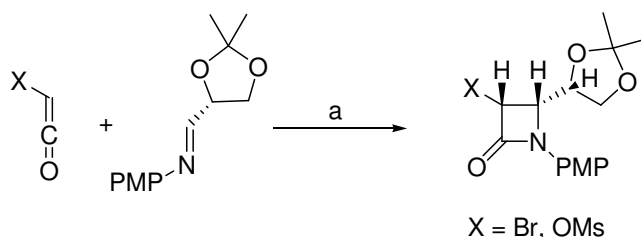
**Scheme 1.54**



The required  $\beta$ -lactam can be obtained by converting a suitably substituted 3-hydroxy  $\beta$ -lactam into its mesyl or tosyl derivative. The requisite  $\beta$ -lactam with a good leaving group at C-3 position can be envisaged to be obtained by well documented Staudinger reaction.

We started our efforts with attempts to synthesize suitably substituted  $\beta$ -lactams having the good leaving group at C-3 position already in place. Thus mesyloxy acetyl chloride was used as a ketene precursor with a D-glyceraldehyde derived imine in a Staudinger cycloaddition reaction. However the reaction failed to deliver the required product and we ended up with complex reaction mixture. Similar results were obtained when we tried chloroacetyl chloride and bromoacetyl chloride as ketene precursors (Scheme 1.55).

**Scheme 1.55**



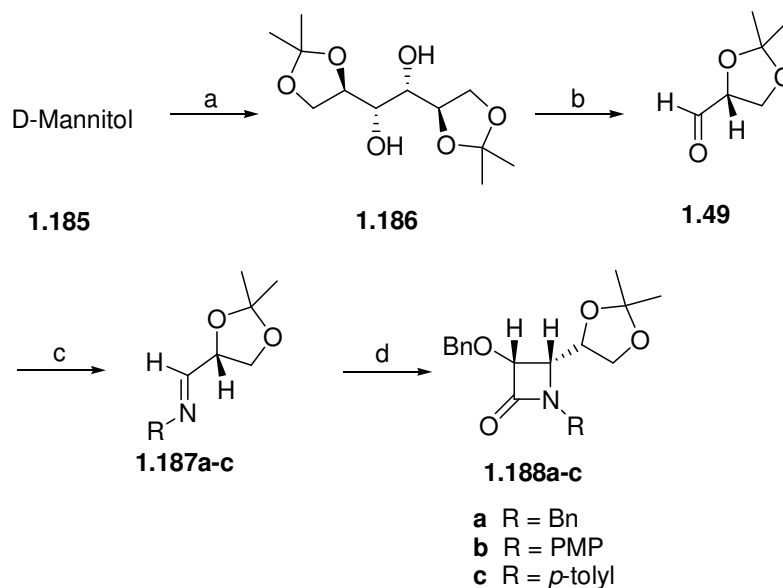
*Reagents and conditions:* a)  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ -rt, 12 h.

Thus we abandoned this route and decided to obtain the required  $\beta$ -lactam by deprotecting an acetoxy or a benzyloxy group at C-3 position, which can be installed



pretty easily and subsequently converting them into mesylate or a tosylate derivative. Thus the starting 3-benzyloxy-azetidin-2-one (**1.188a**) was obtained in good yield and enantiopurity by Staudinger's ketene-imine cycloaddition reaction.<sup>35</sup> The starting material required for Staudinger reaction was prepared from commercially available D-mannitol (Scheme 1.56).

**Scheme 1.56**



*Reagents and conditions:* a) ZnCl<sub>2</sub>, anhyd. acetone, 24 h; b) NaIO<sub>4</sub>, H<sub>2</sub>O, 30 min, 0 °C; c) R-NH<sub>2</sub>, H<sub>2</sub>O-EDC, rt., 2 h; d) BnOCH<sub>2</sub>COCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt., 12 h.

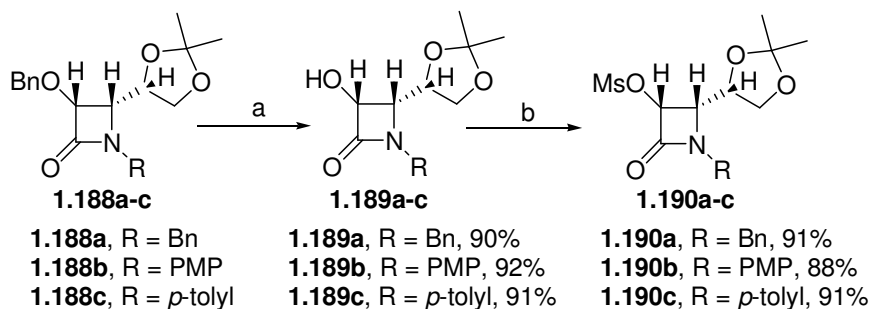
D-mannitol was protected as its diacetonide using anhydrous zinc chloride in dry acetone. The vicinal diol of this acetonide **1.186** was cleaved by sodium metaperiodate to get optically pure D-glyceraldehyde acetonide. The Schiff base **1.187a** was prepared by stirring a mixture of aqueous solution of D-glyceraldehyde acetonide with benzylamine in dichloroethane for 2 h. The imine thus formed was reacted with ketene generated *in situ* from benzyloxyacetyl chloride and triethyl amine to afford  $\beta$ -lactam **1.188a**. Several other optically pure 3-benzyloxy-azetidin-2-ones (**1.188b-c**) were prepared by using following synthetic protocol and well characterized by spectral data (Scheme 1.56).

IR spectrum of **1.188a** showed a sharp peak at 1742 cm<sup>-1</sup> which is characteristic of the  $\beta$ -lactam carbonyl group.

The  $^1\text{H}$  NMR spectrum of **1.188a** showed two singlets at 1.34 ppm and 1.35 ppm for methyl groups of acetonide moiety. The multiplet of two protons at 3.53-3.62 corresponds to the methylene protons of acetonide moiety. One diastereotopic benzylic proton on nitrogen, methine proton of acetonide moiety and proton on C-4 of  $\beta$ -lactam were appeared together as a multiplet at 4.09-4.36, while other diastereotopic benzylic proton on nitrogen appeared as doublet at 4.83 ppm with  $J = 14.7$  Hz. The C-3  $\beta$ -lactam proton appeared as doublet at 4.58 ppm with  $J = 5.1$  Hz. The benzyl protons on oxygen atom attached to C-3 position of  $\beta$ -lactam appeared as two doublets at 4.65 and 4.93 ppm with  $J = 11.7$  Hz. The ten aromatic protons appeared as a multiplet between 7.30-7.36 ppm.

The benzyl group was removed by transfer hydrogenation<sup>82</sup> using ammonium formate and Pd-C (10%) to get the corresponding 3-hydroxy- $\beta$ -lactam **1.189a** in very good yield (Scheme 1.57).

**Scheme 1.57**

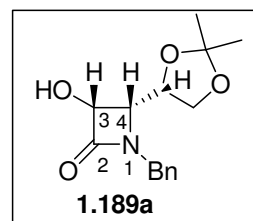


*Reagents and conditions:* a) 10% Pd/C, HCOONH<sub>4</sub>, MeOH, reflux, 0.5 h;  
b) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -10 °C-rt, 2 h.

A mixture of **1.188a**, ammonium formate and 10% Pd/C in methanol was refluxed for 0.5 h. After extractive work up with ethyl acetate got the crude product, it was subsequently purified by column chromatography to afford pure 3-hydroxy  $\beta$ -lactam **1.189a** as a white solid. The structure of **1.189a** was established by spectral and analytical data.

The IR spectrum of **1.189a** showed a sharp band at 1731  $\text{cm}^{-1}$  corresponds to the  $\beta$ -lactam carbonyl. The band at 3307  $\text{cm}^{-1}$  corresponds to the hydroxyl group.

The  $^1\text{H}$  NMR spectrum of **1.189a** showed two singlets at 1.25 ppm and 1.31 ppm for methyl groups of acetonide moiety. A doublet of



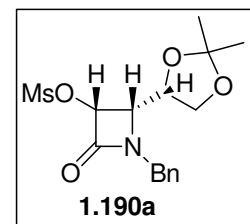
doublet appeared at 3.42 ppm with  $J = 5.2$  Hz and 2.5 Hz corresponding to C-4 proton of the  $\beta$ -lactam. The proton at C-3 position of  $\beta$ -lactam ring resonated as doublet of doublet at 3.62 ppm with  $J = 5.2$  Hz and 9.0 Hz. The methyl protons of acetonide moiety and hydroxy proton appeared together as a multiplet at 4.04-4.08 ppm while, the methine proton of acetonide moiety showed a multiplet at 4.12-4.30 ppm. The benzyl protons on nitrogen appeared as two doublets at 4.71 ppm and 4.75 ppm with  $J = 14.3$  Hz. All the aromatic protons showed a multiplet between 7.16-7.27 ppm.

The  $^{13}\text{C}$  NMR of **1.189a** showed two peaks at 24.9 ppm and 26.5 ppm corresponds to methyl groups of acetonide moiety. The methylene carbon of acetonide appeared at 66.5 ppm, while methylene carbon attached to nitrogen atom of  $\beta$ -lactam appeared at 44.9 ppm. The methine carbon of acetonide moiety showed a peak at 75.1 ppm. The C-3 and C-4  $\beta$ -lactam carbon appeared at 77.6 ppm and 60.5 ppm respectively. The aromatic quaternary carbon appeared at 109.5 ppm, while remaining aromatic carbons appeared at 127.7, 128.5, 135.2 ppm. The peak at 170.1 ppm was assigned to  $\beta$ -lactam carbonyl carbon. This compound **1.189a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  278 ( $M+1$ ).

Mesylation of hydroxyl group at C-3 position of azetidin-2-one was carried out with the help of methane sulphonyl chloride in presence of triethyl amine in anhydrous dichloromethane. The purpose of this reaction was to convert the hydroxy moiety into a good leaving group thereby making it displacable by any good nucleophile. Methane sulphonyl chloride was added at  $-10$  °C to a mixture of **1.189a** and triethyl amine in dichloromethane to get the crude product, which on column chromatographic purification gave pure **1.190a** as a white solid. The structure of **1.190a** was established by spectral and analytical data.

The IR spectrum of 3-mesyloxy  $\beta$ -lactam **1.190a** showed a band at  $1770\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl.

The  $^1\text{H}$  NMR spectrum of **1.190 a** showed two singlets at 1.28 ppm and 1.31 ppm for methyl groups of acetonide moiety while, methyl protons of mesylate group appeared at 3.19 ppm as a singlet. The signals due to protons corresponding



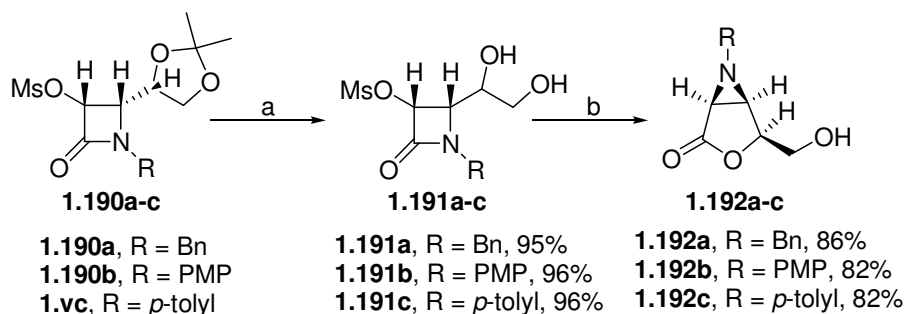
to methine proton attached to C-4 position of  $\beta$ -lactam and proton of C-4 position of  $\beta$ -lactam ring were merged at 3.58-3.67 ppm. The signals due to protons corresponding to methylene group of acetonide moiety and one of the diastereotopic

benzylic protons also got merged at 4.08-4.31 ppm. The other diastereotopic benzylic proton appeared as doublet at 4.78 ppm with  $J = 14.3$  Hz. The doublet at 5.39 ppm with  $J = 5.2$  Hz was assigned to C-3 proton of  $\beta$ -lactam ring. The aromatic protons appeared as a multiplet between 7.20-7.26 ppm.

The  $^{13}\text{C}$  NMR of **1.190a** showed two peaks at 24.9 ppm and 26.5 ppm corresponds to methyl groups of acetonide moiety. The peak at 29.1 ppm corresponds to methyl carbon of mesylate group on C-3 position of  $\beta$ -lactam ring. The methylene carbon of acetonide appeared at 66.3 ppm, while methylene carbon attached to nitrogen atom of  $\beta$ -lactam appeared at 45.6 ppm. The methine carbon of acetonide moiety showed a peak at 76.1 ppm. The C-3 and C-4  $\beta$ -lactam carbon appeared at 78.4 ppm and 58.9 ppm respectively. The quaternary carbon of acetonide moiety appeared at 110.1 ppm. The aromatic quaternary carbon appeared at 134.7 ppm, while remaining aromatic carbons appeared at 128.0, 128.6, 134.7 ppm. The peak at 162.7 ppm was assigned to  $\beta$ -lactam carbonyl carbon. This compound **1.190a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  356 ( $M+1$ ).

The deprotection of acetonide group was achieved by refluxing **1.190a** in THF- $\text{H}_2\text{O}$  with a catalytic amount of PTSA for 12 h. After completion of reaction the reaction mixture was neutralized with  $\text{NaHCO}_3$  and solvent was removed under reduced pressure. Extractive work up with ethyl acetate afforded dihydroxy- $\beta$ -lactam as a crude product, which was purified by column chromatography to obtain **1.191a** in excellent yield as a white crystalline solid (Scheme 1.58). The structure of **1.191a** was established by spectral and analytical data.

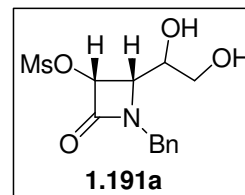
**Scheme 1.58**



*Reagents and conditions:* a) PTSA, THF- $\text{H}_2\text{O}$ , reflux, 12-24 h;  
 b) HCl-MeOH (20%), reflux, 18-24 h.

The IR spectrum of dihydroxy  $\beta$ -lactam **1.191a** showed a band at  $1733\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl. The band at  $3326\text{ cm}^{-1}$  corresponds to the hydroxyl group.

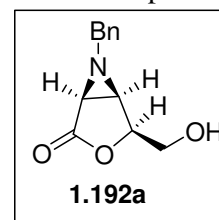
The  $^1\text{H}$  NMR spectrum of **1.191a** showed singlet at 3.34 ppm corresponding to methyl protons of the mesylate group.



The two broad singlets at 3.34 ppm and 3.37 ppm hydroxyl protons. The signals due to proton corresponding to C-4 position of  $\beta$ -lactam appeared at 3.70-3.75 ppm as a multiplet. The proton on methine carbon attached to C-4 position of  $\beta$ -lactam appeared as a triplet at 3.88 ppm with  $J = 5.5$  Hz. The doublet at 4.31 ppm with  $J = 15.5$  corresponds to one of the diastereotopic benzylic protons. The other diastereotopic benzylic proton and one of the methylene proton attached to primary hydroxyl group were merged at 4.65-4.77 ppm displaying a multiplet while, other methylene proton attached to primary hydroxy group appeared as doublet at 5.16 ppm with  $J = 5.8$  Hz. The doublet at 5.71 ppm with  $J = 5.2$  Hz was assigned to C-3 proton of  $\beta$ -lactam ring. The aromatic protons appeared as a multiplet between 7.30-7.36 ppm.

The  $^{13}\text{C}$  NMR of **1.191a** showed the peak at 29.1 ppm corresponding to methyl carbon of mesylate group. The methylene carbon attached to primary hydroxyl group appeared at 63.5 ppm, while benzylic carbon attached on nitrogen appeared at 45.4 ppm. The methine carbon attached to C-4 position of  $\beta$ -lactam showed a peak at 70.2 ppm. The C-3 and C-4  $\beta$ -lactam carbon appeared at 78.3 ppm and 57.5 ppm respectively. The aromatic quaternary carbon appeared at 136.1 ppm, while remaining aromatic carbons appeared at 127.6, 128.0, 128.8 ppm. The peak at 163.9 ppm was assigned to  $\beta$ -lactam carbonyl carbon. This compound **1.191a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  316 ( $M+1$ ).

Dihydroxy- $\beta$ -lactam **1.191a** was refluxed in methanolic HCl (20%) for 18 hours (reaction was monitored by TLC). Solvent was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. The extractive work-up with ethyl acetate gave 2,3-aziridino- $\gamma$ -lactone **1.192a** as a thick oil. This compound was found to be unstable on silica gel column when kept for a longer time. Therefore, it was quickly purified by flash column chromatography. The structure of **1.192a** was established by spectral and analytical data.



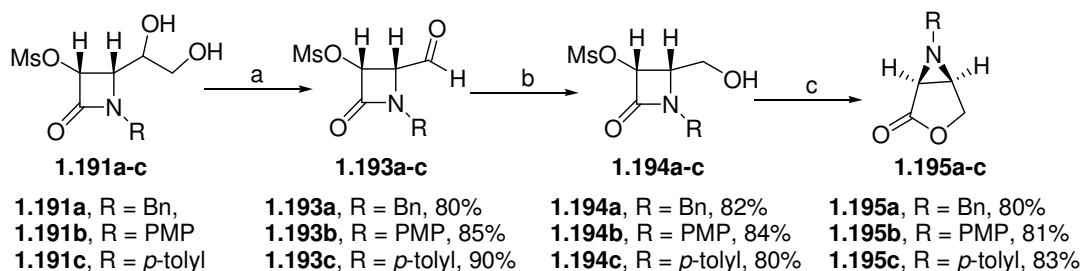
The IR spectrum of the product **1.192a** showed a strong absorption band at  $1780\text{ cm}^{-1}$  for  $\gamma$ -lactone carbonyl group.

$^1\text{H}$  NMR spectrum did not show a singlet for methyl indicating the elimination of mesylate group during the aziridine ring formation. The broad singlet at 2.36 ppm is attributed to hydroxyl proton. One of the aziridine ring protons appeared as a doublet at 2.80 ppm with  $J = 4.5\text{ Hz}$  and other proton appeared as doublet of doublet at 3.14 ppm with  $J = 3.1$  and  $4.5\text{ Hz}$ . The benzyl protons appeared as two doublets at 3.35 and 3.82 ppm with  $J = 13.0\text{ Hz}$ . The lactone ring proton and one of the hydroxy methyl proton attached to lactone ring got merged and appeared as a multiplet at 3.81-3.94 ppm while, other hydroxyl methyl proton appeared as a multiplet at 4.46-4.53 ppm. The aromatic protons appeared as a multiplet between 7.34-7.38 ppm.

The  $^{13}\text{C}$  NMR of **1.192a** showed two peaks at 39.9 ppm and 42.8 ppm corresponding to aziridine ring. The benzylic carbon attached to nitrogen atom of aziridine ring appeared at 60.8 ppm while, methylene carbon of hydroxyl group appeared at 61.6 ppm. The peak at 79.4 ppm corresponds to methine carbon of lactone ring. The aromatic quaternary carbon appeared at 136.8 ppm, while remaining aromatic carbons appeared at 127.8, 127.8, 128.6 ppm. The peak at 171.8 ppm was assigned to  $\gamma$ -lactone carbonyl carbon. This compound **1.192a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  220 ( $M+1$ ).

Spectral data clearly revealed the formation of 2,3-aziridino- $\gamma$ -lactone **1.192a** via one-pot azetidione ring opening followed by aziridine ring formation.

### Scheme 1.57



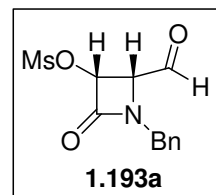
*Reagents and conditions:* a)  $\text{NaIO}_4$  supported on silica gel, MeOH, rt, 3.5 h; b)  $\text{NaBH}_4$ , MeOH or THF, rt, 3 h; c) HCl-MeOH (20%), reflux, 18-24 h.

The formation of 2,3-aziridino- $\gamma$ -lactone was further confirmed by synthesis of aziridino- $\gamma$ -lactone **1.195a** and comparing its spectral data with the reported racemic compound.<sup>79b</sup> This was achieved by following the synthetic scheme shown in Scheme (Scheme 1.57). The dihydroxy- $\beta$ -lactam **1.191a** on oxidative cleavage by silica gel supported sodium metaperiodate<sup>83</sup> gave 4-formyl- $\beta$ -lactam **1.193a**.

To a vigorously stirred suspension of silica gel-supported NaIO<sub>4</sub> reagent in anhydrous dichloromethane was added a solution of vicinal diol in dichloromethane and the reaction mixture was stirred for 3.5 h afforded 4-formyl azetidino-2-one **1.193a**. The structure of **1.193a** was established by spectral and analytical data.

The IR spectrum of the product **1.193a** showed a strong absorption band at 1772 and 1733 cm<sup>-1</sup> corresponding to  $\beta$ -lactam and aldehydic carbonyl respectively.

The <sup>1</sup>H NMR spectrum of **1.193a** showed singlet at 3.14 ppm corresponding to methyl protons of the mesylate group. The signals due to proton corresponding to C-4 position of  $\beta$ -lactam appeared as doublet of doublet at 4.20 ppm with  $J = 1.3$  and 5.3 Hz. The benzyl protons appeared as two doublets at 3.31 and 4.71 ppm with  $J = 14.6$  Hz.



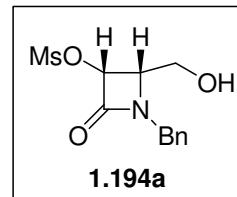
The doublet at 5.67 ppm with  $J = 5.3$  Hz was assigned to C-3 proton of  $\beta$ -lactam ring. The aromatic protons appeared as a multiplet between 7.12-7.31 ppm. The aldehydic proton appeared as doublet at 9.48 with  $J = 1.3$  Hz.

The <sup>13</sup>C NMR of **1.193a** showed the peak at 38.8 ppm corresponding to methyl carbon of mesylate group. The benzylic carbon attached on nitrogen appeared at 46.1 ppm. The C-3 and C-4  $\beta$ -lactam carbon appeared at 78.4 ppm and 61.7 ppm respectively. The aromatic quaternary carbon appeared at 133.4 ppm, while remaining aromatic carbons appeared at 128.4, 128.8, 129.1 ppm. The peak at 161.7 ppm and 195.55 ppm was assigned to  $\beta$ -lactam and aldehydic carbonyl carbon respectively. The compound **1.193a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  284 ( $M+1$ ).

The aldehyde **1.193a** was reduced to the corresponding alcohol **1.194a** by sodium borohydride in good yield. To a cooled solution of 1-benzyl-3-mesyloxy-4-formyl azetidino-2-one (**1.193a**) in methanol at 0 °C was added NaBH<sub>4</sub> portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 3 h. Purification by column chromatography afforded alcohol **1.194a** as a white solid. The structure of **1.194a** was established by spectral and analytical data.

The IR spectrum of 4-hydroxy  $\beta$ -lactam **1.194a** showed a band at  $1751\text{ cm}^{-1}$  corresponds to  $\beta$ -lactam carbonyl. The band at  $3458\text{ cm}^{-1}$  corresponds to the hydroxyl group.

The  $^1\text{H}$  NMR spectrum of **1.194a** showed broad singlet at 1.90 ppm corresponding to hydroxy proton while, singlet at 3.28 ppm corresponding to methyl protons of the mesylate group. The signals due to proton corresponding to C-4 position of  $\beta$ -lactam and methylene proton attached to primary hydroxyl group got merged at 3.81-3.91 ppm displaying a multiplet. The benzyl protons appeared as two doublets at 4.35 and 4.64 ppm with  $J = 14.9\text{ Hz}$ . The doublet at 5.58 ppm with  $J = 4.4\text{ Hz}$  was assigned to C-3 proton of  $\beta$ -lactam ring. The aromatic protons appeared as a multiplet between 7.29-7.40 ppm.



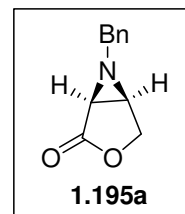
The  $^{13}\text{C}$  NMR of **1.194a** showed the peak at 38.9 ppm corresponding to methyl carbon of mesylate group. The benzylic carbon attached on nitrogen appeared at 45.5. The peak at 59.7 ppm corresponding to the methylene carbon attached to C-4 position of  $\beta$ -lactam. The C-3 and C-4  $\beta$ -lactam carbon appeared at 78.6 ppm and 58.0 ppm respectively. The aromatic quaternary carbon appeared at 134.6 ppm, while remaining aromatic carbons appeared at 128.2, 128.3, 129.0 ppm. The peak at 162.9 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **1.194a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  286 ( $M+1$ ).

4-Hydroxy  $\beta$ -lactam **1.194a** was further subjected to intramolecular nucleophilic ring cleavage. Compound **1.194a** was refluxed with methanolic HCl for 8 h to get 2,3-aziridino- $\gamma$ -lactone **1.195a** in very good yield following the same synthetic procedure for preparation of aziridino- $\gamma$ -lactone as shown in Scheme 1.56.

The structure of **1.195a** was established by spectral and analytical data. The IR and NMR data of **1.195a** was found to be exactly similar with that of the reported racemic compound.<sup>79b</sup> This confirms the formation of aziridino- $\gamma$ -lactones *via* tandem nucleophilic azetidinone ring opening and aziridine ring formation.

The IR spectrum of the product **1.195a** showed a strong absorption band at  $1774\text{ cm}^{-1}$  for  $\gamma$ -lactone carbonyl group.

$^1\text{H}$  NMR spectrum did not show a singlet for methyl indicating the elimination of mesylate group during the aziridine ring formation. One of the aziridine ring protons appeared as a doublet at 2.72 ppm with  $J = 4.5\text{ Hz}$  and





other proton appeared as doublet of doublet at 2.96 ppm with  $J = 3.1$  and  $4.5$  Hz. The benzyl protons appeared as two doublets at 3.47 and 3.74 ppm with  $J = 13.5$  Hz. One the lactone ring proton appeared as doublet of doublet at 4.21 with  $J = 9.8$  and  $3.1$  Hz while other other proton appeared as single doublet at 4.34 ppm with  $J = 9.8$  Hz. The aromatic protons appeared as a multiplet between 7.30 -7.40 ppm.

The  $^{13}\text{C}$  NMR of **1.195a** showed two peaks at 39.68 ppm and 42.1 ppm corresponding to aziridine ring. The benzylic carbon attached to nitrogen atom of aziridine ring appeared at 61.1 ppm while, methylene carbon of lactone ring appeared at 69.5 ppm. The aromatic quaternary carbon appeared at 137.0 ppm, while remaining aromatic carbons appeared at 127.7, 127.8, 128.6 ppm. The peak at 172.3 ppm was assigned to  $\gamma$ -lactone carbonyl carbon. The compound **1.195a** also gave satisfactory elemental analysis and the mass spectrum showed peak at  $m/z$  190 ( $M+1$ ).

Other 2,3-aziridino- $\gamma$ -lactones **1.192b-c** and **1.195b-c** were also prepared in very good yields and characterized completely by spectral analysis. All of them gave satisfactory elemental analyses, and the data for these compounds is summarized in the following table (Table 1).

**Table 1:** Synthesis of 2,3-aziridino- $\gamma$ -lactones **1.202a-c** and **1.205a-c**

Sr. No.	Compd. No.	R	Reaction Time (h)	Mp ( $^{\circ}\text{C}$ )	Yield (%) <sup>b</sup>	$[\alpha]_{\text{D}}^{30}$ ( $\text{CHCl}_3$ )
1.	<b>1.192a</b>	Bn	20	Thick oil	86	- 40.0 ( <i>c</i> 1.5)
2.	<b>1.192b</b>	PMP <sup>a</sup>	24	Thick oil	82	+1.0 ( <i>c</i> 1.75)
3.	<b>1.192c</b>	<i>p</i> -tolyl	18	Thick oil	82	+16.0 ( <i>c</i> 0.5)
4.	<b>1.195a</b>	Bn	8	Thick oil	80	-1.6 ( <i>c</i> 0.9)
5.	<b>1.195b</b>	PMP <sup>a</sup>	15	92-94	81	+18.0 ( <i>c</i> 1.0)
6.	<b>1.195c</b>	<i>p</i> -tolyl	17	95-96	83	+60.0 ( <i>c</i> 1.5)

<sup>a</sup>PMP = 4-Methoxyphenyl.

<sup>b</sup>Isolated yields.

## 1.5: Conclusion

In conclusion, we have demonstrated an efficient synthetic method for 2,3-aziridino- $\gamma$ -lactones using azetidin-2-ones as synthons. Simultaneous nucleophilic

azetidinone ring opening followed by the formation of aziridine ring is the key step in this synthesis. Generality of this synthetic procedure was established by preparing various 2,3-aziridino- $\gamma$ -lactones **1.192a-c** and **1.195a-c**.

## 1.6: Experimental

### General procedure for the preparation of azetidin-2-one **1.188a-c**

#### Preparation of Schiff base **1.187a-c**

NaIO<sub>4</sub> (2.14 g, 10 mmol) was dissolved in H<sub>2</sub>O (20 mL) and cooled at 0 °C. To the above cooled solution, 1,2,5,6-Di-*O*-isopropylidene-D-manitol **1.185** (2.62 g, 10 mmol) was added in portion with stirring. After completion of addition, the reaction mixture was stirred at room temperature for 30 min and was filtered to an aqueous solution of D-glyceraldehyde acetonide **1.149**. To the cooled (0-5 °C) filtrate, was added a solution of amine (20 mmol) in 1,2-dichloroethane (20 mL). The reaction mixture was stirred at room temperature for 2 h after which the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloroethane (2 x 20mL). The combined organic layer containing the Schiff base **1.187** was dried over anhydrous sodium sulphate, evaporation of the organic solvent provided the Schiff's base that was used as such for the next reaction.

#### Preparation of azetidin-2-ones **1.188a-c** from Schiff base **1.187a-c**

To the dichloromethane solution of Schiff base **1.187** and triethyl amine (6.7 mL, 48 mmol) was added drop wise a solution of benzyloxyacetyl chloride (24 mmol) at 0 °C. The reaction mixture was allowed to come at room temperature and stirred for additional 12-15 h. The reaction mixture was diluted with dichloromethane (30 mL) and organic layer was washed with water (3 x 15 mL), saturated sodium bicarbonate solution (3 x 15 mL), saturated brine solution (15 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography to get pure azetidin-2-ones **1.188a-c**.

#### **(3*R*,4*S*)-1-Benzy-3-benzyloxy-4-[(*S*)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (1.188a):**

Following the general procedure, imine **1.187a** prepared from D-glyceraldehyde acetonide **1.49** and benzyl amine ( 2.18 mL, 20 mmol) was treated with triethyl amine (6.7 mL, 48 mmol) and benzyloxyacetyl chloride (3.8 mL, 24 mmol) at 0 °C to get azetidin-2-one **1.188a** as a white solid (4.77 g, 65%).

MP : 69-70 °C.  
[α]<sup>30</sup><sub>D</sub> : +30 (c 1.0, CHCl<sub>3</sub>)

**IR (CHCl<sub>3</sub>)** : 1742 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 1.34 (s, 3H), 1.35 (s, 3H), 3.53-3.62 (m, 2H), 4.09-3.36 (m, 3H), 4.58 (d, *J* = 5.1 Hz, 1H), 4.65(d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 14.7Hz, 1H), 4.93 (d, *J* = 11.9 Hz, 1H), 7.27-7.36 (m, 10 H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 25.1, 26.7, 44.9, 59.3, 66.8, 72.8, 77.0, 80.4, 109.5, 127.6, 127.7, 128.0, 128.5, 128.7, 135.7, 136.9, 167.2.  
**(50.32MHz)**  
**MS (m/z)** : 368 (M+1).  
**Analysis** : Calculated: C, 71.91; H, 6.86; N, 3.81.  
**(C<sub>22</sub>H<sub>25</sub>NO<sub>4</sub>)** Observed: C, 71.89; H, 6.83; N, 3.62.

**(3R,4S)-1-(4-methoxyphenyl)-3-benzyloxy-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (1.188b):**

Following the general procedure, imine **1.187b** prepared from D-glyceraldehyde acetonide **1.49** and *p*-anisidine (2.46 g, 20 mmol) was treated with triethyl amine (6.7 mL, 48 mmol) and benzyloxyacetyl chloride (3.8 mL, 24 mmol) at 0 °C to get azetidin-2-one **1.188b** as a white solid (4.70 g, 62%).

**MP** : 117-118 °C {lit<sup>35a,c</sup> 120 °C}.  
**[α]<sup>30D</sup>** : +108.2 (*c* 0.5, MeOH) {lit<sup>35a</sup> +109.2, *c* 0.5, MeOH}.  
**IR (CHCl<sub>3</sub>)** : 1735 cm<sup>-1</sup>  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 1.35 (s, 3H), 1.54 (s, 3H), 3.73-3.89 (m, 1H), 3.75 (s, 3H), 4.10-3.50 (m, 3H), 4.70-4.80 (m, 2H), 5.0 (d, *J* = 11.8 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 1H), 7.30-7.45 (m, 5 H), 7.70 (d, *J* = 9.2 Hz, 2H).

**(3R,4S)-3-Benzyloxy-1-*p*-tolyl-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (1.188c):**

Following the general procedure, imine **1.187c** prepared from D-glyceraldehyde acetonide **1.49** and *p*-toluidine (2.14 g, 20 mmol) was treated with triethyl amine (6.7 mL, 48 mmol) and benzyloxyacetyl chloride (3.8 mL, 24 mmol) at 0 °C to get azetidin-2-one **1.188c** as a white solid (4.77 g, 65%).

**MP** : 111-113 °C {lit<sup>35a</sup> 110 °C}.

	: +140 ( <i>c</i> 1.0, CHCl <sub>3</sub> )
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (nujol)</b>	: 1751 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR</b> (CDCl <sub>3</sub> ) (200 MHz)	: δ <sub>H</sub> 1.33 (s, 3H), 1.54 (s, 3H), 2.33 (s, 3H), 3.75 (dd, <i>J</i> = 6.5, 8.8 Hz, 1H), 4.20-4.35 (m, 2H), 4.40-4.45 (m, 1H), 4.71 (d, <i>J</i> = 5.1 Hz, 1H), 4.75 (d, <i>J</i> = 11.5 Hz, 1H), 5.00 (d, <i>J</i> = 11.5 Hz, 1H), 7.12 (d, <i>J</i> = 8.5 Hz, 2H), 7.30-7.40 (m, 5 H), 7.62 (d, <i>J</i> = 8.5 Hz, 2H).
<b><sup>13</sup>C NMR</b> (CDCl <sub>3</sub> ) (50.32MHz)	: δ <sub>C</sub> 20.7, 24.9, 26.5, 61.5, 66.9, 73.1, 76.9, 79.6, 109.6, 118.0, 127.8, 128.0, 128.4, 129.1, 133.9, 135.2, 136.6, 165.1.
<b>MS (m/z)</b>	: 367 (M+1).
<b>Analysis</b> (C <sub>22</sub> H <sub>25</sub> NO <sub>4</sub> )	: Calculated: C, 71.91; H, 6.86; N, 3.81. Observed: C, 71.64; H, 7.04; N, 3.59.

#### General procedure for the preparation of 3-hydroxy azetidin-2-one **1.189a-c**

A mixture of compound **1.188a-c** (20 mmol), ammonium formate (60 mmol) and 10% Pd/C (10 mol %) in methanol (60 mL) was refluxed for 0.5 h. The reaction mixture was filtered through a small pad of celite and washed with ethyl acetate (2 x 30 mL). The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (150 mL), washed with water (2 x 15 mL) and brine (25 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> to get crude product, which was purified by flash column chromatography using acetone/petroleum ether as an eluent to afford **1.189a-c**.

#### (3*R*,4*S*)-1-Benzyl-3-hydroxy-4-[(*S*)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (**1.189a**):

Following general procedure, the mixture of **1.188a** (7.34 g, 20 mmol), ammonium formate (3.78 g, 60 mmol) and 10% Pd/C (0.73 g) in methanol (60 mL) gave crude product, which upon purification by flash column chromatography using acetone/pet ether (30:70) gave pure **1.189a** (4.99 g, 90%) as a white solid.

	: 159-160 °C.
<b>MP</b>	
	: -57 ( <i>c</i> 1.0, CHCl <sub>3</sub> )
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (CHCl<sub>3</sub>)</b>	: 1731, 3307 cm <sup>-1</sup> .

**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  1.25 (s, 3H), 1.31 (s, 3H), 3.42 (dd,  $J = 5.2, 2.5$  Hz, 1H),  
**(CDCl<sub>3</sub>)** 3.62 (dd,  $J = 5.2, 9.0$  Hz, 1H), 4.04-4.08 (m, 3H), 4.12-4.30  
**(200 MHz)** (m, 1H), 4.71 (d,  $J = 14.3$  Hz, 1H), 4.75 (d,  $J = 14.3$  Hz, 1H),  
 7.16-7.27 (m, 5H).

**<sup>13</sup>C NMR** :  $\delta_{\text{C}}$  24.9, 26.5, 45.0, 60.5, 66.5, 75.1, 76.5, 109.5, 127.7,  
**(CDCl<sub>3</sub>)** 128.5, 135.2, 170.1.  
**(50.32MHz)**

**MS (m/z)** : 278 (M+1).

**Analysis** : Calculated: C, 64.95; H, 6.91; N, 5.05.  
**(C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>)** Observed: C, 64.83; H, 6.71; N, 4.98.

**(3R,4S)-1-(4-methoxyphenyl)-3-hydroxy-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (1.189b):**

Following general procedure, the mixture of **1.188b** (7.66 g, 20 mmol), ammonium formate (3.78 g, 60 mmol) and 10% Pd/C (0.76 g) in methanol (60 mL) gave crude product, which upon purification by flash column chromatography using acetone/pet ether (25:75) gave pure **1.189b** (5.30 g, 92%) as a white solid.

**MP** : 208-209 °C.  
 : -24.3 (c 0.7, MeOH)

**[ $\alpha$ ]<sup>30</sup><sub>D</sub>**  
**IR (Nujol)** : 1758 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  1.25 (s, 3H), 1.43 (s, 3H), 3.70 (s, 3H), 3.55-3.76 (m, 2H),  
**(DMSO-*d*<sub>6</sub>)** 4.03 (dd,  $J = 5.3, 8.4$  Hz, 1H), 4.18-4.38 (m, 2H), 4.83 (d,  $J =$   
**(200 MHz)** 5.3 Hz, 1H), 6.76 (d,  $J = 9.7$  Hz, 2H), 7.57 (d,  $J = 9.7$  Hz,  
 2H).

**<sup>13</sup>C NMR** :  $\delta_{\text{C}}$  25.2, 26.6, 55.4, 62.6, 66.5, 74.7, 77.5, 109.0, 114.1,  
**(DMSO-*d*<sub>6</sub>)** 119.1, 131.7, 155.9, 167.0.  
**(50.32MHz)**

**MS (m/z)** : 294 (M+1).

**Analysis** : Calculated: C, 61.41; H, 6.53; N, 4.88.  
**(C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>)** Observed: C, 61.30; H, 6.41; N, 4.62.

**(3R,4S)-3-Hydroxy-1-p-tolyl-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetid-2-one (1.189c):**

Following general procedure, the mixture of **1.188c** (7.34 g, 20 mmol), ammonium formate (3.78 g, 60 mmol) and 10% Pd/C (0.73 g) in methanol (60 mL) gave crude product, which upon purification by flash column chromatography using acetone/pet ether (25:75) gave pure **1.189c** (5.04 g, 91%) as a white solid.

<b>MP</b>	: 209-210 °C.
<b>[<math>\alpha</math>]<sup>30</sup><sub>D</sub></b>	: +26.5 ( <i>c</i> 1.0, MeOH)
<b>IR (Nujol)</b>	: 1741, 3407 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (DMSO-<i>d</i><sub>6</sub>) (200 MHz)</b>	: $\delta$ <sub>H</sub> 1.52 (s, 3H), 1.70 (s, 3H), 2.36 (s, 3H), 4.03 (dd, <i>J</i> = 5.3, 8.6 Hz, 1H), 4.35 (dd, <i>J</i> = 5.3, 8.6 Hz, 1H), 4.46-4.65 (m, 2H), 5.12 (d, <i>J</i> = 5.3 Hz, 1H), 7.31 (d, <i>J</i> = 8.2 Hz, 2H), 7.79 (d, <i>J</i> = 8.2 Hz, 2H).
<b><sup>13</sup>C NMR (DMSO-<i>d</i><sub>6</sub>) (50.32MHz)</b>	: $\delta$ <sub>C</sub> 19.0, 23.4, 24.9, 60.9, 64.9, 72.9, 75.7, 107.3, 116.0, 127.4, 131.4, 134.0, 165.5.
<b>MS (m/z)</b>	: 278 (M+1).
<b>Analysis</b>	: Calculated: C, 64.95; H, 6.91; N, 5.05.
(C <sub>15</sub> H <sub>19</sub> NO <sub>4</sub> )	Observed: C, 64.86; H, 6.61; N, 4.95.

**General procedure for the preparation of 3-mesyloxy azetid-2-one 1.190a-c**

To a solution of 3-hydroxy azetid-2-one **1.189a-c** (5 mmol), triethyl amine (1.0 mL, 7.5 mmol), in dry DCM (15 mL), was added slowly methane sulphonyl chloride (0.5 mL, 6.5 mmol) at 0 °C. The reaction mixture was allowed to come at room temperature and stirred it for 2 h. After the reaction was over (TLC), the reaction mixture was washed with saturated sodium bicarbonate solution (15 mL) and brine (10 mL). The organic layer was separated and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished crude mesylated azetid-2-one, which on further purification by column chromatography using acetone/petroleum ether as an eluent to afford **1.190a-c**.

**(3R,4S)-1-Benzy-3-mesyloxy-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetid-2-one (1.190a):**

Following general procedure, reaction of 3-hydroxy azetid-2-one **1.189a** (1.39 g, 5 mmol), triethyl amine (1.0 mL, 7.5 mmol), and methane sulphonyl chloride (0.5 mL, 6.5 mmol) gave crude mesylated product, which upon purification by flash column chromatography using acetone/pet ether (15:85) gave pure **1.190a** (1.62 g, 91%) as a white solid.

<b>MP</b>	: 98-99 °C.
<b>[<math>\alpha</math>]<sup>30</sup><sub>D</sub></b>	: -17 (c 1.0, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 1770 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>)</b>	: $\delta$ <sub>H</sub> 1.28 (s, 3H), 1.31 (s, 3H), 3.19 (s, 3H), 3.58-3.67 (m, 2H), 4.08-4.31 (m, 3H), 4.78 (d, <i>J</i> = 14.3 Hz, 1H), 5.39 (d, <i>J</i> = 5.2 Hz, 1H), 7.20-7.26 (m, 5H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>)</b>	: $\delta$ <sub>C</sub> 24.9, 26.5, 39.1, 45.6, 58.7, 66.3, 76.1, 78.4, 110.1, 128.0, 128.6, 134.7, 162.7.
<b>MS (m/z)</b>	: 356 (M+1).
<b>Analysis</b>	: Calculated: C, 54.07; H, 5.96; N, 3.94; S, 9.00.
(C <sub>16</sub> H <sub>21</sub> NO <sub>6</sub> S)	Observed: C, 54.00; H, 5.66; N, 3.78; S, 8.90.

**(3R,4S)-1-(4-Methoxyphenyl)-3-mesyloxy-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetid-2-one (1.190b):**

Following general procedure, reaction of 3-hydroxy azetid-2-one **1.189b** (1.47 g, 5 mmol), triethyl amine (1.0 mL, 7.5 mmol), and methane sulphonyl chloride (0.5 mL, 6.5 mmol) gave crude mesylated product, which upon purification by flash column chromatography using acetone/pet ether (20:80) gave pure **1.190b** (1.62 g, 88%) as a white solid.

<b>MP</b>	: 132 °C {lit <sup>35b</sup> 133 °C}.
<b>[<math>\alpha</math>]<sup>30</sup><sub>D</sub></b>	: -96.3 (c 0.3, MeOH) {lit <sup>35b</sup> - 97.4 (c 0.3, MeOH)}.
<b>IR (nujol)</b>	: 1740 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>)</b>	: $\delta$ <sub>H</sub> 1.26 (s, 3H), 1.45 (s, 3H), 3.22 (s, 3H), 3.71 (s, 3H), 3.70-3.73 (m, 1H), 4.20-4.56 (m, 3H), 5.55 (d, <i>J</i> = 5.1 Hz, 1H),



(200 MHz) 6.77- 7.57 (m, 4H).  
<sup>13</sup>C NMR : δ<sub>C</sub> 25.1, 26.4, 38.43, 55.5, 60.61, 66.1, 75.9, 77.6, 109.7,  
(DMSO-d<sub>6</sub>) 114.2, 119.8, 130.6, 156.5, 161.0.  
(50.32MHz)  
MS (m/z) : 372 (M+1).  
Analysis : Calculated: C, 51.75; H, 5.66; N, 3.77; S, 8.63.  
(C<sub>16</sub>H<sub>21</sub>NO<sub>7</sub>S) Observed: C, 51.47; H, 5.36; N, 3.59; S, 8.69.

**(3R,4S)-3-Mesyloxy-1-p-tolyl-4-[(S)-2,2-di-methyl-1,3-dioxolan-4-yl]azetidin-2-one (1.190c):**

Following general procedure, reaction of 3-hydroxy azetidin-2-one **1.189c** (1.39 g, 5 mmol), triethyl amine (1.0 mL, 7.5 mmol), and methane sulphonyl chloride (0.5 mL, 6.5 mmol) gave crude mesylated product, which upon purification by flash column chromatography using acetone/pet ether (15:85) gave pure **1.190c** (1.62 g, 91%) as a white solid.

MP : 149-150 °C.  
[α]<sub>D</sub><sup>30</sup> : + 35.5 (c 1, CHCl<sub>3</sub>).  
IR (CHCl<sub>3</sub>) : 1760 cm<sup>-1</sup>.  
<sup>1</sup>H NMR : δ<sub>H</sub> 1.35 (s, 3H), 1.55 (s, 3H), 2.34 (s, 3H), 3.31 (s, 3H), 3.82-  
(CDCl<sub>3</sub>) 3.88 (m, 1H), 4.30-4.44 (m, 3H), 5.65 (d, *J* = 5.3 Hz, 1H),  
(200 MHz) 7.17 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H).  
<sup>13</sup>C NMR : δ<sub>C</sub> 20.8, 24.7, 26.4, 39.2, 61.3, 66.5, 76.2, 77.7, 110.2, 118.3,  
(CDCl<sub>3</sub>) 129.3, 134.4, 135.0, 160.6.  
(75.48MHz)  
MS (m/z) : 356 (M+1).  
Analysis : Calculated: C, 54.07; H, 5.96; N, 3.94; S, 9.00.  
(C<sub>16</sub>H<sub>21</sub>NO<sub>6</sub>S) Observed: C, 54.01; H, 5.68; N, 3.81; S, 8.89.

**General procedure for the preparation of dihydroxy azetidin-2-one 1.191a-c**

A mixture of azetidin-2-one **1.190a-c** (10 mmol) and *p*-toluenesulphonic acid monohydrate (0.57 g, 3.0 mmol) in THF (40 mL), and water (15 mL) was refluxed for 12-24 h. After completion of reaction (TLC), the reaction mixture was neutralized with NaHCO<sub>3</sub> and solvent was removed under reduced pressure. The residue was

dissolved in ethyl acetate (25 mL) and organic layer was washed with brine solution (15 mL), dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude diol, which on further purification by column chromatography using acetone/petroleum ether as an eluent to afford **1.191a-c**.

**(3R,4S)-1-Benzy-3-mesyloxy-4-[(S)-1,2-dihydroxy-ethyl]azetidin-2-one (1.191a):**

Following the general procedure, a mixture of azetidin-2-one **1.190a** (3.55 g, 10 mmol) and PTSA monohydrate (0.57 g, 3.0 mmol) in THF (40 mL), and water (15 mL) was refluxed for 14 h gave crude dihydroxy azetidin-2-one, which upon purification by flash column chromatography using acetone/pet ether (30:70) gave pure **1.191a** (2.99 g, 95%) as a white solid.

<b>MP</b>	: 94-95 °C.
<b>[<math>\alpha</math>]<sup>30</sup><sub>D</sub></b>	: -4.0 (c 1, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 3326, 1733 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (DMSO-<i>d</i><sub>6</sub>) (200 MHz)</b>	: $\delta$ <sub>H</sub> 3.33 (s, 3H), 3.34 (bs, 1H), 3.37 (bs, 1H), 3.70-3.75 (m, 1H), 3.88 (t, <i>J</i> = 5.5 Hz, 1H), 4.31 (d, <i>J</i> = 15.5 Hz, 1H), 4.65-4.77 (m, 2H), 5.16 (d, <i>J</i> = 5.5 Hz, 1H), 5.71 (d, <i>J</i> = 5.5 Hz, 1H), 7.30-7.36 (m, 5H).
<b><sup>13</sup>C NMR (DMSO-<i>d</i><sub>6</sub>) (50.32 MHz)</b>	: $\delta$ <sub>C</sub> 38.3, 45.4, 57.5, 63.5, 70.2, 78.3, 127.6, 128, 128.8, 136.1, 163.9.
<b>MS (m/z)</b>	: 316 (M+1).
<b>Analysis</b>	: Calculated: C, 49.51; H, 5.43; N, 4.44; S, 10.17.
(C <sub>13</sub> H <sub>17</sub> NO <sub>6</sub> S)	Observed: C, 49.29; H, 5.23; N, 4.48; S, 10.01.

**(3R,4S)-1-(4-Methoxyphenyl)-3-mesyloxy-4-[(S)-1,2-dihydroxy-ethyl]azetidin-2-one (1.191b):**

Following the general procedure, a mixture of azetidin-2-one **1.190a** (3.71 g, 10 mmol) and PTSA monohydrate (0.57 g, 3.0 mmol) in THF (40 mL), and water (15 mL) was refluxed for 24 h gave crude dihydroxy azetidin-2-one, which upon purification by flash column chromatography using acetone/pet ether (35:65) gave pure **1.191b** (3.17 g, 96%) as a white solid.

<b>MP</b>	: 133-134 °C.
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$[\alpha]^{30}_{\text{D}}$  : +25.45 (*c* 1.1, MeOH).  
**IR (nujol)** : 3363, 1739  $\text{cm}^{-1}$ .  
 $^1\text{H NMR}$  :  $\delta_{\text{H}}$  3.34 (s, 3H), 3.34 (bs, 2H), 3.73 (s, 3H), 3.80-3.87 (m, (DMSO- $d_6$ ) 1H), 4.64 (t,  $J = 5.0$  Hz, 1H), 4.90 (t,  $J = 5.5$  Hz, 1H), 5.20 (200 MHz) (d,  $J = 9.0$  Hz, 1H), 5.81 (d,  $J = 5.5$  Hz, 1H), 6.93 (d,  $J = 9.0$  Hz, 2H), 7.43 (d,  $J = 9.0$  Hz, 2H).  
 $^{13}\text{C NMR}$  :  $\delta_{\text{C}}$  38.3, 55.5, 57.9, 63.3, 69.2, 76.9, 114.2, 119.7, 131.4, (DMSO- $d_6$ ) 156.4, 161.8.  
(50.32 MHz)  
**MS (m/z)** : 332 (M+1).  
**Analysis** : Calculated: C, 47.12; H, 5.17; N, 4.23; S, 9.68.  
(C<sub>13</sub>H<sub>17</sub>NO<sub>7</sub>S) Observed: C, 47.01; H, 5.00; N, 4.18; S, 9.39.

**(3R,4S)-3-Mesyloxy-1-*p*-tolyl -4-[(S)-1,2-dihydroxy-ethyl]azetidin-2-one (1.191c):**

Following the general procedure, a mixture of azetidin-2-one **1.190c** (3.55 g, 10 mmol) and PTSA monohydrate (0.57 g, 3.0 mmol) in THF (40 mL), and water (15 mL) was refluxed for 18 h gave crude dihydroxy azetidin-2-one, which upon purification by flash column chromatography using acetone/pet ether (25:75) gave pure **1.191c** (3.02 g, 96%) as a white solid.

**MP** : 132-133 °C.  
 $[\alpha]^{30}_{\text{D}}$  : +28 (*c* 1, MeOH).  
**IR (CHCl<sub>3</sub>)** : 3328, 1747  $\text{cm}^{-1}$ .  
 $^1\text{H NMR}$  :  $\delta_{\text{H}}$  2.24 (s, 3H), 3.26 (s, 3H), 3.40-3.58 (m, 2H), 3.86-3.94 (DMSO- $d_6$ ) (m, 3H), 4.63 (t,  $J = 5.3$  Hz, 1H), 5.65 (d,  $J = 5.3$  Hz, 1H), (200 MHz) 7.04 (d,  $J = 8.4$  Hz, 2H), 7.39 (d,  $J = 8.4$  Hz, 2H).  
 $^{13}\text{C NMR}$  :  $\delta_{\text{C}}$  20.8, 38.4, 57.7, 63.3, 69.2, 76.8, 118.2, 129.5, 133.9, (DMSO- $d_6$ ) 135.7, 162.1.  
(50.32 MHz)  
**MS (m/z)** : 316 (M+1).  
**Analysis** : Calculated: C, 49.51; H, 5.43; N, 4.44; S, 10.17.  
(C<sub>13</sub>H<sub>17</sub>NO<sub>6</sub>S) Observed: C, 49.29; H, 5.23; N, 4.48; S, 10.01.

**A typical procedure for the synthesis of (1*S*,4*S*,5*R*)-6-Benzyl-4-hydroxymethyl-3-oxa-6-aza-bicyclo [3.1.0] hexan-2-one (1.192a):**

Dihydroxy-azetidino-2-one **1.191a** (0.5 g, 1.58 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the reaction mixture was refluxed for 20 h. After the reaction was over (TLC) methanol was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. It was then extracted with ethyl acetate (3 x 20 mL) and the combined organic extract was washed with saturated brine solution (10 mL). It was then dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get thick oil, which was quickly purified by flash column chromatography using acetone/petroleum ether (20:80) as an eluent to furnish **1.192a** (0.30 g, 86%) as a thick oil.

	: -40 ( <i>c</i> 1.5, CHCl <sub>3</sub> ).
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (CHCl<sub>3</sub>)</b>	: 3417, 1780 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)</b>	: δ <sub>H</sub> 2.26 (bs, 1H), 2.80 (d, <i>J</i> = 4.5 Hz, 1H), 3.14 (dd, <i>J</i> = 3.1 & 4.5 Hz, 1H), 3.35 (d, <i>J</i> = 13.0 Hz, 1H), 3.82 (d, <i>J</i> = 13.0 Hz, 1H), 3.78-3.94 (m, 2H), 4.46-4.53 (m, 1H), 7.34-7.38 (m, 5H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)</b>	: δ <sub>C</sub> 40.0, 42.8, 60.8, 61.6, 79.3, 127.7, 127.8, 128.6, 136.8, 171.8.
<b>MS (m/z)</b>	: 220 (M+1).
<b>Analysis</b>	: Calculated: C, 65.73; H, 5.98; N, 6.40.
(C <sub>12</sub> H <sub>13</sub> NO <sub>3</sub> )	Observed: C, 65.50; H, 6.01; N, 6.24.

**(1*S*,4*S*,5*R*)-4-Hydroxymethyl-6-(4-methoxyphenyl)-3-oxa-6-aza-bicyclo [3.1.0] hexan-2-one (1.192b):**

Following typical procedure, dihydroxy-azetidino-2-one **1.191b** (0.8 g, 2.41 mmol) was dissolved in methanolic HCl (20%, 15 mL) and the reaction mixture was refluxed for 24 h to get crude compound, which was purified by flash column chromatography using acetone/ pet ether (20:80) as an eluent furnished pure aziridino-γ-lactone **1.192a** (0.49 g, 86%) as a thick oil.

	: +1.0 ( <i>c</i> 1.7, CHCl <sub>3</sub> ).
<b>[α]<sup>30</sup><sub>D</sub></b>	

**IR (CHCl<sub>3</sub>)** : 3442, 1789 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 3.42 (bs, 1H), 3.76 (s, 3H), 3.92-4.11 (m, 2H), 4.50 (merged dd, 1H), 4.67 (d, *J* = 7.9 Hz, 1H), 4.81-4.86 (m, 1H), 6.68 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 55.7, 60.3, 61.7, 80.2, 82.0, 115.0, 114.0, 139.4, 153.1, 171.9.  
**(50.32 MHz)**  
**MS (m/z)** : 236 (M+1).  
**Analysis** : Calculated: C, 61.26; H, 5.58; N, 5.96.  
**(C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub>)** Observed: C, 61.06; H, 5.35; N, 5.78.

**(1*S*,4*S*,5*R*)-4-hydroxymethyl-6-*p*-tolyl-3-oxa-6-aza-bicyclo [3.1.0] hexan-2-one (1.192c):**

Following typical procedure, dihydroxy-azetidin-2-one **1.191c** (0.6 g, 1.89 mmol) was dissolved in methanolic HCl (20%, 15 mL) and the reaction mixture was refluxed for 18 h to get crude compound, which was purified by flash column chromatography using acetone/ pet ether (20:80) as an eluent furnished pure aziridino-γ-lactone **1.192c** (0.33 g, 82%) as a thick oil.

**[α]<sub>D</sub><sup>30</sup>** : +32 (*c* 1.5, CHCl<sub>3</sub>).  
**IR (CHCl<sub>3</sub>)** : 3384, 1791 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 2.27 (s, 3H), 3.1 (bs, 1H), 3.95 (dd, *J* = 12.8, 1.5 Hz, 1H), 4.10 (dd, *J* = 12.8, 1.5 Hz, 1H), 4.55 (dd, *J* = 8.0, 7.4 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.85 (d, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 20.3, 55.6, 60.6, 61.4, 79.9, 113.7, 128.6, 130.1, 143.3, 171.5.  
**(50.32 MHz)**  
**MS (m/z)** : 220 (M+1).  
**Analysis** : Calculated: C, 65.73; H, 5.98; N, 6.40.  
**(C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>)** Observed: C, 65.54; H, 6.00; N, 6.23.

### General procedure for preparation of 4-formyl azetidin-2-one **1.193a-c**.

To a vigorously stirred suspension of silica gel-supported NaIO<sub>4</sub> reagent (10 g) in dichloro methane (25 mL) was added solution of dihydroxy azetidin-2-one **1.191a-c** (5 mmol) in dichloro methane (10 mL). The reaction was monitored by TLC until disappearance of starting material (3.5 h). The mixture was filtered through a sintered glass funnel and silica gel was washed thoroughly with dichloromethane (3 x 20 mL). Removal of solvent afforded the 4-formyl azetidin-2-one which was pure enough for most purposes.

#### (3*R*,4*R*)-1-Benzyl-3-mesyloxy-4-formyl azetidin-2-one (**193a**):

Following general procedure, the oxidation of dihydroxy azetidin-2-one **1.191a** (3.15 g, 10 mmol), using silica gel supported NaIO<sub>4</sub> reagent (10 g) afforded 4-formyl azetidin-2-one **1.193a** (2.28 g, 80%) as a thick oil.

	: +18 ( <i>c</i> 1.0, CHCl <sub>3</sub> ).
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (CHCl<sub>3</sub>)</b>	: 1772, 1733 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>)</b>	: δ <sub>H</sub> 3.14 (s, 3H), 4.20 (dd, <i>J</i> = 1.3, 5.4 Hz, 1H), 4.31 (d, <i>J</i> = 14.7, 1H), 4.70 (d, <i>J</i> = 14.7 Hz, 1H), 5.66 (d, <i>J</i> = 5.3 Hz, 1H), 7.12-7.31 (m, 5H), 9.47 (d, <i>J</i> = 1.3 Hz, 1H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>)</b>	: δ <sub>C</sub> 38.8, 46.1, 61.67, 78.43, 128.4, 128.8, 129.1, 133.4, 161.6, 195.6.
(50.32 MHz)	
<b>MS (m/z)</b>	: 284 (M+1).
<b>Analysis</b>	: Calculated: C, 50.87; H, 4.63; N, 4.94; S, 11.30.
C <sub>12</sub> H <sub>13</sub> NO <sub>5</sub> S	Observed: C, 50.69; H, 4.56; N, 4.87; S, 11.19.

#### (3*R*,4*R*)-1-(4-Methoxyphenyl)-3-mesyloxy-4-formyl azetidin-2-one (**193b**)

Following general procedure, the oxidation of dihydroxy azetidin-2-one **1.191b** (3.31 g, 10 mmol), using silica gel supported NaIO<sub>4</sub> reagent (10 g) afforded 4-formyl azetidin-2-one **1.193b** (2.54 g, 85%) as a white solid.

<b>MP</b>	: 140-142 °C.
<b>[α]<sup>30</sup><sub>D</sub></b>	: +132 ( <i>c</i> 1, CHCl <sub>3</sub> ).
<b>IR (nujol)</b>	: 1762, 1720cm <sup>-1</sup> .
<b><sup>1</sup>H NMR</b>	: δ <sub>H</sub> 3.26 (s, 3H), 3.80 (s, 3H), 4.84 (dd, <i>J</i> = 2.4, 5.4 Hz, 1H),

(CDCl<sub>3</sub>) 5.89 (d, *J* = 5.4 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 9.81 (d, *J* = 2.4 Hz, 1H).  
 (200 MHz)  
<sup>13</sup>C NMR : δ<sub>C</sub> 55.4, 62.5, 78.2, 88.4, 114.5, 118.6, 119.7, 130.1, 161.6,  
 (DMSO-*d*<sub>6</sub>) 196.7.  
 (50.32 MHz)  
 MS (m/z) : 300 (M+1).  
 Analysis : Calculated: C, 48.16; H, 4.38; N, 4.68; S, 10.71.  
 (C<sub>12</sub>H<sub>13</sub>NO<sub>6</sub>S) Observed: C, 48.00; H, 4.09; N, 4.58; S, 10.62.

**(3*R*,4*R*)-1-(4-Methoxyphenyl)-3-mesyloxy-4-formyl azetidin-2-one (193c)**

Following general procedure, the oxidation of dihydroxy azetidin-2-one **1.191c** (3.15 g, 10 mmol), using silica gel supported NaIO<sub>4</sub> reagent (10 g) afforded 4-formyl azetidin-2-one **1.193c** (2.54 g, 90%) as a white solid.

MP : 171-172 °C.  
 [α]<sub>D</sub><sup>30</sup> : +144 (*c* 0.5, CH<sub>3</sub>OH).  
 IR (CHCl<sub>3</sub>) : 1770, 1730cm<sup>-1</sup>.  
<sup>1</sup>H NMR : δ<sub>H</sub> 2.34 (s, 3H), 3.26 (s, 3H), 4.85 (dd, *J* = 2.4, 5.5 Hz, 1H),  
 (CDCl<sub>3</sub>) 5.88 (d, *J* = 5.5 Hz, 1H), 7.19-7.27 (m, 4H), 9.81 (d, *J* = 2.4  
 (200 MHz) Hz, 1H).  
<sup>13</sup>C NMR : δ<sub>C</sub> 20.5, 38.2, 62.3, 78.1, 118.2, 129.0, 129.6, 134.3, 161.9,  
 (DMSO-*d*<sub>6</sub>) 196.6.  
 (50.32 MHz)  
 MS (m/z) : 284 (M+1).  
 Analysis : Calculated: C, 50.87; H, 4.63; N, 4.94; S, 11.32.  
 (C<sub>12</sub>H<sub>13</sub>NO<sub>5</sub>S) Observed: C, 50.68; H, 4.44; N, 4.67; S, 11.18.

**General procedure for preparation of 4-hydroxymethyl azetidin-2-one from 4-formyl azetidin-2-one 1.194a-c:**

To a cooled solution of 3-mesyloxy-4-formyl azetidin-2-one **1.193a-c** (5.0 mmol) in methanol (30 mL) at 0 °C was added NaBH<sub>4</sub> (10 mmol) portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 3 h. After completion of reaction (TLC) water (10 mL) was added carefully and the reaction mixture was further stirred for 1 h. Methanol was removed under

reduced pressure and the residue was extracted with ethyl acetate (2 x 40 mL). The combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography using acetone/petroleum ether to afford alcohol **1.194a-c**.

**(3R,4S)-1-Benzyl-4-hydroxymethyl-3-mesyloxy azetidin-2-one (1.194a):**

Following general procedure, the reaction of 1-benzyl-3-mesyloxy-4-formyl azetidin-2-one (**1.193a**) (1.43 g, 5.0 mmol) in methanol (30 mL) and NaBH<sub>4</sub> (0.370 g, 10 mmol) gave crude product, which was purified by flash column chromatography using acetone/pet ether (20:80) afforded pure **1.194a** (1.18 g, 82%) as a white solid.

	: 79-80 °C.
<b>MP</b>	
	: +7 (c 1.0, CHCl <sub>3</sub> ).
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (CHCl<sub>3</sub>)</b>	: 3458, 1751 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)</b>	: δ <sub>H</sub> 1.90 (s, 1H), 3.28 (s, 3H), 3.81-3.91 (m, 3H), 4.35 (d, <i>J</i> = 14.9 Hz, 1H), 4.64 (d, <i>J</i> = 14.9 Hz, 1H), 5.58 (d, <i>J</i> = 4.4 Hz, 1H), 7.27-7.40 (m, 5H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)</b>	: δ <sub>C</sub> 38.9, 45.4, 57.9, 59.6, 78.5, 128.2, 128.3, 129, 134.6, 162.9.
<b>MS (m/z)</b>	: 286 (M+1).
<b>Analysis</b>	: Calculated: C, 50.51; H, 5.30; N, 4.92; S, 11.22.
(C <sub>12</sub> H <sub>15</sub> NO <sub>5</sub> S)	Observed: C, 50.43; H, 5.17; N, 4.77; S, 11.04.

**(3R,4S)-1-(4-Methoxyphenyl)-4-hydroxymethyl-3-mesyloxyazetidin-2-one (1.194b):**

Following general procedure, the reaction of 1-(4-methoxyphenyl)-3-mesyloxy-4-formyl azetidin-2-one (**1.193b**) (1.50 g, 5.0 mmol) in methanol (30 mL) and NaBH<sub>4</sub> (0.370 g, 10 mmol) gave crude product, which was purified by flash column chromatography using acetone/pet ether (25:75) afforded pure **1.194a** (1.26 g, 84%) as a white solid.

	: 132-133 °C.
<b>MP</b>	
	: +23.8 (c 1.2, MeOH).
<b>[α]<sup>30</sup><sub>D</sub></b>	



**IR (CHCl<sub>3</sub>)** : 3387, 1739 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)** : δ<sub>H</sub> 3.37 (s, 3H), 3.78 (s, 3H), 3.70-3.79 (m, 1H), 3.85-3.93 (m, 1H), 4.49 (dd, *J* = 5.9, 9.7 Hz, 1H), 5.14 (t, *J* = 5.3 Hz, 1H), 5.84 (d, *J* = 5.3 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 38.4, 55.1, 58.3, 58.6, 77.6, 114.0, 118.8, 130.2, 156.3, 160.1.  
**(50.32 MHz)**  
**MS (m/z)** : 302 (M+1).  
**Analysis** : Calculated: C, 47.83; H, 5.02; N, 4.65; S, 10.62.  
**(C<sub>12</sub>H<sub>15</sub>NO<sub>6</sub>S)** Observed: C, 47.66; H, 4.98; N, 4.56; S, 10.39.

**(3*R*,4*S*)-4-hydroxymethyl-1-(*p*-tolyl)-3-mesyloxy azetidin-2-one (1.194c):**

Following general procedure, the reaction of 3-mesyloxy-1-(*p*-tolyl)-4-formyl azetidin-2-one (**1.193c**) (1.43 g, 5.0 mmol) in methanol (30 mL) and NaBH<sub>4</sub> (0.370 g, 10 mmol) gave crude product, which was purified by flash column chromatography using acetone/pet ether (15:85) afforded pure **1.194a** (1.17 g, 80%) as a white solid.

**MP** : 132-133 °C.  
**[α]<sup>30</sup><sub>D</sub>** : +118 (*c* 1.0, CHCl<sub>3</sub>).  
**IR (CHCl<sub>3</sub>)** : 3450, 1735 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 2.11 (bs, 1H), 2.33 (s, 3H), 3.31 (s, 3H), 4.12 (d, *J* = 4.8 Hz, 2H), 4.50 (dd, *J* = 4.8, 5.4 Hz, 1H), 5.72 (d, *J* = 5.4 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H).  
**<sup>13</sup>C NMR (Acetone-*d*<sub>6</sub>)** : δ<sub>C</sub> 20.4, 38.8, 59.3, 59.5, 78.6, 118.2, 130.2, 134.8, 135.9, 161.6.  
**(50.32 MHz)**  
**MS (m/z)** : 286 (M+1).  
**Analysis** : Calculated: C, 50.51; H, 5.30; N, 4.92; S, 11.22.  
**(C<sub>12</sub>H<sub>15</sub>NO<sub>5</sub>S)** Observed: C, 50.33; H, 5.15; N, 4.68; S, 11.00.

**A typical procedure for the synthesis of (1*S*,5*R*)-6-Benzyl-3-oxa-6-aza-bicyclo[3.1.0] hexan-2-one (1.195a):**

Hydroxy-azetidin-2-one **1.194a** (0.250 g, 0.8 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the reaction mixture was refluxed for 8 h. After the reaction was over (TLC) methanol was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. It was then extracted with ethyl acetate (3 x 20 mL) and the combined organic extract was washed with saturated brine solution (10 mL). It was then dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get thick oil, which was quickly purified by flash column chromatography using acetone/pet ether (12:88) as eluent to furnish **1.195a** (0.13 g, 80%) as a thick oil.

	: -1.6 (c 0.9, CHCl <sub>3</sub> ).
<b>[α]<sup>30</sup><sub>D</sub></b>	
<b>IR (CHCl<sub>3</sub>)</b>	: 1774 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)</b>	: δ <sub>H</sub> 2.72 (d, <i>J</i> = 4.5 Hz, 1H), 2.96 (dd, <i>J</i> = 4.5, 3.1 Hz, 1H), 3.47 (d, <i>J</i> = 13.5 Hz, 1H), 3.74 (d, <i>J</i> = 13.5 Hz, 1H), 4.21 (dd, <i>J</i> = 9.8, 3.1 Hz, 1H), 4.34 (d, <i>J</i> = 9.8 Hz, 1H), 7.30-7.40 (m, 5H).
<b><sup>13</sup>C NMR (CHCl<sub>3</sub>) (50.32 MHz)</b>	: δ <sub>C</sub> 39.7, 42.1, 61.1, 69.5, 127.7, 127.8, 128.6, 137.0, 172.3.
<b>MS (m/z)</b>	: 190 (M+1).
<b>Analysis (C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>)</b>	: Calculated: C, 69.81; H, 5.86; N, 7.40. Observed: C, 69.62; H, 5.43; N, 7.19.

**(1*S*,5*R*)-6-(4-Methoxyphenyl)-3-oxa-6-aza-bicyclo[3.1.0] hexan-2-one (1.195a):**

Following typical procedure, 4-hydroxymethyl azetidin-2-one **1.191b** (0.8 g, 2.6 mmol) was dissolved in methanolic HCl (20%, 15 mL) and the reaction mixture was refluxed for 15 h to get crude compound, which was purified by flash column chromatography using acetone/ pet ether (15:85) as an eluent furnished pure aziridino-γ-lactone **1.192c** (0.41 g, 81%) as a white solid.

<b>MP</b>	: 92-94 °C.
<b>[α]<sup>30</sup><sub>D</sub></b>	: +18 (c 1.0, CHCl <sub>3</sub> ).

**IR (CHCl<sub>3</sub>)** : 1789. cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 3.78 (s, 3H), 4.23-4.31 (m, 2H), 4.81 (dd, *J* = 5.1, 9.1 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H).  
(200 MHz)  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 52.7, 55.7, 59.5, 71.8, 115.2, 115.3, 138.2, 153.7, 171.3.  
(50.32 MHz)  
**MS (m/z)** : 206 (M+1).  
**Analysis** : Calculated: C, 64.38; H, 5.40; N, 6.83.  
(C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>) Observed: C, 64.16; H, 5.19; N, 6.68.

**(1*S*,5*R*)-6-(*p*-Tolyl)-3-oxa-6-aza-bicyclo[3.1.0] hexan-2-one (1.195c):**

Following typical procedure, 4-hydroxymethyl azetidin-2-one **1.191b** (0.25 g, 0.8 mmol) was dissolved in methanolic HCl (20%, 15 mL) and the reaction mixture was refluxed for 15 h to get crude compound, which was purified by flash column chromatography using acetone/ pet ether (15:85) as an eluent furnished pure aziridino- $\gamma$ -lactone **1.192c** (0.14 g, 81%) as a faint pink solid.

**MP** : 95-96 °C.  
: +60.0 (*c* 1.5, CHCl<sub>3</sub>).  
**[ $\alpha$ ]<sup>30</sup><sub>D</sub>**  
**IR (CHCl<sub>3</sub>)** : 1791 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 2.28 (s, 3H), 4.25-4.33 (m, 3H), 4.85 (dd, *J* = 5.8, 10.6 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H).  
(200 MHz)  
**<sup>13</sup>C NMR (CHCl<sub>3</sub>)** : δ<sub>C</sub> 20.4, 52.9, 58.9, 71.8, 113.7, 120.0, 130.1, 142.2, 171.4.  
(50.32 MHz)  
**MS (m/z)** : 190 (M+1).  
**Analysis** : Calculated: C, 69.81; H, 5.86; N, 7.40.  
(C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>) Observed: C, 69.68; H, 5.45; N, 7.22.

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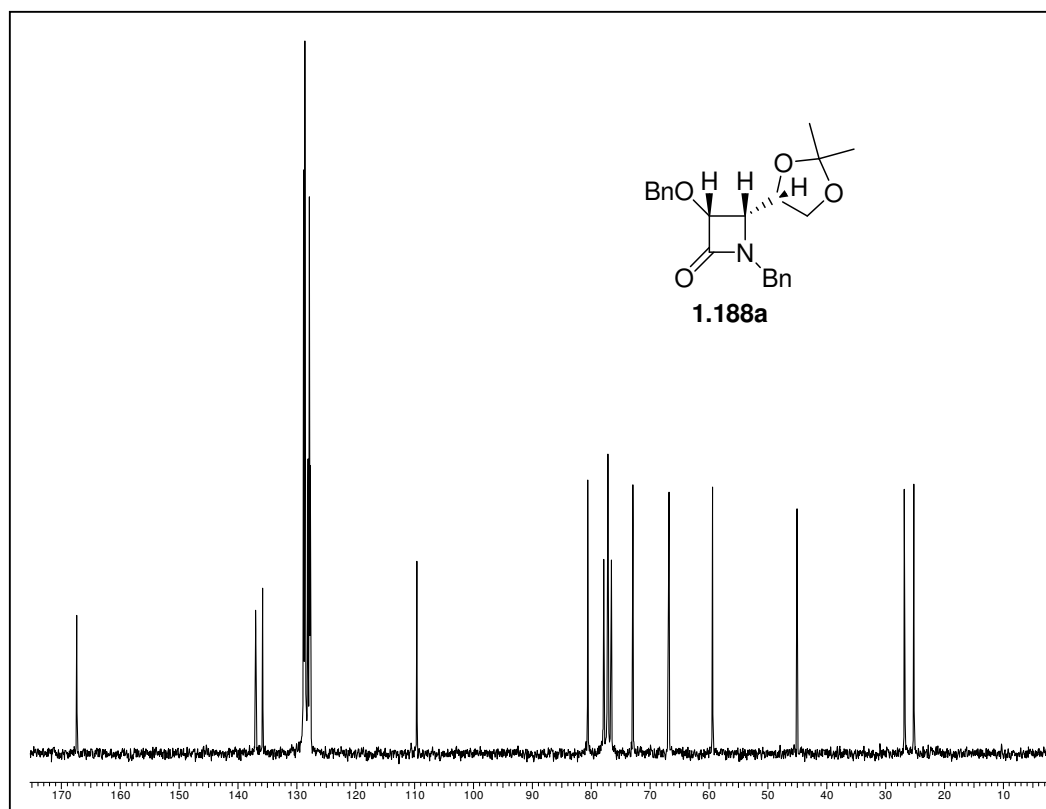
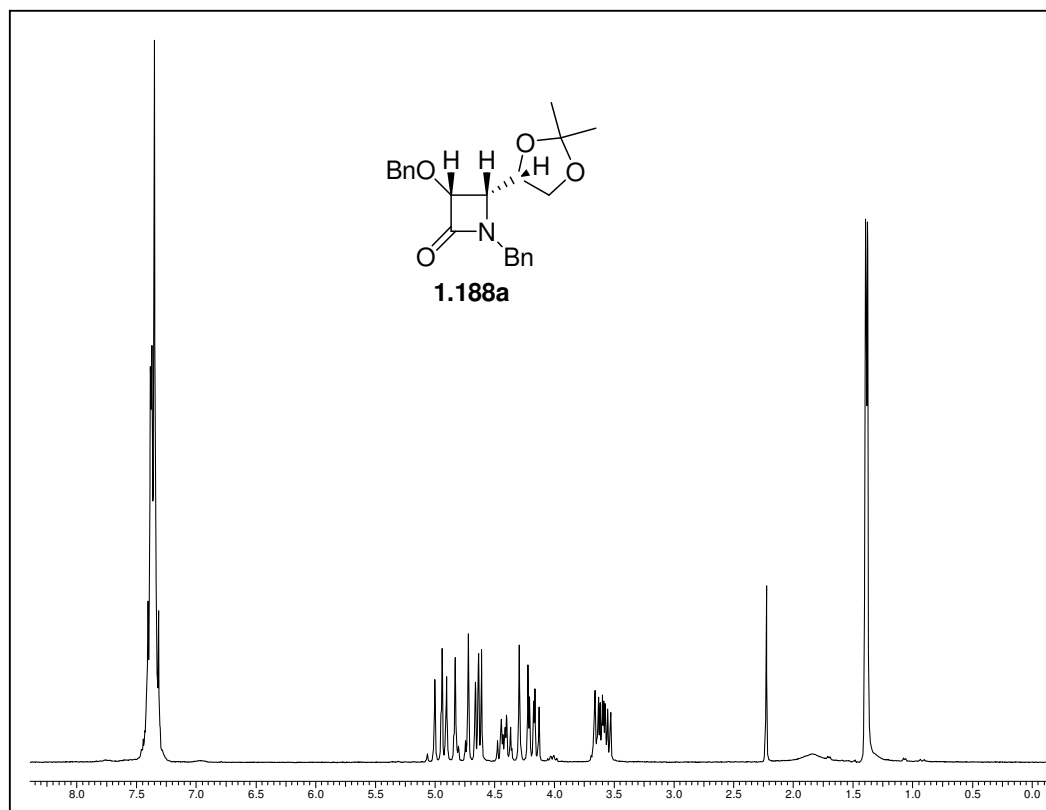


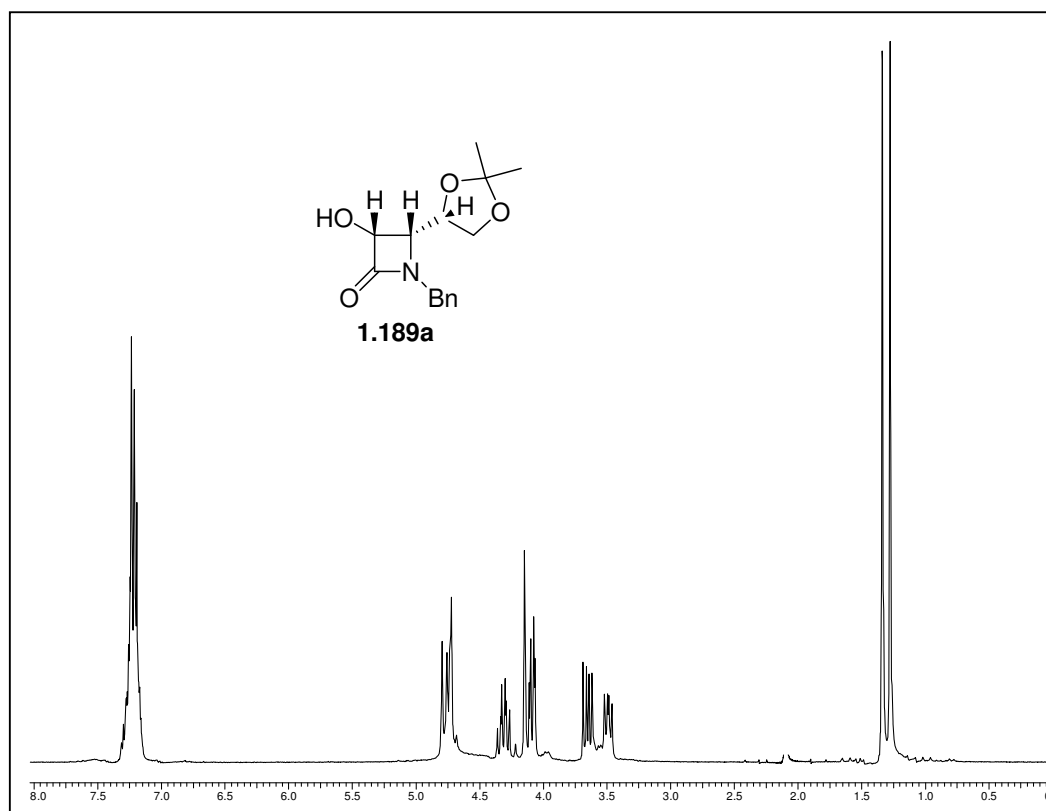
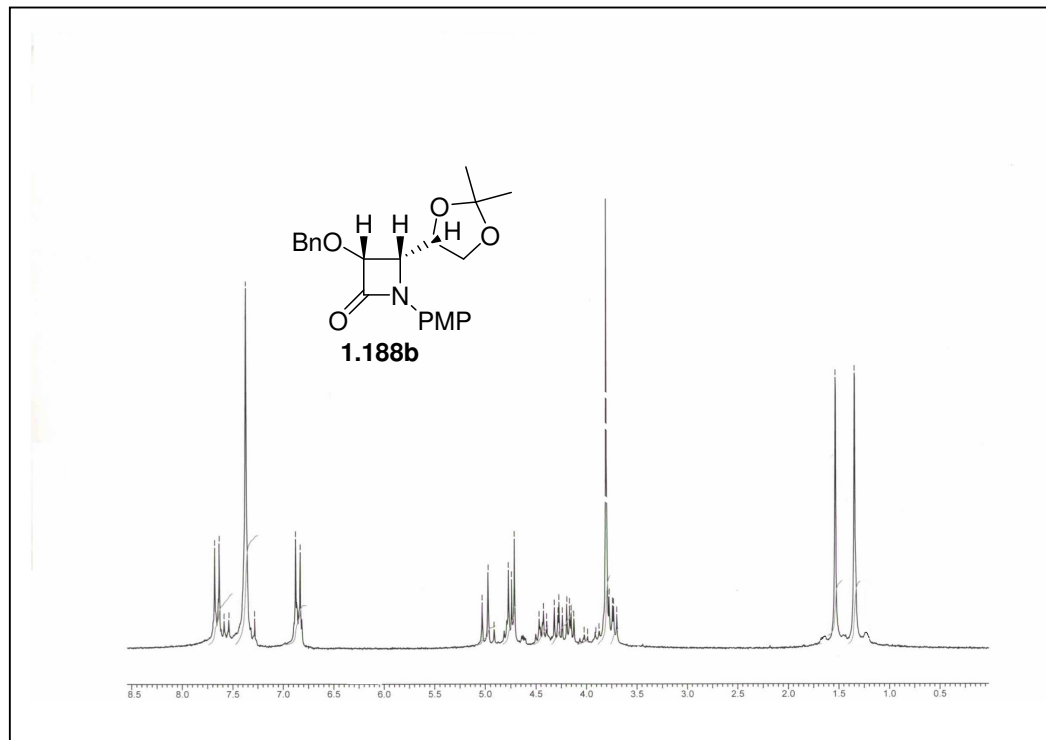
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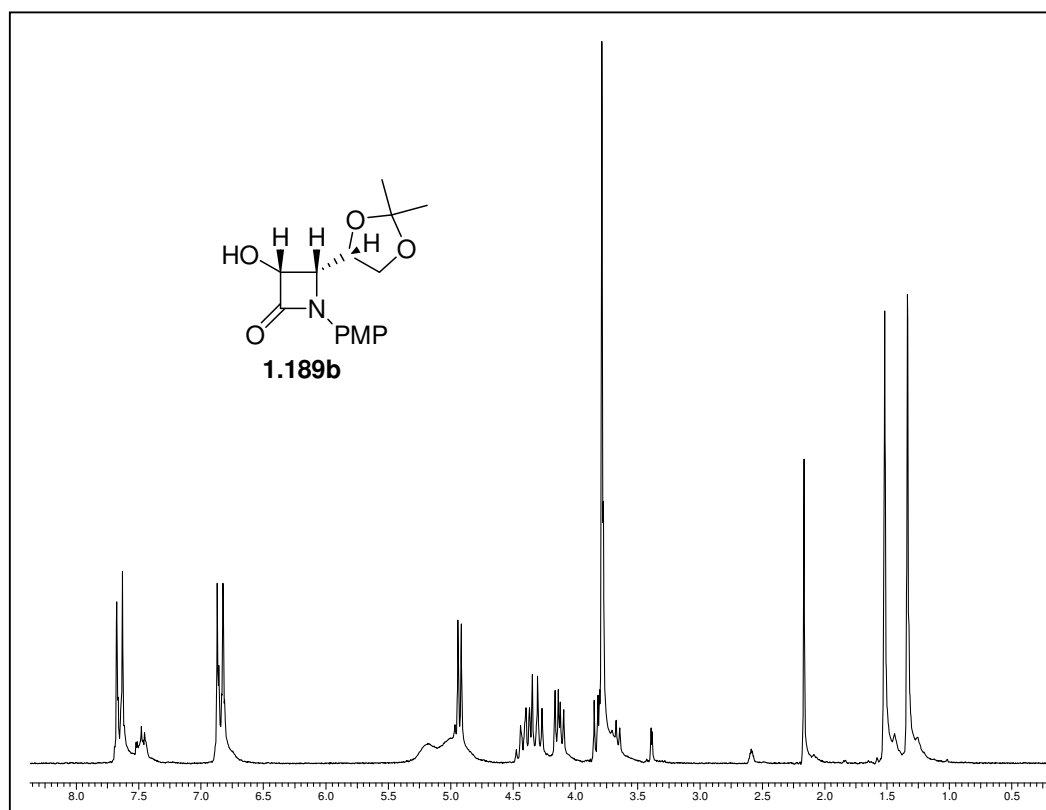
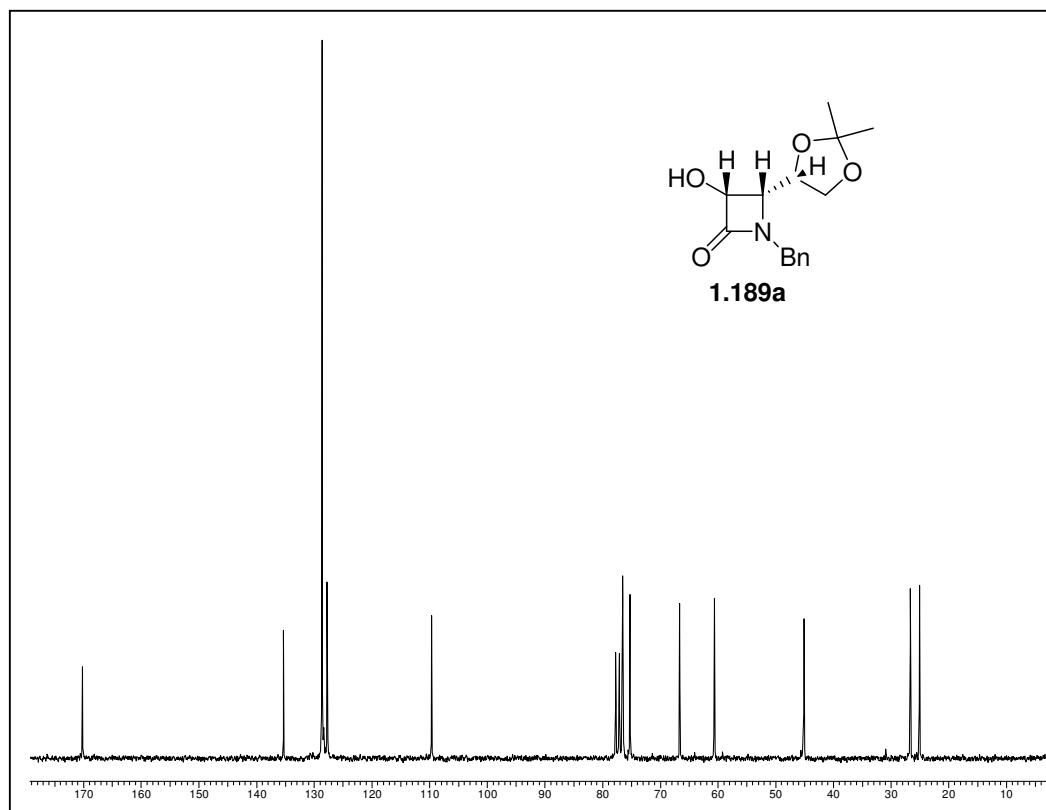
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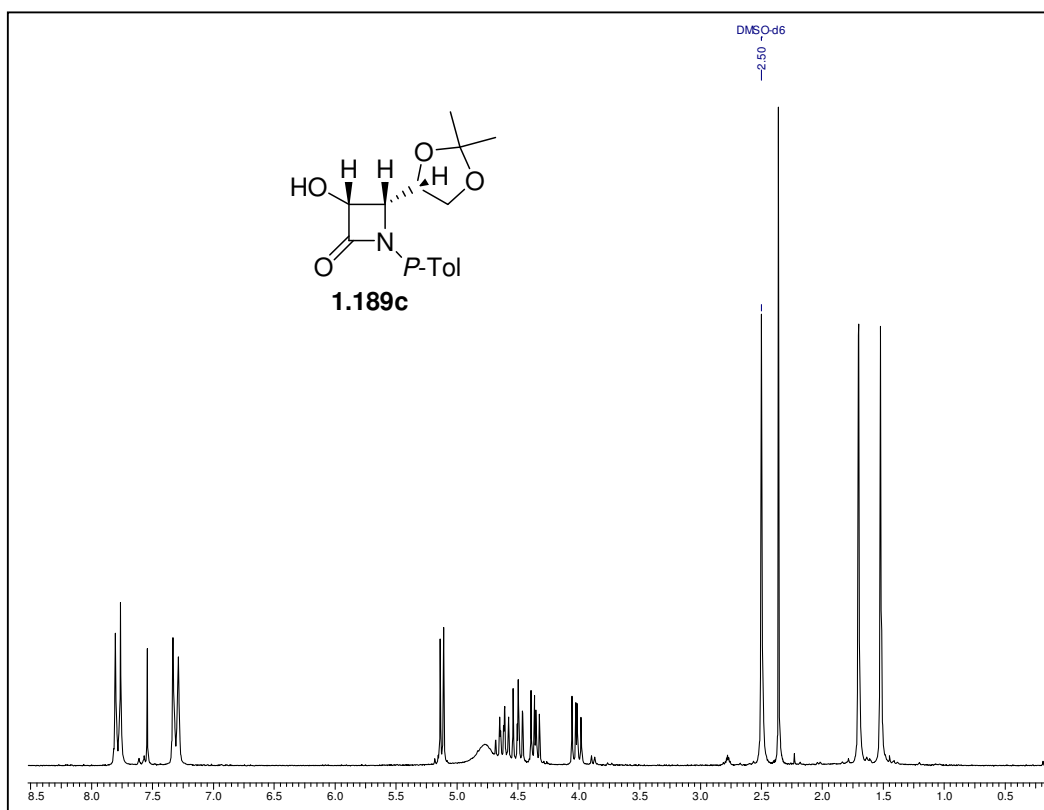
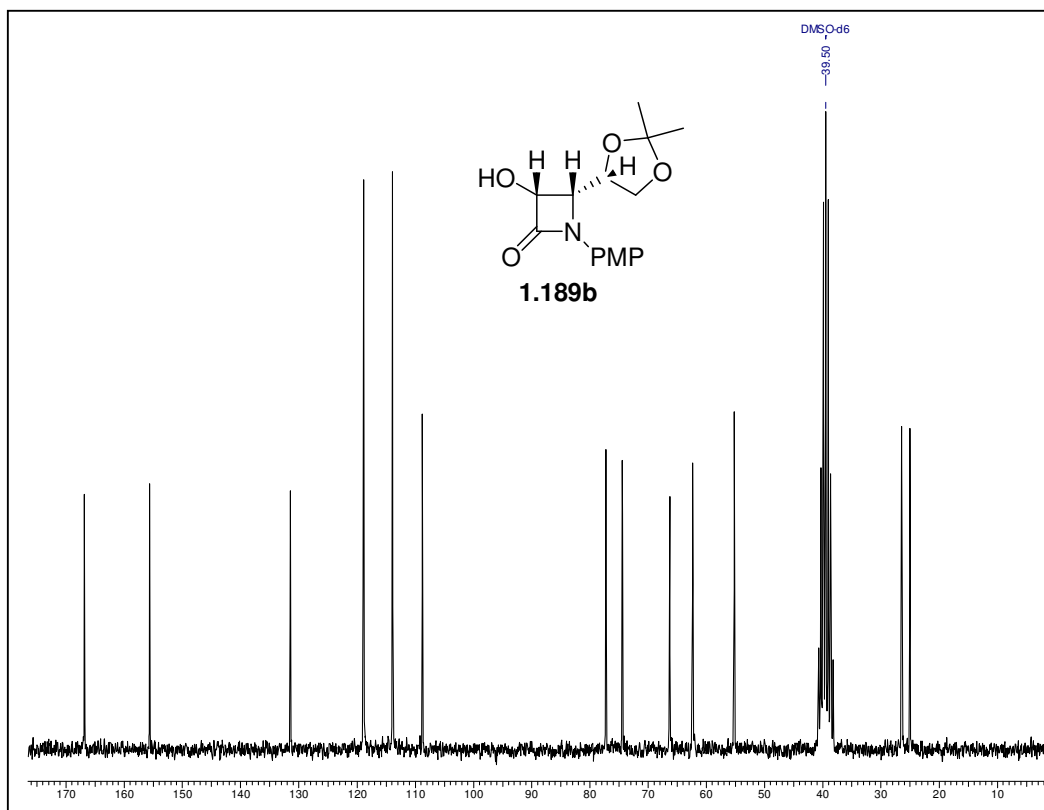
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Chapter 1  
**Spectra**

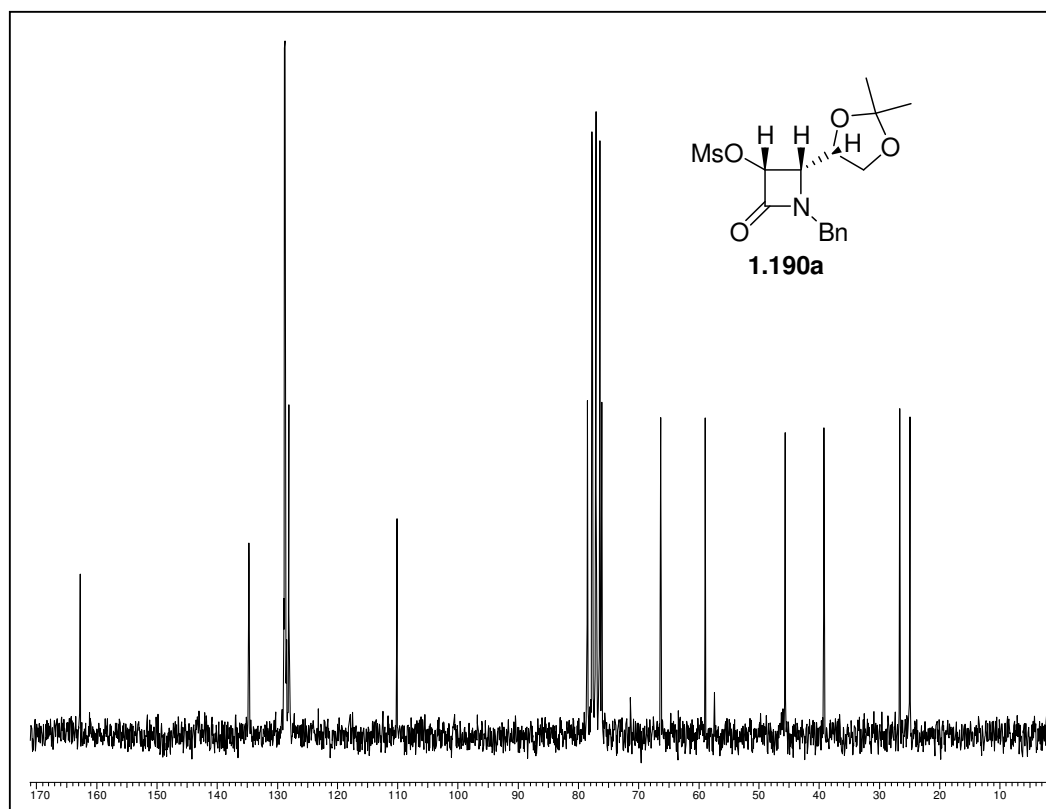
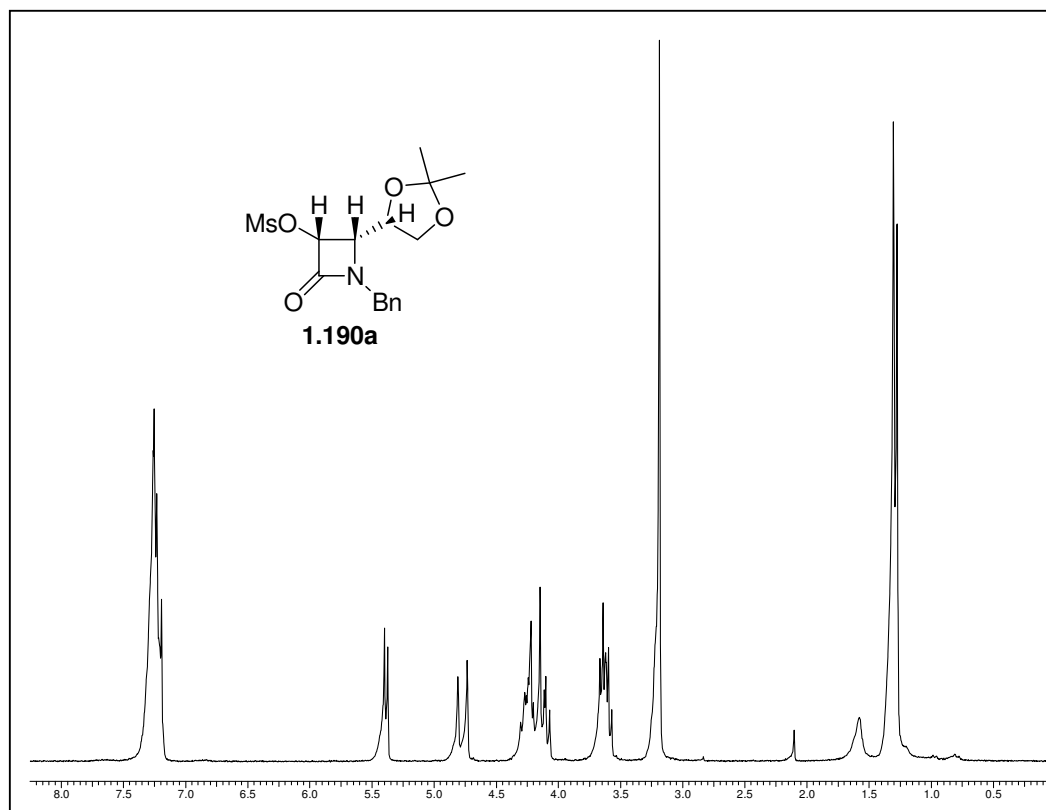


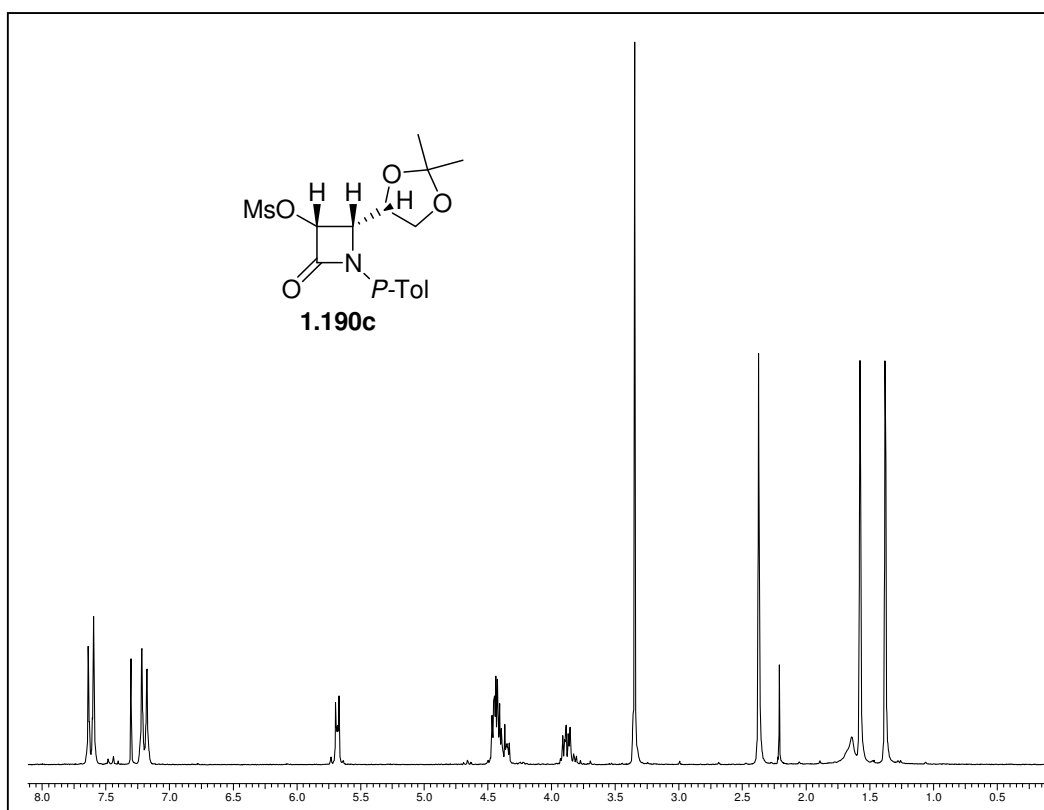
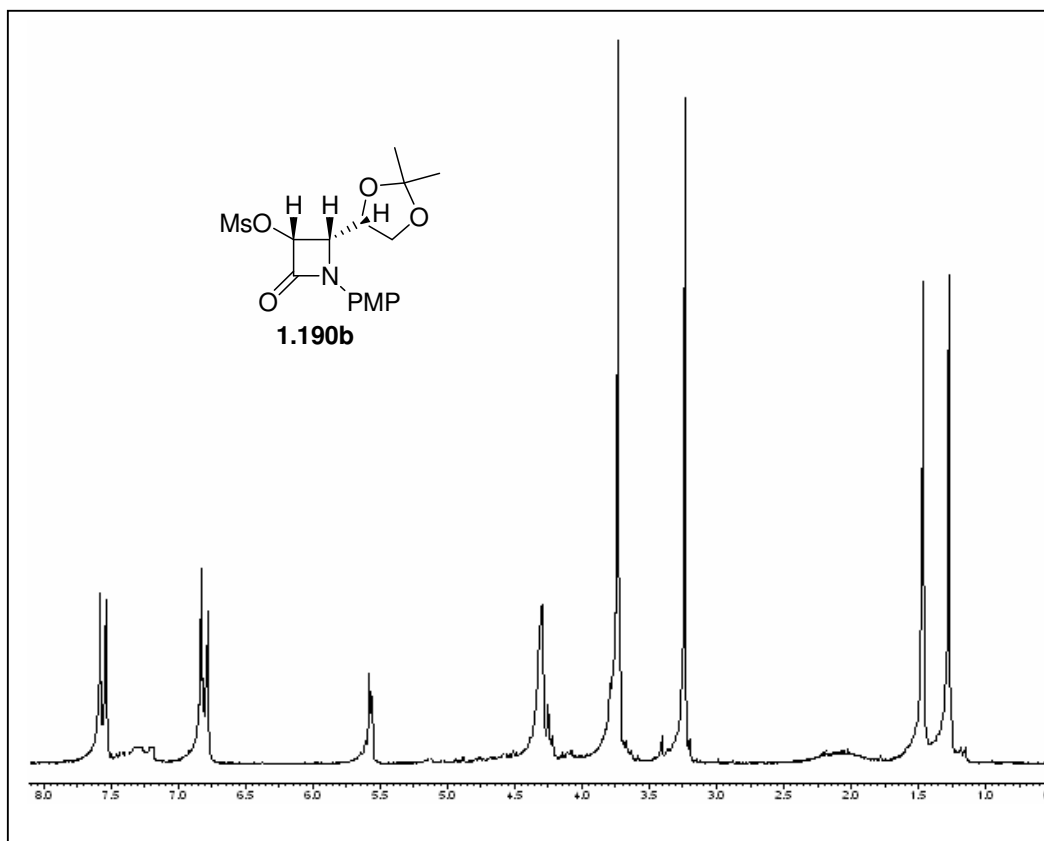


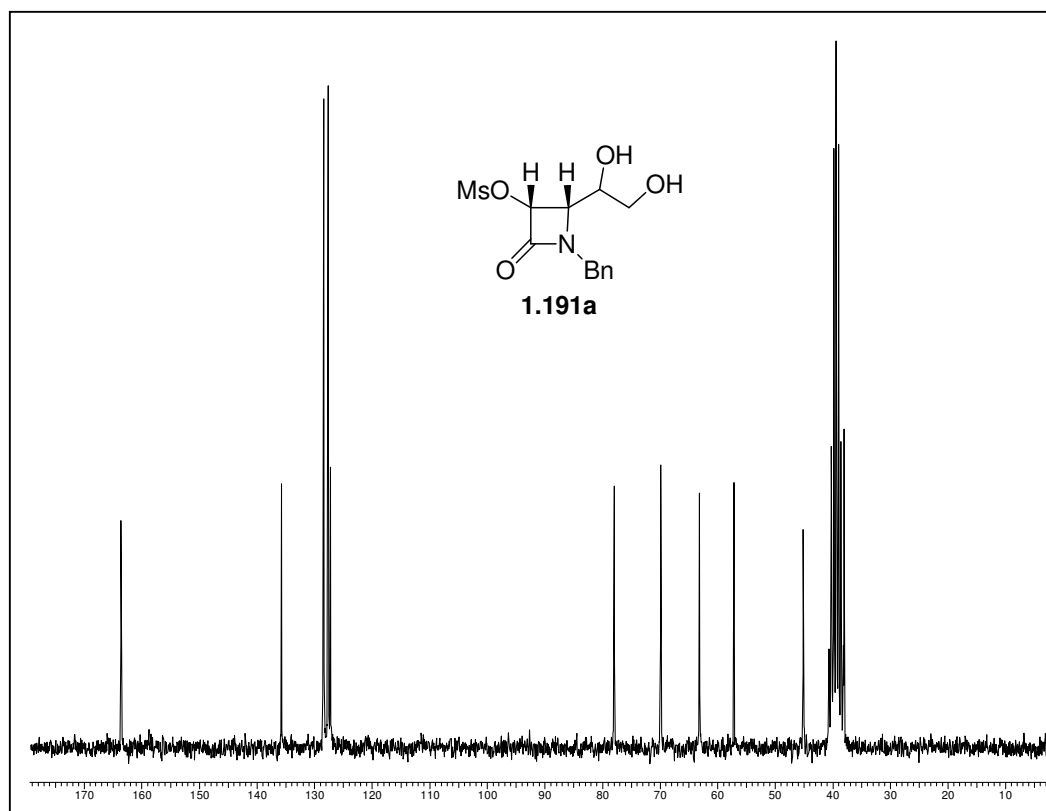
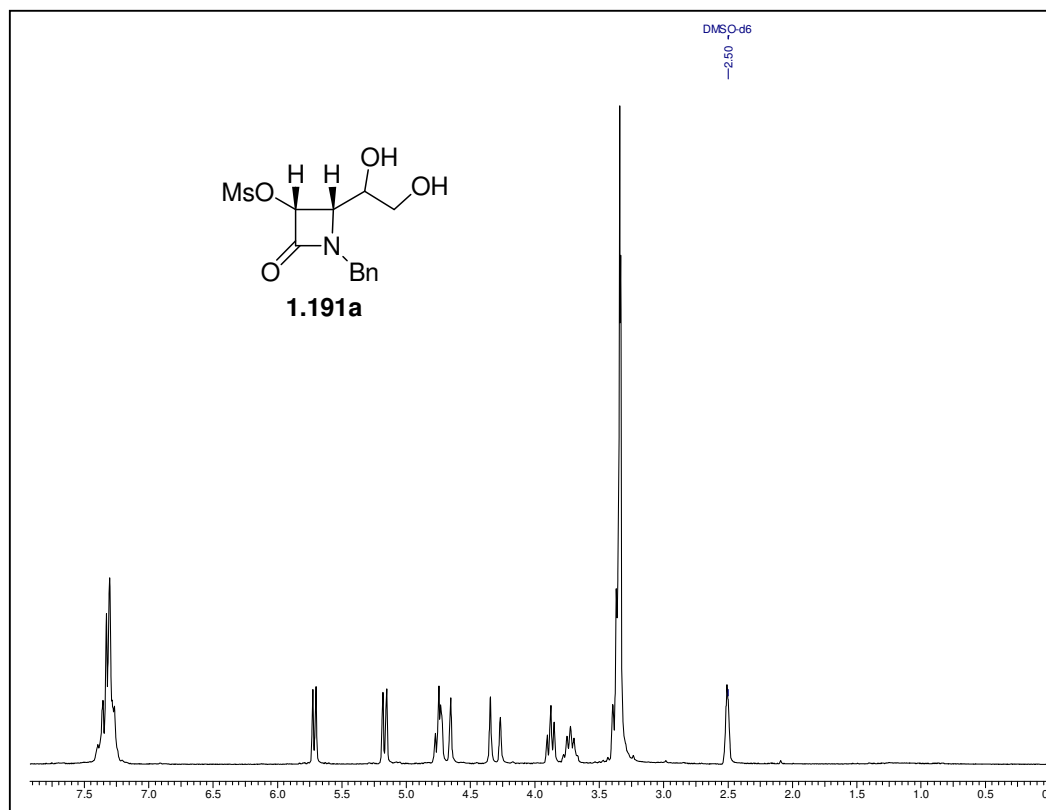


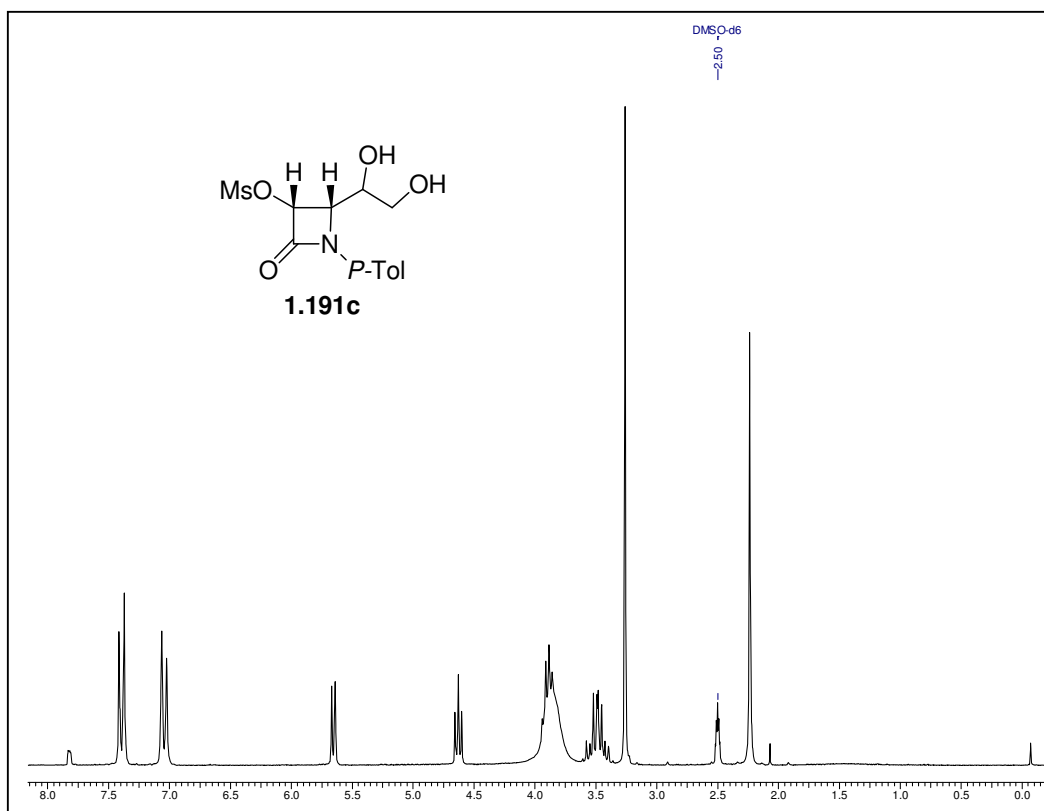
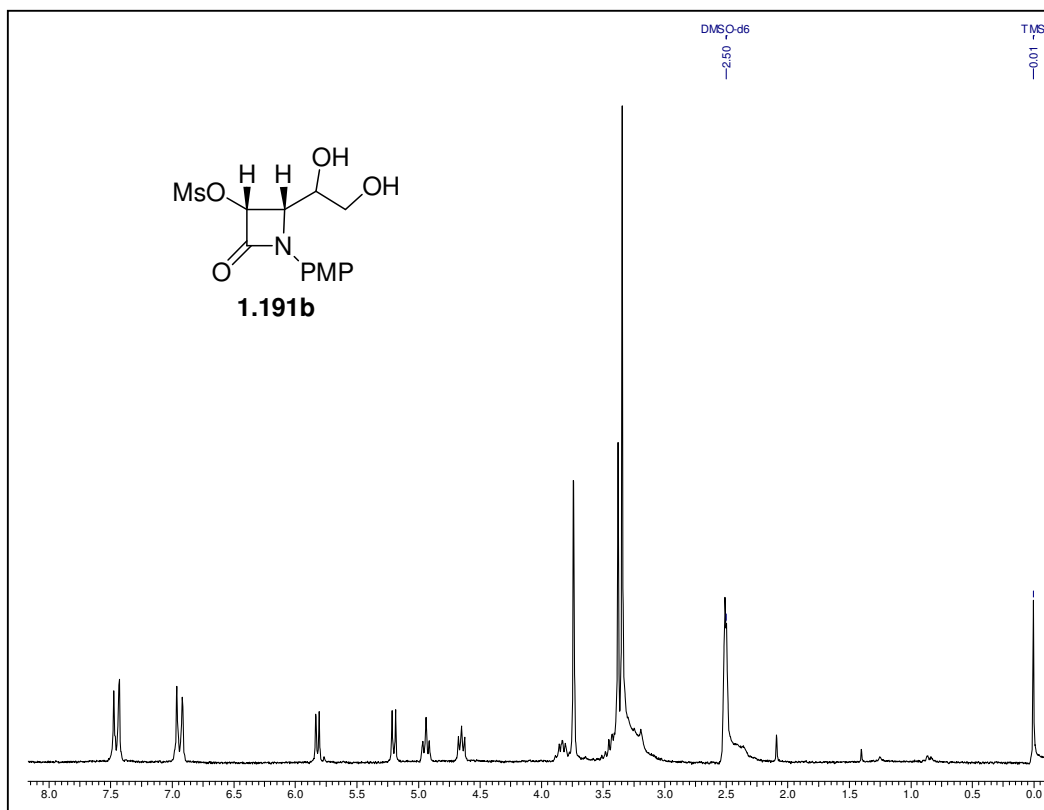


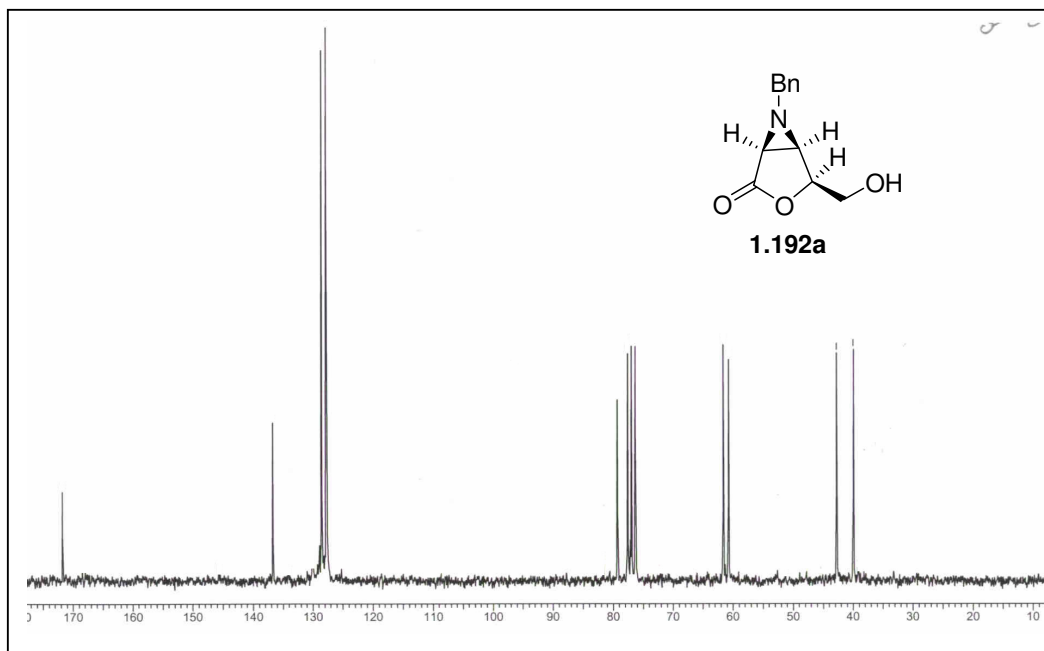
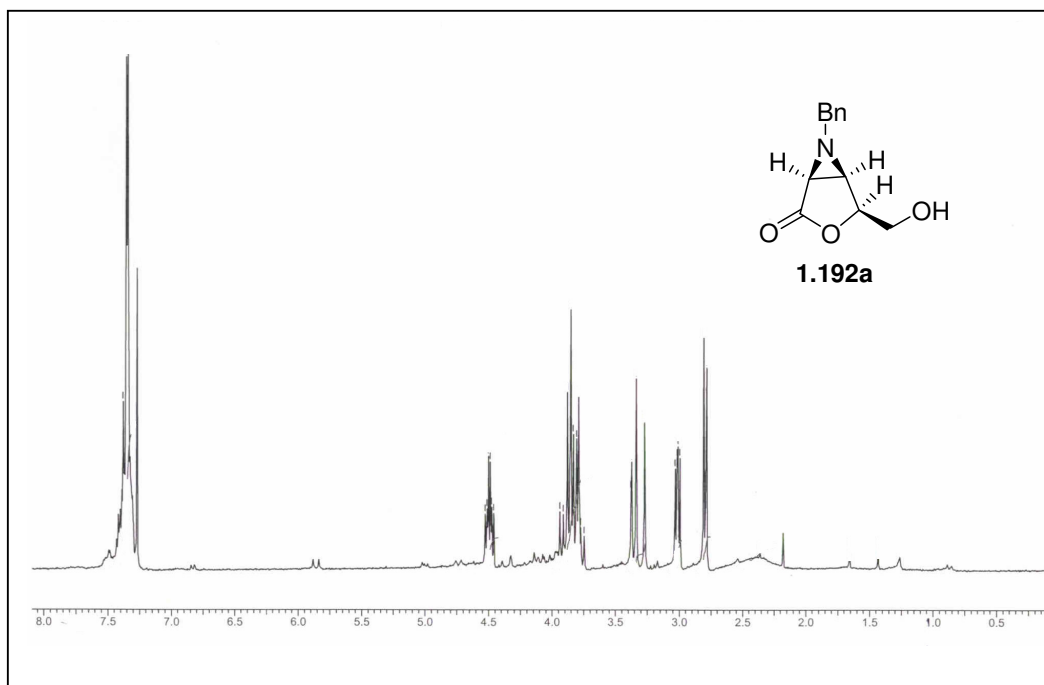


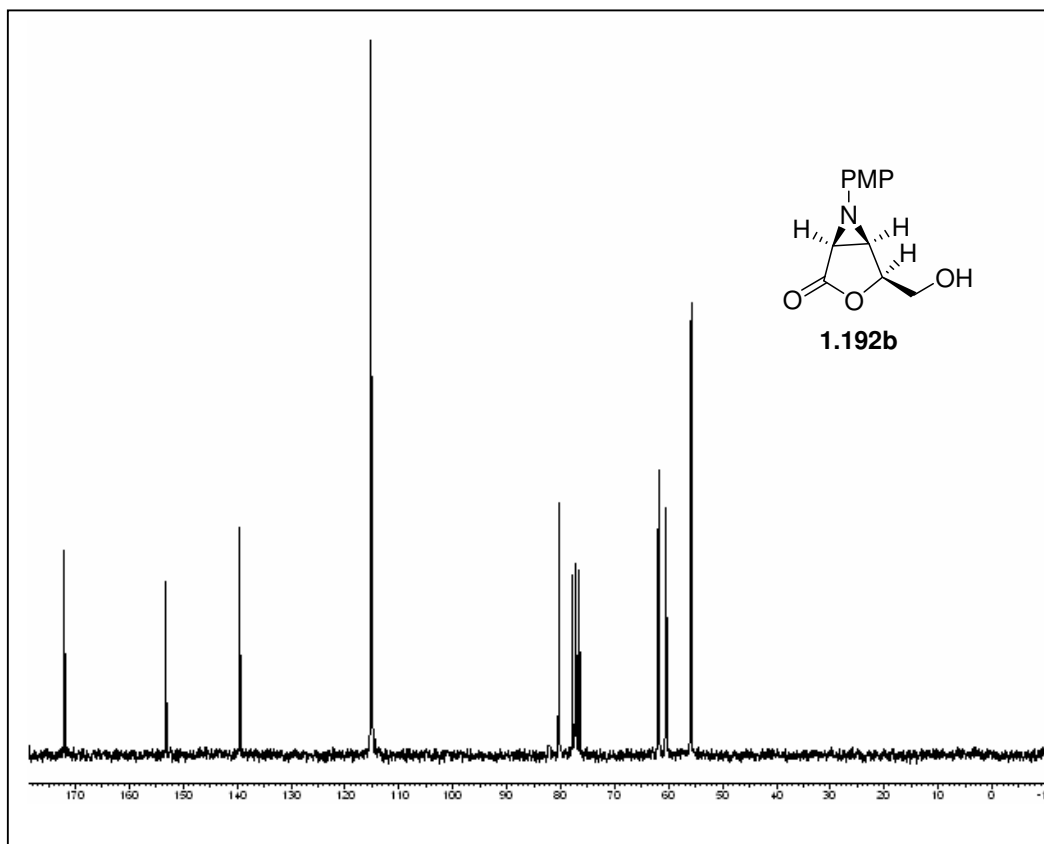
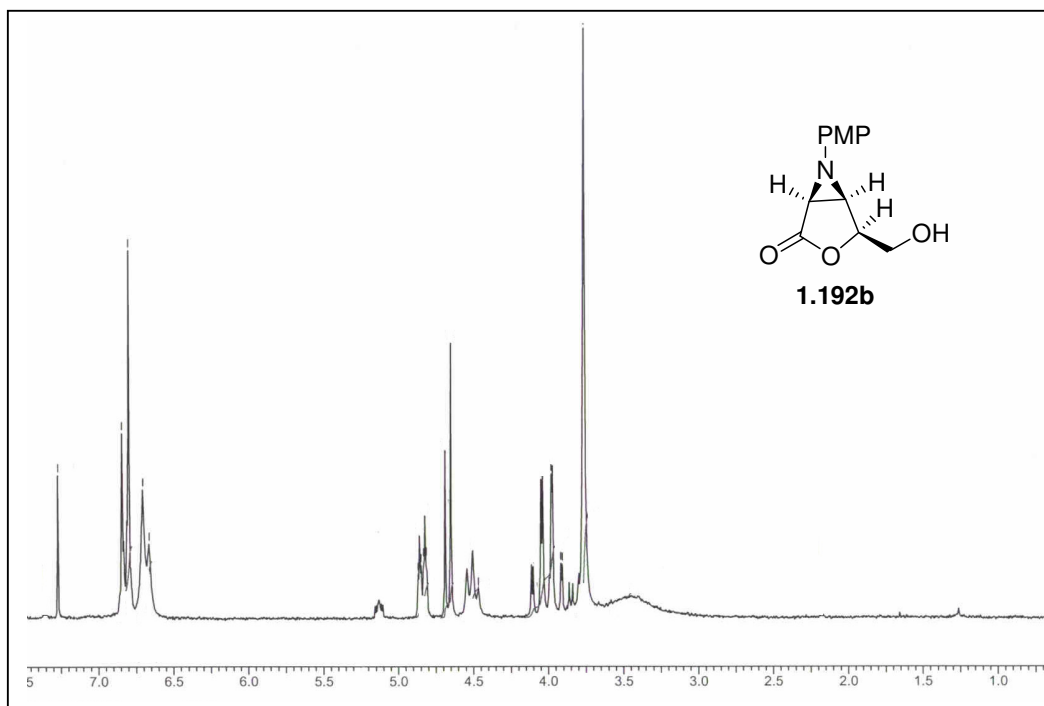


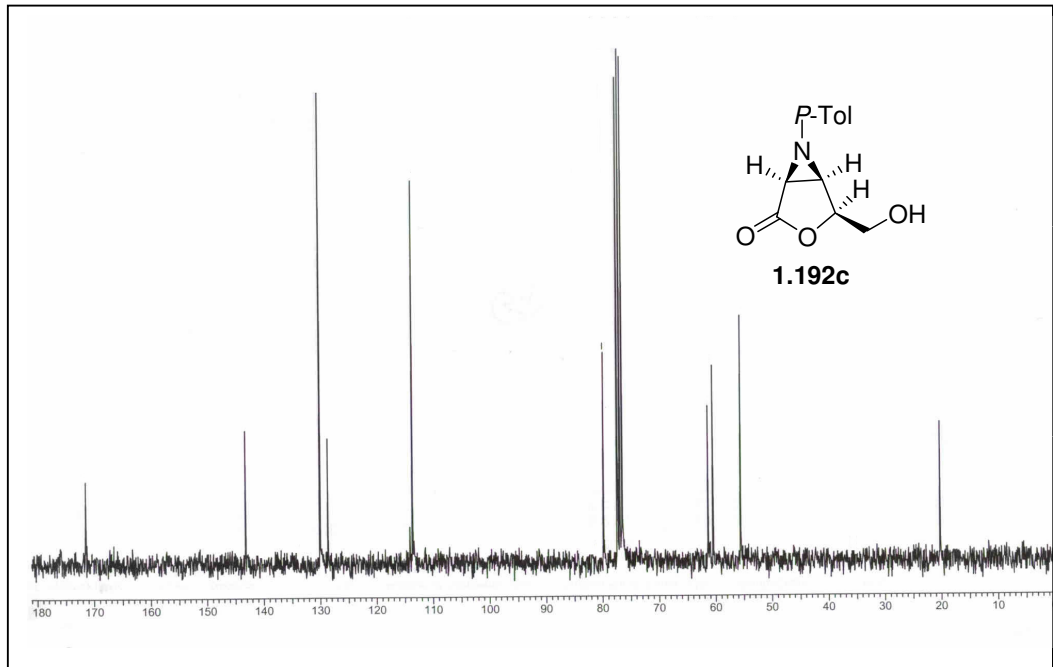
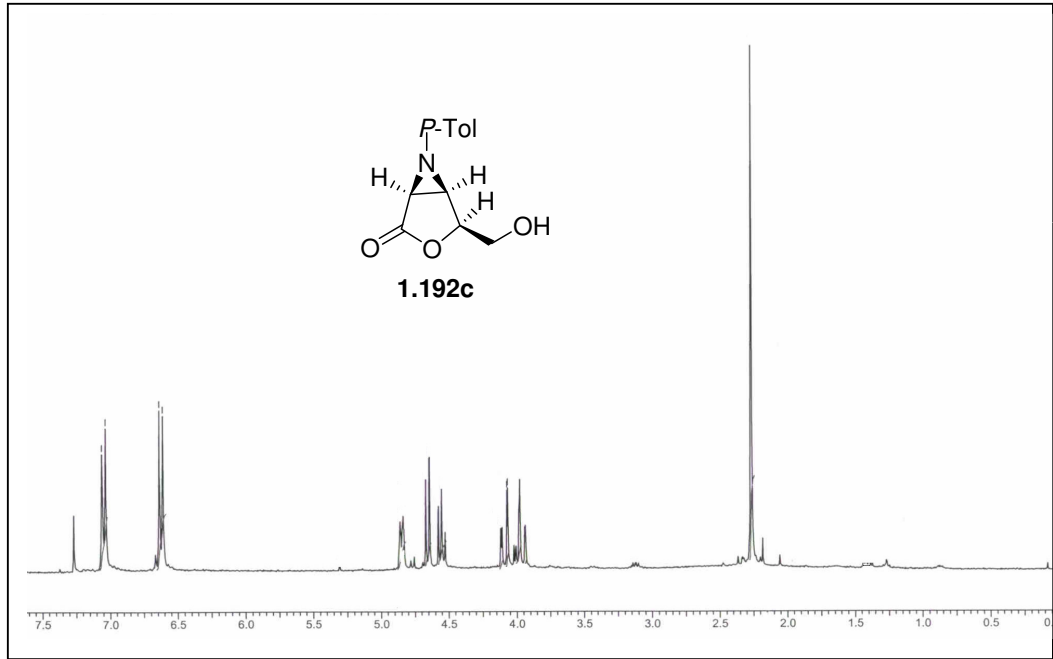


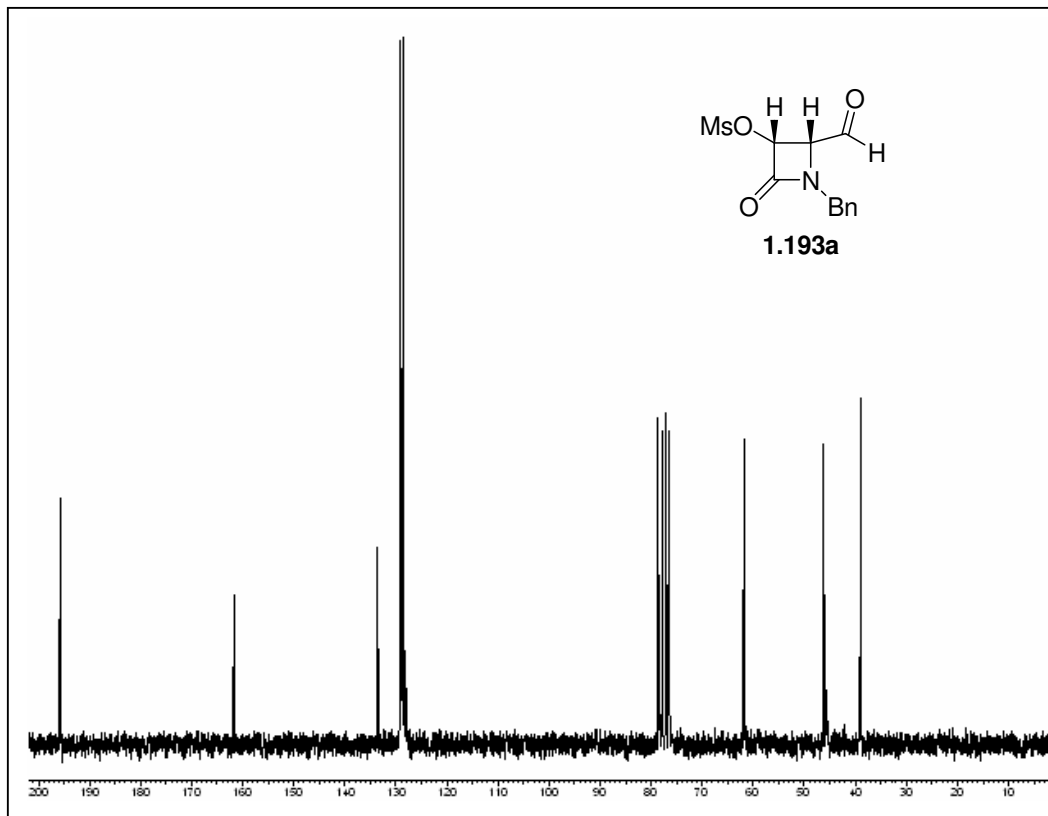
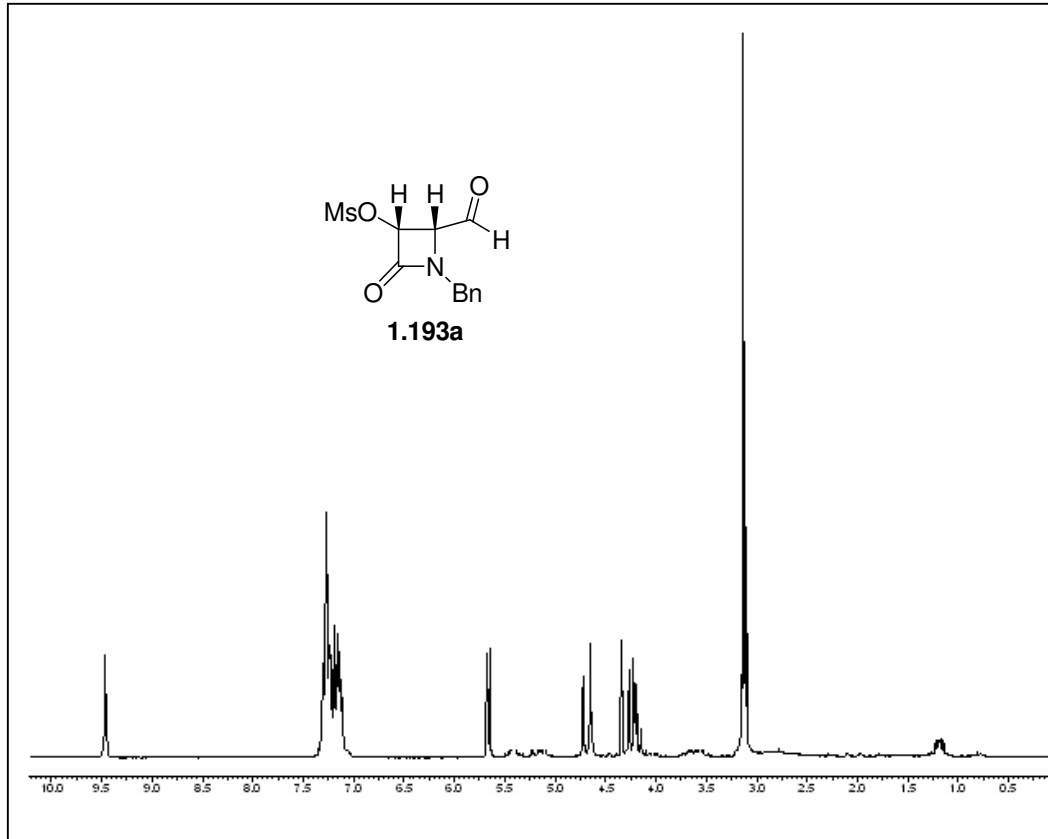




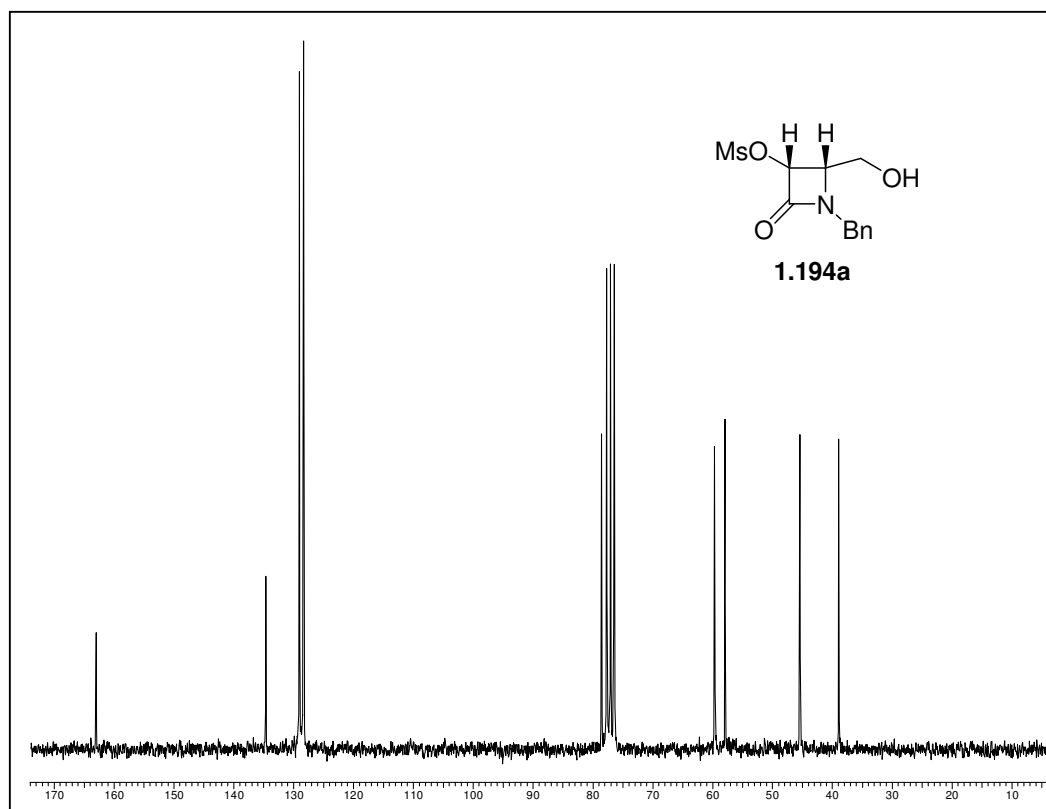
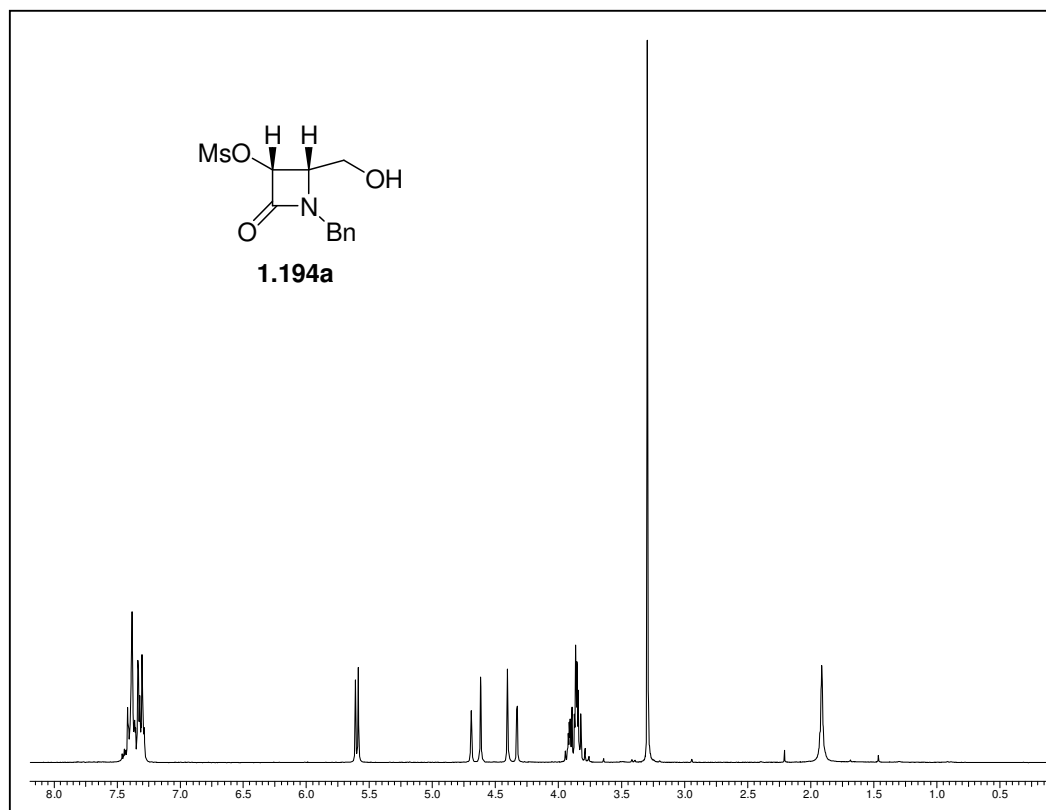


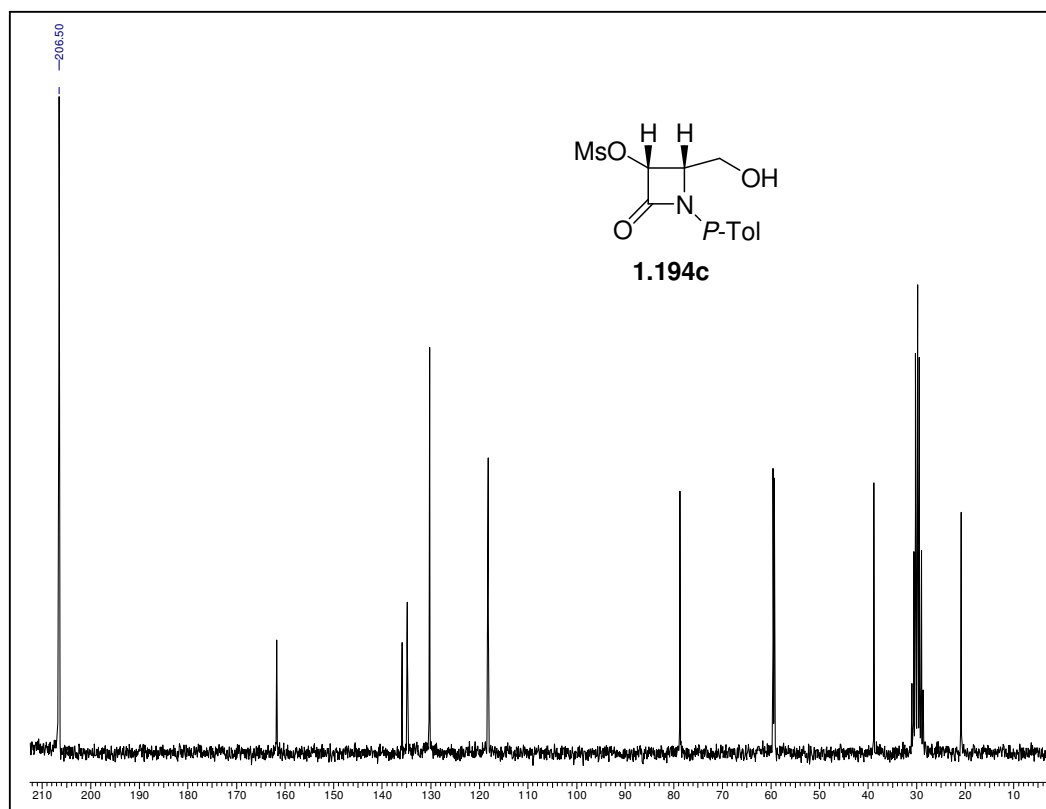
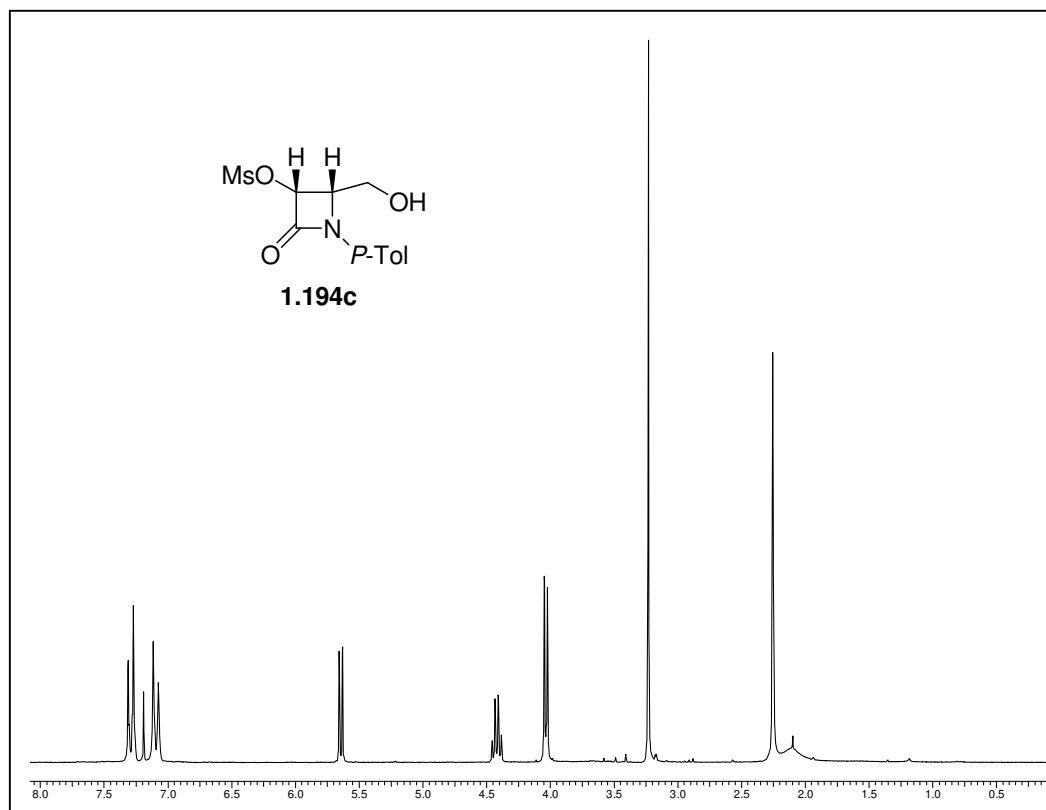


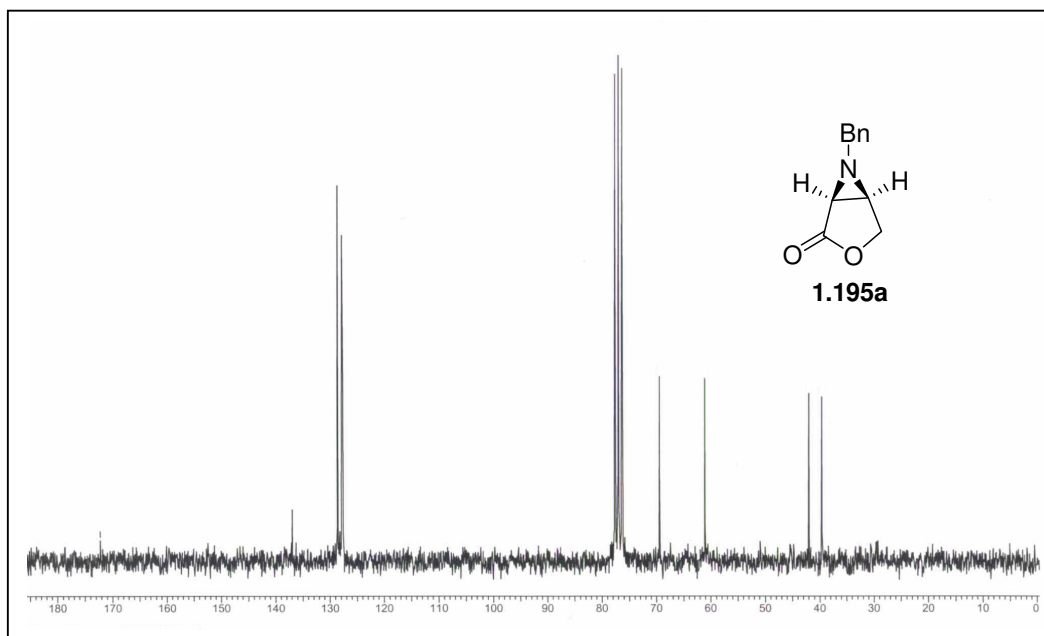
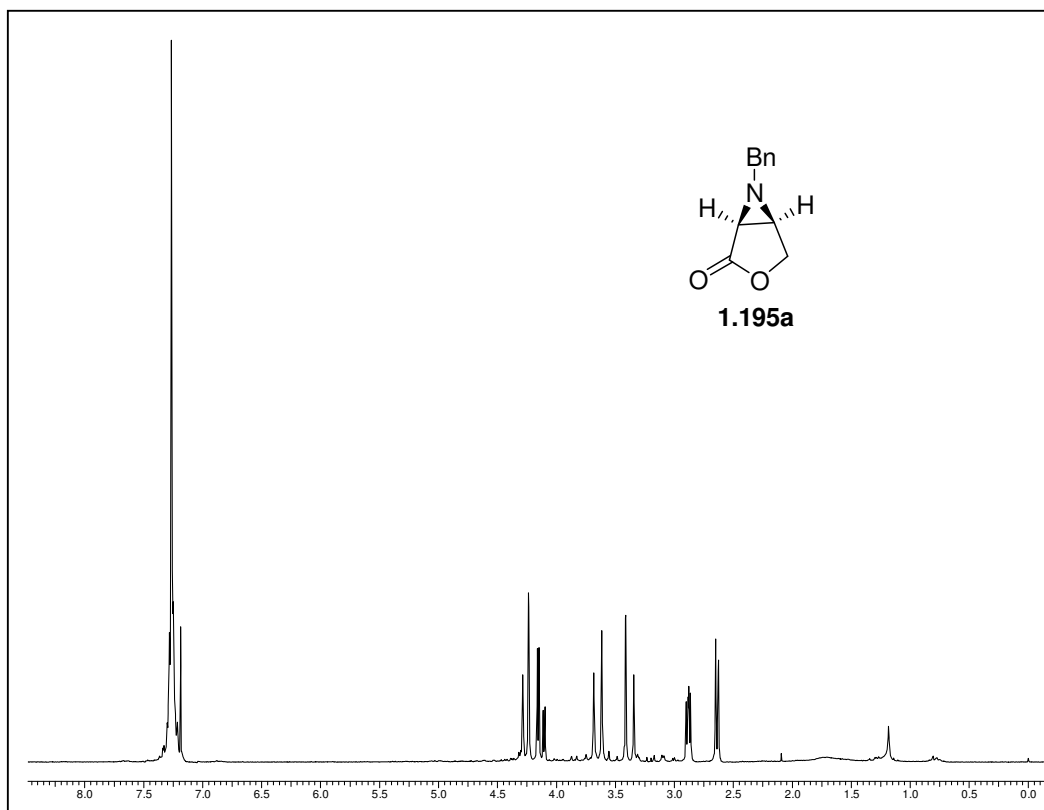


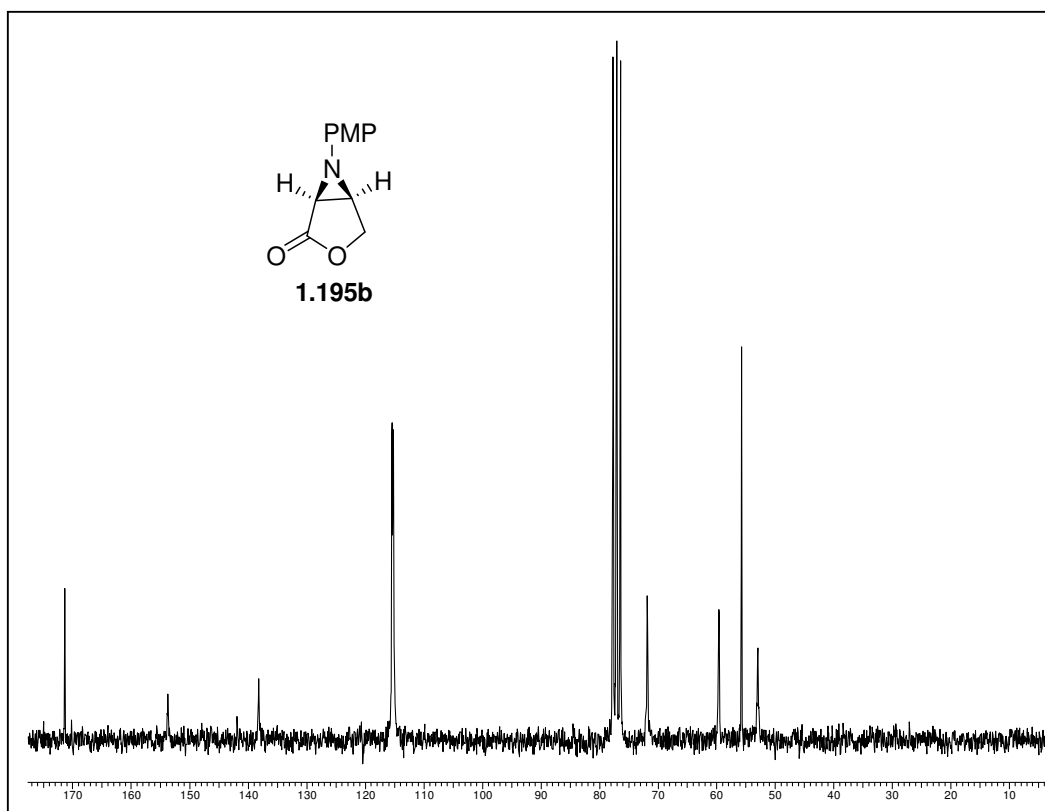
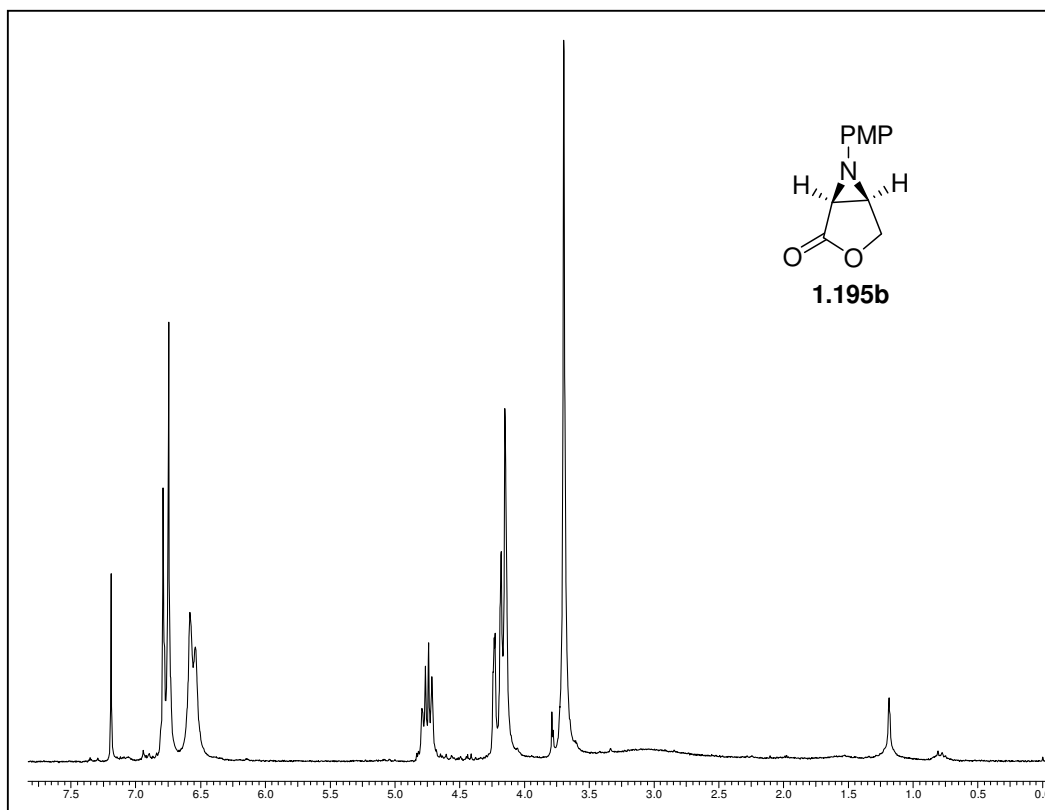


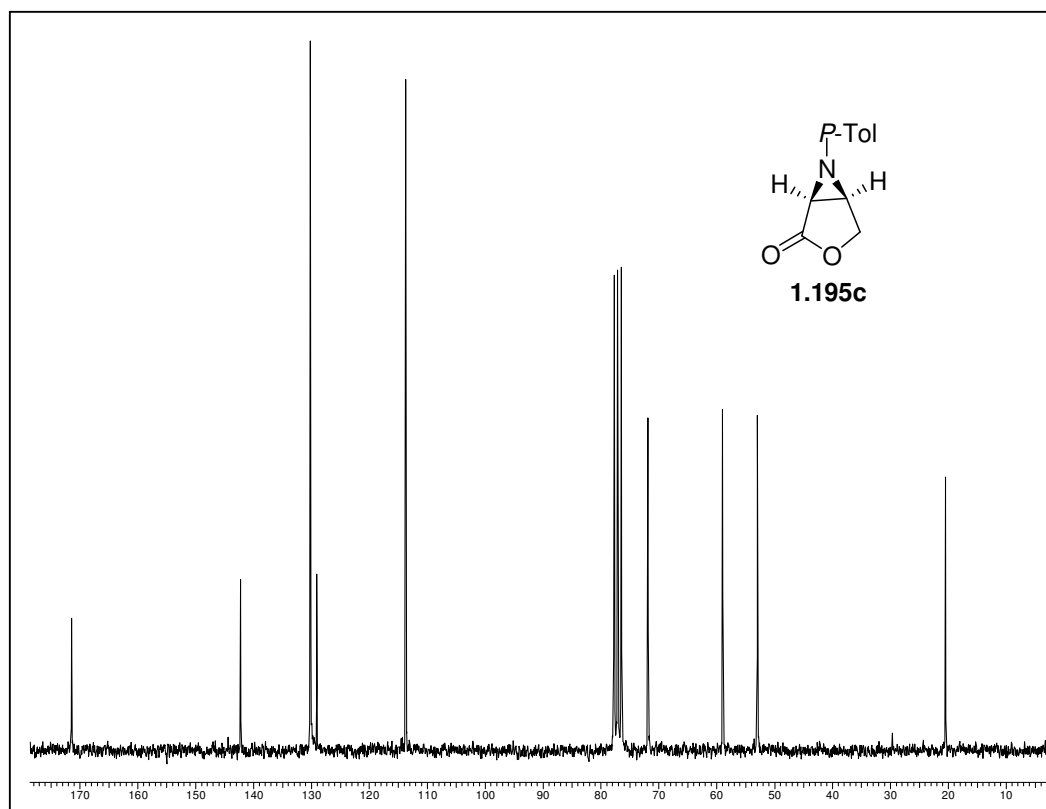
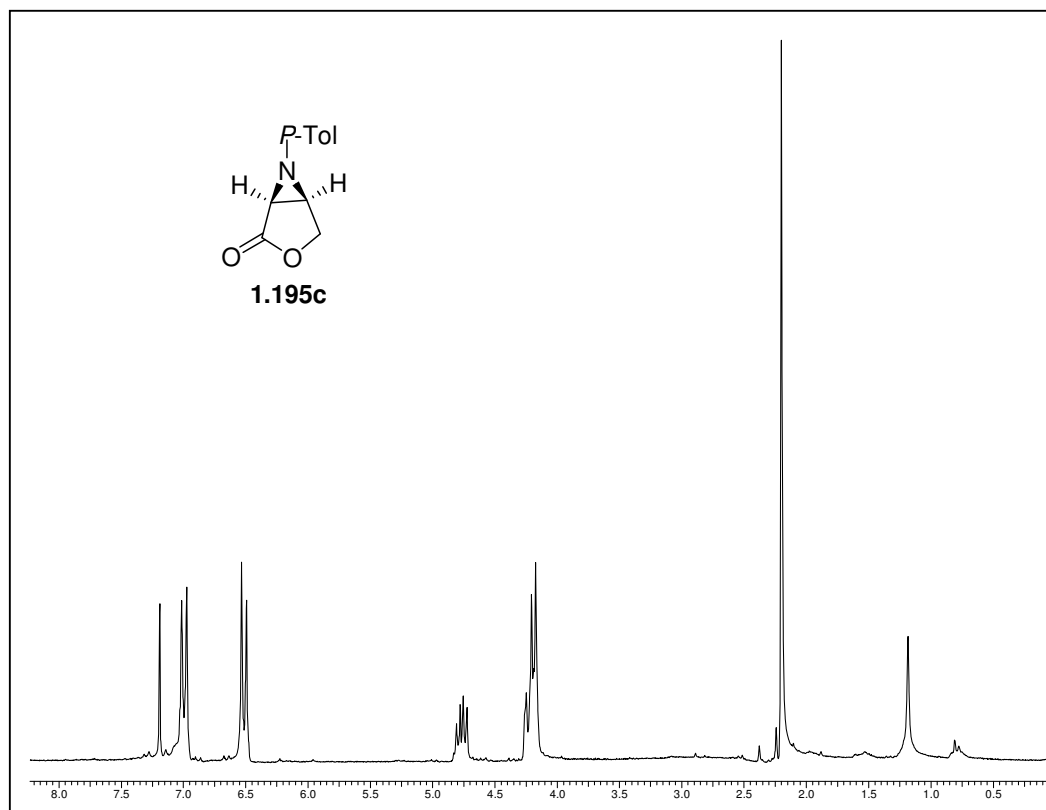












**CHAPTER 2**

**A PRACTICAL FORMAL SYNTHESIS  
OF D-(+)-BIOTIN FROM 4-FORMYL  
AZETIDIN-2-ONE.**

*Conquering any difficulty always gives one a secret joy, for it means pushing back a boundary-line and adding to one's liberty.*

-Henri Fraderic Amiel

This work has been published in *Synthesis* **2007**, 8, 1159-1164.

## 2.1: Introduction

The Chemistry of Biotin dates back to 1936 when it was isolated by Kogl<sup>1</sup> from egg yolk. A few years later it was also isolated from beef liver<sup>2</sup> and from milk concentrate.<sup>3</sup> It is also known as anti-egg white injury factor, bios IIB, vitamin H etc. Chemically biotin is (+)-*cis*-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]-imidazole-4-valeric acid (2.1).

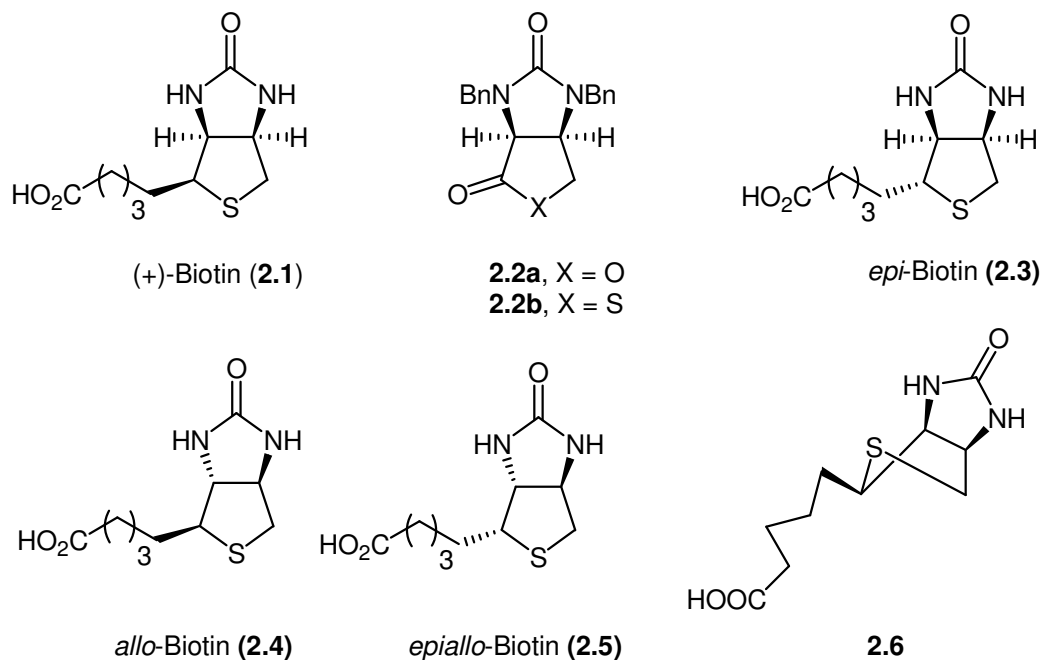


Figure 2.1

Biotin is one of the water-soluble B-complex group of vitamins (Figure 2.1). In bound form it is distributed widely as a cell constituent of animal and human tissues. The main sources of biotin are liver, kidney, pancreas, egg yolk, yeast and milk. A high content of biotin in cow's milk occurs in early lactation. It is also present in different plant materials, especially in seeds, pollen, molasses, rice, mushroom, fresh vegetables and in some fruits. Moist fish contain biotin in small amounts.

Biochemically, biotin functions as a cofactor for enzymes principal to carboxylation reactions. These reactions are a part of important biochemical processes such as gluconeogenesis and fatty acid synthesis.

### 2.1a Structure determination:

The empirical formula for biotin  $C_{10}H_{16}N_2O_3S$  was established in 1941 and the full structure in 1942 by du Vigneaud.<sup>4,5</sup> The structure was confirmed by the first total synthesis of biotin in Merck Laboratories by Harris and coworkers in 1945.<sup>6</sup> The absolute configuration was established more than 20 years later by X-ray crystallographic analysis.<sup>7</sup>

Biotin has three contiguous chiral carbon atoms and therefore, four diastereomeric racemic forms are possible, of which only (+)-biotin **2.1** is biologically active, while, *epi*, *allo* and *epi-allo*-biotin **2.3**, **2.4**, and **2.5** respectively and their enantiomers are biologically inactive. Of the four diastereomeric racemic forms, only D(+)-biotin occurs in nature whereas other isomers are synthetic.

In 1976 two groups reestablished the crystal structure of biotin and results reported were in agreement with the previous ones, but more accurate.<sup>8</sup> According to these data, ureido ring is planar while the thiophane ring has an envelope conformation **2.6**. The valeric acid side chain is not fully extended but twisted and there is a strong interaction between C-6 and N-3, an important feature governing the biochemical reactivity of biotin. This envelope conformation **2.6** of thiophane ring is also found in solution as shown by Glassel and Marquet.<sup>9</sup>

### 2.1b Biosynthesis:

A number of fungi and bacteria synthesize biotin from pimelic acid by a metabolic pathway, whose last step involves the conversion of dethiobiotin to biotin. This pathway has been thoroughly investigated.<sup>10-13</sup> All the intermediates from pimelic acid to dethiobiotin are formed by classical biochemical reactions. Recently Marquet and coworkers solved the elucidation of the mechanism for the transformation of dethiobiotin to biotin. Evidence has been presented that the biosynthesis of biotin *Aspergillus niger* and *E. Coli* proceeds by the introduction of sulfur at C-1 and C-4 of dethiobiotin without apparent involvement of C-2 and C-3.<sup>14,15</sup>

A more recent study clearly demonstrates that sulfur is introduced at C-4 of dethiobiotin with loss of the 4 pro *S* hydrogen atom. Since the configuration of biotin at C-3 is *S*, it follows that sulfur is introduced with retention of configuration at C-4, prochiral center of dethiobiotin.



### **2.1c Biotin deficiency:**

Because of the biosynthesis by intestinal flora, a deficiency of biotin seldom occurs in humans. In rare cases, biotin deficiency when inducted, results in dermatitis, a loss of appetite, nausea, vomiting, depigmentation, alopecia, weight loss, anemia, elevated blood cholesterol and depression.<sup>16</sup> These symptoms can be reversed by giving biotin at the level of adult requirement, 150-300 µg/dose. Recently a rare life threatening genetic defect in biotin metabolism, that is biotin-dependent-carboxylase deficiency, has been determined in a small number of young children. Johnson *et al.*<sup>17</sup> reported: “A diet which is marginally deficient in the vitamin biotin may cause sudden unexpected death of young broiler chickens when they are exposed to stress. Chickens affected with this disorder have low levels of biotin in their livers. In condition of biotin insufficiency, we postulate that a similar disorder, triggered by mild stress may occur in the human infants”. They have used radiochemical technique to measure the biotin content of 204 livers obtained from infants at autopsy. The levels of biotin in the livers of infants who had died of sudden infant death syndrome (SIDS; cot death) were significantly lower than those in livers of infants of similar age, who had died of explainable causes. These findings support an association of biotin with SIDS.

In poultry, biotin is an essential vitamin for normal growth, feed conversion, and reproduction as well as healthy skin, feathers and bones. Biotin deficiency in poultry causes reduced growth rate, impaired feed conversion, reduced feed intake, perosis and other deformities causing leg-weakness, poor feathering and food dermatitis. In broilers, a biotin deficiency causes breast blisters, fatty liver and kidney syndrome, parrot beak and death. Biotin deficiency also causes dramatic symptoms in swine, e.g. reduced growth rate, dermatitis, excessive hair loss, furry tongue, food tensions, stiff-legged gait, squatness, and hind-leg spasms. These deficiencies are corrected by using biotin as a feed additive for poultry and swine.

### **2.1d Uses:**

In recent years a utilization of strong biotin avidin complex has emerged in biochemistry as an important and versatile method for isolation, localization,

immunoassay and drug delivery.<sup>18a</sup> It has been recently recognized that biotin finds use in cosmetic<sup>18b</sup> and it is administered orally for brittle nails and hair loss.

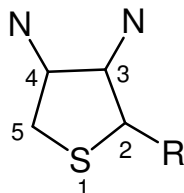
One of the most useful interactions in immunochemistry involves the specific binding of water-soluble vitamin: biotin, to the egg white protein avidin. Avidin is a tetramer containing four identical subunits of molecular weight 15,000. Each subunit contains a high affinity binding site for biotin with a dissociation constant of approximately 10<sup>-15</sup> M. The binding is undisturbed by extremes of pH buffer salts or even chaotropic agents, such as guanidine hydrochloride (up to 3 M). The strength of the avidin biotin interaction has provided the researcher with a unique tool for use in immunoassays, receptor studies, immunocytochemical staining and protein isolation.<sup>19</sup> In addition, the recovery of spilled solvents, disposal of used cooking oil and novel drug delivery systems have been suggested as possible applications for gelling compound. Several of these compounds are capable of forming stable gels with a variety of organic solvents.

Another most important use of biotin derivatives as anti HIV protease inhibitors.<sup>21</sup> Biotin possesses a deceptively simple-looking structure. Its skeleton consists of a biheterocyclic core, to which is attached a carboxybutyl side chain. The heterocyclic system comprises a cyclic urea and a tetrahydrothiophene ring (which will be subsequently called as thiophane). It further possesses three contiguous stereocenters on the thiophane ring in the all-*cis* configuration. Because of the fundamental and commercial importance, biotin has, ever since it was discovered, attracted the attention of both academic and industrial synthetic chemists.

A continuous endeavor over a period of more than 50 years has now resulted in more than 40 original contributions on the total synthesis of biotin. Many of earlier syntheses known were lengthy involving a number of steps, without any stereochemical control. Then there was a drought of published information for 20 years when no significant progress in biotin synthesis was made. However, the recent recognition of the importance of biotin in poultry, biochemistry and pharmaceutical formulations, revived the interest in this molecule, and this is evident by a boom in a number of international patents (around 50) between 1970-2000. The above figure excludes the applications of biotin in biochemistry and related subjects.

## 2.2: Background for the present work

Some of the recent syntheses are discussed briefly since the syntheses of biotin up to 1992 were already reviewed by R. B. Tejwani of this laboratory,<sup>22</sup> and also reviewed by De Clercq in 1997<sup>23</sup> the current section is mostly restricted to the syntheses reported after 1995.



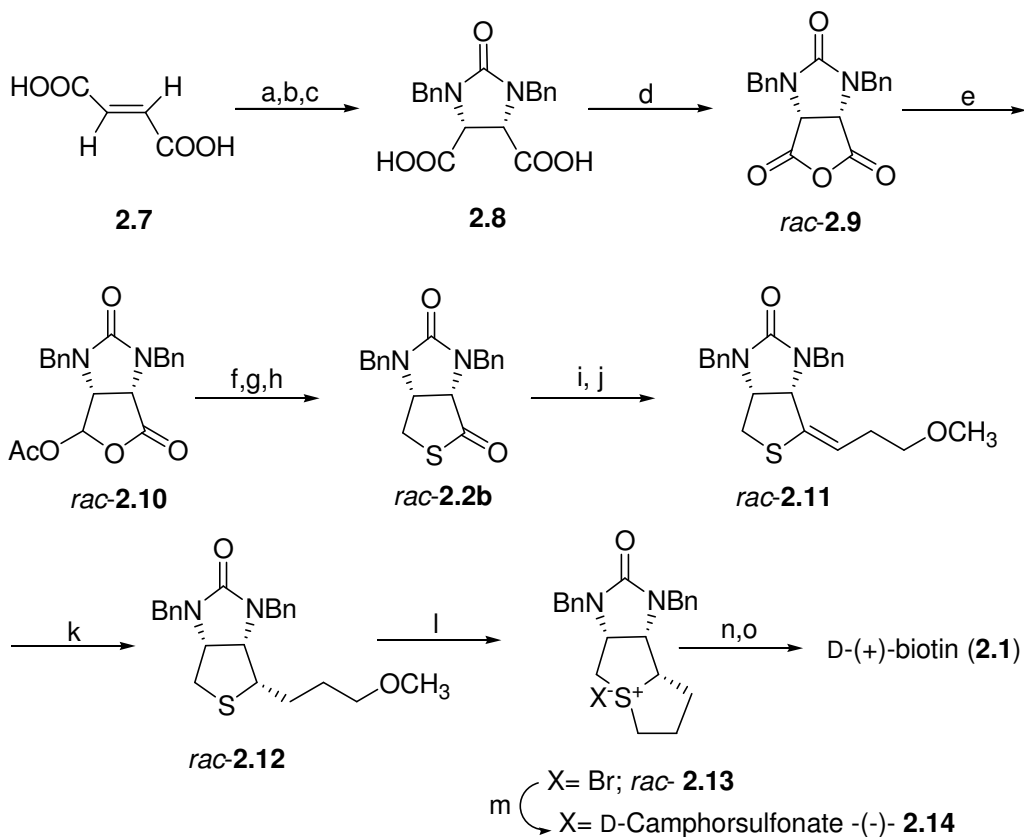
The following stereochemical designations are used in the Schemes: an unprefix Arabic numeral is used for achiral molecules and for chiral molecules which possesses the correct enantiomeric configuration for eventual conversion into (+)-biotin; the opposite enantiomeric configuration is indicated by prefix *ent* and racemic mixtures by the prefix *rac*. Throughout the section, the atom numbering along the thiophane nucleus shown above will be used.

### Goldberg, Sternbach's Approach I:

In 1946 Goldberg, Sternbach<sup>24-26</sup> described the total synthesis of (+)-biotin starting from cheaply available fumaric acid (Scheme 2.1). Fumaric acid is converted into the cyclic anhydride **2.9** via a four step. At this stage *cis* relation of the vicinal amino groups at C-3 and C-4 centers are fixed. In the second stage, the thiophane nucleus is formed by conversion of *meso*-**2.9** into thiolactone **2.2b**. This involves reduction of anhydride **2.9** with zinc in acetic acid, treatment of the resultant acetoxy lactone **2.10** with hydrogen sulfide, and its further reduction with zinc to yield thiolactone **2.2b** in racemic form. In the third stage, part of the carboxy butyl chain of biotin was introduced via Grignard reaction with subsequent dehydration to form the exocyclic olefin **2.11** with undefined double bond stereochemistry. Catalytic hydrogenation of the latter yields **2.12** with the desired all *cis* relative configuration. In the fourth stage ether **2.12** is converted into the thiophanium salt **2.13** by treatment with hydrobromic acid (HBr). At this point, resolution is effected by conversion of bromide **2.13** into the diastereomeric sulfonate salt **2.14** which are readily separated in excellent yield by simple fractional crystallization. In

the final stage of the synthesis the side chain is accomplished by reaction of diastereomer (-)-**2.14** with sodium diethyl malonate (Scheme 2.1).<sup>24-26</sup>

**Scheme 2.1**



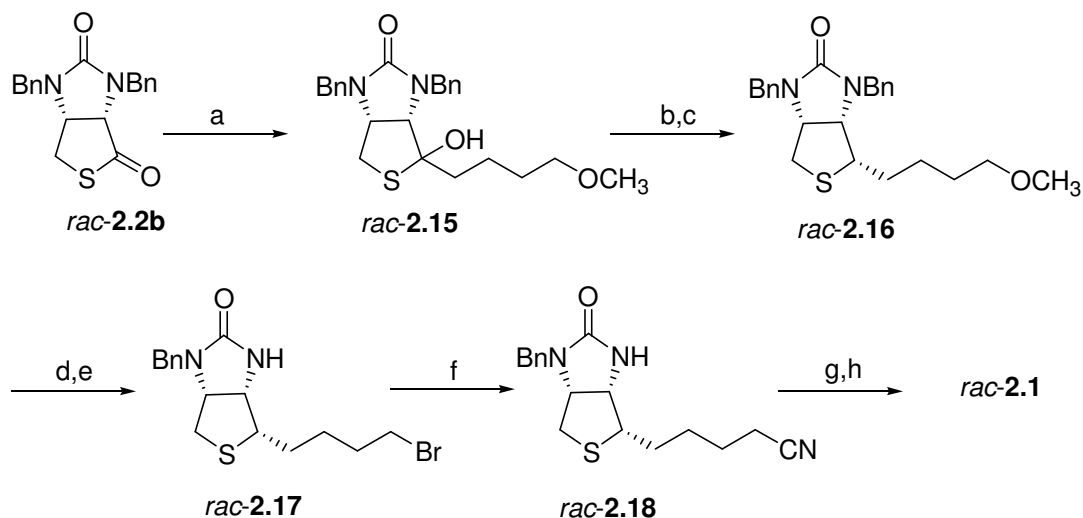
*Reagents and conditions:* a) Br<sub>2</sub>; b) BnNH<sub>2</sub>, EtOH; c) COCl<sub>2</sub>, KOH; d) Ac<sub>2</sub>O; e) Zn, Ac<sub>2</sub>O, HOAc; f) H<sub>2</sub>S, HCl; g) KSH, EtOH; h) Zn, HOAc; i) CIMg(CH<sub>2</sub>)<sub>3</sub>OCH<sub>3</sub>; j) HOAc; k) H<sub>2</sub>, Pd/C; l) HBr; m) silver *d*-camphorsulfonate, followed by fractional crystallization; n) NaCH(COOEt)<sub>2</sub>; o) 48% HBr.

Finally heating with conc. hydrobromic acid effected hydrolysis, subsequent decarboxylation, and debenylation all in one operation furnished biotin. Several intermediates in the above Scheme, and in particular, thiolactone **2.2b** has been obtained later in racemic or homochiral form by other groups thus constituting new formal synthesis of *rac*-biotin or (+)-biotin respectively.

## Goldberg, Sternbach's Approach II:

Another approach by Goldberg described a route in which the thiophanium salt was not involved. The conversion of thiolactone **2.2b** into *rac*-biotin involved a sequence of eight steps (Scheme 2.2).<sup>25</sup>

Scheme 2.2



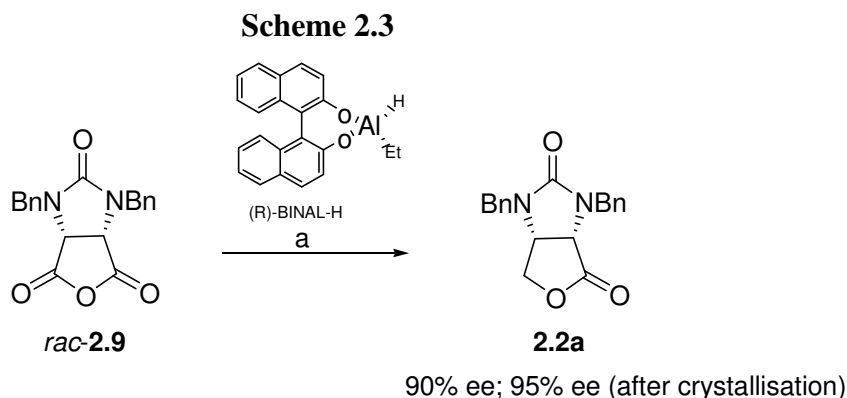
Thus Grignard reaction of **2.2b** with 4-methoxybutyl bromide furnished the alcohol **2.15**. Dehydration of **2.15** followed by catalytic hydrogenation yielded **2.16**. Removal of one benzyl group with sodium in liquid ammonia and conversion of the terminal methoxy alkyl group into the corresponding bromide **2.17** and its one carbon homologation with potassium cyanide furnished **2.18**, whose basic hydrolysis resulted in the formation of the corresponding carboxylic acid. Subsequent debenzylation with sodium in liq. ammonia furnished ( $\pm$ )-biotin.

## Matsuki's approach:

Matsuki and co-workers reported the highly enantioselective reduction of *meso*-1,2-dicarboxylic anhydride to yield optically active lactones using Noyori's lithium aluminium hydride-ethanol-1,1'-bis-2-naphthol complex (BINAL-H).<sup>27a</sup> When applied to

*meso*-**2.9**, the desired lactone **2.2a** was directly obtained in 76% yield with 90% *ee*, which was enriched to 95% *ee* by recrystallization from benzene/cyclohexane (Scheme 2.3).<sup>27b</sup>

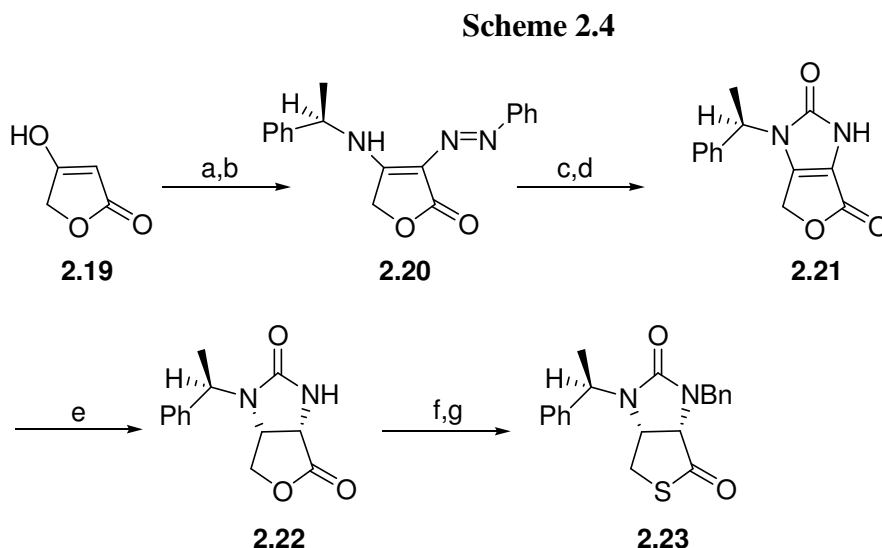
Although the chiral recognition mechanism is not clear, the general mechanism proposed by Noyori can be applied to explain the outcome of the reaction.<sup>27a</sup>



*Reagents and conditions:* a) (R)-BINAL-H, -78 °C to rt., THF, 76%

### Lonza's approach:

Another interesting asymmetric approach has been developed by a group, Lonza *et al*<sup>28,29</sup> that uses the hydrogenation of furoimidazole derivative **2.21**. The synthesis of this intermediate **2.21** involves a straightforward four-step sequence starting from tetronic acid, which upon further steps leads to intermediate thiolactone **2.23** (Scheme 2.4).<sup>28</sup>

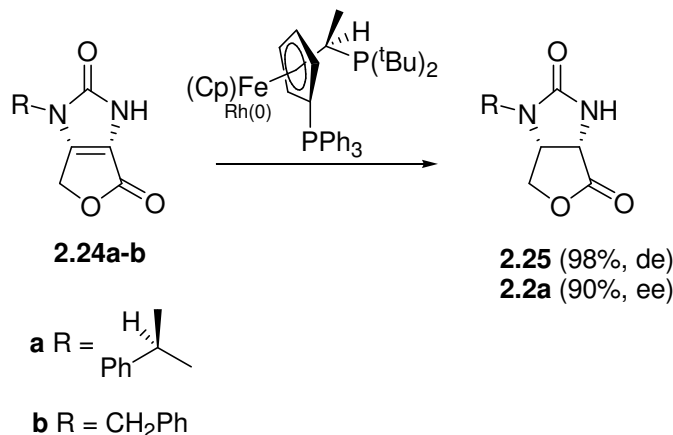


*Reagents and conditions:* a) PhNH<sub>2</sub>, NaNO<sub>2</sub>, HCl, 92%; b) (R)-PhCH(NH<sub>2</sub>)CH<sub>3</sub>, B(OEt)<sub>3</sub>, PhCH<sub>3</sub>, 80 °C; c) H<sub>2</sub>, Pt/C, EtOAc, 40 bar, 84%; d) ClCOOEt, Et<sub>3</sub>N, THF, CH<sub>3</sub>CN, reflux, 66%; e) H<sub>2</sub>, Rh/Al<sub>2</sub>O<sub>3</sub>, DMF, 40 bar, 54%; f) NaH, DME, BnBr; g) CH<sub>3</sub>COSK, CH<sub>3</sub>CON(CH<sub>3</sub>)<sub>2</sub>, 150 °C, 69%.

### McGarity's approach:

Very recently this group has reported the hydrogenation of **2.23** which was performed in the presence of a rhodium complex and a chiral ferrocenylphosphine ligand. The reduction of achiral **2.24** into **2.25** (95% yield; 90% *ee*) constitutes the second example in which the chirality is induced involving a catalytic pathway (Scheme 2.5).<sup>30,31</sup>

Scheme 2.5

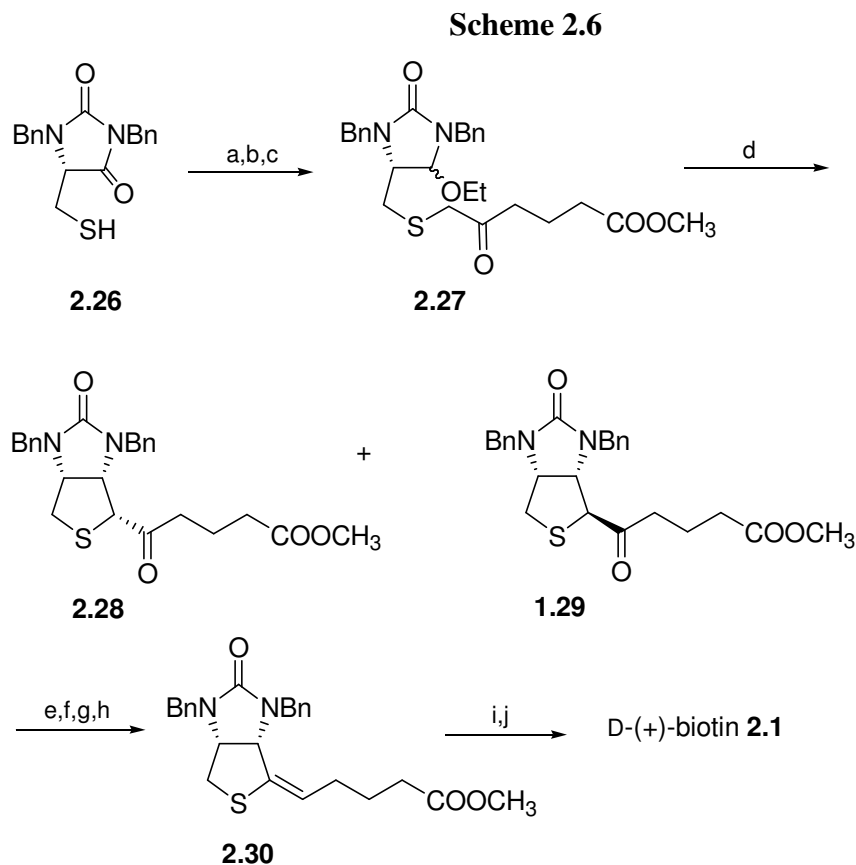


Reagent and conditions: a) Rh(0) = [Rh(norbornadiene)Cl]<sub>2</sub>, chiral ligand, PhCH<sub>3</sub>, 70 °C, H<sub>2</sub>, 50 bar, 95%.

### Speckamp, Poetsch and Casutt's approach:

In a joint effort, Speckamp and co workers and Poetsch and Casutt have used the intramolecular version of the condensation of silyl enol ether with *N*-acyliminium intermediate to effect the ring closure of thio ether **2.27** to the thiophane nucleus from the known intermediate **2.26**. The intermediate **2.26** is readily available from L-cysteine. Reduction with DIBAL-H led to the formation of corresponding hydroxy imidazolidinone (10:1) ratio of cis:trans diastereomers. Coupling with appropriate  $\alpha$ -chloro ketone furnished the thioether, which was converted into the ethoxy derivative **2.27**. The crucial cyclization step involved the use of ethyl(trimethylsilyl)acetate/tetra-*n*-butylammonium fluoride for the *in situ* enol ether formation and addition of trimethylsilyl triflate (TMSOTf) to induce the cyclization. This led to a 78% yield of the two diastereomers **2.28** and **2.29** (3:2 ratio). The further conversion of **2.28** and **2.29** into biotin. Indeed, the mixture is converted to the same exocyclic olefin **2.30** via sodium borohydride reduction, mesylation, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU)

elimination and saponification. Final conversion of **2.30** to biotin **2.1** proceeds in the usual way (Scheme 2.6).<sup>32a, b</sup>



Reagents and Conditions: a) DIBAL-H, THF, -70 °C, 1h; b) MeO<sub>2</sub>C(CH<sub>2</sub>)<sub>3</sub>C(O)CH<sub>2</sub>Cl, Et<sub>3</sub>N, 4 h; c) H<sub>2</sub>SO<sub>4</sub>/EtOH, methyl orange, pH = 3.1, 0 °C, 2 h, 72%. d) 2.1 eq. of (TMS)CH<sub>2</sub>CO<sub>2</sub>Et, 0.03 eq. of TBAF, THF, -78 °C to 25 °C, 18 h, then 1.5eq. of TMSOTf, DCM, -78 °C, 1 h, 78%; e) NaBH<sub>4</sub>, MeOH, 25 °C; f) MeSO<sub>2</sub>Cl, Et<sub>3</sub>N, DCM; g) DBU, 60 °C, 2h; h) KOH/MeOH, 2 h, 87%; i) H<sub>2</sub> (10 bar), 10% Pd/C, 2-propanol, 50 °C, 18h; j) 48% HBr, 100 °C, 2 h, 85%.

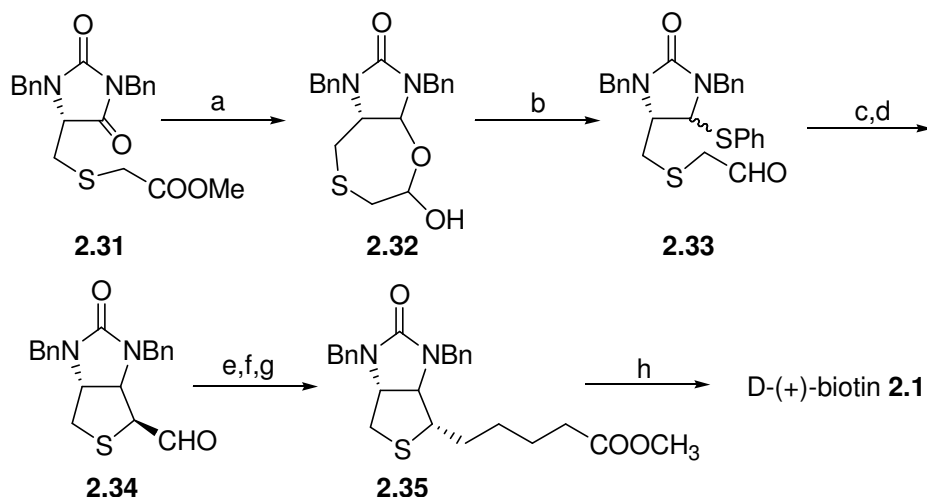
### Chavan's approach:

Chavan *et al.*<sup>32c,d</sup> have reported the synthesis of biotin on similar lines of *N*-acyliminium cyclisation. The hydrantoin **2.31** could be readily synthesized from cystine/cysteine. DIBAL-H reduction of carbonyl and ester of **2.31** furnished lactol **2.32**. Treatment of lactol **2.32** with thiophenol resulted in the formation of thioaminal aldehyde. Conversion of thioaldehyde **2.34** to the corresponding silyl enol ether followed by trialkyl triflate mediated cyclization in the presence of *p*-nitrobenzaldehyde as the thiophenol scavenger leads to the thermodynamically more stable thiophane aldehyde **2.34**. The transformation



of **2.34** into biotin involved first Wittig reaction with the 4-carbon ylide, followed by deconjugation with base to yield the exocyclic olefin. Further catalytic hydrogenation led to dibenzyl biotin methyl ester **2.35**, which on treatment with 48% HBr furnished D-(+)-biotin (Scheme 2.7).<sup>32d</sup>

**Scheme 2.7**



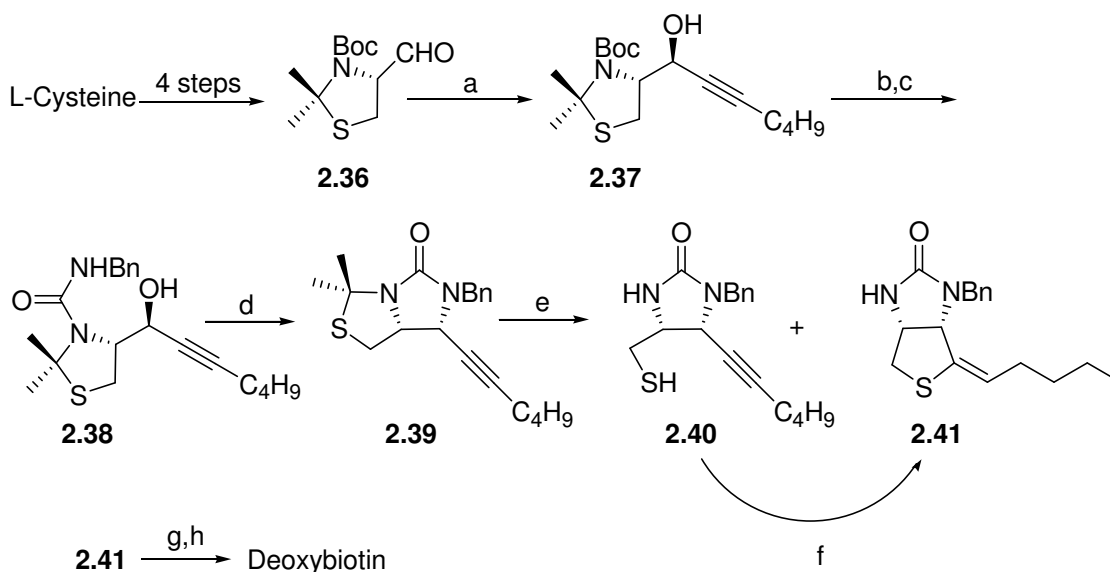
*Reagents and Conditions:* a) DIBAL-H, PhCH<sub>3</sub>, b) *p*-TsOH, PhSH; c) <sup>t</sup>BuMe<sub>2</sub>SiCl, DBU, DCM; d) <sup>t</sup>BuMe<sub>2</sub>SiOTf (cat.), *p*-NO<sub>2</sub>PhCHO, DCM; e) Ph<sub>3</sub>P=CH-CH=CH-CO<sub>2</sub>Me, DCM; f) DBU, DCM; g) H<sub>2</sub> (3 bar), Pd/C, MeOH; h) 48% HBr.

### Fujisawa's approach:

In 1994 Fujisawa and coworkers reported an interesting approach to (+)-deoxybiotin from L-Cysteine. The synthesis involves the diastereoface discrimination in the addition of an acetylide to chiral aldehyde **2.36** is obtained from L-Cysteine by known four synthetic steps.<sup>34c</sup> When the chlorozinc acetylide derived from 1-hexyne was condensed with aldehyde **2.36**, the propargylic alcohol **2.37** was obtained as the sole isomer in very good yield. Introduction of the amino group at C-3 in the required configuration resulted from an internal SN<sup>2</sup> displacement *via* potassium hydride treatment of the tosylated alcohol **2.38**. The latter was obtained from **2.37** after hydrolysis and formation of the mixed urea. Deprotection of the acetonide in **2.39** with 1 eq. of *p*-toluenesulphonic acid (*p*-TsOH) led to the cyclized thiophane **2.41** (23% yield) along with thiol **2.40** in 65% yield.

Further cyclization of **2.40** presented a regiochemical problem, since an undesired six membered isomer was formed in addition to desired **2.41**. The final conversion of **2.41** into (+)-deoxybiotin further involved catalytic hydrogenation and debenzylation (Scheme 2.8).<sup>33</sup>

**Scheme 2.8**

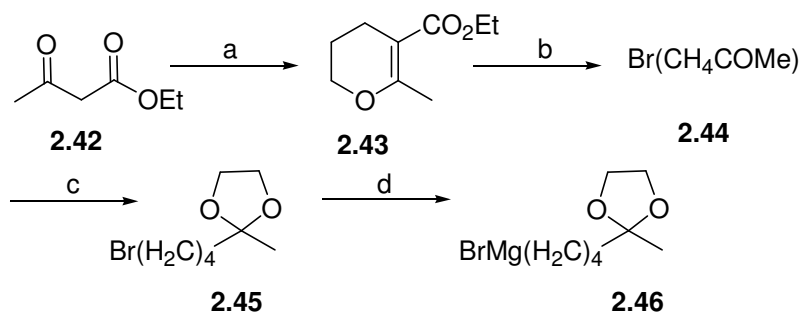


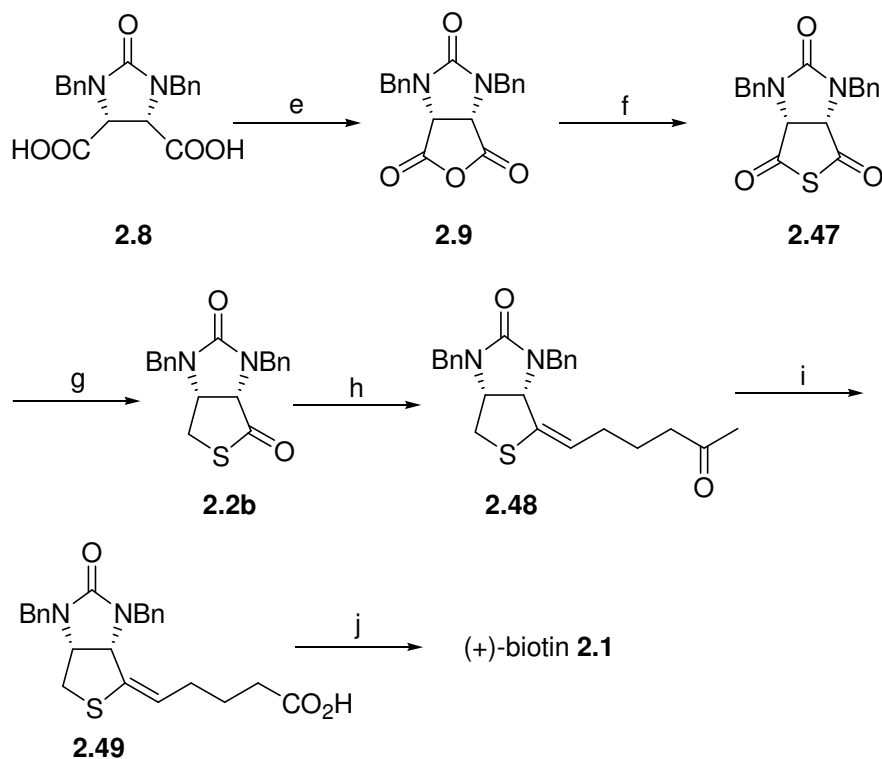
*Reagents and conditions:* a)  $C_4H_9C\equiv CZnCl$ ,  $Et_2O$ , 10 h, 86%; b) PTSA, MeOH, 35 °C, 11 h; c)  $PhCH_2NCHO$ ,  $C_5H_5N$ , 0 °C, 70%; d) KH, (5eq), p-TsCl, HMPA (30equ), THF, 86%; e) PTSA, MeOH/ $H_2O$ , 40 °C, 15 h; f) CsOH,  $H_2O/THF$ , 40 °C, 50%; g)  $H_2$ , Pd/C 10%, 2-propanol/ $H_2O$ ; h) HBr (47%), 73%

### Chen's approach:

In 2000 Chen and coworkers reported<sup>35</sup> an efficient and enantioselective synthesis of D-(+)-biotin using BINAL-H reduction of meso thioanhydride **2.47**.

**Scheme 2.9**





*Reagents and conditions:* a) 1-Bromo-3-chloropropane,  $K_2CO_3$ , toluene, 80 °C, 94%; b) 47% HBr, NaBr,  $H_2SO_4$ , 50 °C, 86%; c)  $(CHOH)_2$ , TsOH, toluene, reflux, 92%; d) Mg, THF, rt; e).  $Ac_2O$ , (83%)  $H_3PO_4$  (cat.) ,reflux, 98%; f)  $Na_2S \cdot 9H_2O$ , THF,  $H_2O$ , rt, 49%; g) (*R*)-BINAL-*H*, THF, -78 °C to rt, 83%; h) **2.46**, THF, reflux, then 30%  $H_2SO_4$ , 60 °C, 82%; i)  $I_2$ , KI, 10% NaOH, dioxane, 60 °C, 75%; j) 75% HCOOH,  $CH_3SO_3H$ , 10% Pd/C, reflux, 85%.

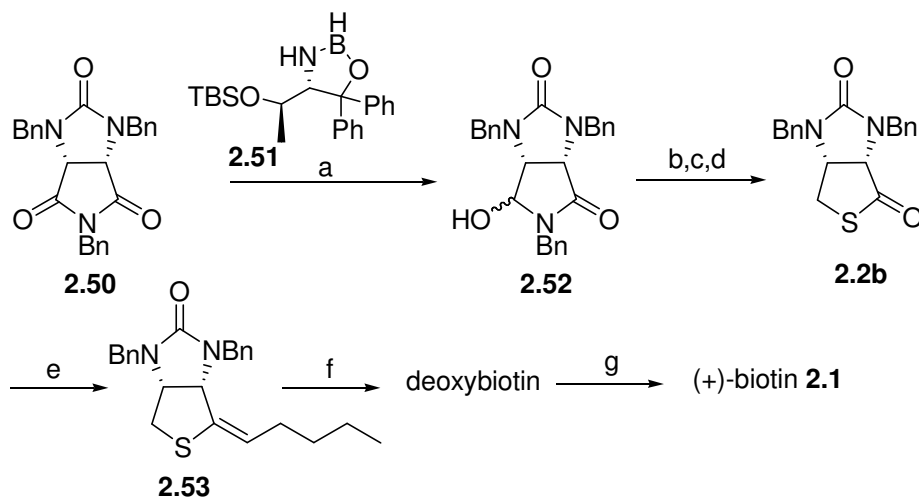
The synthesis starts with *cis*-1,3-dibenzyl-2-imidazolidine-4,5-dicarboxylic acid **2.8**. The key steps are the enantioselective reduction of meso-1,2-dicarboxylithioanhydride **2.47** to prepare the (3*aS*,6*aR*)-thiolactone **2.2b**, and the introduction of the six carbon side chain on **2.2a** was performed by modified Grignard reaction. This novel synthesis proceeded in six steps starting from **2.8** to afford **2.1** with 21% overall yield (Scheme 2.9).<sup>35</sup>

#### Shimazu's approach:

The known *meso*-imide **2.50** was reduced using oxazaborolidine derived from L-threonine and borane-THF complex **2.51** to give lactam **2.52** in high enantiomeric purity.<sup>36</sup> The hydroxy lactam **2.52** was reduced with  $NaBH_4$  to give hydroxy amide and the subsequent treatment with sulfuric acid gave the lactone. Thiolactone **2.2b** formation

was carried out as described in the literature<sup>38</sup> in 87% yield. The side chain was introduced by the addition of a Grignard reagent followed by treatment with acetic acid gave **2.2b** in 82% yield. Stereospecific hydrogenation of double bond and further *N*-debenzylation with Na in liq. NH<sub>3</sub> gave (+)-deoxybiotin and (+)-biotin **2.1** in good yield (Scheme 2.10).

**Scheme 2.10**

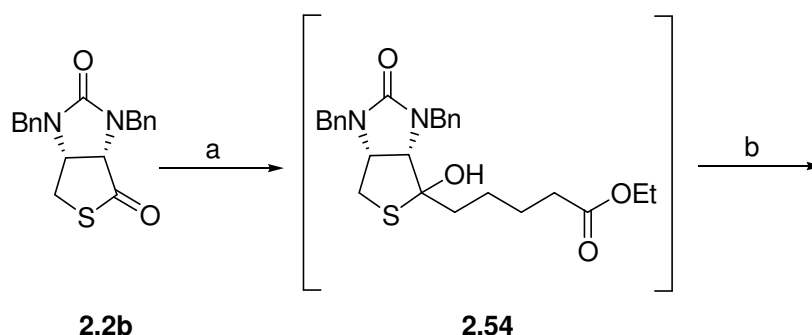


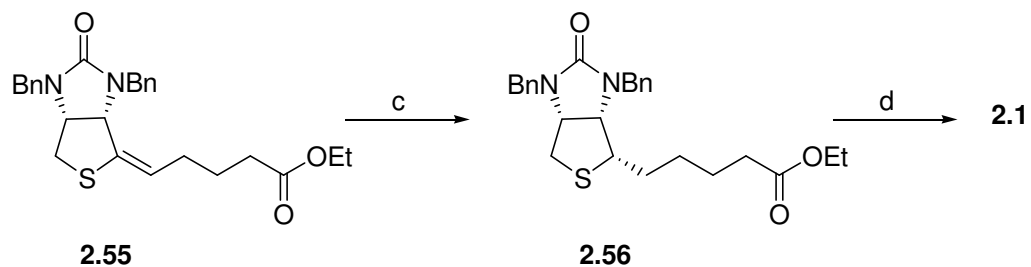
*Reagents and conditions:* a) BH<sub>3</sub>-THF (2.1 equ) b) NaBH<sub>4</sub> (4.0 eq), THF-H<sub>2</sub>O (10:1), 71%; c) 2N H<sub>2</sub>SO<sub>4</sub>-1,4-dioxane (8:1), 0 °C, 92%; d) CH<sub>3</sub>COSK, DMF, 150 °C, 87%; e) n-C<sub>5</sub>H<sub>11</sub>MgBr, THF, AcOH, reflux, 82%; f) i) Pd black, H<sub>2</sub>, 40 °C, iPrOH-H<sub>2</sub>O (6:1), 90%; ii) Na liq. NH<sub>3</sub>, THF, 62%; g) ref. 37

**Seki's approach I:**<sup>39-45</sup>

Very recently Seki *et al* have reported<sup>39</sup> a facile synthesis of D-(+)-biotin using Fukuyama coupling of carbonyl compounds (Scheme 2.11).

**Scheme 2.11**



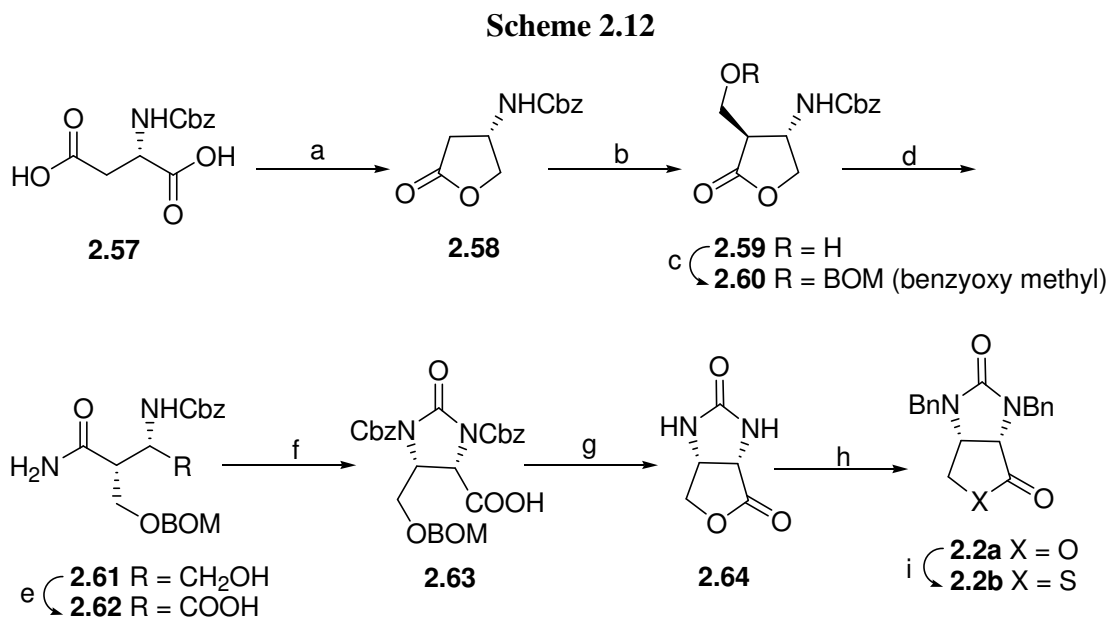


*Reagents and conditions:* a)  $\text{IZn}(\text{CH}_2)_4\text{COOEt}$  (3 eq),  $\text{PdCl}_2(\text{PPh}_3)_2$  (10 mmol%), THF, toluene, DMF, 20 °C; b) *p*-TSA, toluene, 20 °C, 18 h; c)  $\text{H}_2$  (70 atm), Pd/C, EtOH, 100 °C, 3 h; d) i) 48% HBr, reflux, 48 h, ii)  $\text{ClCOOEt}$ , NaOH, iii) HCl 80%.

The known thiolactone **2.2b** with zinc reagent in presence of  $\text{PdCl}_2(\text{Ph}_3)_2$  in mixed solvent at 20 °C for 35 h gave alcohol **2.54** which without purification was allowed to react with *p*-TSA in toluene at 20 °C to furnish known olefin **2.55** in 86% yield. The final conversion of **2.55** into (+)-biotin **2.1** further involved catalytic hydrogenation and debenzylation (Scheme 2.11).<sup>39</sup> The same group Seki *et al.* reported another synthesis of biotin from L-Cystein utilizing Strecker's reaction as a key step.<sup>44</sup>

### Seki's approach II:

In 2002 Seki *et al.* have reported the synthesis of biotin starting from L-aspartic acid as a chiral synthon. (Scheme 2.12).<sup>41</sup>



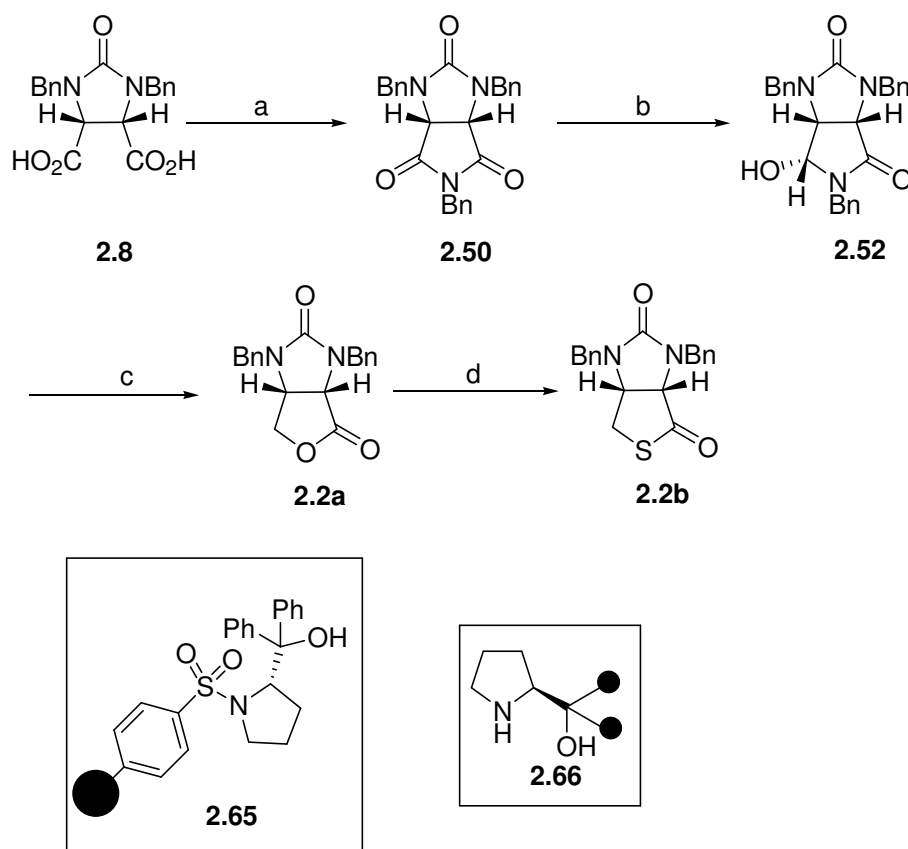
*Reagents and conditions:* a) i)  $\text{Ac}_2\text{O}$ , ii)  $\text{NaBH}_4$ , THF, iii) HCl; b) i) LDA, THF, ii) HCHO, -78 °C, 62%, *trans/cis* = 12:1; c) BOMCl, *i*-Pr<sub>2</sub>NEt, THF; d)  $\text{NH}_4\text{OH}$ , MeOH; e) Jones' reagent, acetone; f) NaOCl, NaOH, H<sub>2</sub>O; g)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$ , MeOH; h) BnBr, NaH, DMF; i) AcSK, DMF.

The aldol reaction of an *N*-Cbz-3-amino-4-butanolide **2.57**, derived from L-aspartic acid, with formaldehyde gave the *trans*-disubstituted 3-amino-4-butanolide **2.59** stereoselectively. Following protection of the hydroxyl group of **2.59**, amidation and oxidation provided the substituted L-asparagine derivative **2.62**. The Hofmann rearrangement of **2.62** with sodium hypochlorite in the presence of sodium hydroxide and subsequent hydrogenation gave the bicyclic lactone **2.64**, which upon dibenylation and thionation, gave the thiolactone **2.2b**, a key intermediate for the synthesis of (+)-biotin **2.1**.

**Chen's approach:**

The essential steps in the two syntheses involve the enantioselective reduction of *meso*-cyclic imide **2.50** catalyzed by a polymer-supported chiral oxazaborolidine derived

**Scheme 2.13**



*Rgagents and conditions:* a)  $\text{PhCH}_2\text{NH}_2$ , 4 $^\circ\text{A}$  MS, xylene, reflux; b) **2.65**,  $\text{BH}_3\cdot\text{SMe}_2$ , THF, reflux or 80% NaH,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , **2.66**, THF, reflux; c)  $\text{KBH}_4$ , LiCl, THF, rt, then 1N aqu. HCl, 55  $^\circ\text{C}$ ; d) EtSC(S)SK, 125  $^\circ\text{C}$ .

from (*S*)-diphenylprolinol and polymer-bound sulfonyl chloride **2.65**, or chiral polymer supported oxaborolidine **2.66** derived from polymer supported ligand. The reduction using 80% NaH, BF<sub>3</sub>.Et<sub>2</sub>O, **2.66**, THF, reflux, was claimed to be advantageous over **2.65**, BH<sub>3</sub>.SMe<sub>2</sub>, THF, reflux in avoiding the use of BH<sub>3</sub>.DMS and easy for large scale production which was replaced by NaH, and BF<sub>3</sub>.Et<sub>2</sub>O (Scheme 2.13).<sup>46a, b</sup>

### 2.3: Present work

The biological and commercial importance of biotin has made it a fascinating target molecule for total synthesis for more than fifty years.<sup>22-49</sup> Although numerous synthetic approaches have been reported to date, the first synthesis of biotin described by Goldberg and Sternbach, and subsequent modifications is still one of the best known syntheses.<sup>24-26</sup> The potential of this approach depends upon the efficiency of the method available for making optically active lactone **2.2a** or thiolactone **2.2b**. This is considered to be one of the most expedient approaches to the synthesis of biotin.<sup>24-46</sup> Most of the syntheses reported for the bicyclic lactone **2.2a** revolve around the desymmetrization of *meso* diacid **2.8** and diester, cyclic anhydride **2.9** and bicyclic imide **2.50**, followed by further transformations. The conversion of *meso* diacid **2.8** to lactone **2.2a** via enzymatic resolution involved multi-step process and also resulted in poor overall yield.<sup>50</sup> Asymmetric hydrolysis of *meso* diester using PLE (pig liver esterase) gave low enantioselectivity for hemiesters.<sup>52</sup> The desymmetrization of cyclic anhydride<sup>27,53</sup> **2.9** and cyclic imide<sup>27b,54</sup> **2.50** by asymmetric reduction involved use of expensive chiral ligands in large quantities. A modified cinchona alkaloid was also reported as a catalyst for the desymmetrization of cyclic anhydride **2.9** to a hemiester.<sup>55</sup> Apart from these methods a multi-step synthesis of lactone **2.2a** from L-aspartic acid in 11% overall yield was reported.<sup>41</sup>

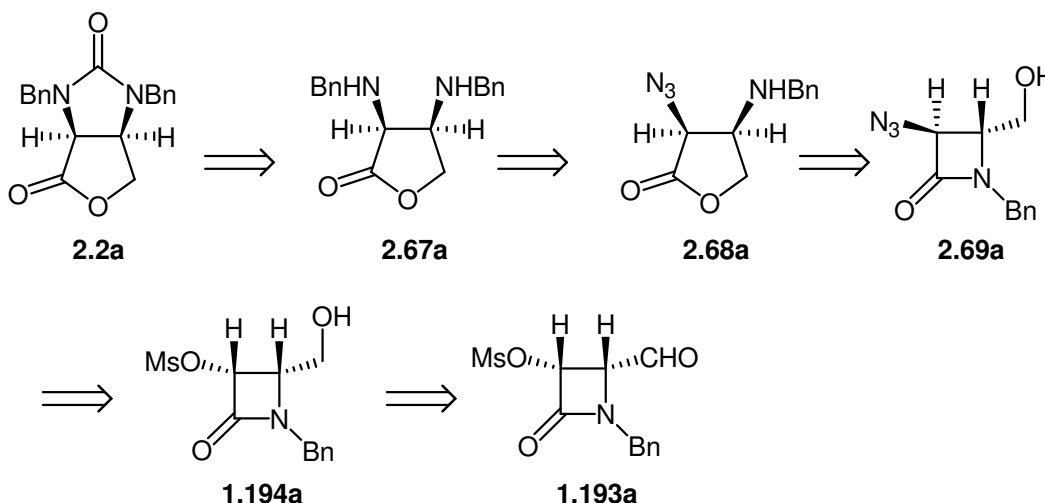
In spite of the biological significance and the commercial importance of biotin, there are very few practical methods available for the synthesis of enantiopure lactone **2.2a**, a key intermediate in the synthesis of D-(+)-biotin (**2.2**). A practical synthesis of (3*S*,6*R*)-1,3-dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione, an important intermediate in the synthesis of biotin, from 3-mesyloxy-4-formylazetid-2-one has been achieved. Acid catalyzed azetid-2-one ring opening followed by a one-pot conversion of diaminehydrochloride to a cyclic urea and hydroxymethylene to chloromethylene by

triphosgene to get (4*S*,5*R*)-methyl-1,3-dibenzyl-5-chloromethyl-2-oxo-imidazolidine-4-carboxylate is the key step in this synthesis.

## 2.4: Results and discussion

To the best of our knowledge there is no synthesis of D (+)-biotin using  $\beta$ -lactam synthon method and our experience in the  $\beta$ -lactam synthesis inspired us to design a retro-synthetic route for **2.1a**, from 4-formyl- $\beta$ -lactam. The retrosynthetic analysis is as shown in scheme (Scheme 2.14). Conversion of bicyclic lactone **2.2a** to D (+)-biotin is known in literature. The bicyclic lactone **2.2a** can be obtained from diamino lactone **2.67a** which in turn can be obtained from **2.68a**. We envisaged that **2.68a** can be obtained from a  $\beta$ -lactam having a hydroxy methylene group at C-4 position and an azido group at the C-3 position having a *trans* relationship with each other. This  $\beta$ -lactam can in turn be obtained with correct stereochemistry from *cis* 3-mesyloxy- $\beta$ -lactam **1.194a** by nucleophilic displacement of the mesyloxy group by an azide. **1.194a** can easily be obtained from *cis* 3-mesyloxy-4-formyl  $\beta$ -lactam **1.193a**.

Scheme 2.14

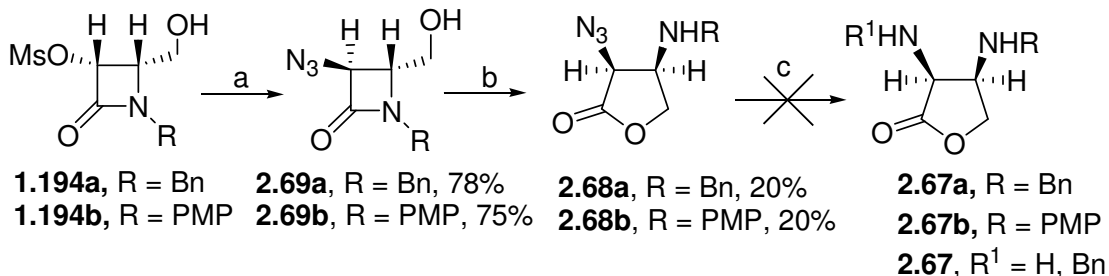


In previous chapter we have shown that aziridino- $\gamma$ -lactone can be obtained in excellent yield from 3-mesyloxy-4-formylazetididin-2-one (**1.193a**) in two steps (Scheme 1.57). The same procedure was employed for the preparation of optically pure starting *N*-benzyl-4-formyl-3-mesyloxyazetididin-2-one (**1.193a**) and its reduction to *N*-benzyl-4-hydroxymethyl-3-mesyloxyazetididin-2-one (**1.194a**) by sodium borohydride.



The displacement of the mesyloxy group with an azide was achieved by heating **1.194a** with sodium azide in dry DMF at 80 °C for 36 h. The *trans*-azido- $\beta$ -lactam **2.69a** was obtained in very good yield with a complete inversion of the configuration at C-3 of the azetidin-2-one ring (Scheme 2.15). The main objective of this reaction is to obtain required stereochemistry of target molecule, which can be obtained only from its *trans*- $\beta$ -lactam precursor. To a solution of **1.194a** in dry DMF was added sodium azide and stirred at 80 °C for 36 h to get crude product, which was purified by column chromatography to afford 3-azido  $\beta$ -lactam **2.69a** as a white solid. The structure of **2.69a** was established by spectral and analytical data.

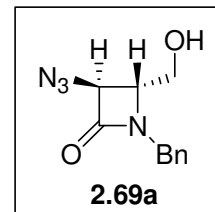
**Scheme 2.15**



*Reagents and Conditions:* a) NaN<sub>3</sub>, DMF, 80 °C, 36 h; b) HCl-MeOH (20%), rt, 34 h; c) HCOONH<sub>4</sub>, Pd/C (10%), MeOH, reflux, 40 min.; or H<sub>2</sub>, Pd/C (10%), EtOH, 60 psi, 5 h, or Bu<sub>3</sub>P, THF, Et<sub>3</sub>N, BnBr, 5 h.

The IR spectrum of **2.69a** showed a sharp band at 1731 cm<sup>-1</sup> corresponds to the  $\beta$ -lactam carbonyl group. The sharp band at 2102 cm<sup>-1</sup> corresponds to the azide group.

The <sup>1</sup>H NMR spectrum of **2.69a** showed a broad singlet at 1.79 ppm corresponding to hydroxyl proton. The signals due to proton corresponding to C-4 position of  $\beta$ -lactam resonated as a multiplet at 3.34-3.51 ppm while, methylene protons at C-4 position of  $\beta$ -lactam appeared as a doublet at 3.67 ppm with *J* = 3.3 Hz.



Protons at C-3 position of  $\beta$ -lactam appeared as a singlet at 4.56 ppm. The benzyl protons appeared as two doublet at 4.33 ppm and 4.52 ppm with *J* = 14.9 Hz. The aromatic protons appeared as multiplet between 7.26-7.39 ppm.

The  $^{13}\text{C}$  NMR of **2.69a** showed a peak at 44.7 ppm corresponds to hydroxy methylene carbon at C-4 position  $\beta$ -lactam ring. The benzylic carbon on nitrogen appeared at 58.6 ppm. The C-3 and C-4  $\beta$ -lactam carbons appeared at 64.8 ppm and 60.1 ppm respectively. The peak displaying at 134.5 ppm was assigned to aromatic quaternary carbon while, other aromatic carbons appeared at 128.0, 128.9 ppm. The peak at 164.7 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **2.69a** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  233 (M+1).

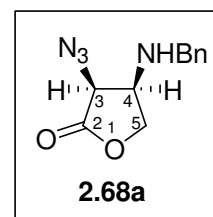
The azetidin-2-one ring expansion reaction of **2.69a** with methanolic-HCl at room temperature resulted azidolactone **2.68**. 3-Azido-4-hydroxymethyl azetidin-2-one (**2.69**) was dissolved in methanolic HCl (20%) and the reaction mixture was stirred for 34 h at room temperature to get crude product which was quickly purified by flash column chromatography furnished **2.68a** as a white solid. The structure of **2.68a** was established by spectral and analytical data.

The IR spectrum of **2.68a** showed a sharp band at  $1774\text{ cm}^{-1}$  corresponds to the  $\gamma$ -lactone carbonyl group. The band at  $2119\text{ cm}^{-1}$  corresponds to the azide group.

The  $^1\text{H}$  NMR spectrum of **2.68a** showed multiplet at 4.22-4.29 ppm for the benzyl protons and one of the methylene proton of lactone ring while, other methylene proton of  $\gamma$ -lactone ring resonated as doublet of doublet at 4.54 ppm with  $J = 6.9$  and  $11.1$  Hz. The C-4  $\gamma$ -lactone ring proton appeared as multiplet at 4.80-4.94 while, C-3  $\gamma$ -lactone ring proton resonated as a doublet at 5.30 ppm with  $J = 7.4$  Hz. The aromatic protons appeared as multiplet between 7.42-7.58 ppm.

The  $^{13}\text{C}$  NMR of **2.68a** showed a peak at 51.7 ppm corresponds to methylene carbon at C-5 position  $\gamma$ -lactone ring. The benzylic carbon attached on nitrogen appeared at 68.2 ppm. The C-3 and C-4  $\gamma$ -lactone carbon appeared at 57.7 ppm and 55.6 ppm respectively. The peak displaying at 132.3 ppm was assigned to aromatic quaternary carbon while, other aromatic carbons appeared at 130.3, 131.0, 131.3 ppm. The peak at 172.6 ppm was assigned to  $\gamma$ -lactone carbonyl carbon. The compound **2.68a** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  233 (M+1).

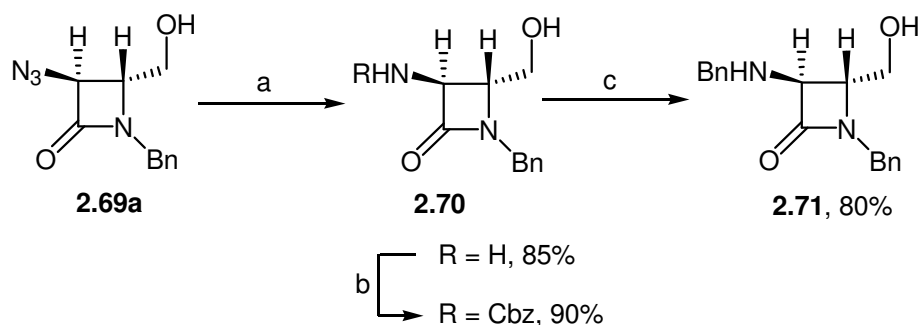
The azetidin-2-one ring expansion reaction of **2.69a** with methanolic-HCl at room temperature resulted in very poor yield (20%) of the azidolactone **2.68**. All our efforts to



improve the yield of **2.68a** were unsuccessful. Moreover, the reduction of azido group by catalytic hydrogenation or transfer hydrogenation gave a complex mixture of products. The Staudinger reaction of azide **2.68a** with *n*-tributylphosphine in the presence of benzyl bromide also did not give the desired product **2.67a** (R = Bn).

Since all our efforts to improve the yield of azidolactone **2.56a** and its further reduction to amino lactone failed, to overcome the difficulties encountered in above rout, we planed to reduce azido- $\beta$ -lactam **2.69a** to the corresponding amino- $\beta$ -lactam **2.70** (R = H). The reduction of azido- $\beta$ -lactam **2.69a** was successfully achieved by transfer hydrogenation using Pd/C and ammonium formate in methanol to get amino- $\beta$ -lactam **2.70** (R = H) in very good yield (Scheme 2.16).

**Scheme 2.16**

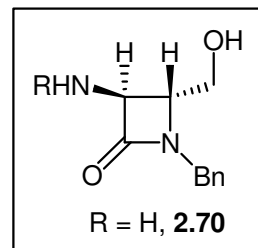


*Reagents and conditions:* a) HCOONH<sub>4</sub>, Pd/C (10%), MeOH, reflux, 45 min; b) CbzCl, NaHCO<sub>3</sub>, acetone-water (2:1), 1.5 h; c) i) PhCHO, MgSO<sub>4</sub>, DCM, rt, 12 h  
ii) NaBH<sub>4</sub>, MeOH, 0 °C to rt, 2.5 h;

The structure of **2.70** (R = H) was confirmed by IR and <sup>1</sup>H NMR data.

The IR spectrum of **2.70** (R =H) showed a sharp band at 1739 cm<sup>-1</sup> corresponds to the  $\beta$ -lactam carbonyl group.

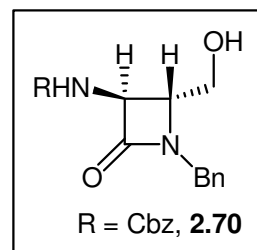
The <sup>1</sup>H NMR spectrum of **2.70** (R = H) displayed a multiplet of three protons at 2.10-2.22 ppm for amino and hydroxyl protons. The C-3 and C-4  $\beta$ -lactam ring protons resonated as a two singlets at 3.99 ppm and 3.29 ppm respectively. The hydroxyl methylene protons at C-4 position of  $\beta$ -lactam appeared as doublet at 3.61 ppm with *J* = 3.6 Hz. The benzyl protons appeared as two doublet at 4.26 and 4.41 ppm with *J* = 14.9 Hz. The aromatic protons appeared as multiplet between 7.20-7.29 ppm. Mass spectrum of this compound showed a peak at *m/z* 207 (M+1). The compound was found unstable



and the changed to dark brown colour on keeping at room temperature. The amino- $\beta$ -lactam **2.70** (R = H) was further converted to the corresponding *N*-Cbz-derivative for the purpose of fully characterization. The structure was established by spectral and analytical data.

The IR spectrum of **2.70** (R = Cbz) showed a sharp band at  $1747\text{ cm}^{-1}$  corresponds to the  $\beta$ -lactam carbonyl group.

The  $^1\text{H}$  spectrum of **2.70** (R = Cbz) displayed a multiplet for three protons at 3.48-3.63 ppm corresponding for hydroxyl methylene protons and C-4  $\beta$ -lactam proton. One of the benzylic proton on nitrogen showed a doublet at 4.25 ppm with  $J = 14.9\text{ Hz}$  while, other proton, C-3  $\beta$ -lactam proton and  $-\text{OH}$  proton were merged and displayed a multiplet at 4.39-4.47 ppm. The benzyl protons of Cbz group appeared as a two doublets at 4.99 ppm and 5.06 ppm with  $J = 12.2\text{ Hz}$ . The broad singlet at 5.63 ppm corresponds for carbamate proton. The all aromatic protons appeared as multiplet between 7.19-7.26 ppm.

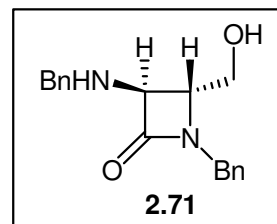


The  $^{13}\text{C}$  NMR of **2.70** (R = Cbz) showed a peak at 67.3 ppm corresponds to methylene carbon at C-4 position  $\beta$ -lactam ring. The benzylic carbon attached on nitrogen appeared at 60.5 ppm while benzyl carbon of carbamate appeared at 67.3 ppm. The C-3 and C-4  $\beta$ -lactone carbon appeared at 61.8 ppm and 60.0 ppm respectively. The peaks displaying at 135.2 ppm and 135.8 ppm was assigned to aromatic quaternary carbons while, other aromatic carbons appeared at 128, 128.1, 128.2, 128.5, 128.9 ppm. The peak at 156.2 corresponds for carbonyl carbon of carbamate. The peak at 165.7 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **2.70** (R = Cbz) also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  341 (M+1).

The amino- $\beta$ -lactam **2.70** (R = H) was then transformed to *N*-benzyl derivative **2.71** in good yield by reacting with benzaldehyde followed by *in situ* reduction of the corresponding Schiff base with sodium borohydride. The crude product was purified by silica gel column chromatography to afford pure **2.71** as colorless oil. The structure of **2.71** was established by spectral and analytical data.

The IR spectrum of **2.71** showed a broad band at  $3384\text{ cm}^{-1}$  for hydroxyl and amino group while, a sharp band at  $1731\text{ cm}^{-1}$  corresponds to the  $\beta$ -lactam carbonyl group.

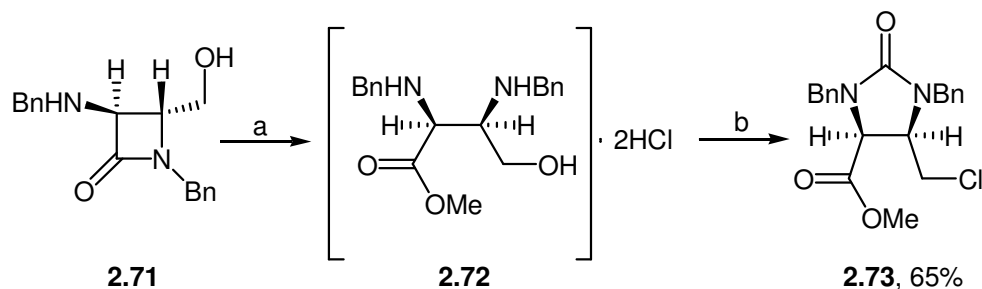
The  $^1\text{H}$  NMR of **2.71** showed a broad singlet at 1.95 ppm corresponds for the hydroxyl proton. One of the hydroxy methylene proton resonated as a multiplet at 3.37-3.43 ppm while, other hydroxy methylene proton and C-4 proton of  $\beta$ -lactam were merged and appeared at 3.49-3.61 ppm. The signal displaying at 4.02 ppm as a doublet with  $J = 1.9\text{ Hz}$  corresponds for the C-4  $\beta$ -lactam ring proton. The benzyl protons on nitrogen atom of  $\beta$ -lactam ring appeared as a two doublets at 3.84 ppm and 3.94 ppm with  $J = 13.0\text{ Hz}$ . The amino benzyl protons also appeared as two doublets at 4.02 ppm and 4.36 ppm with  $J = 15.0\text{ Hz}$ . The all aromatic protons appeared as multiplet between 7.27-7.38 ppm.



The  $^{13}\text{C}$  NMR of **2.71** showed a peak at 60.4 ppm corresponds to hydroxy methylene carbon at C-4 position  $\beta$ -lactam ring. The benzylic carbon attached on nitrogen appeared at 51.2 ppm while benzyl carbon of amino benzyl appeared at 44.8 ppm. The C-3 and C-4  $\beta$ -lactam carbon appeared at 66.6 ppm and 61.1 ppm respectively. The peaks displaying at 135.8 ppm and 139.0 ppm was assigned to aromatic quaternary carbons while, other aromatic carbons appeared at 127.3, 127.9, 128.2, 128.3, 128.9, 129.1 ppm. The peak at 168.8 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **2.71** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  297 ( $M+1$ ).

*N*-Benzylamino- $\beta$ -lactam **2.71** was treated with methanolic-HCl (20%) at room temperature to get highly polar ring cleavage product, dihydrochloride **2.72**. Our efforts to isolate the free base from the dihydrochloride **2.72** in pure form were unsuccessful. Therefore, the dihydrochloride **2.72** was directly reacted with triphosgene in the presence of triethylamine. Interestingly, a one-pot conversion of diamine to cyclic urea and hydroxymethylene to the corresponding chloromethylene took place simultaneously to afford chloroester **2.73** in 65% yield as a white crystalline solid (Scheme 2.17).

### Scheme 2.17

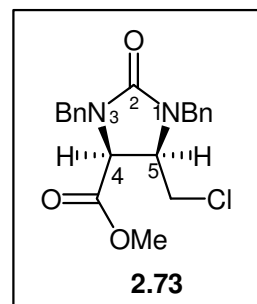


*Reagents and conditions:* a) HCl-MeOH (20%), rt, 14 h; b) Et<sub>3</sub>N, triphosgene, -20 °C, 2 h.

The structure of **2.73** was established by spectral data and further confirmed by single crystal X-ray analyses (Fig. 2.2).

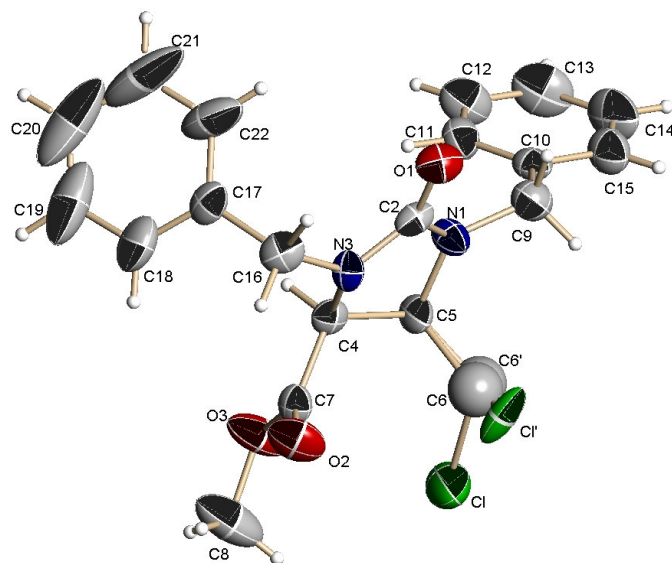
The IR spectrum of **2.73** showed a band at 1708 cm<sup>-1</sup> for carbonyl group of cyclic urea and sharp band at 1743 cm<sup>-1</sup> corresponds to the ester carbonyl group.

The <sup>1</sup>H NMR spectrum of **2.73** displayed a singlet at 3.66 ppm corresponding to methyl protons of ester group. The chloro methylene protons at C-5 were appeared as multiplet at 3.45-3.56 ppm. The C-5 ring proton was resonated at 3.70-3.80 ppm as a multiplet while, C-4 ring proton was appeared as doublet at 3.91 ppm with *J* = 11.1 Hz. The benzyl protons on N-3 appeared as two doublets at 3.95 ppm and 4.97 ppm with *J* = 14.9 Hz. The other benzyl protons also appeared as two doublets at 4.12 ppm and 4.79 ppm with *J* = 15.7 Hz. The ten aromatic protons appeared as multiplet between 7.13-7.30 ppm.



The <sup>13</sup>C NMR of **2.73** showed a peak at 52.5 ppm corresponds to methyl carbon of ester group. The methylene carbon of chloro methylene showed a peak at 40.5 ppm. The benzylic carbon on N-1 and N-3 displayed two peaks at 46.3 ppm and 46.6 ppm respectively. The peaks corresponding to C-4 and C-5 ring carbons appeared at 57.5 ppm and 55.8 ppm respectively. The peaks displaying at 136.0 ppm and 136.5 ppm was assigned to aromatic quaternary carbons while, other aromatic carbons appeared at 127.8, 128.5, 128.8, 129.1 ppm. The peak at 159.8 ppm was assigned to ester carbonyl carbon and peak at 168.9 ppm was attributed for carbonyl carbon of cyclic urea. The compound

**2.73** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  373 ( $M+1$ ). The structure of **2.73** was further confirmed by single crystal X-ray analyses. **X-Ray crystal data for 2.73:** Single crystals of the compound were grown by slow evaporation of the solution mixture of DCM and pet-ether. Colourless needle of approximate size 0.40 x 0.09 x 0.04 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo  $K_{\alpha}$  radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, multiscan data acquisition. Total scans = 5, total frames = 2142, Oscillation / frame  $-0.3^{\circ}$ , exposure / frame = 25.0 sec / frame, maximum detector swing angle =  $-30.0^{\circ}$ , beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration,  $\theta$  range =  $2.21$  to  $22.49^{\circ}$ , completeness to  $\theta$  of  $22.49^{\circ}$  is 99.8 %. SADABS correction applied,  $C_{20}H_{21}ClN_2O_3$ ,  $M = 372.84$ . Crystals belong to orthorhombic, space group  $P2_12_12_1$ ,  $a = 5.7271(4)$ ,  $b = 13.1934(9)$ ,  $c = 25.7863(17)$  Å,  $V = 1948.4(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.271$  mg m<sup>-3</sup>,  $\mu$  (MoK $\alpha$ ) =  $0.217$  mm<sup>-1</sup>,  $T = 293(2)$  K, 13315 reflections measured, 2553 unique [ $I > 2\sigma(I)$ ], R value 0.0973, wR2 = 0.2043. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)<sup>56</sup> was used for structure solution and full matrix least squares refinement on  $F^2$ . Hydrogen atoms were included in the refinement as per the riding model.

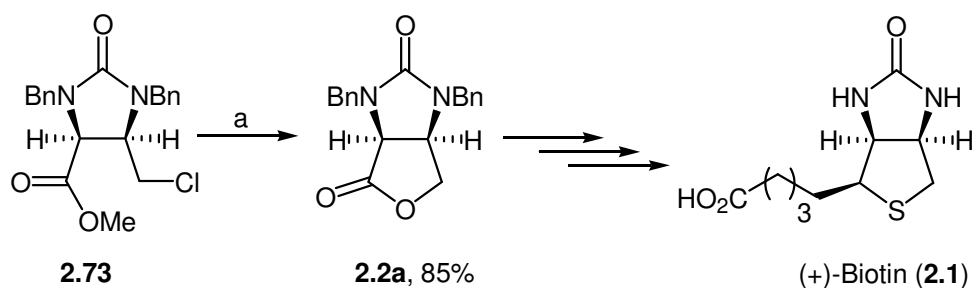


**Figure 2.2** ORTEP diagram of **2.73**

X-Ray analysis revealed the stereochemistry of C-4 and C-5 carbon centers as 4*S* and 5*R* respectively. The molecule has a disorder in the alkyl halide group attached to C-5 carbon atom (Fig. 2.2).

The conversion of the chloroester **2.73** to the desired (3*S*,6*R*)-1,3-dibenzyl-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (**2.2a**), was achieved by stirring with aqueous KOH afforded crude product which was purified by column chromatography to get lactone **2.2a** as a white crystalline solid (Scheme 2.18).

**Scheme 2.18**



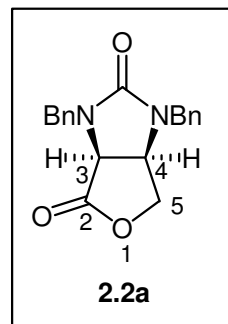
*Reagents and conditions:* a) Aq. KOH (2.5%), THF, 0 °C to rt, 5 h.

The optical purity (ee > 99%) was determined by chiral HPLC. The spectral data and the specific rotation were found to be identical with the reported values.  $[\alpha]_D^{25} = + 58.1$  (*c* 1.2, CHCl<sub>3</sub>) {Lit.  $[\alpha]_D^{25} = + 58.2$  (*c* 1, benzene)<sup>38</sup>;  $[\alpha]_D^{25} = + 56.4$  (*c* 1.12, CHCl<sub>3</sub>)<sup>55</sup>}.

The synthesis of D-(+)-biotin **2.1** from the lactone **2.2a** can be achieved by using a reported synthetic protocol.<sup>24-46</sup>

The IR spectrum of **2.2a** showed a sharp band at 1782 cm<sup>-1</sup> corresponds to the  $\gamma$ -lactone carbonyl group. The band at 1703 cm<sup>-1</sup> corresponds to the carbonyl group of cyclic urea.

The <sup>1</sup>H NMR spectrum of bicyclic lactone **2.2a** showed a doublet at 3.84 ppm with *J* = 8.0 Hz corresponds to one of the distreotropic  $\gamma$ -lactone methylene (C-5) proton while, other proton appeared as doublet at 4.24 ppm with *J* = 6.4 Hz. The  $\gamma$ -lactone ring proton (C-4) and *N*-benzyl protons at C-4 were merged and appeared as multiplet at 4.02-4.07 ppm. The other  $\gamma$ -lactone ring proton (C-3) resonated as a doublet at 4.30 with *J* =





5.9 Hz. The N-benzyl proton at C-3 position appeared as two doublet at 4.55 ppm and 4.96 with  $J = 14.9$  Hz. The aromatic protons appeared as multiplet between 7.18-7.29 ppm.

The  $^{13}\text{C}$  spectrum of bicyclic lactone **2.2a** showed two peaks at 45.2 ppm and 46.9 ppm corresponds to the benzylic carbons. The  $\gamma$ -lactone ring methylene carbon (C-5) showed a peak at 70.1 ppm. The peaks corresponding for C-3 and C-4 ring carbons appeared at 54.4 ppm and 52.5 ppm respectively. The peaks displaying at 135.9 ppm and 136.0 ppm was assigned to aromatic quaternary carbons while, other aromatic carbons appeared at 127.8, 128.1, 128.2, 128.7, 128.8, 129.0 ppm. The peak at 158.2 ppm was assigned to carbonyl carbon of cyclic urea and peak at 172.7 ppm was attributed for carbonyl carbon of  $\gamma$ -lactone ring. The compound **2.2a** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  323 (M+1).

## 2.5: Conclusion

In conclusion we have demonstrated the utility of azetidin-2-one as a synthon for the synthesis of the bicyclic lactone **2.2a**, an important intermediate in biotin synthesis. In this synthesis a crucial step is the azetidin-2-one ring opening followed by a one-pot conversion of diaminehydrochloride to cyclic urea and hydroxymethylene to chloromethylene by triphosgene to get the cyclic chloroester **2.73**. The starting  $\beta$ -lactam is also easily available in optically pure form and all the other steps of the synthesis are operationally simple and gave very good yields.

## 2.6: Experimental

### (3*S*,4*R*)-3-Azido-1-benzyl-4-hydroxymethylazetid-2-one (2.69a):

To a solution of **1.194a** (0.6 g, 2 mmol) in dry DMF (20 mL) was added sodium azide (0.650 g, 10 mmol) and stirred at 80 °C for 36 h. After completion of reaction (TLC) the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with water (4 x 20 mL) and saturated brine solution (10 mL) successively. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to afford a crude product, which was purified by column chromatography using acetone/petroleum ether (20:80) to afford 3-azido  $\beta$ -lactam **2.69a** (0.380 g, 78%) as a white solid.

**MP** : 72-73 °C.

**$[\alpha]_D^{30}$**  : -228 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3392, 2102, 1731 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** :  $\delta_H$  1.79 (s, 1H), 3.47-3.51 (m, 1H), 3.67 (d, *J* = 3.3 Hz, 2H), 4.33 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 14.9 Hz, 1H), 4.56 (s, 1H), 7.26-7.39 (m, 5H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** :  $\delta_C$  44.7, 58.6, 60.2, 64.8, 128, 128.9, 134.5, 164.7.

**(CDCl<sub>3</sub>)**  
(50.32 MHz)

**MS (m/z)** : 233 (M+1).

**Analysis** : Calculated: C, 56.87; H, 5.21; N, 24.13.

(C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>) Observed: C, 56.70; H, 5.17; N, 24.04.

### (3*S*,4*R*)-3-Azido-1-(4-methoxyphenyl)-4-hydroxymethylazetid-2-one (2.69b):

Following the above procedure, **1.194b** (0.9 g, 3 mmol) in dry DMF (20 mL) was added sodium azide (1.0 g, 15 mmol) and stirred at 80 °C for 36 h gave a crude product, which was purified by column chromatography using acetone/petroleum ether (15:85) to afford 3-azido  $\beta$ -lactam **2.69b** (0.556 g, 75%) as a colourless oil.

**$[\alpha]_D^{30}$**  : -128.2 (*c* 1.1, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3412, 2111, 1751 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_H$  1.95 (s, 1H), 3.80 (s, 3H), 3.98-4.14 (m, 3H), 4.77 (s, 1H),

(CDCl<sub>3</sub>) 6.90 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H).  
(200 MHz)  
<sup>13</sup>C NMR : δ<sub>C</sub> 55.4, 58.4, 60.8, 64.9, 114.5, 119.2, 129.5, 156.8, 161.3.  
(CDCl<sub>3</sub>)  
(50.32 MHz)  
MS (m/z) : 249 (M+1).  
Analysis : Calculated: C, 53.21; H, 4.88; N, 19.34.  
(C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>) Observed: C, 53.10; H, 4.75; N, 19.19.

**(3*S*,4*R*)-3-Azido-4-(benzylamino)dihydrofuran-2(3*H*)-one (2.68a):**

3-Azido-4-hydroxymethyl azetidin-2-one (**2.69a**) (0.5 g, 2.2 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the reaction mixture was stirred for 34 h at room temperature. After the reaction was over (TLC) methanol was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. It was then extracted with ethyl acetate (3 x 20 mL) and the combined organic extract was washed with saturated brine solution (10 mL). It was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get thick oil, which was quickly purified by flash column chromatography using acetone/petroleum ether (20:80) as an eluent to furnish **2.68a** (0.1 g, 20%) as a white solid.

MP : 143-144 °C (dec.).  
[α]<sub>D</sub><sup>30</sup> : - 55.1 (*c* 1.0, MeOH).  
IR (CHCl<sub>3</sub>) : 3394, 2119, 1774 cm<sup>-1</sup>.  
<sup>1</sup>H NMR : δ<sub>H</sub> 4.22-4.50 (m, 3H), 4.53-4.80 (m, 1H), 4.82 (d, *J* = 9.6 Hz,  
(DMSO-*d*<sub>6</sub>) 1H), 5.30 (d, *J* = 7.4 Hz, 1H), 7.42-7.58 (m, 5H).  
(200 MHz)  
<sup>13</sup>C NMR : δ<sub>C</sub> 42.4, 49.5, 53.9, 69.8, 128.8, 128.9, 129.1, 130.4, 171.8.  
(CD<sub>3</sub>OD) 51.7, 55.9, 57.7, 68.2, 130.3, 131.0, 131.3, 132.3, 172.6.  
(125 MHz)  
MS (m/z) : 233 (M+1).  
Analysis : Calculated: C, 56.87; H, 5.21; N, 24.13.  
(C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>) Observed: C, 56.68; H, 5.14; N, 24.

**(3*S*,4*R*)-3-Azido-4-(4-methoxyphenylamino)dihydrofuran-2(3*H*)-one (2.68b):**

3-Azido-4-hydroxymethyl azetid-2-one (**2.69b**) (0.9 g, 3 mmol) was dissolved in methanolic HCl (20%, 12 mL) and the reaction mixture was stirred for 34 h at room temperature to get thick oil, which was purified by flash column chromatography using acetone/petroleum ether (15:85) as an eluent to furnish **2.68b** (0.15 g, 20%) as a white solid.

<b>MP</b>	: 123-124 °C (dec.)
<b>[<math>\alpha</math>]<sup>30</sup><sub>D</sub></b>	: -10.0 ( <i>c</i> 1.5, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 3382, 2123, 1789 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>)</b>	: $\delta$ <sub>H</sub> 3.77 (s, 3H), 4.29 (d, <i>J</i> = 8.0 Hz, 2H), 4.43-4.65 (m, 3H), 6.63 (d, <i>J</i> = 8.8 Hz, 2H), 6.82 (d, <i>J</i> = 8.8 Hz, 2H).
(300 MHz)	
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>)</b>	: $\delta$ <sub>C</sub> 53.1, 55.7, 58.7, 70.7, 115.2, 115.5, 139.1, 153.7, 171.9.
(75.48 MHz)	
<b>MS (m/z)</b>	: 249 (M+1).
<b>Analysis</b>	: Calculated: C, 53.21; H, 4.88; N, 19.34.
(C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> )	Observed: C, 53.09; H, 4.65; N, 19.09.

**(3*S*,4*R*)-3-Amino-1-benzy-4-hydroxymethylazetid-2-one (2.70, R = H):**

A mixture of **2.69** (0.5 g, 2.16 mmol), ammonium formate (0.41 g, 6.47 mmol), 10% Pd/C (0.05 g) in methanol (10 mL) was refluxed for 1 h. The reaction mixture was filtered through a small pad of celite and washed with ethyl acetate (2 x 10 mL). The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (50 mL) and washed with water (2 x 5 mL) and saturated brine (5 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to afford **2.70** (R = H) (0.34 g, 85%) as a white solid. The compound was unstable and the color changed to dark brown on keeping for a longer time at room temperature.

<b>MP</b>	: 115-116 °C.
<b>[<math>\alpha</math>]<sup>25</sup><sub>D</sub></b>	: - 60.28 ( <i>c</i> 1.0, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 3332, 3271, 1739 cm <sup>-1</sup> .

**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  2.10-2.22 (m, 3H), 3.29 (brs, 1H), 3.60 (d,  $J = 3.6$  Hz, 2H),  
(**CDCl<sub>3</sub>**) 3.99 (brs, 1H), 4.26 (d,  $J = 14.9$  Hz, 1H), 4.41 (d,  $J = 14.9$  Hz,  
(200 MHz) 1H), 7.20-7.29 (m, 5H).  
**MS (m/z)** : 207 (M+1).

**(3*S*,4*R*)-3-Amino(benzyloxycarbonyl)-4-hydroxymethylazetidin-2-one (2.70, R = Cbz):**

To a solution of 3-amino azetidin-2-one **2.70** (R = H) (0.2 g, 0.97 mmol) in acetone-H<sub>2</sub>O (8:2, 10 mL) was added sodium bicarbonate (0.37 g, 3.88 mmol) portion-wise. After complete addition the reaction mixture was stirred for 15 min. and benzylchloroformate (0.15 mL, 1.45 mmol) was slowly added. After completion of the reaction (1.5 h by TLC), acetone was removed under reduced pressure. The residue was dissolved in water (5 mL), extracted with ethyl acetate (2 x 20 mL) and washed with saturated brine solution (5 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was distilled off under reduced pressure to afford a crude product, which was purified by column chromatography using acetone/petroleum ether (20:80) to furnish pure **2.70**, (R = Cbz) (0.27 g, 90%) as colorless oil.

**$[\alpha]_{\text{D}}^{26}$**  : -14.47 (*c* 1.0, CHCl<sub>3</sub>).  
**IR (CHCl<sub>3</sub>)** : 3415, 3332, 1747 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  3.48-3.63 (m, 3H), 4.25 (d,  $J = 14.9$  Hz, 1H), 4.39-4.47 (m,  
(**CDCl<sub>3</sub>**) 3H), 4.99 (d,  $J = 12.2$  Hz, 1H), 5.06 (d,  $J = 12.2$  Hz, 1H), 5.63  
(200 MHz) (brs, 1H), 7.19-7.26 (m, 10H).  
**<sup>13</sup>C NMR** :  $\delta_{\text{C}}$  45, 60, 60.5, 61.8, 67.3, 128, 128.1, 128.2, 128.5, 128.9,  
(**CDCl<sub>3</sub>**) 135.2, 135.8, 156.2, 165.7.  
(50.32 MHz)  
**MS (m/z)** : 341 (M+1).  
**Analysis** : Calculated: C, 67.03; H, 5.93; N, 8.23.  
(C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>) Observed: C, 67.10; H, 5.83; N, 8.18.

**(3*S*,4*R*)-3-Aminobenzyl-1-benzyl-4-hydroxymethylazetid-2-one (2.71):**

To a mixture of amine **2.70**, (R = H) (0.38 g, 1.83 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added activated magnesium sulphate (0.4 g) and benzaldehyde (2.1 mL, 2.0 mmol) at 0 °C under argon atmosphere. The reaction mixture was then allowed to warm up to room temperature and stirred for another 10 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (5 mL) and sodium borohydride (0.08 g, 2.1 mmol) was added slowly at 0° C with stirring. It was further stirred at the same temperature for 2.5 h. The reaction mixture was poured into water (5 mL) and extracted with ethyl acetate (2 x 20 mL). The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography using ethyl acetate/petroleum ether (40:60) to afford pure **2.71** (0.46 g, 80%) as colorless oil.

**[α]<sub>D</sub><sup>25</sup>** : -57.56 (c 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3404, 1737 cm<sup>-1</sup>

**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** : δ<sub>H</sub> 1.95 (brs, 2H), 3.37-3.43 (m, 1H), 3.49-3.61 (m, 2H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 4.02 (d, *J* = 1.9 Hz, 1H), 4.36 (d, *J* = 15 Hz, 1H), 4.48 (d, *J* = 15 Hz, 1H), 7.27-7.38 (m, 10H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)** : δ<sub>C</sub> 44.8, 51.2, 60.4, 61.1, 66.6, 127.3, 127.9, 128.2, 128.3, 128.9, 129.1, 135.8, 139, 168.8.

**MS (m/z)** : 297 (M+1).

**Analysis** : Calculated: C, 72.94; H, 6.81; N, 9.46.

(C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>) Observed: C, 72.91; H, 6.78; N, 9.26.

**(4*S*,5*R*)-1,3-Dibenzyl-5-chloromethyl-2-oxo-imidazolidine-4-carboxylic acid methyl ester (2.73):**

A solution of methanolic HCl (20%, 12 mL) was added slowly to *N*-benzyl-3-benzylamino-4-hydroxymethylazetid-2-one (**2.71**) (0.4 g, 1.18 mmol) and the reaction mixture was stirred at room temperature for 14 h. The progress of the reaction was

monitored by TLC. The solvent was completely removed under reduced pressure and the residue was taken in dry THF (7 mL) and the suspension was cooled to  $-20\text{ }^{\circ}\text{C}$ . Triethylamine (0.86 mL, 6 mmol) was added to the reaction mixture followed by a solution of triphosgene (0.36 g, 1.21 mmol) in dry THF (5 mL) over a period of 1 h. The reaction mixture was then stirred further for 2 h at  $-20\text{ }^{\circ}\text{C}$ . The solvent was removed under reduced pressure and the residue was dissolved in water (5 mL). It was extracted with ethyl acetate (2 x 10 mL) and washed with saturated brine solution (5 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was distilled off under reduced pressure to afford a crude product which was purified by column chromatography using ethyl acetate/petroleum ether (15:85) to furnish pure chloroester **2.73** (0.27 g, 65%) as a white crystalline solid.

**MP** : 85-86  $^{\circ}\text{C}$ .

**$[\alpha]_{\text{D}}^{25}$**  : +2.72 (*c* 1.1,  $\text{CHCl}_3$ ).

**IR ( $\text{CHCl}_3$ )** : 1743, 1708  $\text{cm}^{-1}$ .

**$^1\text{H NMR}$**  :  $\delta_{\text{H}}$  3.45-3.56 (m, 2H), 3.66 (s, 3H), 3.70-3.80 (m, 1H), 3.91 (d,  $J = 11.1\text{ Hz}$ , 1H), 3.95 (d,  $J = 14.9\text{ Hz}$ , 1H), 4.12 (d,  $J = 15.7\text{ Hz}$ , 1H), 4.79 (d,  $J = 15.7\text{ Hz}$ , 1H), 4.97 (d,  $J = 14.9\text{ Hz}$ , 1H), 7.13-7.30 (m, 10H).

**$^{13}\text{C NMR}$**  :  $\delta_{\text{C}}$  40.51, 46.3, 46.6, 52.5, 55.8, 57.5, 127.8, 128.5, 128.8, 129.1, 136, 136.5, 159.8, 168.9.  
(50.32 MHz)

**MS (*m/z*)** : 373 (*M*+1).

**Analysis** : Calculated: C, 64.49; H, 5.69; N, 7.55; Cl, 9.39.

( $\text{C}_{20}\text{H}_{21}\text{ClN}_2\text{O}_3$ ) Observed: C, 64.38; H, 5.49; N, 7.43; Cl, 9.21.

**(3*aS*,6*aR*)-1,3-Dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (2.2a):**

To a cooled solution of **2.73** (0.140 g, 0.39 mmol) in THF (4 mL) was added a solution of KOH (0.051 g, 0.78 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was neutralized by adding aqueous HCl (20%) at  $0\text{ }^{\circ}\text{C}$ , stirred for 15 min and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with saturated brine (5 mL) and dried over anhydrous sodium sulphate. The solvent was

removed under reduced pressure and the crude product was purified by column chromatography using ethyl acetate/petroleum ether (15:85) to get lactone **2.2a** (0.107 g, 85%) as a white crystalline solid. The ee was determined to be 99.9% (HPLC conditions: Column: Diacel Chiralcel OD-H, 250 x 4.6 mm id; Detector: UV set at  $\lambda = 254$  nm; Mobile phase: hexane: propan-2-ol, 7:3; Flow rate: 0.5 mL/min; Rt: = 31.0 min).

**MP** : 118-119 °C {Lit.<sup>38</sup> mp 120-121}.

**$[\alpha]_D^{25}$**  :  $[\alpha]_D^{25} = + 58.1$  (*c* 1.2, CHCl<sub>3</sub>) {Lit.  $[\alpha]_D^{25} = + 58.2$  (*c* 1, benzene)<sup>38</sup>;  $[\alpha]_D^{25} = + 56.4$  (*c* 1.12, CHCl<sub>3</sub>)<sup>55</sup>}.

**IR (CHCl<sub>3</sub>)** : 1782, 1703 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (400 MHz)** :  $\delta_H$  3.84 (d, *J* = 8.0 Hz, 1H), 4.02-4.07 (m, 3H), 4.24 (d, *J* = 6.4 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 1H), 4.55 (d, *J* = 14.9 Hz, 1H), 4.96 (d, *J* = 14.9 Hz, 1H), 7.18-7.29 (m, 10H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>) (100 MHz)** :  $\delta_C$  45.2, 46.9, 52.4, 54.4, 70.1, 127.8, 128.1, 128.2, 128.7, 128.8, 129.0, 135.9, 136.0, 158.2, 172.7.

**MS (m/z)** : 323 (M+1).

**Analysis (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>)** : Calculated: C, 70.78; H, 5.63; N, 8.69.  
Observed: C, 70.68; H, 5.60; N, 8.59.



## 2.7: Refreences

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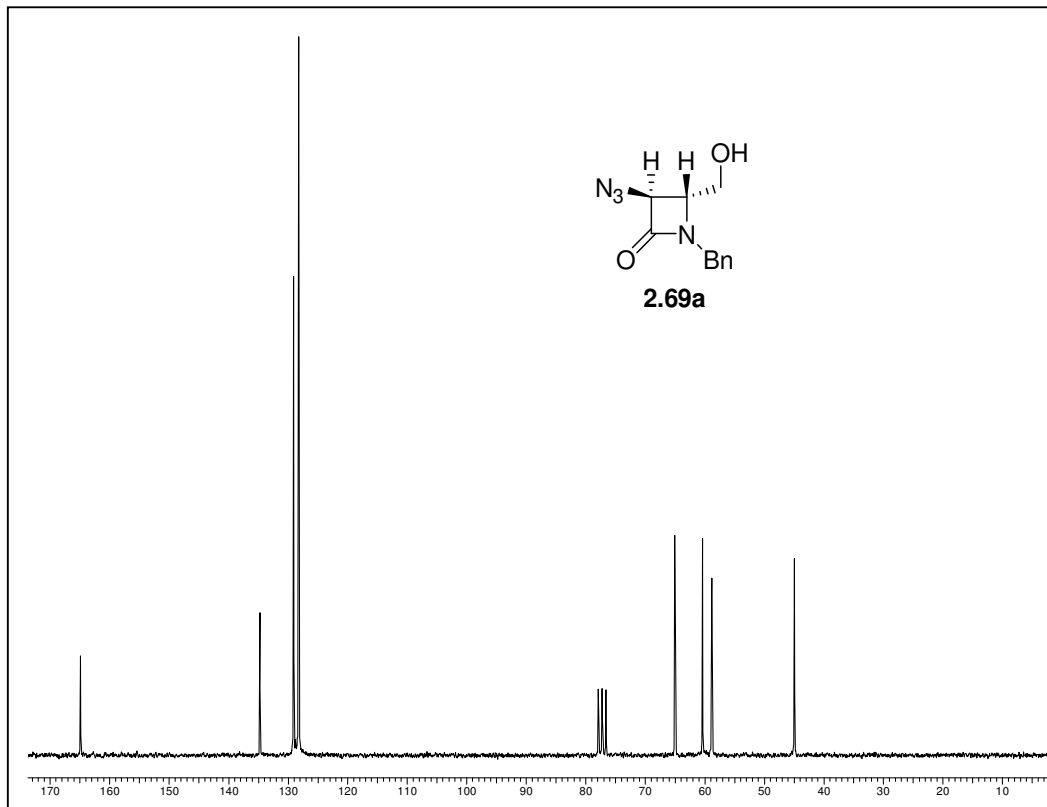
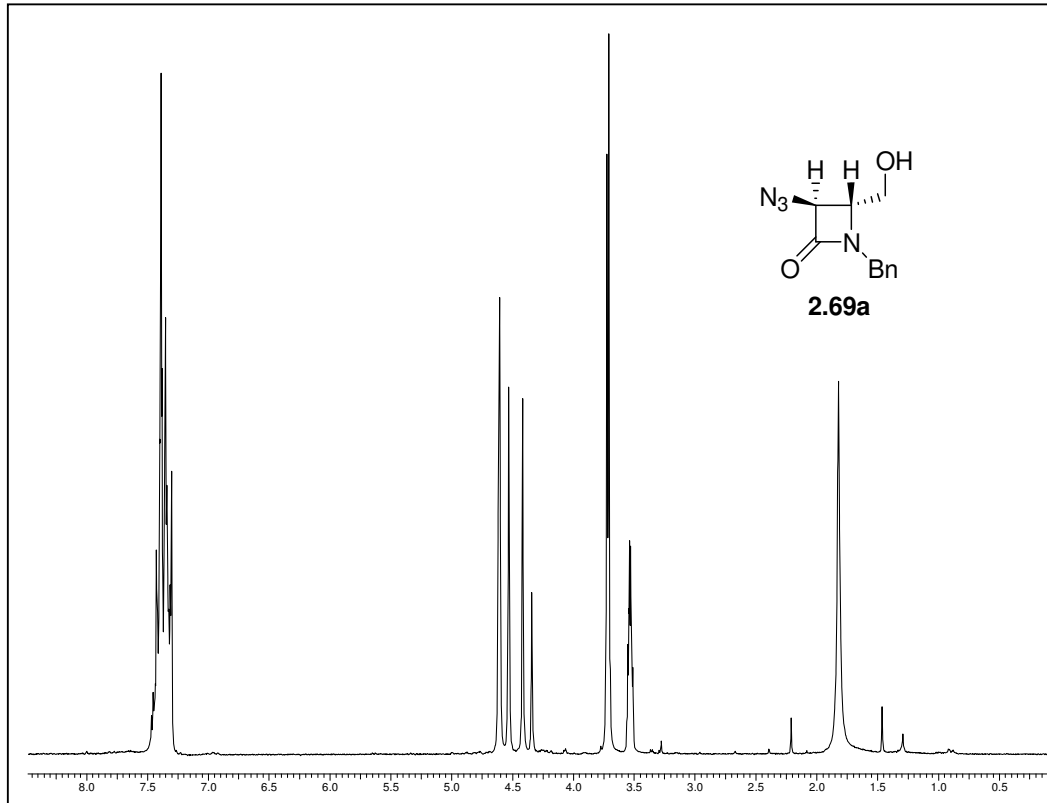
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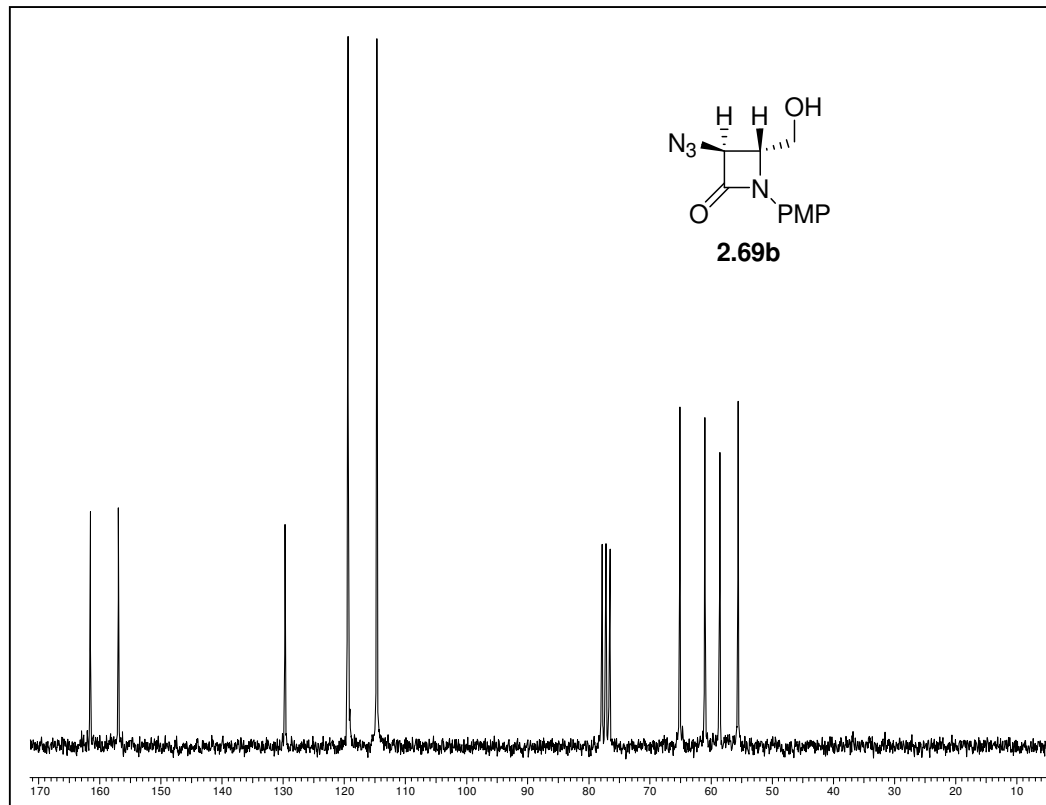
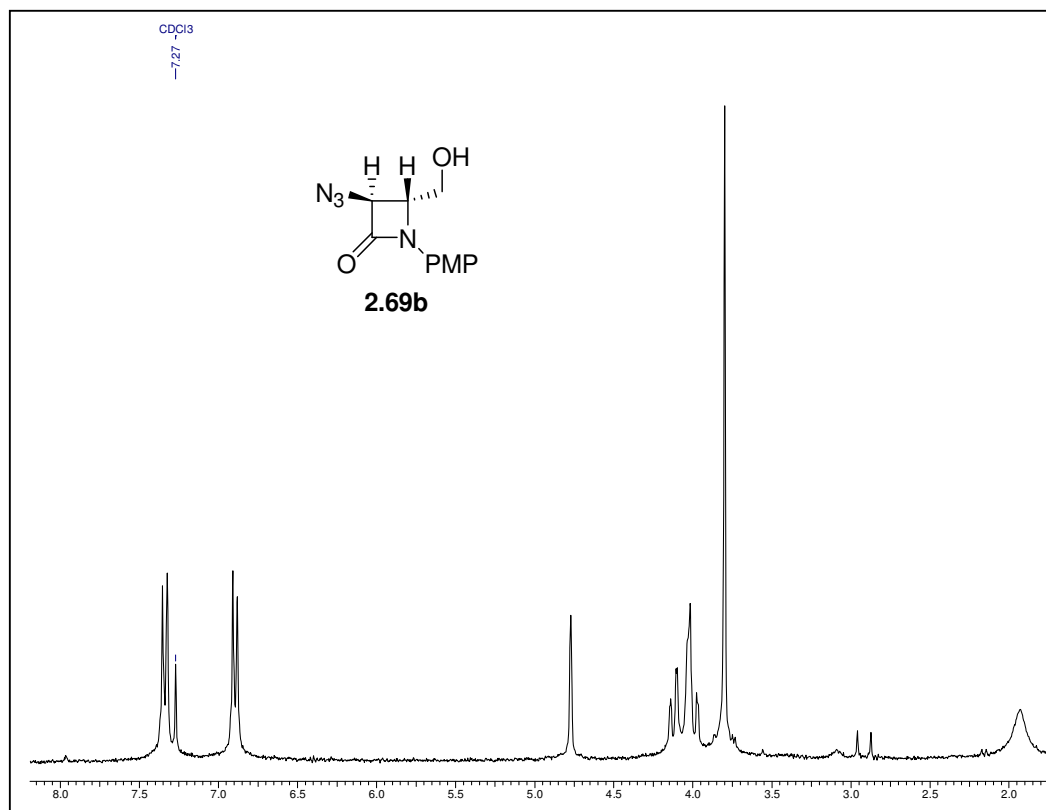
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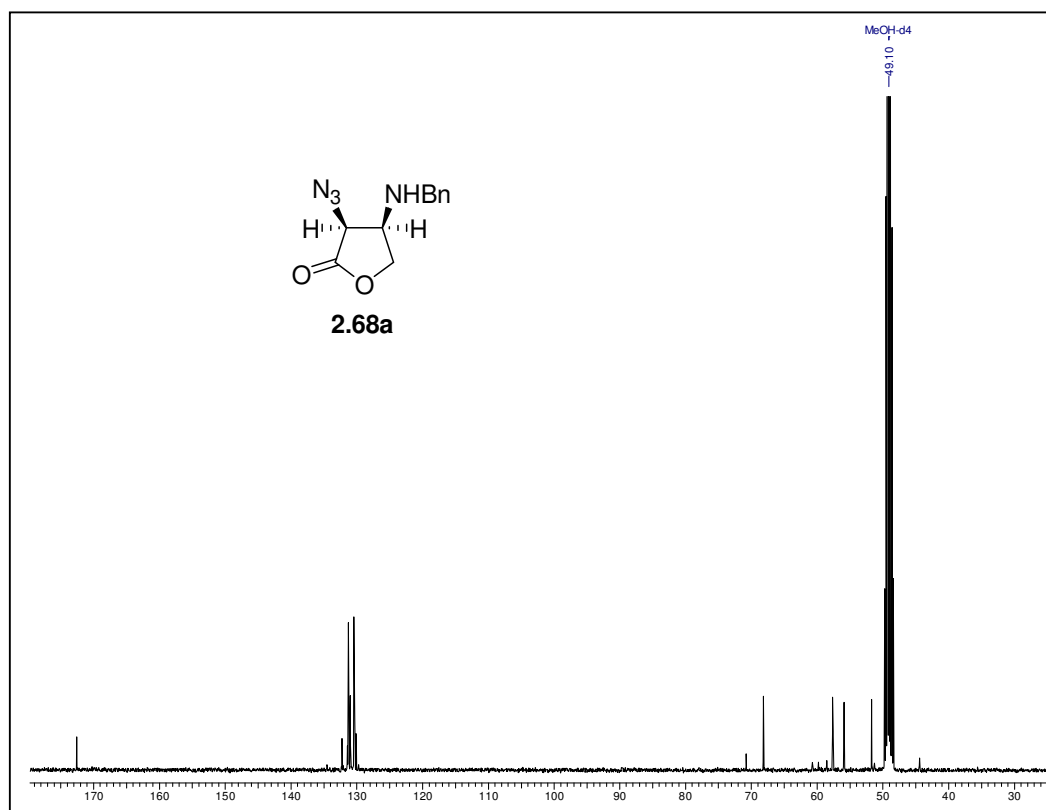
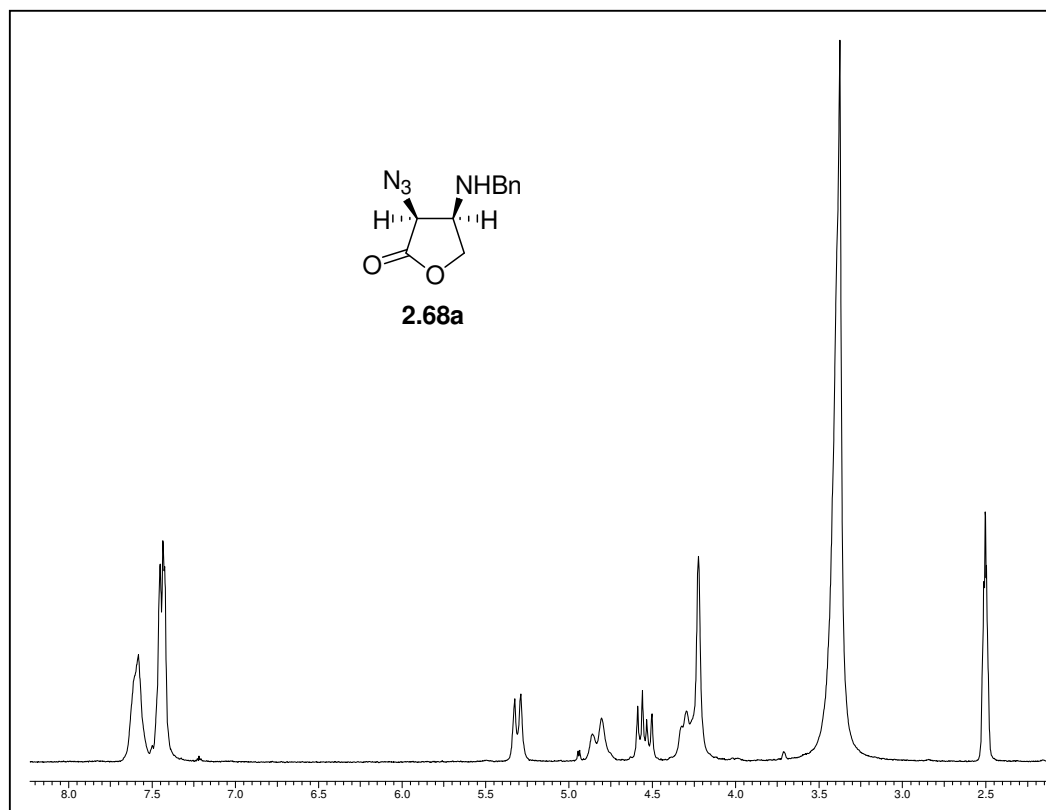
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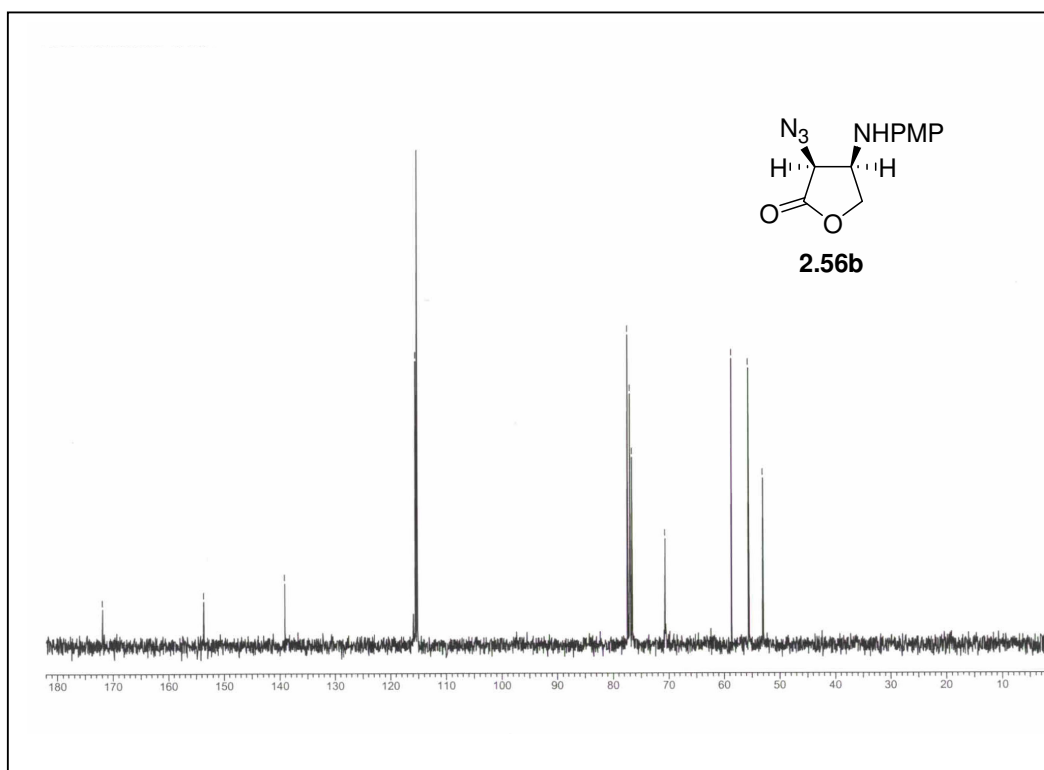
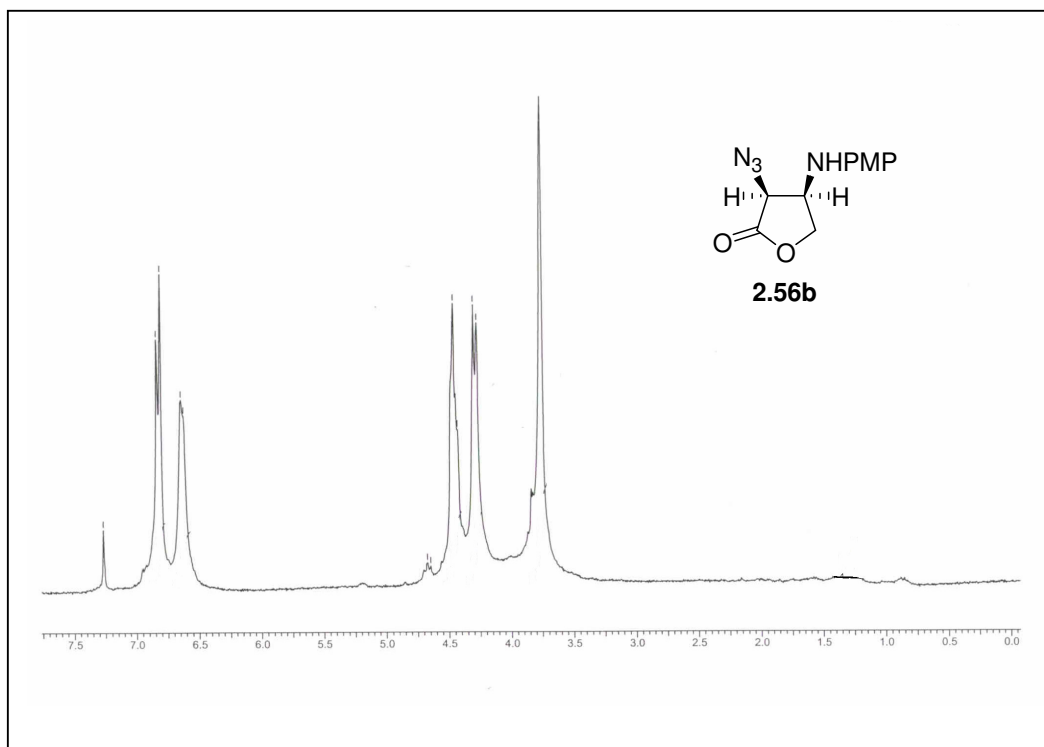
Chapter 2  
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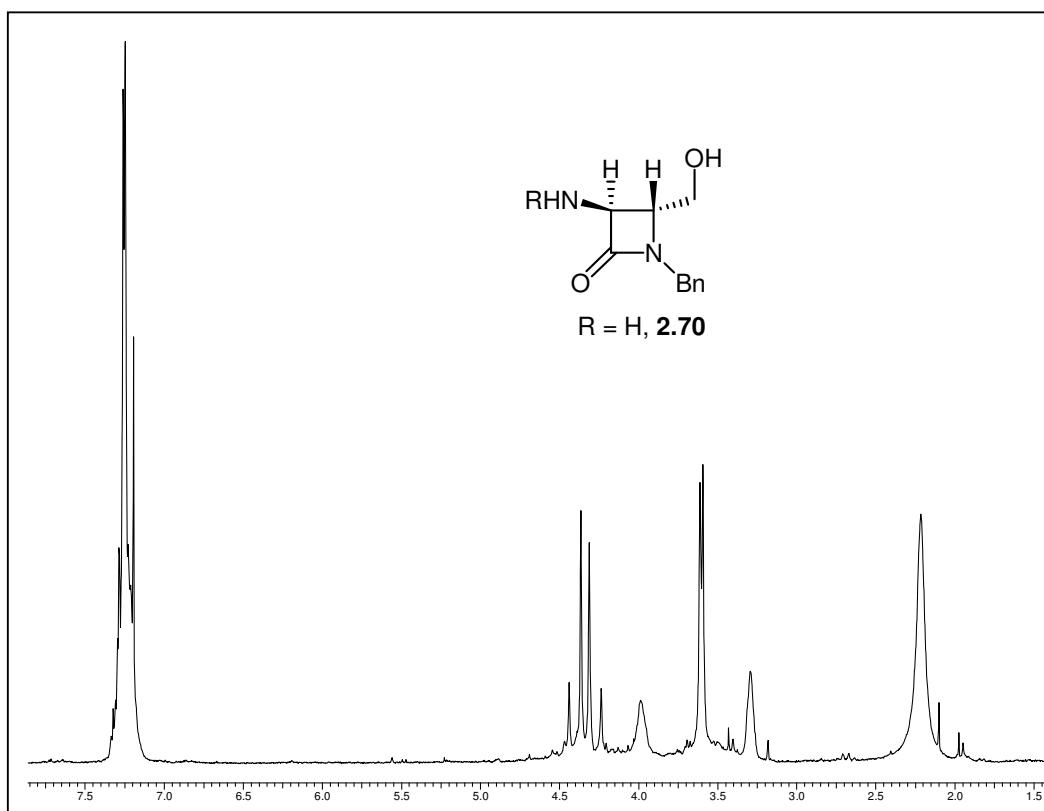
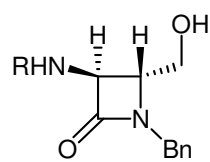


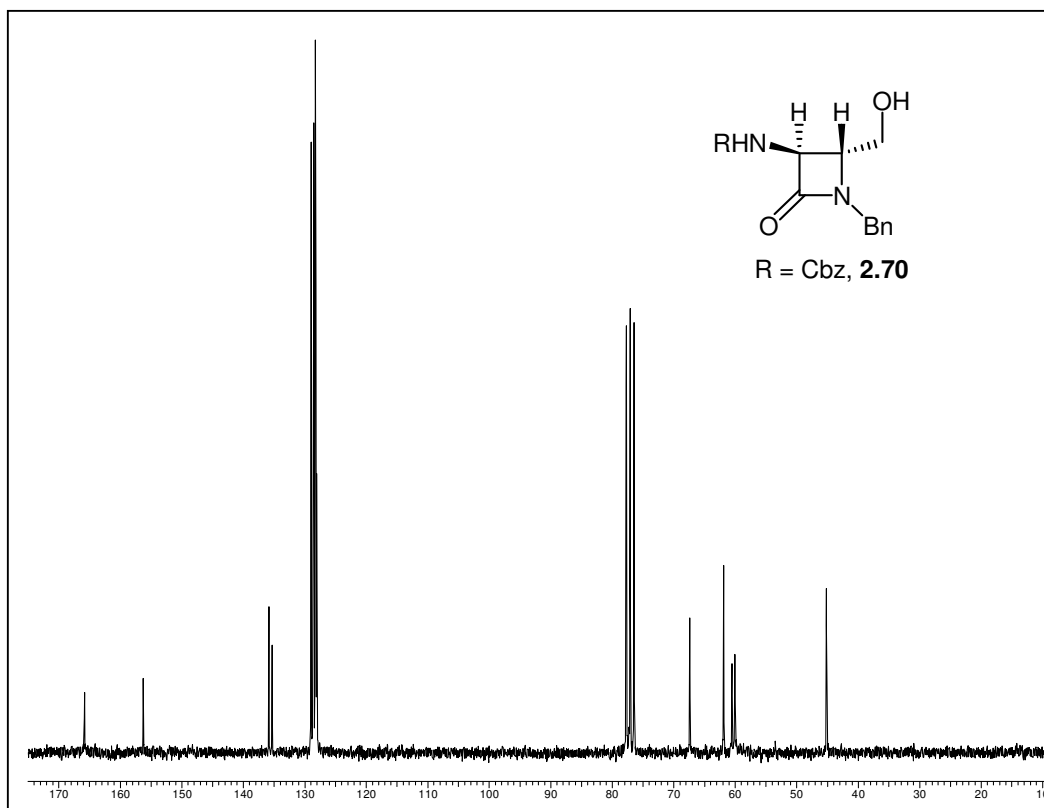
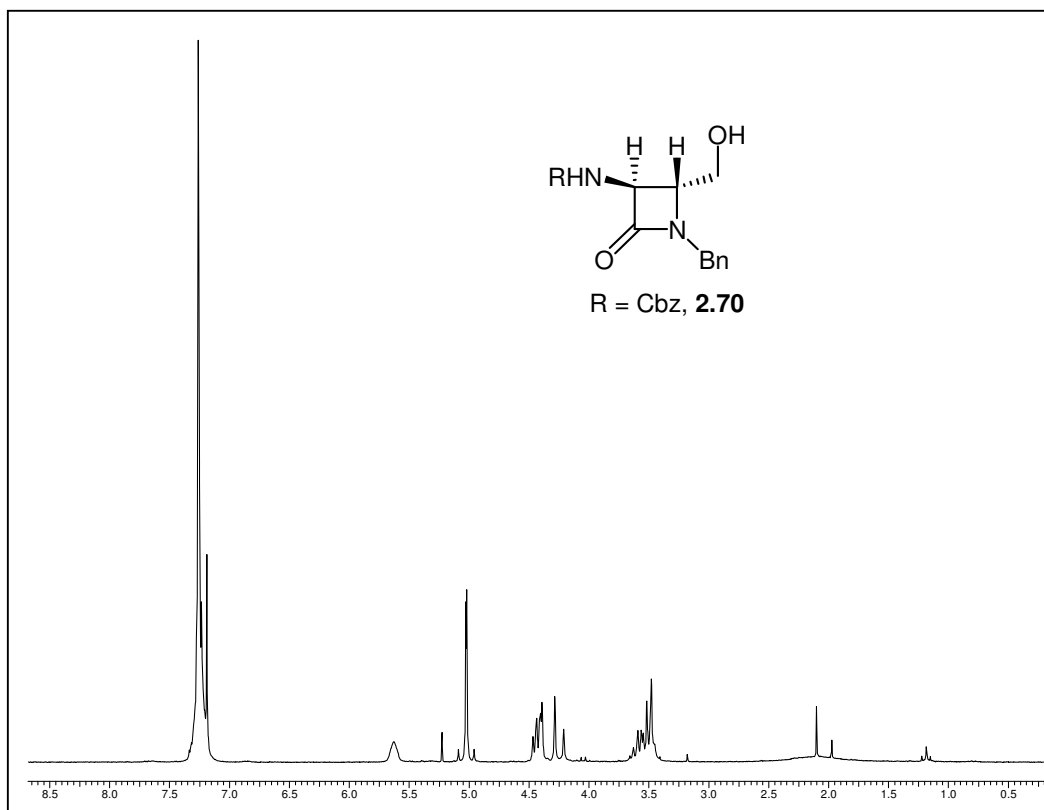


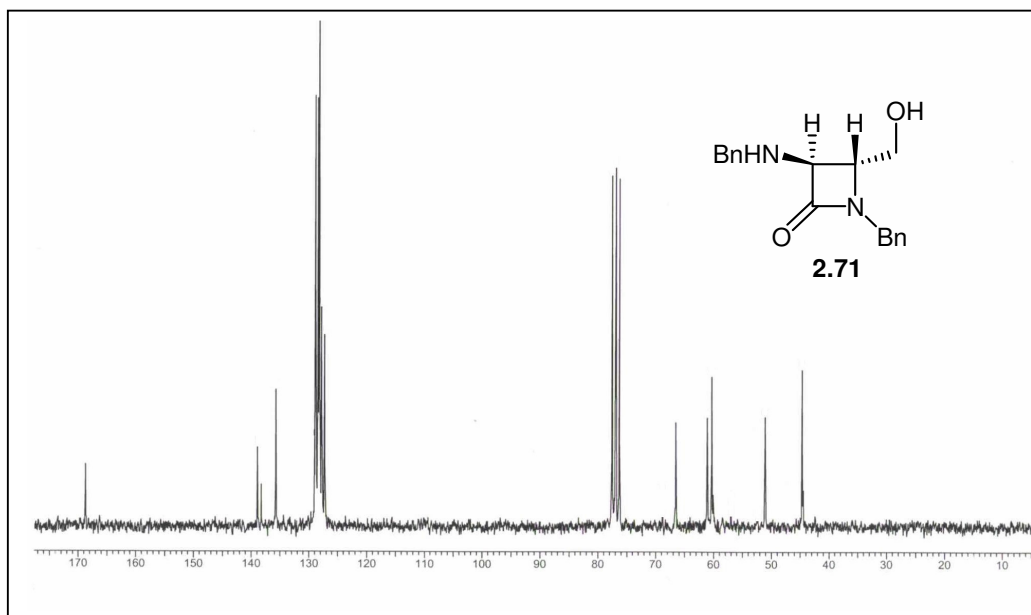
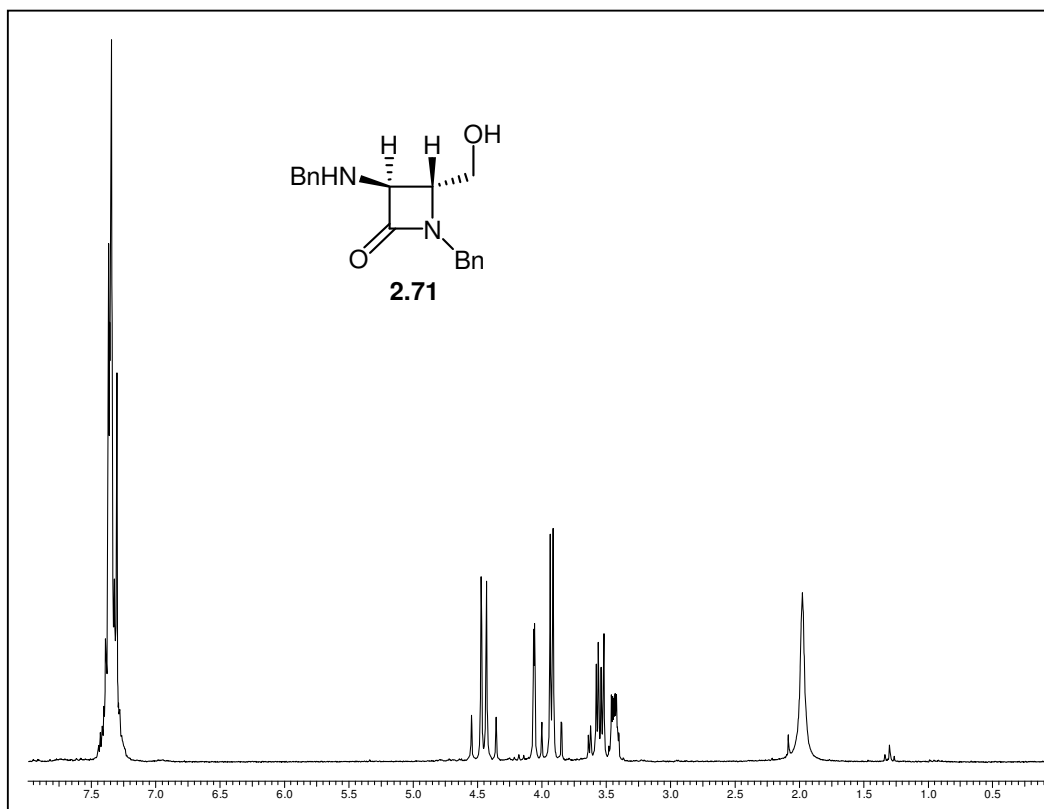


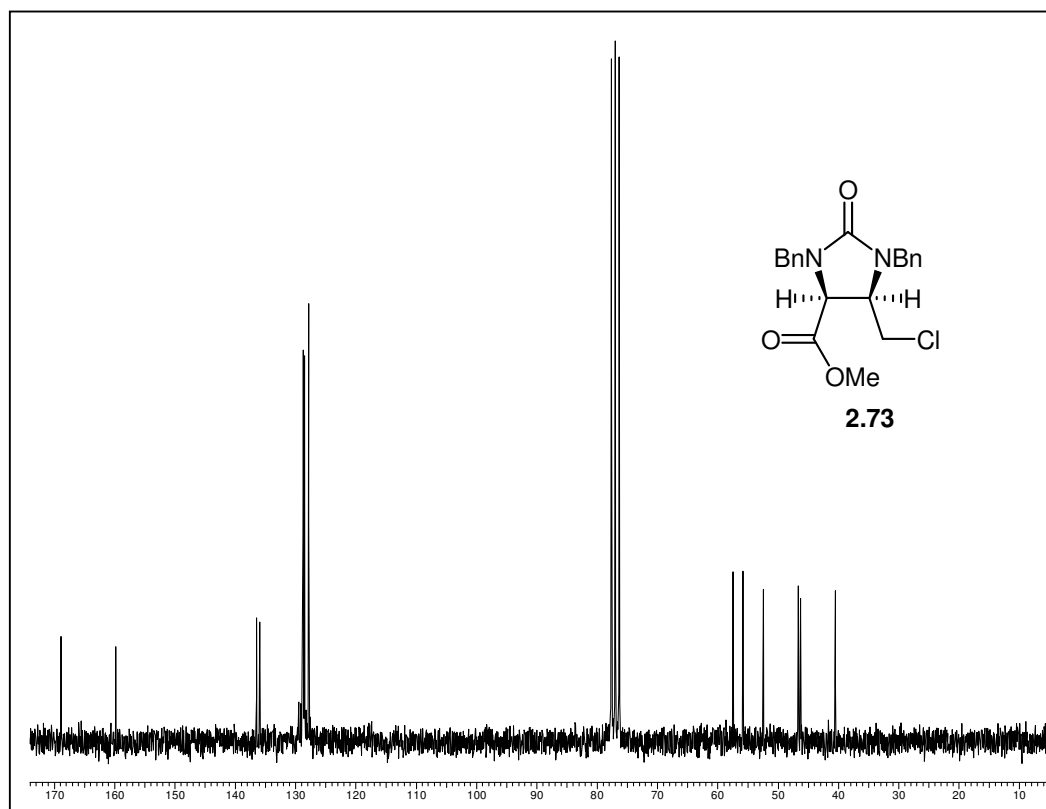
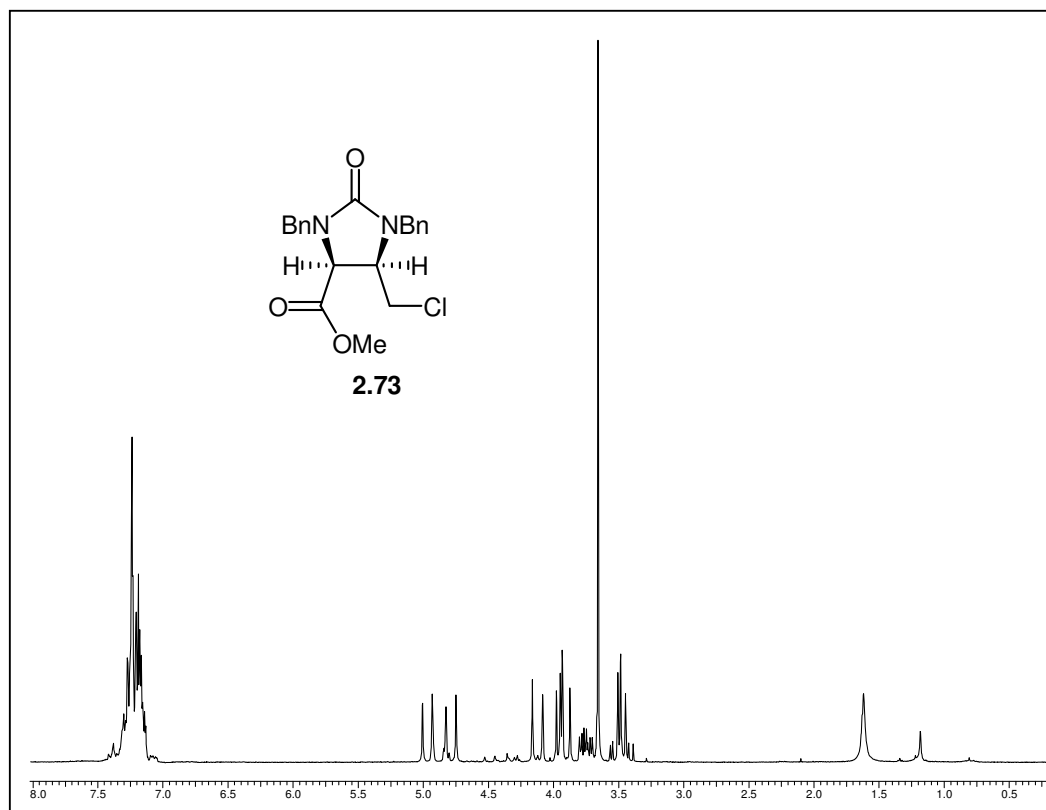


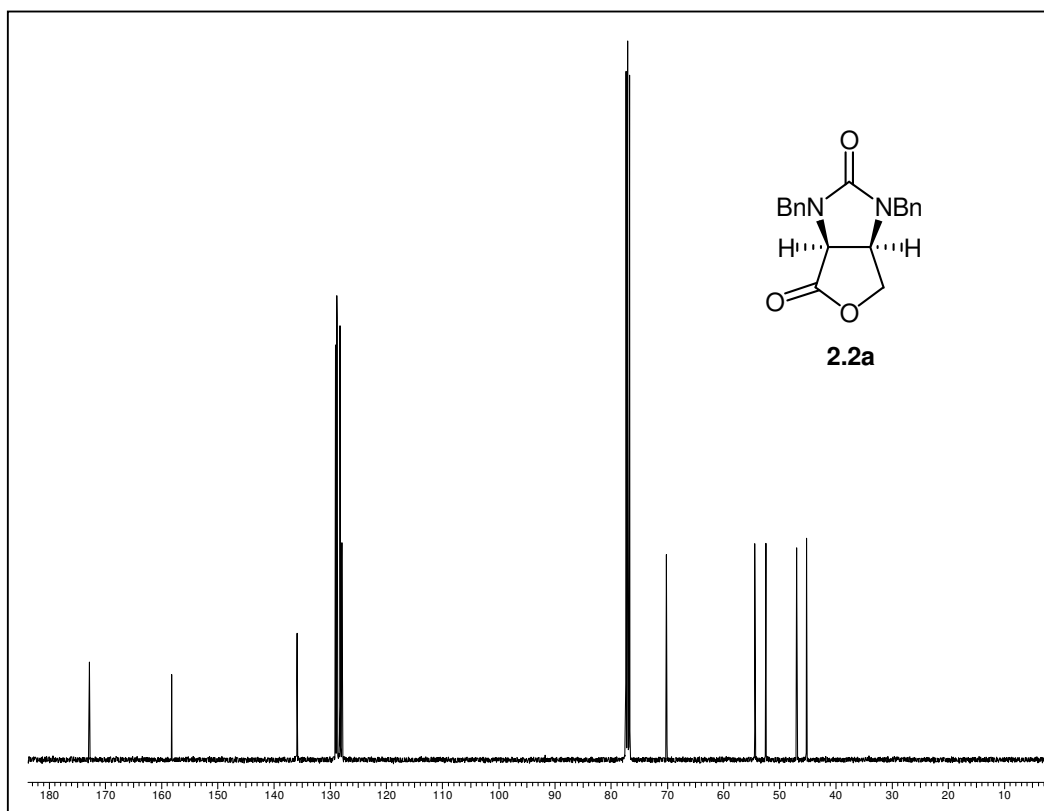
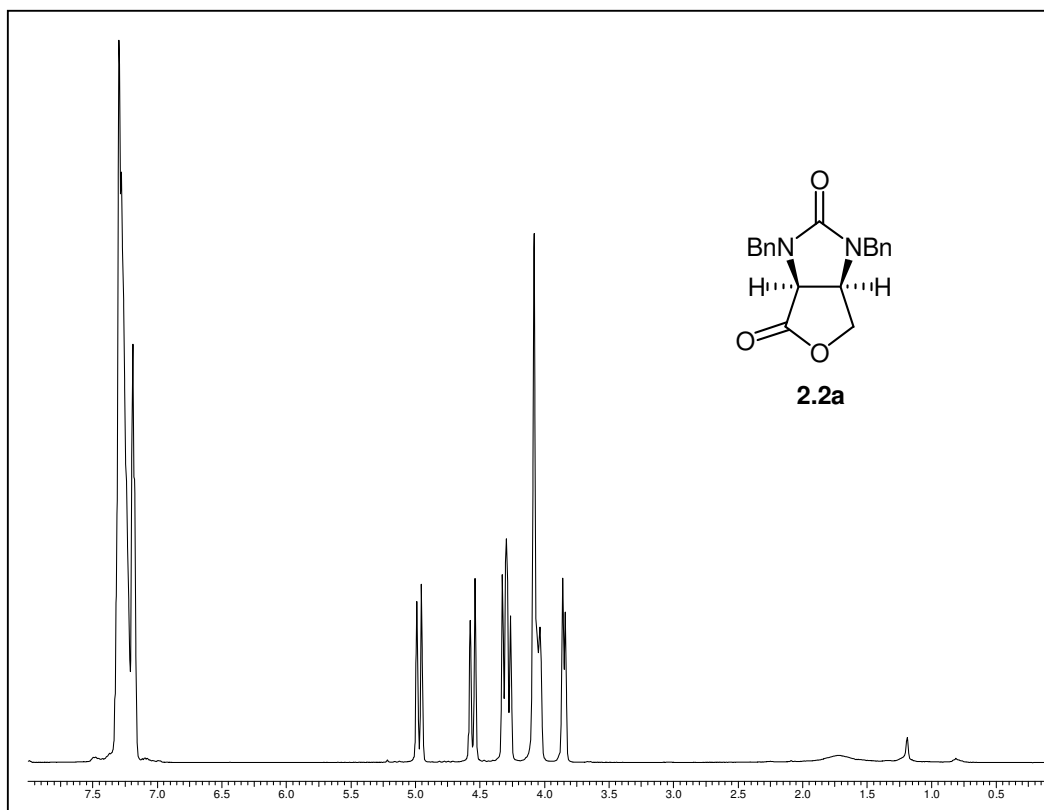












## CHAPTER 3

# **4-FORMYLAZETIDIN-2-ONE AN USEFUL BUILDING BLOCK FOR THE FORMAL SYNTHESIS OF *XYLO-* *(2S,3R,4R)*-PHYTOSPHINGOSINE AND *THREO*-*(2S,3S)*-SPHINGOSINE.**

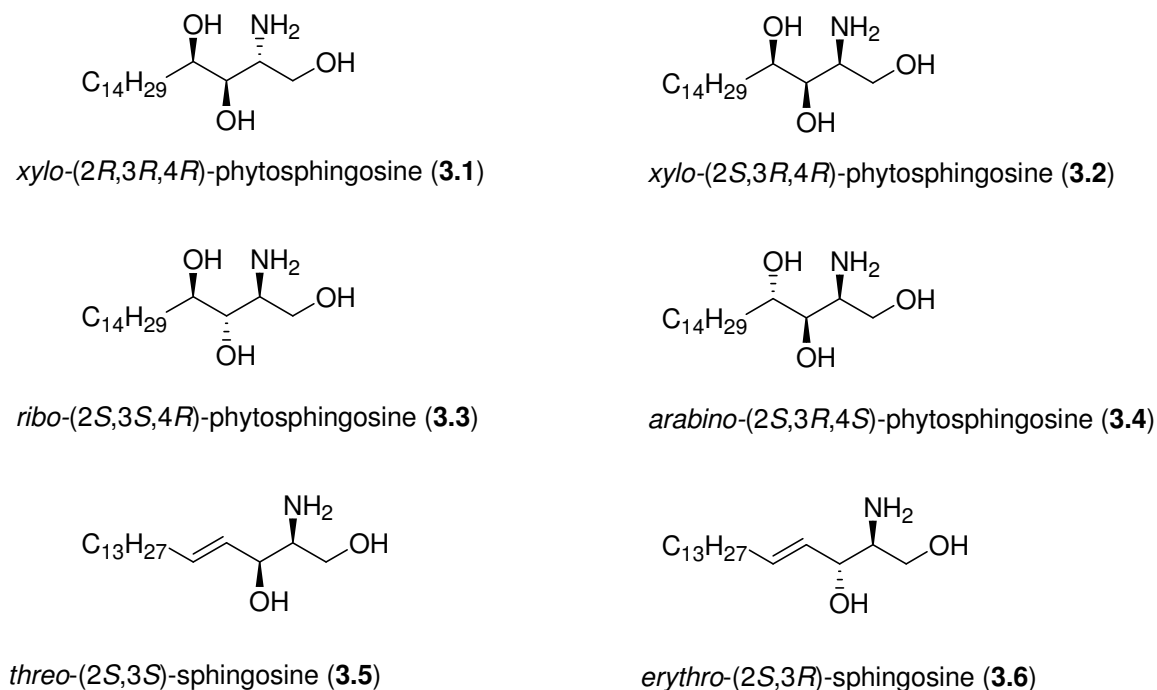
*That which we persist in doing becomes easier, not that the task itself has become easier, but that our ability to perform it has improved.*

-Ralph Waldo Emerson

This work has been published in *Synthesis* **2007**, *17*, 2631-2636.

### 3.1: Introduction

Sphingosines (Figure 3.1) constitute a group of related long-chain aliphatic 2-amino-1,3-diols, of which 2-amino-D-erythro-4(*E*)-octadecene-1,3-diol (commonly called sphingosine **3.6**) occurs most frequently in animal glycosphingolipids.<sup>1</sup> Sphingosines are known inhibitors of protein kinase C and are the backbone structures to glycosphingolipids. This larger family of biomolecules is involved in a plethora of processes related to cell growth, differentiation, adhesion, and neuronal repair.<sup>2</sup>

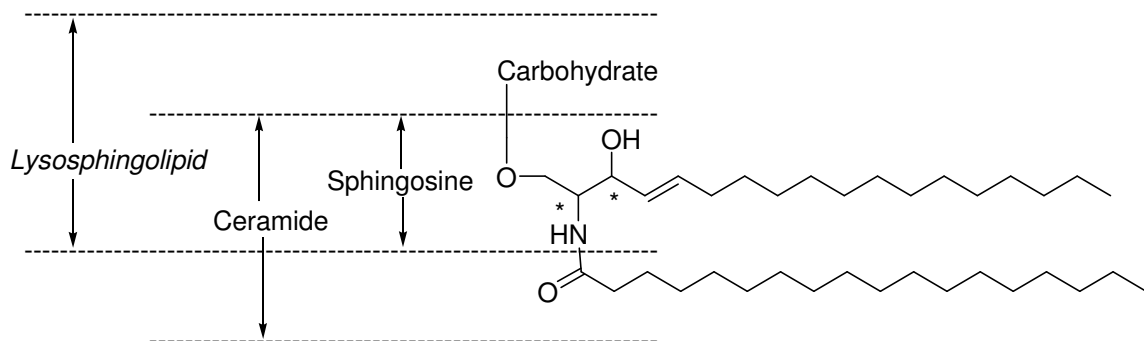


**Figure 3.1**

Glycosphingolipids contain two basic structural motifs: carbohydrate and ceramide (Figure 2). The ceramide portion consists of a sphingoid base and an amide-linked fatty acyl chain, e.g. stearyl or palmitoyl. The structural variation in fatty acids (*N*-acyl portion, sphingosines and carbohydrates results in a great variety of chemically distinct glycosphingolipids.<sup>1</sup> Glycosphingolipids are found in the cell membrane of all animal and many plant cells, where they serve as identifying markers and regulate cellular recognition, growth and development.<sup>3a</sup> They are thought to function by anchoring the hydrophobic ceramide portion (Figure 3.2) in the plasma membrane



exposing the hydrophilic carbohydrate portion to the surrounding exterior which specifies the intended biological function.<sup>3b</sup>



**Figure 3.2 Glycosphingolipid structure**

They are involved in several biological functions such as (i) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,<sup>4</sup> (ii) being unambiguous links between specific sphingolipids and malignant tumors which enables them to be used as ‘biological markers’ for possible early detection of cancer,<sup>3a</sup> and (iii) potent and reversible inhibition of protein kinase C by breakdown products of glycosphingolipids, e.g. sphingosine **3.6** and lysosphingolipids (Figure 3.2).

Dihydrosphingosine is a biosynthetic precursor to sphingosine **3.6** which is the most abundant long chain amino alcohol possessing generally 18 or 20 carbon atoms. Dihydrosphingosine is an intermediate in the biosynthesis of sphingolipids such as ceramides, sphingomyelin, cerebroside and gangliosides, which play important roles in cell regulation and signal transduction.<sup>5</sup> Dihydrosphingosine is itself found to be an inhibitor of protein kinase C.<sup>6</sup> The on-going recognition of glycosphingolipids as fundamental mediators of cellular interactions continues to sustain research in this field.

Phytosphingosine **3.1-3.4** (Figure 3.1) exists abundantly as one of the molecular species of sphingolipids in microorganisms, plants and many mammalian tissues such as brain, hair, intestine,<sup>7</sup> uterus,<sup>8</sup> liver,<sup>9</sup> skin,<sup>10</sup> kidney<sup>11</sup> and in blood plasma.<sup>12</sup> It was first isolated from mushrooms in 1911<sup>13</sup> and its structure was elucidated by Oda<sup>14a</sup> and by Carter *et al.*<sup>14b</sup> In addition to its structural function as the long-chain base of sphingolipids in membranes, phytosphingosine itself is a bioactive lipid; for example, phytosphingosine **3.3** is a potential heat stress signal in yeast cells<sup>15a,b</sup> and some of its derivatives exhibit important physiological activities.  $\alpha$ - and  $\beta$ -Galactosyl and

glucosylphytoceramides possess very high tumor inhibitory potency.<sup>15c</sup> Moreover it has been shown that diastereomers of ceramides, sphingosines and dihydrosphingosines exhibit different activities and metabolisms.<sup>16</sup>

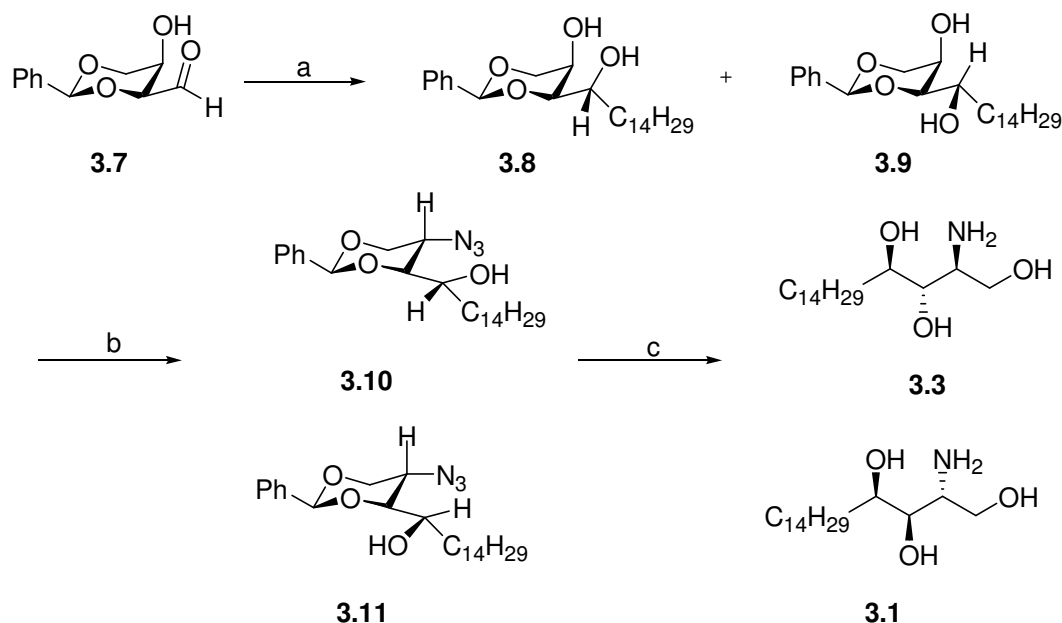
### 3.2: Background for the present work

Thus, owing to the number of applications of sphingosines, it has attracted a large number of synthetic chemists.<sup>17</sup> The subtle variations in biological activities over a range of diastereomers have inevitably led to synthesis of all diastereomers of sphingosines. This fact is reflected in a steep rise in the number of publications dealing with the synthesis of sphingosines.<sup>17, 18, 19</sup> Sphingosines being popular synthetic targets, many synthetic routes have been reported. A few interesting syntheses of sphingosines are described below.

#### Schmidt's approach:

Schmidt *et al.* employed a D-threose-based synthesis of D-ribo and L-lyxo-phytosphingosine. Reaction of tetradecyl magnesium bromide with D-threose derivative **3.7** gave a separable 1:1 mixture of **3.8** and **3.9**.

Scheme 3.1



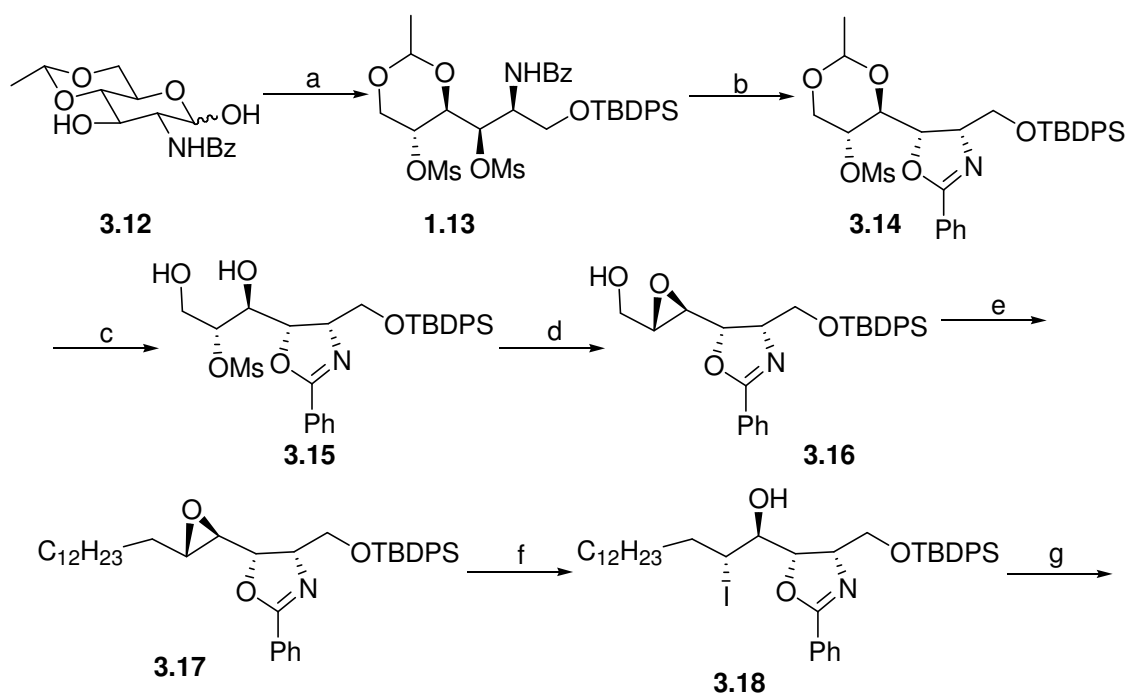
*Reagents and conditions:* a)  $C_{14}H_{29}MgBr$ , THF, 35% (**3.8**), 36% (**3.9**); b) i)  $MsCl$ , pyridine,  $-30\text{ }^{\circ}C$ , 12 h, 75%, ii)  $DMF$ ,  $NaN_3$ ,  $90\text{ }^{\circ}C$ , 48 h, 63%; c) i)  $MeOH$ , conc.  $HCl$ , 15 h, 65%, ii)  $LiAlH_4$ , THF, rt, 30 min, 1 h, reflux, 95%.

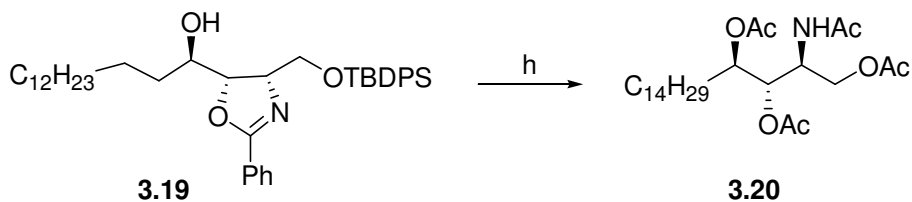
Conversion of secondary hydroxyl group to its mesylate derivative and subsequent azide displacement furnished **3.10** and **3.11** respectively. Deprotection of benzylidene and reduction of azide afforded *D-ribo*- and *L-lyxo*-phytosphingosines **3.3** and **3.1** respectively (Scheme 3.1).<sup>20a</sup>

### Murakami's approach:

Murakami *et al.* synthesized *D-ribo*-phytosphingosine from *D*-glucosamine by utilizing its whole carbon skeleton and functional groups. 4,6-*O*-Ethylidene-*N*-benzoyl-*D*-glucosamine **3.12** (readily prepared from *D*-glucosamine<sup>21</sup>) was reduced to give the triol. Selective protection of the primary hydroxyl and mesylation gave the dimesylate **3.13**, which was further converted into phenyl oxazoline **3.14**. Deprotection of acetal followed by base treatment gave the epoxide **3.16**. Conversion of the free hydroxyl into tosylate and displacement with dodecyl magnesium bromide gave rise the epoxide **3.17**, which was subjected to ring opening with iodide to furnish **3.18**. Deiodination, hydrolysis of phenyloxazoline and TBDPS groups followed by acetylation afforded the tetraacetate derivative of *D-ribo*-phytosphingosine **3.20** (Scheme 3.2).<sup>22</sup>

Scheme 3.2



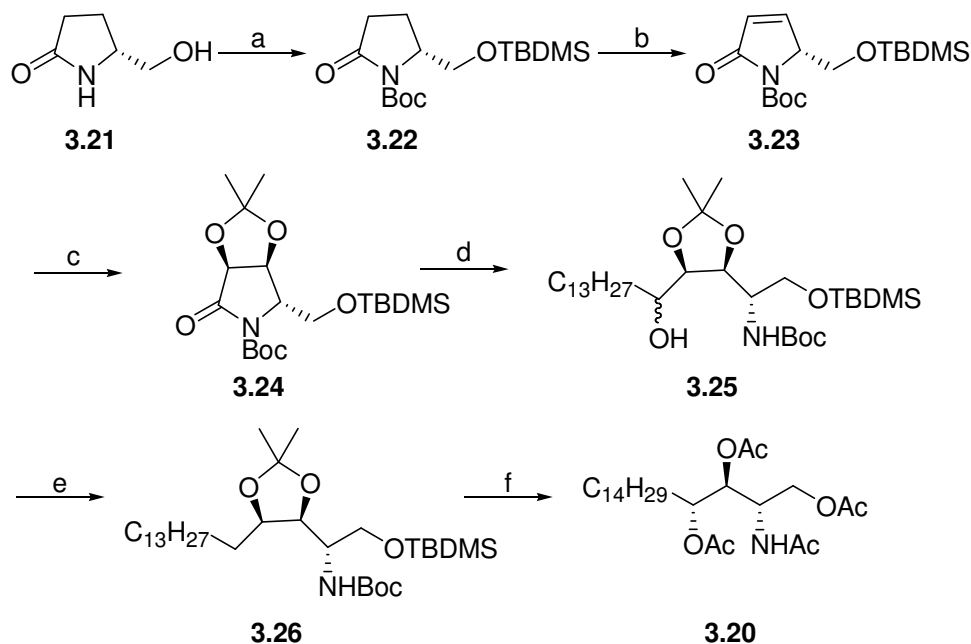


*Reagents and conditions:* a) i) NaBH<sub>4</sub>, *i*-PrOH, H<sub>2</sub>O, 0 °C, 1 h, 95%, ii) *t*-BuPh<sub>2</sub>Si-Cl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h then MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h; b) Pyridine, Et<sub>3</sub>N, toluene, 110 °C, 24 h, 90%; c) TiCl<sub>4</sub>, PhSH, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 83%; d) K<sub>2</sub>CO<sub>3</sub>, MeOH, 0 °C, 2 h; e) i) *p*-TsCl, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 88% from 182, ii) C<sub>12</sub>H<sub>25</sub>MgBr, CuBr, THF, -30 °C to 0 °C, 4 h, 84%. f) NaI, Me<sub>3</sub>SiCl, H<sub>2</sub>O, CH<sub>3</sub>CN, 0 °C to 10 °C, 2 h; g) *n*-Bu<sub>3</sub>SnH, AIBN, PhCH<sub>3</sub>, 60 °C, 30 min, 88% from **3.16**; h) i) 4N HCl, THF, rt, 24 h, ii) aq. NaOH, rt, iii) aq. NaOH, EtOH, 95 °C, 12 h, iv) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 75%.

### Yoda's approach:

In Yoda's approach, the hydroxylactam **3.21**<sup>23a</sup> on successive TBDMS and Boc protection followed by unsaturation gave **3.23**.

### Scheme 3.3



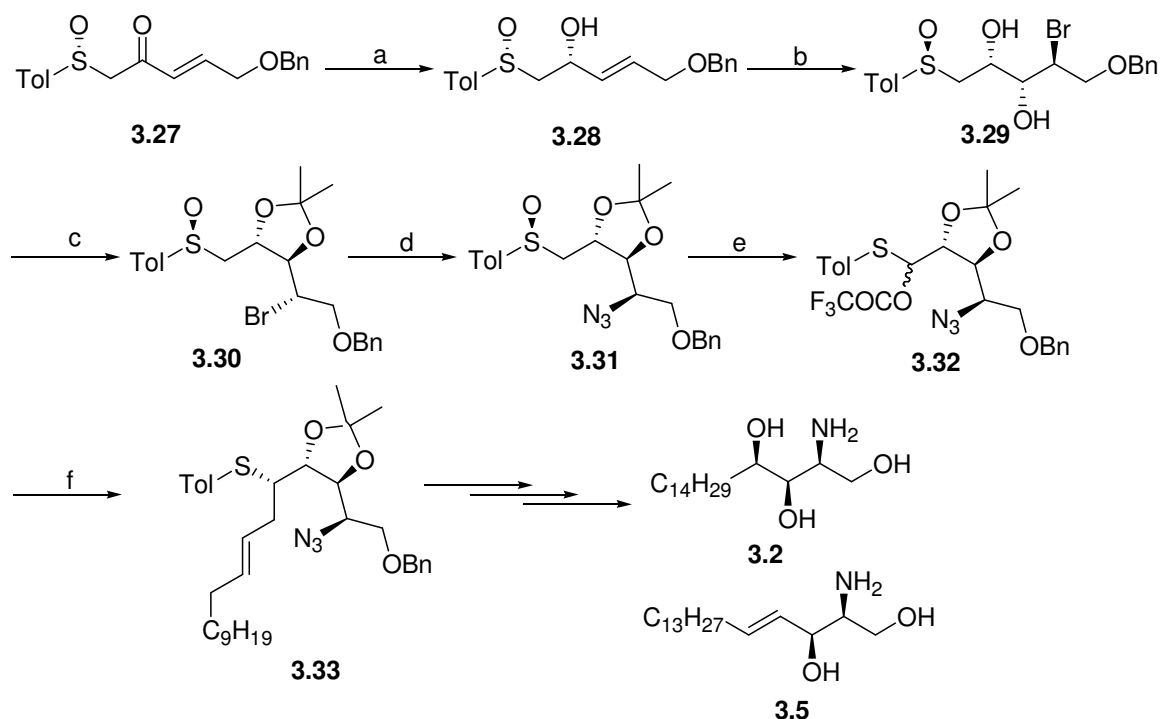
*Reagents and conditions:* a) i) *t*-BuMe<sub>2</sub>Si-Cl, imidazole, DMF, 88%, ii) (BOC)<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 90%; b) i) LDA, THF, PhSeBr, -78 °C, ii) *m*-CPBA, -78 °C; c) i) OsO<sub>4</sub>, NMO, acetone-H<sub>2</sub>O, 55% from **3.22**, ii) 2,2-DMP, *p*-TsOH, 100%; d) i) C<sub>13</sub>H<sub>27</sub>MgBr, -78 °C, 60%. ii) NaBH<sub>4</sub>, EtOH, 88%; e) i) (thiocarbonyl)diimidazole, 50 °C, 98%, ii) *n*-Bu<sub>3</sub>SnH, AIBN, toluene, 100 °C, 87%; f) i) CF<sub>3</sub>CO<sub>2</sub>H, H<sub>2</sub>O then KOH, MeOH, 100%, ii) Ac<sub>2</sub>O, pyridine, DMAP.

Dihydroxylation and acetonide protection followed by treatment with tridecyl magnesium bromide and reduction afforded **3.25**, which on deoxygenation *via* thioimidazolide led to compound **3.26**. Deprotection of acetonide, Boc, TBDMS and subsequent acetylation gave *D-ribo*-phytosphingosine tetraacetate **3.20** (Scheme 3.3).<sup>23</sup>

#### Raghavan's approach:

Raghavan *et al* have described use of olefin in the Pummerer ene reaction which permits introduction of carbon chain into the stereoselective synthesis of *xylo*-(2*R*,3*S*,4*S*)-C<sub>18</sub>-phytosphingosine and *threo*-(2*R*,3*R*)-C<sub>18</sub>-sphingosine. The key steps in the syntheses are i) asymmetric induction from sulfur to C-2 in the transformation of **3.27** to **3.28**, ii) asymmetric induction from C-2 to C-3 and C-4 in the transformation of **3.28** to **3.29**, iii) ene reaction for the introduction of the hydrocarbon chain which on further synthetic transformations provides *xylo*-(2*R*,3*S*,4*S*)-C<sub>18</sub>-phytosphingosine and *threo*-(2*R*,3*R*)-C<sub>18</sub>-sphingosine (Scheme 3.4).<sup>17k</sup>

Scheme 3.4

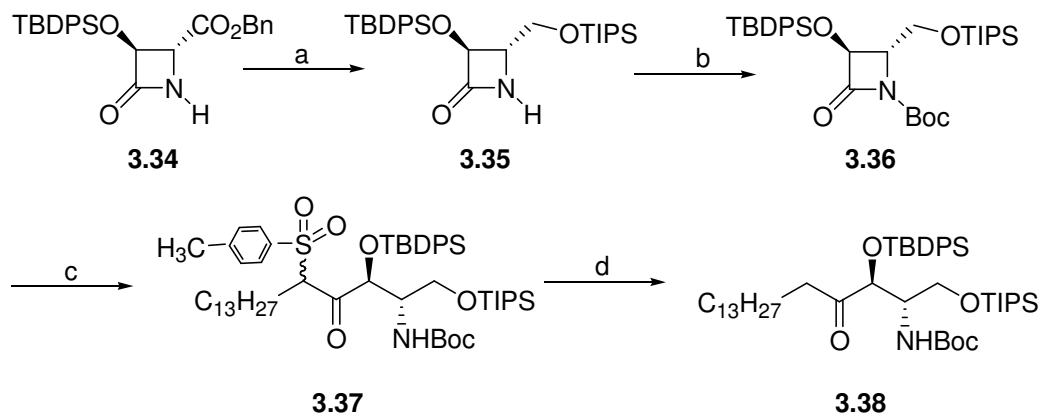


*Reagents and conditions:* a) DIBAL, THF, -78 °C; b) NBS, H<sub>2</sub>O, toluene; c) 2,2-DMP, acetone, CSA (cat.); d) NaN<sub>3</sub>, DMSO, 85 °C; e) TFAA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; f) C<sub>13</sub>H<sub>16</sub>, SnCl<sub>4</sub>, 0 °C.

### Shiozaki's approach:

Shiozaki *et al.* utilized the chiral  $\beta$ -lactam **3.34** obtained from D-tartaric acid.<sup>24</sup> Reduction of **3.34** and hydroxyl protection followed by Boc protection yielded **3.36**. The compound **3.36** was converted into  $\alpha$ -sulfonyl ketone **3.37**. Removal of *p*-toluene sulfonyl moiety by lithium naphthalenide furnished a keto compound **3.38** (Scheme 3.5).<sup>17j</sup>

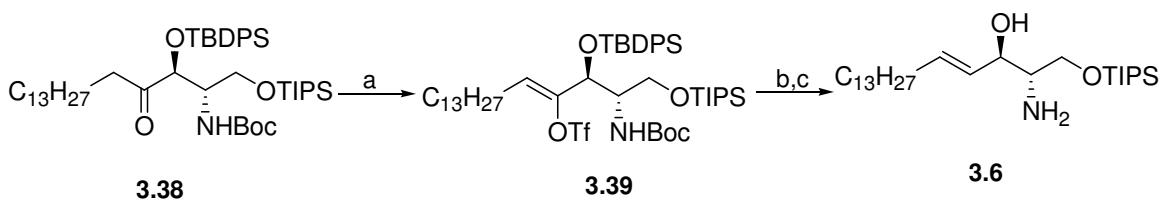
Scheme 3.5

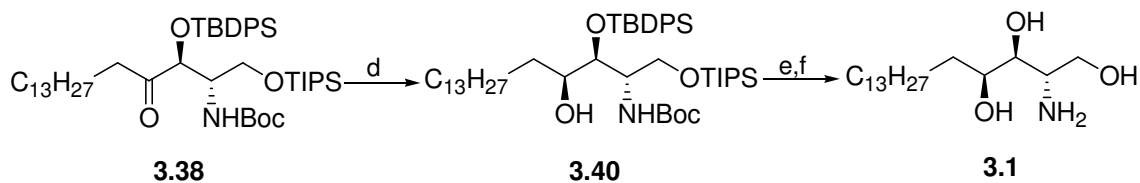


*Reagents and conditions:* a) i) NaBH<sub>4</sub>, EtOH, ii) TIPSCl, imidazole, DMF; b) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; c) *n*-C<sub>14</sub>H<sub>29</sub>SO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Me, *n*-BuLi, THF; d) lithium naphthalenide, THF, -78 °C.

Deprotonation of **3.38** with potassium bis(trimethyl)amide and successive sulfonylation with *N*-phenyl-trifluoromethanesulfonide gave enol triflate **3.39**, exclusively. The reductive elimination of triflate and successive deprotection of two silyl group produced exclusive *trans*-olefinated *N*-Boc sphingosine, and into *D*-erythro-sphingosine **3.6** by Boc deprotection. The diastereoselective reduction of ketone furnished **3.40** in 92% diastereo selectivity. The subsequent removal of silyl groups and Boc deprotection afforded *L*-lyxo-phytosphingosine **3.1** (Scheme 3.6).<sup>17j</sup>

Scheme 3.6



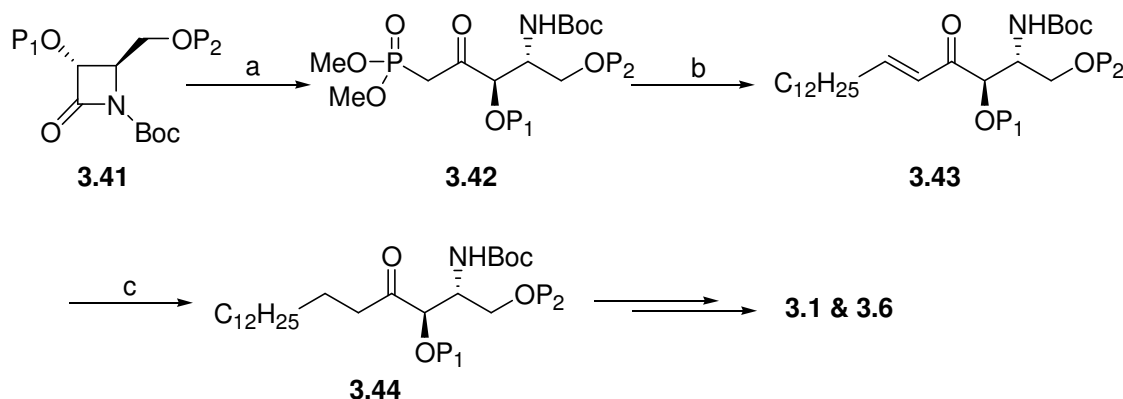


*Reagents and conditions:* a)  $\text{KN}(\text{TMS})_2$ , THF,  $-78\text{ }^\circ\text{C}$ , 1 h then  $\text{PhN}(\text{Tf})_2$ , THF,  $-20\text{ }^\circ\text{C}$ ; b)  $\text{HCO}_2\text{H}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Pd}(\text{OAc})_2(\text{Ph}_3)_2$ , DMF,  $60\text{ }^\circ\text{C}$ ; c) TBAF, THF, rt; d)  $\text{LiEt}_3\text{BH}$ , THF,  $-78\text{ }^\circ\text{C}$ ; e) TBAF, THF, rt.; f) 10% HCl, MeOH, rt.

### Pak's approach:

Pak *et al.* have reported a facile transformation of azetidin-2-one to unsaturated ketone **3.43** through the addition of phosphonate stabilized carbanion to azetidin-2-one ring and Horner-Wadsworth-Emmons olefination of the resulting  $\beta$ -ketophosphonates **3.42** with aldehyde is the key step in the formal synthesis of *L-erythro*-sphingosine and *D-lyxo*-phytosphingosine (Scheme 3.7).<sup>17i</sup>

**Scheme 3.7**



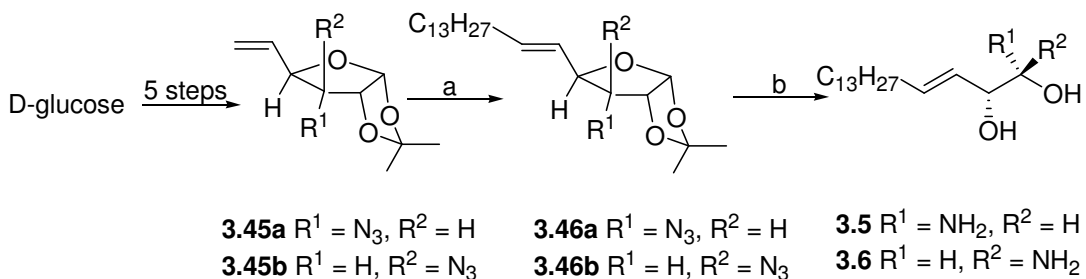
*Reagents and conditions:* a)  $\text{CH}_3\text{P}(\text{O})\text{OMe}_2$  (2 equiv.), *n*-BuLi (2 equiv.), THF,  $-78\text{ }^\circ\text{C}$ ; b)  $\text{CH}_3(\text{CH}_2)_{11}\text{CHO}$ ,  $\text{K}_2\text{CO}_3$ , EtOH; c)  $\text{H}_2$ , 10% Pd/C, EtOAc.

### Dhavale's approach:

Dhavale *et al.* illustrates the efficiency of the *E*-selective CM olefination methodology in the synthesis of *D-erythro*- and *D-threo*-sphingosine **3.5** and **3.6**, respectively. The four-step synthesis from **3.45a** and **3.45b** gives corresponding **3.5** in 65.4% and **3.6** 65.2% in overall yield. The easy availability of starting materials and reagents, a few high-yielding steps, and compatibility of Grubb's catalyst (second

generation) with sugar azides make this approach versatile for the synthesis of different types of sphingosine analogues and lipids (Scheme 3.8).<sup>17h</sup>

**Scheme 3.8**

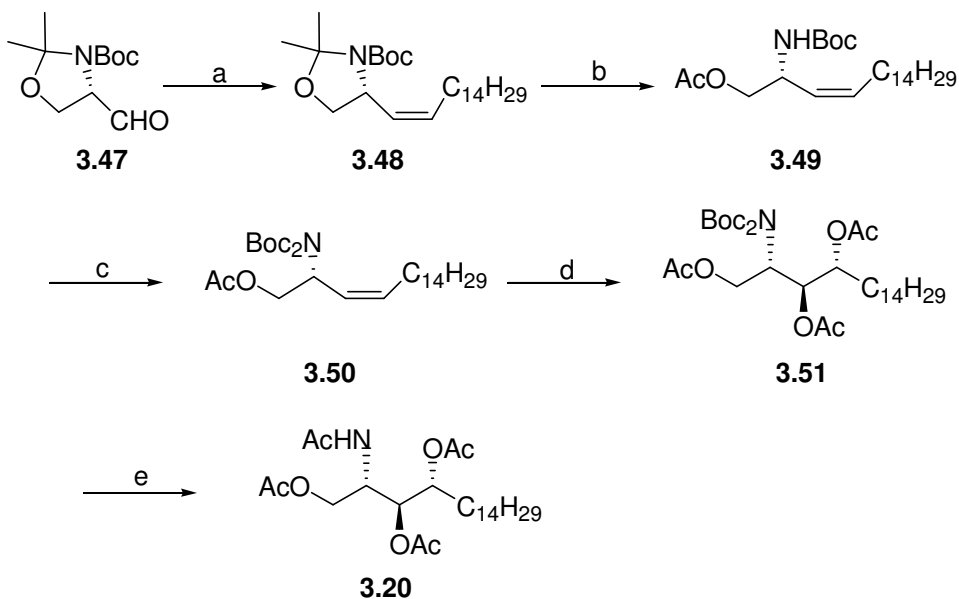


*Reagents and conditions:* a) 1-pentadecene, (10 mol %) Grubb's catalyst,  $CH_2Cl_2$ , 30 °C; b) i) TFA:H<sub>2</sub>O (4:1) 0 °C - 30 °C, ii) NaIO<sub>4</sub>, acetone-water, 0 °C - 30 °C; iii) LAH, THF, 0 °C - 30 °C.

### Kim's approach:

Kim *et al* have reported the N,N-diBoc-controlled dihydroxylation reaction for an efficient stereoselective synthesis of the tetraacetyl derivative of *D*-ribo-phytosphingosine **3.20** was realized in eight steps over a 45% overall yield from Garner's aldehyde with more than a 20:1 ratio (Scheme 3.9).<sup>25</sup>

**Scheme 3.9**



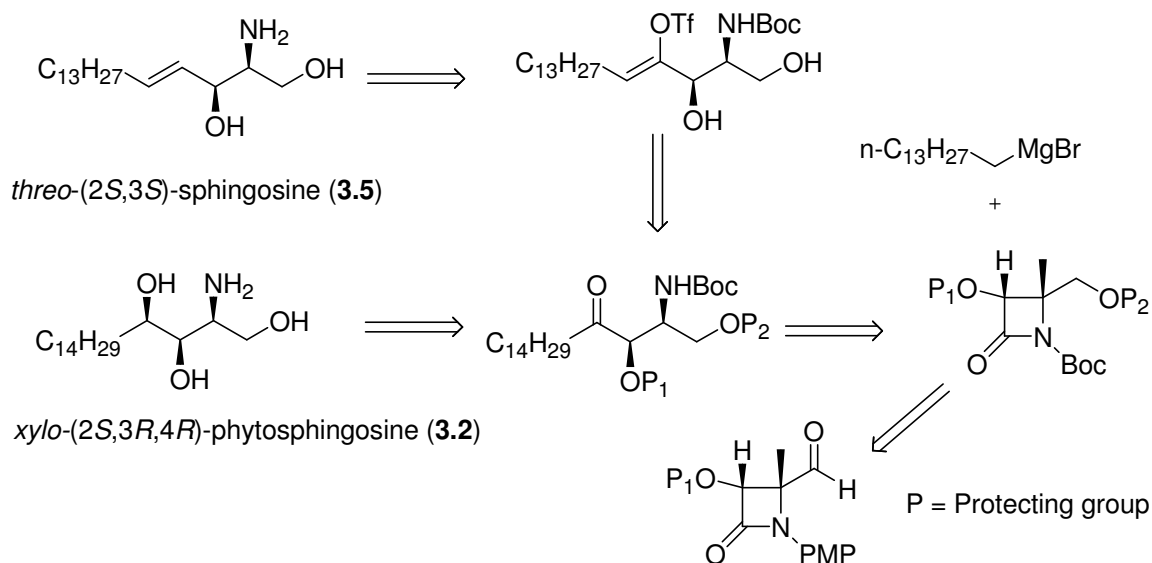
*Reagents and conditions:* a)  $Ph_3PC_{15}H_{31}Br$ , KHMDS, -78 °C; b) i) Dowex 50Wx<sub>4-100</sub> (H<sup>+</sup> form), ii)  $Ac_2O$ , TEA, DMAP; c)  $Boc_2O$ , TEA, DMAP; d) i)  $OsO_4$ , NMO, ii)  $Ac_2O$ , TEA, DMAP; e) i) HCl in MeOH, ii)  $Ac_2O$ , TEA, DMAP.



### 3.3: Present work

Sphingosines being popular synthetic targets, many synthetic routes have been reported. However, the literature survey brought forth only two examples using  $\beta$ -lactams as synthons. In one of the reports the starting  $\beta$ -lactam has been subjected to ring opening by phosphonate stabilized carbanion followed by a Horner-Wadsworth-Emmons reaction to obtain unsaturated ketone which on further elaboration yields sphingosines (Scheme 3.7).<sup>17i</sup> In another approach *n*-tetradecyl *p*-toluenesulphonate and *n*-butyllithium have been used to open the  $\beta$ -lactam ring. Subsequent desulphonylation using lithium naphthalenide and further synthetic manipulations led to the corresponding sphingosines (Scheme 3.6).<sup>17j, 26h</sup> While both the reports present beautiful approaches to sphingosines, the installation of the tetradecyl chain essentially happens in a two-step process in both the cases. In view of the above mentioned facts we envisaged that an attack of Grignard reagent would open the  $\beta$ -lactam ring and simultaneously bring in place the side chain in one step as shown in retro synthetic strategy (Scheme 3.10).

**Scheme 3.10**



The objective of this study was stereoselective formal synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine starting from enantiopure 4-formyl  $\beta$ -lactam.

### 3.4: Result and discussion

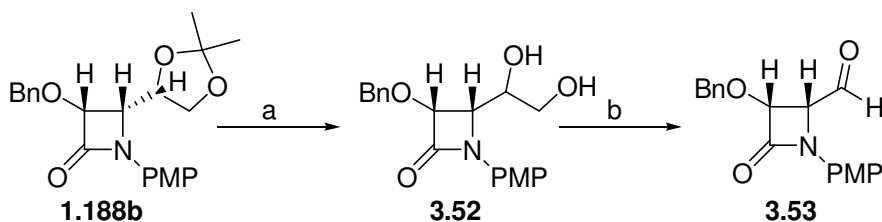
The optically pure 4-formyl- $\beta$ -lactam **3.53** can be easily prepared from commercially available D-glyceraldehyde acetonide *via* Staudinger ketene-imine cycloaddition reaction, in excellent yield and high enantiopurity by following a reported procedure.<sup>27</sup>

The acetonide group of the  $\beta$ -lactam **1.188b** was cleaved by PTSA<sup>28</sup> to get the diol **3.52**, which was then subjected to oxidative cleavage using NaIO<sub>4</sub> to get required enantiopure 4-formyl- $\beta$ -lactam **3.53** which was characterized by the spectral data (Scheme 3.11).

The IR spectrum of **3.53** showed a band at 1743 cm<sup>-1</sup> and 1745 cm<sup>-1</sup> corresponding to the  $\beta$ -lactam and aldehydic carbonyl respectively.

The <sup>1</sup>H NMR spectrum of **3.53** showed a singlet at 3.75 ppm corresponding to methoxy protons attached to aromatic ring. C-3 and C-4  $\beta$ -lactam protons appeared as doublet at 4.96 ppm with  $J = 5.3$  Hz and doublet of doublet at 4.39 ppm with  $J = 5.3, 3.5$  Hz respectively.

Scheme 3.11

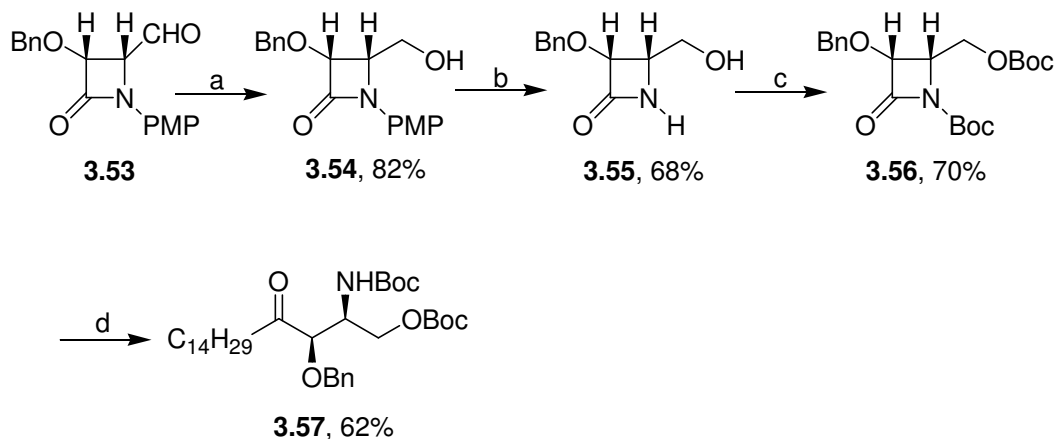


Reagents and conditions: a) PTSA, THF-H<sub>2</sub>O, reflux, 24 h;  
b) NaIO<sub>4</sub>, acetone-H<sub>2</sub>O, rt, 1 h.

The coupling constant 5.3 Hz indicates the *cis* stereochemistry of C-3 and C-4  $\beta$ -lactam protons. The benzyl protons resonated as two doublets at 4.67 and 4.79 ppm with  $J = 11.9$  Hz. The protons *ortho* to the methoxy group of the PMP appeared as two doublets at 6.81 and 7.18 ppm with  $J = 8.8$  Hz. The remaining aromatic protons appeared as multiplet in the range of 7.23-7.31 ppm. The aldehydic proton appeared as a doublet at 9.67 ppm with  $J = 3.5$  Hz.

The aldehyde **3.53** was reduced to the corresponding alcohol **3.54** by sodium borohydride in good yield (Scheme 3.12).

**Scheme 3.12**

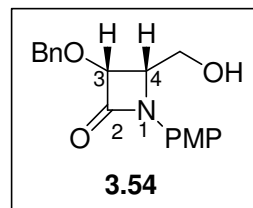


*Reagents and conditions:* a) NaBH<sub>4</sub>, MeOH, 8 h; b) CAN, CH<sub>3</sub>CN-H<sub>2</sub>O, 45 min; c) (Boc)<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 12 h; d) C<sub>14</sub>H<sub>29</sub>MgBr, THF, -78°-40°C, 1 h.

4-formyl azetidin-2-one **3.53**<sup>7a</sup> was reduced using NaBH<sub>4</sub> to obtain crude product, which was purified by column chromatography using acetone/petroleum ether to afford alcohol **3.54** as a white crystalline solid. The structure of **3.54** was established by spectral and analytical data.

The IR spectrum of 4-hydroxy methyl azetidin-2-one **3.54** showed a band at 1743 cm<sup>-1</sup> corresponding to β-lactam carbonyl. The band at 3337 cm<sup>-1</sup> was attributed for hydroxyl group.

The <sup>1</sup>H NMR spectrum of **3.54** showed a doublet of doublet at 2.38 ppm with *J* = 5.6 and 8.1 Hz corresponding to hydroxyl proton while, singlet at 3.79 ppm corresponding to methoxy protons attached to aromatic ring. The hydroxyl methylene protons displayed a multiplet at 3.99-4.08 ppm. The signals due proton corresponding to C-4 position of β-lactam appeared as multiplet at 4.08-4.24 ppm while, C-3 β-lactam proton appeared as doublet at 4.87 ppm with *J* = 5.1 Hz. The methylene protons from the benzyl resonated as two doublets at 4.78 and 5.03 ppm with *J* = 11.6 Hz. The *p*-methoxy phenyl ring protons appeared as doublet at 6.87 ppm with *J* = 9.1 Hz.



The remaining seven aromatic protons appeared as multiplet in the range of 7.36-7.42 ppm.

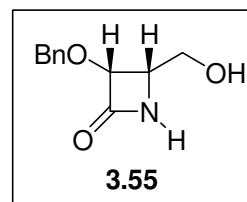
The  $^{13}\text{C}$  NMR **3.54** showed a peak at 55.3 ppm corresponding to methoxy carbon. The benzylic carbon appeared at 73.5 ppm while, the peak at 59.2 ppm corresponding to the hydroxyl methylene carbon. The C-3 and C-4  $\beta$ -lactam carbons appeared at 80.7 and 59.2 ppm respectively. The aromatic quaternary carbons resonated at 130.4, 136.4, 156.7 ppm, while the remaining aromatic carbons appeared at 114.3, 118.7, 128, 128.2, 128.5 ppm. The peak at 164.1 was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.54** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  314 (M+1).

The oxidative removal of *p*-methoxy phenyl group was then carried out using ceric ammonium nitrate to get *N*-deprotected  $\beta$ -lactam **3.55**.

A solution of  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  in water was added drop wise to a solution of 3-Benzyloxy-1-(4-methoxyphenyl)-4-hydroxymethyl azetidin-2-one (**3.54**) in acetonitrile at 0 °C. The mixture was stirred at this temperature for 45 min. After extractive workup with ethyl acetate, and concentration under vacuum to get crude product, it was purified by flash column chromatography using acetone/petroleum ether to furnish **3.55** as a white solid. The structure of **3.55** was established by spectral and analytical data.

The IR spectrum of **3.55** showed a band at  $1753\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl. The band at  $3373\text{ cm}^{-1}$  was attributed to hydroxyl group.

The  $^1\text{H}$  NMR spectrum of **3.55** showed signals due to -OH, -NH, hydroxyl methylene protons and C-4  $\beta$ -lactam proton which were merged and appeared as a multiplet at 3.51-3.90 ppm. The C-



3  $\beta$ -lactam proton appeared as doublet at 4.66 ppm with  $J = 5.5$  Hz. The methylene protons from the benzyl resonated as two doublets at 4.62 and 4.78 ppm with  $J = 11.6$  Hz. The aromatic protons appeared as multiplet in the range of 7.34-7.42 ppm.

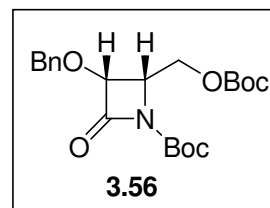
The  $^{13}\text{C}$  NMR **3.55** showed a peak at 54.8 ppm corresponding to C-4  $\beta$ -lactam carbon while, C-3  $\beta$ -lactam carbon appeared at 82.1 ppm. The benzylic carbon appeared at 73.4 ppm while, the peak at 61.5 ppm corresponding to the hydroxyl methylene carbon. The aromatic quaternary carbon resonated at 136.5 ppm, while remaining aromatic carbons appeared at 82.1, 128, 128.2, 128.5 ppm. The peak at 169.1 ppm was

assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.55** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  208 (M+1).

Subsequently the  $\beta$ -lactam nitrogen and the hydroxyl were protected as *N*-Boc and *O*-Boc derivatives respectively to get compound **3.56**.  $\text{Boc}_2\text{O}$  and DMAP were added to a solution of azetidin-2-one **3.55** in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ , and the reaction mixture was stirred for 5 h to get crude product, which was purified by column chromatography using acetone/petroleum ether to furnish title  $\beta$ -lactam **3.56** as a white solid. The structure of **3.56** was established by spectral and analytical data.

The IR spectrum of **3.56** showed a band at  $1741\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl. The band at  $1812\text{ cm}^{-1}$  was attributed to carbonate.

The  $^1\text{H}$  NMR spectrum of **3.56** showed two singlets at 1.44 ppm and 1.46 ppm corresponding to *N*-Boc and *O*-Boc respectively. The protected hydroxyl methylene protons at C-4 Position of  $\beta$ -lactam displayed a multiplet at 4.26-4.33 ppm. The signal due to proton corresponding to C-4 position of  $\beta$ -lactam appeared as multiplet at 4.36-4.44 ppm while, C-3  $\beta$ -lactam proton appeared as doublet at 4.63 ppm with  $J = 5.1\text{ Hz}$ . The benzyl methylene protons resonated as two doublets at 4.72 and 4.79 ppm with  $J = 11.7\text{ Hz}$ . The aromatic protons showed multiplet at 7.27-7.37 ppm.



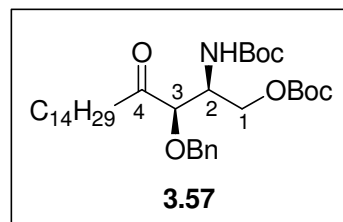
The  $^{13}\text{C}$  NMR **3.56** showed peaks at 27.6 and 27.8 ppm corresponding to methyl carbons of *N*-Boc and *O*-Boc respectively. The quaternary carbons of *O*-Boc and *N*-Boc appeared at 82.2 and 83.7 ppm respectively. The benzylic carbon appeared at 73.4 ppm while, the peak at 55.4 ppm corresponding to the protected hydroxyl methylene carbon. The C-3 and C-4  $\beta$ -lactam carbons appeared at 80.4 and 55.4 ppm respectively. The aromatic quaternary carbon resonated at 136.4 ppm, while remaining aromatic carbons appeared at 127.8, 128.0, 128.3 ppm. The *O*-Boc and *N*-Boc carbonyl carbons showed peaks at 147.5 and 152.8 ppm respectively. The peak at 164.1 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.56** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  408 (M+1).

Grignard reaction with tetradecylmagnesium bromide on **3.56** proceeded smoothly furnishing the required keto compound **3.57** in good yields. The tetradecylmagnesium bromide in THF was added to a solution of  $\beta$ -lactam **3.56** at  $-78^\circ\text{C}$ . The

reaction mixture was stirred at  $-40\text{ }^{\circ}\text{C}$  1 h. It was then extracted with ethyl acetate and the solvent was removed in *vacuo* yielding the product. Purification by flash column chromatography with acetone/petroleum ether gave  $\beta$ -amino ketone **3.57** as oil. The structure of **3.57** was established by spectral and analytical data.

The IR spectrum of **3.57** showed a band at  $1722\text{ cm}^{-1}$  corresponding to ketone. The band at  $1739\text{ cm}^{-1}$  was assigned for carbonate carbonyl while, band at  $3438\text{ cm}^{-1}$  was attributed for  $-\text{NH}$  stretching.

The  $^1\text{H}$  NMR displayed a multiplet for the terminal methyl protons of the long chain around 0.86-0.92 ppm. The methylene protons of the tetradecyl side chain appeared as two sets of multiplets at 1.17-1.26 and 1.35-1.43 ppm integrating for twenty one and three protons



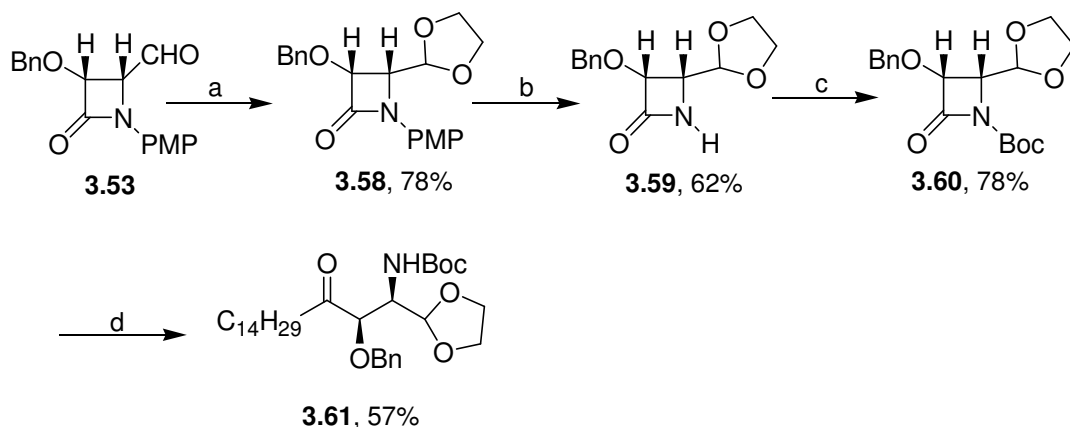
respectively. The remaining methylene of the tetradecyl side chain adjacent to the carbonyl appeared as a multiplet at 2.42-2.53 ppm. The two singlets corresponding to *N*-Boc and *O*-Boc appeared at 1.40 ppm and 1.49 ppm respectively. The proton on nitrogen appeared as a broad singlet at 3.56 ppm. The methine protons on C-2 and C-3 appeared together as a multiplet at 4.07-4.09 ppm. The benzyl protons resonated as two doublets at 4.41 and 4.95 ppm with  $J = 11.4\text{ Hz}$ . The protected hydroxyl methylene protons displayed a multiplet at 4.67- 4.73 ppm. All the aromatic protons appeared as a multiplet at 7.33-7.36 ppm.

The  $^{13}\text{C}$  NMR **3.57** showed peaks at 27.6 and 28.1 ppm corresponding to methyl carbons of *N*-Boc and *O*-Boc respectively. The methyl carbon of the newly introduced tetradecyl side chain appeared at 13.9 ppm. The methylene carbons of the side chain appeared together as a cluster at 22.5, 23.0, 28.2, 29.0, 29.2, 29.3, 29.4, 30.2, 31.7 and 39.0 ppm. The methylene carbon of the side chain, adjacent to the carbonyl appeared at 75.9 ppm. The quaternary carbons of *N*-Boc and *O*-Boc appeared at 81.5 and 81.9 ppm respectively. The benzylic carbon appeared at 72.8 ppm while, the peak at 64.9 ppm corresponding to the protected hydroxyl methylene carbon. The C-2 and C-3 carbons appeared at 50.3 and 81.3 ppm respectively. The aromatic quaternary carbon resonated at 154.9 ppm, while remaining aromatic carbons appeared at 127.8, 128.1 and 128.3 ppm. The *N*-Boc and *O*-Boc carbonyl carbons showed peaks at 136.9 and 152.9 ppm

respectively. The peak at 208.9 ppm was assigned to ketone carbonyl carbon. The compound **3.57** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  606 ( $M+1$ ).

The compound **3.56** on nucleophilic azetidinone ring opening using appropriate Grignard reagent gave core structure of sphingosine **3.57**. Various reactions were carried out on compound **3.57** such as  $AlCl_3$ ,  $BF_3 \cdot OEt_2$ , dil HCl, PTSA and CAN for Boc deprotection. However, all our attempts yielded complex reaction mixture. Efforts to reduce the keto group using various conditions such as  $NaBH_4$ , LAH and super hydride also yielded complex reaction mixture. Therefore, the aldehyde group was protected as an acetal and compound **3.58** so obtained was subjected CAN oxidation to remove PMP and subsequently protected as a Boc derivative to yield compound **3.60** (Scheme 3.13).

**Scheme 3.13**

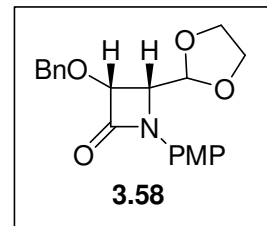


*Reagents and conditions:* a) Ethylene glycol, PTSA, benzene, reflux, 8 h; b) CAN,  $CH_3CN-H_2O$ , 0 °C, 45 min; c)  $(Boc)_2O$ , DMAP, DCM, rt, 12 h; d)  $C_{14}H_{29}MgBr$ , THF, -78 °C-40 °C, 1 h.

The 4-formyl group of  $\beta$ -lactam **3.53** was protected as its acetal using ethylene glycol in presence of catalytic amount of PTSA. To a mixture of 4-formyl  $\beta$ -lactam **3.53**, catalytic PTSA in benzene was added ethylene glycol. The reaction mixture was refluxed for 8 h. Extractive workup using ethyl acetate gave **3.58** in good yield as a white solid. The structure of **3.58** was established by spectral and analytical data.

The IR spectrum of **3.58** showed a band at  $1751\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl.

The  $^1\text{H}$  NMR spectrum of **3.58** showed a singlet at 3.79 ppm corresponding to methoxy protons attached to aromatic ring. The four methylene protons of acetal moiety displayed a multiplet at 3.94-3.98 ppm. The signals due proton corresponding to C-4 position of  $\beta$ -lactam appeared as triplet at 4.23 ppm with  $J = 5.1$  Hz while, C-3  $\beta$ -lactam proton appeared as doublet at 5.24 ppm with  $J = 5.1$  Hz.



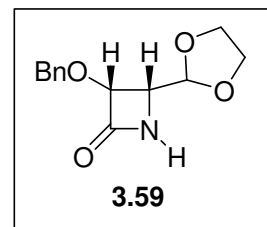
The benzyl protons and methine proton of acetal group merged together and appeared as multiplet at 4.83-4.94 ppm. The *p*-methoxy phenyl ring protons appeared as doublet at 6.87 ppm with  $J = 9.1$  Hz. The remaining seven aromatic protons appeared as multiplet in the range of 7.28-7.61 ppm.

The  $^{13}\text{C}$  NMR **3.58** showed a peak at 55.2 ppm corresponding to methoxy carbon. The benzylic carbon appeared at 73.1 ppm while, the peak corresponding to the methine carbon of acetal moiety appeared at 102.5 ppm. The methylene carbons of acetal moiety appeared at 64.8 and 66.5 ppm. The C-3 and C-4  $\beta$ -lactam carbons appeared at 80.2 and 60.2 ppm respectively. The aromatic quaternary carbons resonated at 131.0, 137.0, 156.2 ppm while, remaining aromatic carbons appeared at 113.8, 119.2, 127.7 and 128.0 ppm. The peak at 164.5 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.58** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  356 ( $M+1$ ).

The oxidative removal of *p*-methoxy phenyl group was then carried out with ceric ammonium nitrate using standard procedure to get *N*-deprotected  $\beta$ -lactam **3.59**. The structure of **3.59** was established by spectral and analytical data.

The IR spectrum of **3.59** showed a band at  $1774\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl. The band at  $3417\text{ cm}^{-1}$  was attributed for  $-\text{NH}$  stretching.

The  $^1\text{H}$  NMR spectrum of **3.59** showed the multiplet for four methylene protons of acetal moiety and C-4  $\beta$ -lactam proton which were merged and appeared at 3.60-4.01 ppm. The C-3  $\beta$ -



-lactam proton appeared as doublet at 5.12 ppm with  $J = 5.1$  Hz. The benzyl protons and methine proton of acetal group were merged and appeared as multiplet at 4.73-4.85 ppm. All the aromatic protons appeared as multiplet in the range of 7.32-7.37 ppm.



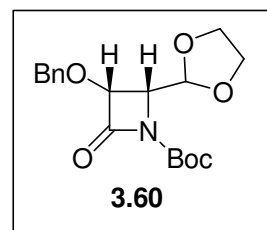
The  $^{13}\text{C}$  NMR **3.59** showed peak at 73.3 ppm corresponding to benzylic carbon while, the peak at 61.0 ppm corresponding to the methine carbon of acetal moiety. The methylene carbons of acetal moiety appeared at 63.8 and 65.5 ppm. The C-3 and C-4  $\beta$ -lactam carbons appeared at 79.2 and 56.2 ppm respectively. The aromatic quaternary carbon resonated at 136.0 ppm while, remaining aromatic carbons appeared at 127.8, 128.0, 128.3 ppm. The peak at 164.5 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.59** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  250 ( $M+1$ ).

Subsequently the  $\beta$ -lactam nitrogen was protected as *N*-Boc derivative to get compound **3.60**.

Boc<sub>2</sub>O and DMAP were added to a solution of azetidin-2-one **3.59** in  $\text{CH}_2\text{Cl}_2$  at 0 °C, and the reaction mixture was stirred for 12 h to get crude product, which was purified by column chromatography using acetone/petroleum ether furnished *N*-Boc protected  $\beta$ -lactam **3.60** as thick oil. The structure of **3.60** was established by spectral and analytical data.

The IR spectrum of **3.60** showed a band at  $1744\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl.

The  $^1\text{H}$  NMR spectrum of **3.60** showed a sharp singlet at 1.52 ppm corresponding to the methyl protons of carbamate. The four methylene protons of acetal moiety and C-4  $\beta$ -lactam proton were merged and appeared as a multiplet at 3.88-4.10 ppm. The C-3  $\beta$ -lactam proton appeared as doublet at 4.13 ppm with  $J = 5.5$  Hz. The benzyl protons appeared as two doublets at 4.72 and 4.77 ppm with  $J = 14.9$  Hz. The methine proton of acetal group resonated as doublet at 5.30 ppm with  $J = 5.7$  Hz. All the aromatic protons appeared as multiplet in the range of 7.30-7.36 ppm.



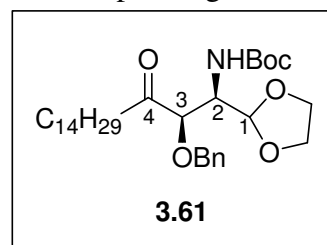
The  $^{13}\text{C}$  NMR **3.60** showed peaks at 27.8 corresponding to methyl carbons of *N*-Boc group. The two methylene carbons of acetal moiety showed peaks at 65.0 and 65.3 ppm. The quaternary carbon of *N*-Boc appeared at 83.2 ppm. The benzylic carbon showed peak at 73.2 ppm. The C-3 and C-4  $\beta$ -lactam carbons appeared at 79.9 and 57.9 ppm respectively while, the methine carbon of acetal moiety resonated at 101.3 ppm. The aromatic quaternary carbon resonated at 136.4 ppm, while remaining aromatic carbons

appeared at 127.8, 127.9, 128.3 ppm. The *N*-Boc carbonyl carbons showed peak at 147.7 ppm. The peak at 164.4 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.60** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  350 ( $M+1$ ).

Grignard reaction with tetradecylmagnesium bromide on **3.60** proceeded smoothly furnishing the required keto compound **3.61** by using standard procedure in good yields. The structure of **3.61** was established by spectral and analytical data.

The IR spectrum of **3.61** showed a band at  $1720\text{ cm}^{-1}$  corresponding to ketone. The band at  $3448\text{ cm}^{-1}$  was attributed for  $-\text{NH}$  stretching.

The  $^1\text{H}$  NMR displayed a multiplet for the terminal methyl protons of the long chain around 0.85-0.91 ppm. The methylene protons of the the tetradecyl side chain appeared as two sets of multiplets at 1.15-1.22 and 1.33-



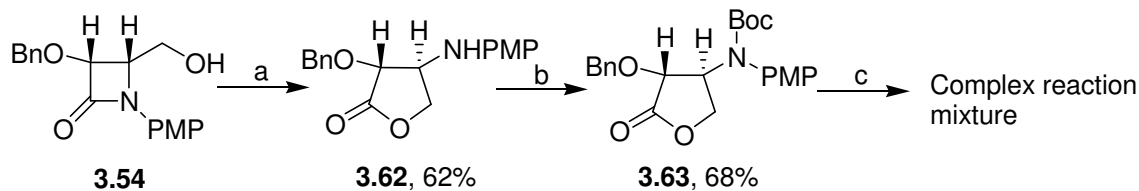
1.43 ppm integrating for twenty one and three protons respectively. The remaining methylene of the tetradecyl side chain, adjacent to the carbonyl appeared as a multiplet at 2.48-2.55 ppm. The singlet corresponding to *N*-Boc appeared at 1.50 ppm. The four methylene protons of acetal moiety and C-2 proton appeared together as a multiplet at 3.90-4.06 ppm. The proton on nitrogen appeared as a broad singlet at 1.86 ppm. The methine protons on C-2 and C-3 appeared together as a multiplet at 4.07-4.09 ppm. The benzyl protons resonated as two doublets at 4.58 and 4.95 ppm with  $J = 11.5$  Hz. The methine proton of acetal moiety displayed a doublet at 5.06 ppm with  $J = 5.6$  Hz. All the aromatic protons appeared as a multiplet at 7.35-7.37 ppm.

The  $^{13}\text{C}$  NMR **3.61** showed peak at 27.6 ppm corresponding to the methyl carbons of *N*-Boc. The methyl carbon of the newly introduced tetradecyl side chain appeared at 13.8 ppm. The methylene carbons of the side chain appeared together as a cluster at 22.5, 23.0, 28.2, 29.0, 29.2, 29.3, 29.4, 30.2, 31.7 and 39.0 ppm. The methylene carbon of the side chain adjacent, to the carbonyl appeared at 75.8 ppm. The quaternary carbon of *N*-Boc showed signal at 81.4 ppm. The two methylene carbons of acetal moiety showed peaks at 65.1 and 65.2 ppm. The benzylic carbon appeared at 72.6 ppm while, the peak at 101.3 ppm corresponding to the methine carbon of acetal moiety. The C-2 and C-3 carbons appeared at 51.3 and 82.3 ppm respectively. The aromatic quaternary carbon

resonated at 154.3 ppm, while remaining aromatic carbons appeared at 127.2, 128.2 and 128.5 ppm. The *N*-Boc carbonyl carbon showed peak at 136.9 ppm. The peak at 208.9 ppm was assigned to ketone carbonyl carbon. The compound **3.61** also gave satisfactory elemental analysis and a mass spectrum showed peak at *m/z* 548 (*M*+1).

Unfortunately our attempts to selectively deprotect the acetal using various conditions such as dil HCl, PTSA, CAN and Lewis acids such as AlCl<sub>3</sub>, BF<sub>3</sub>-OEt<sub>2</sub> were unsuccessful and always yielded inseparable mixture of products. So we changed our strategy, the 4-hydroxymethylene azetidin-2-one (**3.54**) was lactonized using methanolic HCl to obtain compound **3.62** (Scheme 3.14).

**Scheme 3.14**

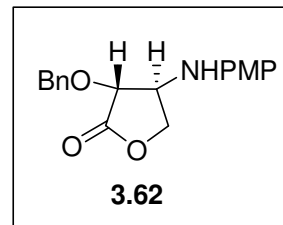


a) H<sup>+</sup>/MeOH, rt, 12 h; b) (Boc)<sub>2</sub>O, DMAP, DCM, 12 h; c) C<sub>14</sub>H<sub>29</sub>MgBr, THF, -78 °C-40 °C, 1 h.

The azetidin-2-one ring expansion reaction of **3.54** with methanolic-HCl at room temperature resulted in very good yield (62%) of the  $\gamma$ -lactone **3.62**. 3-Benzyloxy-4-hydroxymethyl azetidin-2-one (**3.54**) was dissolved in methanolic HCl (20%) and the reaction mixture was stirred for 12 h at room temperature. After the reaction was over it was then extracted with ethyl acetate. The solvent was removed under reduced pressure to get thick oil, which was purified by flash column chromatography furnished **3.62** as a white solid. The structure of **3.62** was established by spectral and analytical data.

The IR spectrum of **3.62** showed a sharp band at 1785 cm<sup>-1</sup> corresponding to the  $\gamma$ -lactone carbonyl group. The band at 3373, 3519 cm<sup>-1</sup> corresponds to the -NH stretching.

The <sup>1</sup>H NMR spectrum of **3.62** showed a broad singlet at 3.99 ppm corresponding to the proton on nitrogen. The sharp singlet at 3.77 ppm was attributed to the methoxy protons. The C-4 methine proton displayed a doublet at 4.14 ppm with *J* = 6.6 Hz. One of the diastereotopic methylene ring proton resonated as doublet at 3.96 with *J* = 6.3 ppm while, other proton displayed



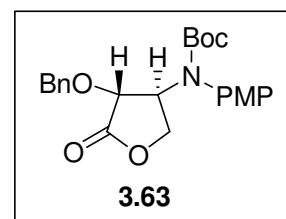
doublet of doublet at 4.12 ppm with  $J = 6.3$  and  $6.6$  Hz. The C-3 ring proton appeared as doublet of doublet at 4.66 ppm with  $J = 3.3$  and  $6.6$  Hz. The benzylic protons appeared as two doublets at 4.47 and 5.0 ppm with  $J = 11.9$  Hz. The *p*-methoxy phenyl ring protons resonated as two doublets at 6.59 and 6.79 ppm with  $J = 8.8$  Hz and remaining aromatic protons appeared as multiplet between 7.27-7.38 ppm.

The  $^{13}\text{C}$  NMR of **3.62** showed a peak at 55.2 ppm corresponding for the methoxy carbon. The peaks at 70.0 ppm and 72.0 ppm corresponds to the methylene carbon at C-5 position of  $\gamma$ -lactone ring and benzyl carbon respectively. The C-3 and C-4  $\gamma$ -lactone carbons appeared at 76.9 ppm and 56.6 ppm respectively. The peaks at 136.3, 139.2 and 152.9 ppm was assigned to aromatic quaternary carbons while, other aromatic carbons appeared at 114.6, 115.0, 127.8, 127.9 and 128.1 ppm. The peak at 173.1 ppm was assigned to  $\gamma$ -lactone carbonyl carbon. The compound **3.62** also gave satisfactory elemental analysis and mass spectrum showed a peak at  $m/z$  314 (M+1).

The secondary amino group of **3.62** was protected as its carbamate derivative **3.63** and structure was established by spectral and analytical data.

The IR spectrum of **3.63** showed a sharp band at  $1764\text{ cm}^{-1}$  corresponding to the  $\gamma$ -lactone carbonyl group.

The  $^1\text{H}$  NMR spectrum of **3.63** showed a singlet at 1.45 ppm corresponding to the protons of *N*-Boc. The sharp singlet at



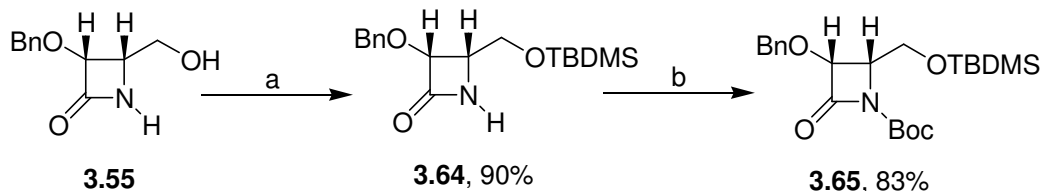
3.78 ppm was attributed to the methoxy protons. The C-4 methine proton displayed a doublet at 3.91 ppm with  $J = 3.6$  Hz. One of the diastereotopic methylene ring protons and one of benzyl protons appeared together and displayed a multiplet at 4.32-4.41 ppm while, the other benzyl proton resonated as a doublet at 4.74 ppm with  $J = 11.9$  Hz. The other C-5 methylene proton and C-3 proton merged and appeared at 4.45-4.65 ppm. The *p*-methoxy phenyl ring protons resonated as doublet at 6.87 ppm with  $J = 8.8$  Hz and remaining seven aromatic protons appeared as multiplet between 7.26-7.36 ppm.

The  $^{13}\text{C}$  NMR of **3.63** showed a peak at 27.7 ppm corresponding to the methyl carbons of *N*-Boc. The peak at 55.4 ppm was attributed to the methoxy carbon. The peaks at 58.7 ppm and 72.6 ppm were attributed to the methylene carbon at C-5 position of  $\gamma$ -lactone ring and benzylic carbon respectively. The C-3 and C-4  $\gamma$ -lactone carbons appeared at 75.6 ppm and 58.7 ppm respectively. The quaternary carbon of *N*-Boc

showed a peak at 83.2 ppm. The peaks at 129.1, 128.5 and 136.6 ppm were assigned to the aromatic quaternary carbons while, other aromatic carbons appeared at 128.1, 127.8, 124.8, 124.6 and 114.5 ppm. The peaks at 157.5 ppm and 173.1 ppm were assigned to *N*-Boc carbonyl carbon and  $\gamma$ -lactone carbonyl carbon respectively. The compound **3.63** also gave satisfactory elemental analysis and mass spectrum showed a peak at *m/z* 414 (*M*+1).

The carbamate derivative **3.63** on Grignard reaction with tetradecyl magnesium bromide did not give the desired product. To our dismay the Grignard reaction too gave a very complex reaction mixture. Therefore, the hydroxymethylene group at C-4 position of  $\beta$ -lactam **3.55** was protected as *O*-tertiarybutyldimethylsilyl ether **3.64** (Scheme 3.15).

**Scheme 3.15**



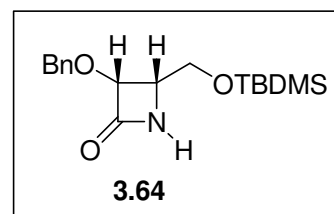
*Reagents and conditions:* a) TBDMS-Cl, imidazole, DMF, 3 h; b) (Boc)<sub>2</sub>O, DMAP, DCM, 5 h.

To a mixture of azetidin-2-one **3.63** and imidazole in anhydrous DMF was added *tert*-butyldimethylsilyl chloride at room temperature. The reaction mixture was stirred at room temperature for 3 h. The extractive work up with ethyl acetate afford crude product, which was purified by column chromatography using ethyl acetate/petroleum ether to furnish **3.64** as colorless oil. The structure of **3.64** was established by spectral and analytical data.

The IR spectrum of **3.64** showed a band at 1762 cm<sup>-1</sup> corresponding to  $\beta$ -lactam carbonyl. The band at 3259 cm<sup>-1</sup> was attributed to the hydroxyl group.

The <sup>1</sup>H NMR spectrum of **3.64** showed two singlets at 0.05 ppm and 0.06 ppm corresponding for two methyl groups while and a singlet at 0.88 ppm integrating nine protons corresponding to the methyl protons of *t*-butyl group.

One of the protected hydroxy methylene proton, C-3 and C-4  $\beta$ -lactam protons appeared together as a multiplet at 3.70-3.82 ppm while, other methylene proton resonated as a multiplet at 4.71-4.74 ppm. The benzyl protons



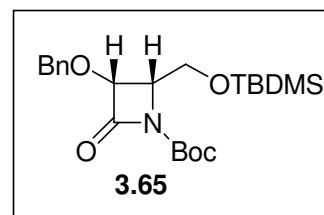
appeared as two doublets at 4.67 ppm and 4.81 ppm with  $J = 11.9$  Hz. The cyclic amide proton displayed a broad singlet at 6.12 ppm. The aromatic protons appeared as multiplet in the range of 7.26-7.35 ppm.

The  $^{13}\text{C}$  NMR **3.64** showed a peak at -5.4 ppm corresponding to two methyl carbons on silicon atom while, methyl carbons of *t*-butyl group showed peak at 25.8 ppm. The quaternary carbon of *t*-butyl group on silicon atom resonated at 18.2 ppm. The C-3 and C-4  $\beta$ -lactam carbons showed peaks at 82.0 ppm and 55.7 ppm respectively. The peak at 62.8 ppm was attributed to the protected hydroxy methylene carbon. The benzylic carbon appeared at 73.1 ppm. The aromatic quaternary carbon resonated at 137.0 ppm while, remaining aromatic carbons appeared at 127.9, 128.3 and 128.4 ppm. The peak at 168.7 ppm was assigned to  $\beta$ -lactam carbonyl carbon. The compound **3.64** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  322 ( $M+1$ ).

The protection of hydroxymethylene was followed by the protection of  $\beta$ -lactam nitrogen as *t*-butoxycarbonyl **3.65**. The structure of **3.65** was established by spectral and analytical data.

The IR spectrum of **3.65** showed a band at  $1718\text{ cm}^{-1}$  corresponding to  $\beta$ -lactam carbonyl.

The  $^1\text{H}$  NMR spectrum of **3.65** showed two singlets at 0.05 ppm and 0.06 ppm corresponding to two methyl groups while and a singlet at 0.89 ppm integrating nine protons corresponding to methyl protons of *t*-butyl group. The peak at

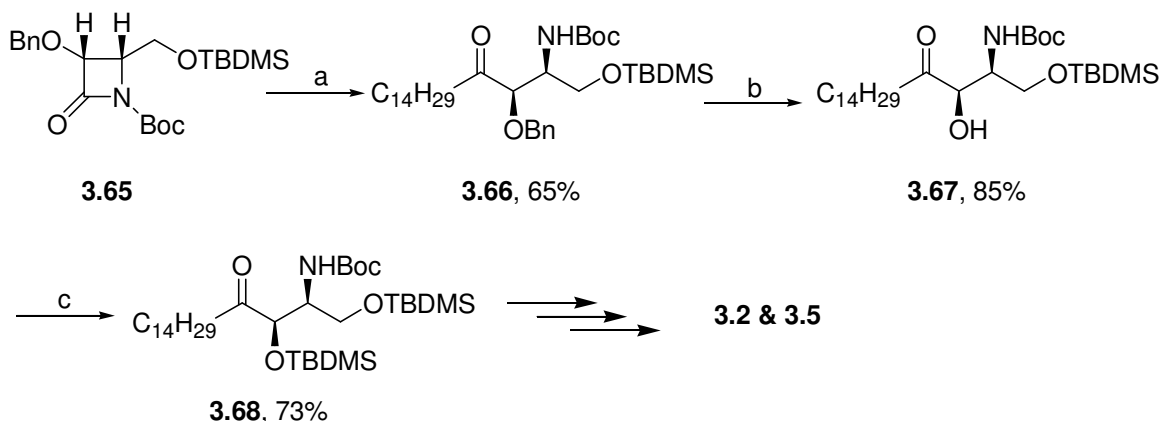


1.52 ppm was attributed for methyl protons of carbamate. The protected hydroxy methylene protons appeared as a multiplet at 3.97-4.03 ppm. The C-4  $\beta$ -lactam proton appeared as multiplet at 4.04-4.09 ppm while, C-3  $\beta$ -lactam proton resonated as doublet at 4.69 ppm with  $J = 5.2$  Hz. The benzylic protons displayed a singlet at 4.77 ppm. The aromatic protons appeared as multiplet in the range of 7.31-7.36 ppm.

The  $^{13}\text{C}$  NMR **3.65** showed two peaks at -5.6 ppm and -5.5 ppm corresponding to the two methyl carbons on silicon atom while, methyl carbons of *t*-butyl group showed a peak at 25.7 ppm. The quaternary carbon of *t*-butyl group on silicon atom resonated at 18.2 ppm. The peak at 28.0 ppm was assigned to the methyl carbons of *N*-Boc. The C-3 and C-4  $\beta$ -lactam carbons showed peaks at 80.3 ppm and 58.2 ppm respectively. The

peak at 63.1 ppm was attributed to the protected hydroxy methylene carbon. The benzylic carbon appeared at 73.3 ppm. The quaternary carbon of *N*-Boc appeared at 83.3 ppm while, the aromatic quaternary carbon resonated at 136.8 ppm. The remaining aromatic carbons appeared at 127.9, 128.2 and 128.4 ppm. The peaks at 148.0 ppm and 168.7 ppm were assigned to *N*-Boc carbonyl carbon and  $\beta$ -lactam carbonyl carbon respectively. The compound **3.65** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  422 ( $M+1$ ).

**Scheme 3.16**

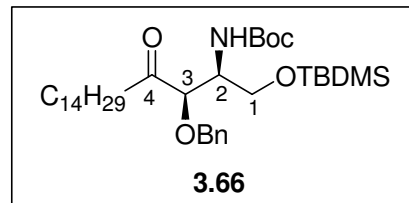


*Reagents and conditions:* a)  $C_{14}H_{29}MgBr$ , THF,  $-78$  °C- $40$  °C, 1 h; b)  $HCOONH_4$ , 10% Pd/C, MeOH, reflux, 1 h; c) TBDMS-Cl, imidazole, DMF,  $35$  °C, 12 h.

The compound **3.65** was then subjected to Grignard reaction with *n*-tetradecyl magnesium bromide in THF to obtain compound **3.66** using standard procedure (Scheme 3.16). The structure of **3.66** was established by spectral and analytical data.

The IR spectrum of **3.66** showed a band at  $1706\text{ cm}^{-1}$  corresponding to ketone. The band at  $1718\text{ cm}^{-1}$  was assigned to the carbonate carbonyl while, band at  $3436\text{ cm}^{-1}$  was attributed for  $-NH$  stretching.

The  $^1H$  NMR of **3.66** displayed two singlets at 0.05 ppm and 0.07 ppm corresponding to two methyl groups of TBDMS. The multiplet for the terminal



methyl protons of the long chain and nine protons of TBDMS appeared together around 0.85-0.89 ppm. The methylene protons of the the tetradecyl side chain appeared as two sets; one as multiplet at 1.20-1.30 and triplet at 1.55 ppm with  $J = 6.8$  Hz integrating for twenty two and one protons respectively. The remaining methylene of the tetradecyl side chain, adjacent to the carbonyl appeared as a doublet of doublet at 2.48 ppm with  $J = 6.8$

and 14.4 Hz. The singlet corresponding to *N*-Boc appeared at 1.39 ppm. The C-2 methine proton and one of the C-1 proton appeared as multiplet at 3.51-3.69 ppm while, other C-1 proton displayed a doublet at 4.26 ppm with  $J = 2.9$  Hz. The proton on nitrogen appeared as multiplet at 4.05-4.18 ppm. The methine proton on C-3 appeared as doublet at 4.91 ppm with  $J = 9.6$  ppm. The benzyl protons resonated as two doublets at 4.40 and 4.68 ppm with  $J = 11.2$  Hz. All the aromatic protons appeared as a multiplet at 7.29-7.39 ppm.

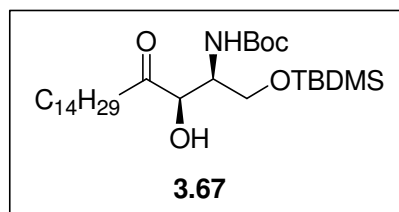
The  $^{13}\text{C}$  NMR **3.66** showed two peaks at -5.5 ppm and -5.4 ppm corresponding to the two methyl carbons on silicon atom while, methyl carbons of *t*-butyl group showed a peak at 25.8 ppm. The quaternary carbon of *t*-butyl group on silicon atom resonated at 18.1 ppm. The peak corresponding to the methyl carbons of *N*-Boc appeared at 28.2 ppm. The methyl carbon of the newly introduced tetradecyl side chain appeared at 14.1 ppm. The methylene carbons of the side chain appeared together as a cluster at 22.6, 23.4, 29.2, 29.3, 29.4, 29.6, 31.9, and 39.1 ppm. The methylene carbon of the side chain, adjacent to the carbonyl appeared at 39.3 ppm. The quaternary carbon of *N*-Boc appeared at 79.5 ppm. The benzylic carbon appeared at 73.0 ppm while, the peak at 61.4 ppm was attributed to the protected hydroxyl methylene carbon. The C-2 and C-3 carbons appeared at 53.1 and 81.4 ppm respectively. The aromatic quaternary carbon resonated at 137.4 ppm, while remaining aromatic carbons appeared at 127.9, 128.1 and 128.4 ppm. The *N*-Boc carbonyl carbon showed peak at 155.2 ppm. The peak at 210.3 ppm was assigned to ketone carbonyl carbon. The compound **3.66** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  620 ( $M+1$ ).

The benzyloxy group was successfully deprotected by transfer hydrogenation with ammonium formate and Pd-C (10%) to get **3.67**. The structure of **3.67** was established by spectral and analytical data.

The IR spectrum of **3.67** showed a band at  $1712\text{ cm}^{-1}$  corresponding to ketone. The band at  $3442\text{ cm}^{-1}$  was attributed for  $-\text{NH}$  stretching.



The  $^1\text{H}$  NMR of **3.67** displayed two singlets at 0.09 ppm and 0.1 ppm corresponding for two methyl protons of TBDMS. The multiplet for the terminal methyl protons, one of the methylene proton of the long chain and nine protons of TBDMS appeared together around 0.79-0.97 ppm. The



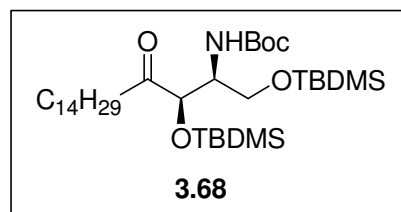
methylene protons of the tetradecyl side chain appeared as multiplet at 1.20-1.35 ppm integrating for twenty three protons. The remaining methylene of the tetradecyl side chain, adjacent to the carbonyl appeared as a multiplet at 2.41-2.62 ppm. The singlet corresponding to *N*-Boc appeared at 1.39 ppm. The C-1 methylene proton and proton on nitrogen appeared as multiplet at 3.61-3.73 ppm while, hydroxyl proton displayed a multiplet at 4.10-4.25 ppm. The C-2 and C-3 methine protons resonated as two multiplets at 4.30-4.50 ppm and 4.56-4.65 ppm respectively.

The  $^{13}\text{C}$  NMR **3.67** showed peaks two peaks at -5.5 ppm and -5.4 ppm corresponding to the two methyl carbons on silicon atom while, methyl carbons of *t*-butyl group showed a peak at 25.8 ppm. The quaternary carbon of *t*-butyl group on silicon atom resonated at 18.1 ppm. The peak corresponding to the methyl carbons of *N*-Boc appeared at 28.2 ppm. The methyl carbon of the newly introduced tetradecyl side chain appeared at 14.1 ppm. The methylene carbons of the side chain appeared together as a cluster at 14.1, 18.2, 22.7, 23.6, 29.1, 29.3, 29.4, 29.5, 29.6, and 31.9 ppm. The methylene carbon of the side chain, adjacent to the carbonyl appeared at 37.7 ppm. The quaternary carbon of *N*-Boc appeared at 79.7 ppm. The peak corresponding to the protected hydroxyl methylene carbon resonated at 62.3 ppm. The C-2 and C-3 carbons displayed signals at 53.1 ppm and 74.7 ppm respectively. The *N*-Boc carbonyl carbon showed peak at 155.2 ppm. The peak at 211.5 ppm was assigned to ketone carbonyl carbon. The compound **3.67** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  530 ( $M+1$ ).

Compound **3.67** on protection with TBDMS chloride yielded (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3-bis-(*tert*-butyldimethylsilyloxy)octadecane-4-one (**3.68**) in good yield.

The IR spectrum of **3.68** showed a band at  $1715\text{ cm}^{-1}$  corresponding to ketone. The band at  $3436\text{ cm}^{-1}$  was attributed for  $-\text{NH}$  stretching.

The  $^1\text{H}$  NMR of **3.68** displayed four singlets at 0.01, 0.04, 0.07 ppm and 0.1 ppm corresponding for four methyl groups of TBDMS. The methyl protons of *t*-butyl groups on silicon appeared as two singlets at 0.90 ppm and 0.94 ppm. The methylene protons and terminal methyl protons of the tetradecyl side chain appeared as two multiplets at 1.20-1.27 ppm and 1.45-1.61 ppm integrating for twenty two protons and five protons respectively. The remaining methylene of the tetradecyl side chain, adjacent to the carbonyl appeared as a multiplet at 2.42-2.54 ppm. The singlet corresponding to *N*-Boc appeared at 1.41 ppm. The protected hydroxyl methylene protons displayed two multiplets at 3.62-3.67 ppm and 4.42-4.44 ppm. The C-2 methine proton resonated as a triplet at 3.51 ppm with  $J = 8.5$  Hz while, C-3 methine proton appeared as doublet at 4.90 ppm with  $J = 9.1$  Hz. The proton on nitrogen appeared as broad singlet at 3.70 ppm.



The  $^{13}\text{C}$  NMR **3.68** showed three peaks at -5.5, -5.3 and -4.7 ppm corresponding to the four methyl carbons on silicon atom while, methyl carbons of *t*-butyl group showed a peaks at 25.8 and 28.3 ppm. The quaternary carbons of *t*-butyl group on silicon atoms resonated at 18.2 and 18.3 ppm. The peak at 29.2 ppm was assigned to the methyl carbons of *N*-Boc. The methyl carbon of the newly introduced tetradecyl side chain appeared at 14.1 ppm. The methylene carbons of the side chain appeared together as a cluster at 22.7, 23.5, 29.4, 29.5, 29.6 and 31.9 ppm. The methylene carbon of the side chain, adjacent to the carbonyl appeared at 38.6 ppm. The quaternary carbon of *N*-Boc appeared at 79.5 ppm. The peak corresponding to the protected hydroxy methylene carbon appeared at 61.0 ppm. The C-2 and C-3 carbons displayed signals at 54.2 ppm and 75.7 ppm respectively. The *N*-Boc carbonyl carbon showed peak at 155.2 ppm. The peak at 211.3 ppm was assigned to ketone carbonyl carbon. The compound **3.68** also gave satisfactory elemental analysis and a mass spectrum showed peak at  $m/z$  645 ( $M+1$ ).

The transformation of **3.68** to *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine is a well documented three-step synthetic protocol.<sup>17i,j</sup> (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3-bis-(*tert*-butyldimethylsilyloxy)octadecane-4-one (**3.68**) is also an important intermediate in the synthesis of *threo*-(2*S*,3*S*)-sphingosine (**3.5**), which is a well established three-step synthetic sequence.<sup>17i,j</sup> Thus, (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3-bis-(*tert*-

butyldimethylsilyloxy)ctadecane-4-one (**3.68**) is a common intermediate in the synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**3.2**) and *threo*-(2*S*,3*S*)-sphingosine (**3.5**).

### **3.5: Conclusion**

In conclusion we have established a stereoselective synthesis of a common intermediate **3.68** for *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**3.2**) and *threo*-(2*S*,3*S*)-sphingosine (**3.5**) starting from enantiopure 4-formyl  $\beta$ -lactam. A Grignard reaction on the  $\beta$ -lactam carbonyl followed by further transformations provided this crucial common precursor in good yield.

### 3.6: Experimental

#### (3*R*,4*R*)-3-Benzoyloxy-1-(4-methoxyphenyl)-4-formylazetidin-2-one (3.53)

A mixture of azetidin-2-one **1.188b** (3.83 g, 10 mmol) and *p*-toluenesulphonic acid monohydrate (0.57 g, 3 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC) the reaction mixture was neutralized with sodium bicarbonate and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and organic layer was washed with brine solution (10 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to afford the diol **3.52**, which was dissolved in acetone (50 mL) and water 25 mL) and cooled to 0 °C. To the cooled solution, NaIO<sub>4</sub> (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and residue was taken in dichloromethane (30 mL) and organic layer was washed with water (2 x 10 mL), saturated sodium bicarbonate solution (2 x 10 mL), brine solution (15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to afford the 4-formylazetidin-2-one **3.53** (2.65 g, 85%) as a white solid.

**MP** : 152-153 °C {Lit<sup>27</sup> 154-155 °C}.

**[α]<sup>25</sup><sub>D</sub>** : +176.3 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>) {Lit<sup>27</sup> [α]<sup>25</sup><sub>D</sub> = +178.5 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>)}.

**IR (CHCl<sub>3</sub>)** : 1753 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 3.75 (s, 3H), 4.39 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 5.3 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.23-7.31 (m, 5H), 9.67 (d, *J* = 3.5 Hz, 1H).

#### (3*R*,4*S*)-3-Benzoyloxy-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (3.54):

To a cooled solution of 4-formyl azetidin-2-one (**3.53**)<sup>27a</sup> (3.11 g, 10 mmol) in methanol (50 mL) at 0 °C was added NaBH<sub>4</sub> (1.85 g, 50 mmol) portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 8 h. After completion of reaction (TLC), water (20 mL) was added carefully and the reaction mixture was further stirred for 1 h. Methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 80 mL). The combined

organic layer was washed with brine (15 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography using acetone/petroleum ether (25:75) to afford alcohol **3.54** (2.56 g, 82%) as a white crystalline solid.

**MP** : 119-120 °C.

**[α]<sup>25</sup><sub>D</sub>** : +160 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3337, 1743 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 2.38 (dd, *J* = 8.1, 5.6, 1H), 3.79 (s, 3H), 3.99-4.08 (m, 2H), 4.08-4.26 (m, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 5.1 Hz, 1H), 5.03 (d, *J* = 11.6 Hz, 1H), 6.87 (d, *J* = 9.1 Hz, 2H), 7.36-7.42 (m, 7H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 55.3, 57.9, 59.2, 73.5, 80.7, 114.3, 118.7, 128, 128.2, 128.5, 130.4, 136.4, 156.7, 164.1.

(50.32 MHz)

**MS (m/z)** : 314 (M+1).

**Analysis** : Calculated: C, 68.99; H, 6.11; N, 4.47.

(C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>) Observed: C, 68.93; H, 6.09; N, 4.38.

**(3R,4S)- 3-Benzyloxy-4-(hydroxymethyl)azetidin-2-one (3.55):**

A solution of (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> (10.5 g, 19.2 mmol) in water (65 mL) was added drop wise to a solution of 3-Benzyloxy-1-(4-methoxyphenyl)-4-hydroxymethyl azetidin-2-one (**3.54**) (2 g, 6.4 mmol) in acetonitrile (67 mL) at 0 °C. The mixture was stirred at this temperature for 45 min. Water (50 mL) was added, it was extracted with ethyl acetate (3 x 125 mL) and washed with saturated solution of NaHCO<sub>3</sub> (2 x 50 mL). The aqueous layer of NaHCO<sub>3</sub> was extracted again with ethyl acetate (1 x 25 mL), and the combined organic extracts were washed with 40% NaHSO<sub>3</sub> (3 x 60 mL) and brine (10 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography using acetone/petroleum ether (40:60) as an eluant to furnish **3.55** (0.9 g, 68%) as a white solid.

**MP** : 80 °C.

**[α]<sup>25</sup><sub>D</sub>** : -36 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3373, 1753 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  3.51-3.9 (m, 5H), 4.62 (d,  $J = 11.6$  Hz, 1H), 4.66 (d,  $J = 5.5$  Hz, 1H), 4.78 (d,  $J = 11.6$  Hz, 1H), 7.34-7.42 (m, 5H).  
(CDCl<sub>3</sub>)  
(200 MHz)

**<sup>13</sup>C NMR** :  $\delta_{\text{C}}$  54.8, 61.5, 73.4, 82.1, 128, 128.2, 128.5, 136.5, 169.1.  
(CDCl<sub>3</sub>)  
(50.32 MHz)

**MS (m/z)** : 208 (M+1).

**Analysis** : Calculated: C, 63.76; H, 6.32; N, 6.76.  
(C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub>) Observed: C, 63.62; H, 6.28; N, 6.68.

**(3R,4S)-3-Benzoyloxy-1-(tert.butoxycarbonyl)-4-[(tert-butoxycarbonyl)hydroxymethyl]azetidin-2-one (3.56):**

Boc<sub>2</sub>O (3.8 mL, 16.9 mmol) and DMAP (0.77 g, 6.3 mmol) were added to a solution of azetidin-2-one **3.55** (1 g, 4.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C, and the reaction mixture was stirred for 12 h. Then, CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added, and it was washed with a saturated solution of NaHCO<sub>3</sub> (20 mL), and brine (10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography by acetone/petroleum ether (5:95) as an eluent to furnish title  $\beta$ -lactam **3.56** (1.38 g, 70%) as a white solid.

**MP** : 98-99 °C.

**$[\alpha]_{\text{D}}^{25}$**  : +77 ( $c$  1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 1812, 1741 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_{\text{H}}$  1.44 (s, 9H), 1.46 (s, 9H), 4.26-4.33 (m, 2H), 4.36-4.44 (m, 1H), 4.63 (d,  $J = 5.1$  Hz, 1H), 4.72 (d,  $J = 11.7$  Hz, 1H), 4.79 (d,  $J = 11.7$  Hz, 1H), 7.27-7.37 (m, 5H).  
(CDCl<sub>3</sub>)  
(200 MHz)

**<sup>13</sup>C NMR** :  $\delta_{\text{C}}$  27.6, 27.8, 55.5, 62.5, 73.4, 80.5, 82.2, 83.7, 127.8, 128.0, 128.3, 136.4, 147.5, 152.8, 164.1.  
(CDCl<sub>3</sub>)  
(50.32 MHz)

**MS (m/z)** : 408 (M+1).

**Analysis** : Calculated: C, 61.90; H, 7.17; N, 3.44.  
(C<sub>21</sub>H<sub>29</sub>NO<sub>7</sub>) Observed: C, 61.77; H, 7.12; N, 3.31.

**(2*S*,3*R*)-3-Benzoyloxy-2-(*tert*-butoxycarbonylamino)-1-(*tert*-butoxycarbonyloxy)octadecane-4-one (3.57):**

*n*-Tetradecyl magnesium bromide (1 M in THF 3.2 mL, 3.2 mmol) was added to a solution of starting  $\beta$ -lactam **3.56** (1.2 g, 2.9 mmol) in THF (15 mL) at -78 °C (acetone-CO<sub>2</sub> bath). The reaction mixture was stirred at -40 °C for (acetonitrile-CO<sub>2</sub> bath) 1 h. After completion of reaction (TLC), a saturated solution of NH<sub>4</sub>Cl (4 mL) was poured in to reaction mixture and then extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (10 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed in *vacuo* yielding the product. Purification by flash column chromatography with acetone/petroleum ether (3:97) gave  $\beta$ -amino ketone **3.57** (1.1 g, 62%) as oil.

**[ $\alpha$ ]<sup>25</sup><sub>D</sub>** : +56 (*c* 0.8, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3438, 1739, 1722 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** :  $\delta$ <sub>H</sub> 0.86-0.92 (m, 3H), 1.17-1.26 (m, 21H), 1.35-1.43 (m, 3H), 1.40 (s, 9H), 1.49 (s, 9H), 2.42-2.53 (m, 2H), 3.56 (bs, 1H), 4.07 (d, *J* = 6.3 Hz, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.67- 4.73 (m, 2H), 4.95 (d, *J* = 11.4 Hz, 1H), 7.33-7.36 (m, 5H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)** :  $\delta$ <sub>C</sub> 13.9, 22.5, 23.0, 27.6, 28.1, 28.2, 29.0, 29.2, 29.3, 29.4, 30.2, 31.7, 39.0, 50.3, 64.9, 72.8, 75.9, 81.3, 81.5, 81.9, 127.8, 128.1, 128.3, 136.9, 152.9, 154.9, 208.9.

**MS (m/z)** : 606 (M+1).

**Analysis** : Calculated: C, 69.39; H, 9.82; N, 2.31.

(C<sub>35</sub>H<sub>59</sub>NO<sub>7</sub>) Observed: C, 69.28; H, 9.78; N, 2.24.

**(3*R*,4*R*)-3-Benzoyloxy-4-[(1,3)-dioxolan-2-yl]-1-(4-methoxyphenyl)azetidin-2-one (3.58):**

To a mixture of 4-formyl  $\beta$ -lactam **3.53** (3.11 g, 10 mmol), ethylene glycol (6.1 mL, 11 mmol) and *p*-toluenesulphonic acid monohydrate (0.57 g, 3 mmol) in benzene was added ethylene glycol. The reaction mixture was refluxed in dean stork apparatus for 8 h. After completion of reaction (TLC), the reaction mixture was neutralized with sodium bicarbonate and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and organic layer was washed with brine solution

(10 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure to afford crude product. Purification by flash column chromatography with acetone/petroleum ether (20:80) gave **3.58** (2.77 g, 78 %) as a white solid.

**MP** : 132-135 °C.

**[α]<sup>25</sup><sub>D</sub>** : +78 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 1751 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 3.79 (s, 3H), 3.94-3.98 (m, 4H), 4.23 (t, *J* = 5.1 Hz, 1H), 4.83-4.94 (m, 3H), 5.24 (d, *J* = 5.1, 1H), 6.87 (d, *J* = 9.1 Hz, 2H), 7.28-7.61 (m, 7H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> 55.2, 59.9, 60.2, 64.8, 66.5, 73.1, 80.2, 102.5, 113.8, 119.2, 127.7, 128.0, 131.0, 137.0, 156.2, 164.5.  
(50.32 MHz)

**MS (m/z)** : 356 (M+1).

**Analysis** : Calculated: C, 67.59; H, 5.96; N, 3.94.

(C<sub>20</sub>H<sub>21</sub>NO<sub>5</sub>) Observed: C, 67.36; H, 5.63; N, 3.78.

**(3R,4R)-3-Benzyloxy-4-[(1,3)-dioxolan-2-yl]-azetidin-2-one (3.59):**

A solution of CAN (16.4 g, 30 mmol) in water (35 mL) was added drop wise to a solution of azetidin-2-one **3.58** (3.55 g, 10 mmol) in acetonitrile (37 mL) at 0 °C. The mixture was stirred at this temperature for 45 min. Water (25 mL) was added, it was extracted with ethyl acetate (3 x 75 mL) and washed with saturated solution of NaHCO<sub>3</sub> (2 x 25 mL). The aqueous layer of NaHCO<sub>3</sub> was extracted again with ethyl acetate (1 x 25 mL), and the combined organic extracts were washed with 40% NaHSO<sub>3</sub> (3 x 30 mL) and brine (10 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography using acetone/petroleum ether (35:65) as an eluant to furnish **3.59** (1.54 g, 62%) as a white solid.

**MP** : 127-128 °C.

**[α]<sup>25</sup><sub>D</sub>** : +11 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3417, 1774 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 3.60-4.01 (m, 3H), 4.73-4.85 (m, 3H), 5.12 (d, *J* = 5.1 Hz, 1H), 6.50 (bs, 1H), 7.32-7.37 (m, 5H).



(200 MHz)

$^{13}\text{C}$  NMR :  $\delta_{\text{C}}$  56.2, 61.0, 63.3, 63.8, 73.3, 79.2, 127.8, 128.0, 128.3, 136.0,  
( $\text{CDCl}_3$ ) 164.5.

(50.32 MHz)

MS (m/z) : 250 (M+1).

Analysis : Calculated: C, 62.64; H, 6.07; N, 5.62.

( $\text{C}_{13}\text{H}_{15}\text{NO}_4$ ) Observed: C, 62.44; H, 5.99; N, 5.44.

**(3R,4R)-3-Benzoyloxy-1-(tert.butoxycarbonyl)-4-[(1,3)-dioxolan-2-yl]-azetidin-2-one  
(3.60):**

Boc<sub>2</sub>O (4.5 mL, 20 mmol) and DMAP (0.133 g, 1 mmol) were added to a solution of azetidin-2-one **3.59** (2.49 g, 10 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) at 0 °C, and the reaction mixture was stirred for 12 h. Then,  $\text{CH}_2\text{Cl}_2$  (35 mL) was added, and it was washed with a saturated solution of  $\text{NaHCO}_3$  (20 mL), and brine (10 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography by acetone/petroleum ether (15:85) as an eluent to furnish  $\beta$ -lactam **3.60** (2.72 g, 78%) as a white solid.

MP : 103-104 °C.

$[\alpha]_{\text{D}}^{25}$  : +56 (c 1.0,  $\text{CHCl}_3$ ).

IR ( $\text{CHCl}_3$ ) : 1744  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR :  $\delta_{\text{H}}$  1.52 (s, 9H), 3.88-4.10 (m, 5H), 4.13 (d,  $J = 5.5$  Hz, 1H), 4.72  
( $\text{CDCl}_3$ ) (d,  $J = 14.9$  Hz, 1H), 4.77 (d,  $J = 14.9$  Hz, 1H), 5.30 (d,  $J = 5.7$   
(200 MHz) Hz, 1H), 7.30-7.36 (m, 5H).

$^{13}\text{C}$  NMR :  $\delta_{\text{C}}$  27.8, 57.9, 65.0, 65.3, 73.2, 80.0, 83.2, 101.3, 127.8, 127.9,  
( $\text{CDCl}_3$ ) 128.3, 136.4, 147.7, 164.4.

(75.48 MHz)

MS (m/z) : 350 (M+1).

Analysis : Calculated: C, 61.88; H, 6.64; N, 4.01.

( $\text{C}_{18}\text{H}_{23}\text{NO}_6$ ) Observed: C, 61.69; H, 6.34; N, 3.98.

**(2R,3R)-3-Benzoyloxy-2-(tert-butoxycarbonylamino)-1-[(1,3)-dioxolan-2-yl]octadecane-4-one(3.61):**

*n*-Tetradecyl magnesium bromide (1 M in THF 2.2 mL, 2.2 mmol) was added to a solution of  $\beta$ -lactam **3.65** (0.58 g, 1.66 mmol) in THF (5 mL) at -78 °C (acetone-CO<sub>2</sub> bath). The reaction mixture was stirred at -40 °C (acetonitrile-CO<sub>2</sub> bath) for 1 h. After completion of reaction (TLC), a saturated solution of NH<sub>4</sub>Cl (4 mL) was poured in to mixture and then extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine (10 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed in *vacuo* yielding the product. Purification by flash column chromatography with ethyl acetate/ petroleum ether (5:95) gave  $\beta$ -amino ketone **3.66** (0.56 g, 62%) as oil.

**[ $\alpha$ ]<sup>25</sup><sub>D</sub>** : +16 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3448, 1720 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** :  $\delta$ <sub>H</sub> 0.85-0.91 (m, 3H), 1.15-1.22 (m, 21H), 1.33-1.43 (m, 3H), 1.50 (s, 9H), 1.86 (bs, 1H) 2.48-2.55 (m, 2H), 3.90-4.06 (m, 5H), 4.07-4.09 (m, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.95 (d, *J* = 11.5 Hz, 1H), 7.35-7.37 (m, 5H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** :  $\delta$ <sub>C</sub> 13.8, 22.5, 23.0, 27.6, 28.0, 29.0, 29.2, 29.3, 29.4, 30.2, 31.7, 39.0, 51.3, 72.6, 75.8, 81.4, 82.2, 101.3, 127.2, 128.2, 128.5, 136.9, 154.3, 208.9.

**MS (m/z)** : 548 (M+1).

**Analysis** : Calculated: C, 70.17; H, 9.75; N, 2.56.

(C<sub>32</sub>H<sub>53</sub>NO<sub>6</sub>) Observed: C, 70.00; H, 9.45; N, 2.28.

**(3R,4R)3-Benzoyloxy-4-(4-methoxy-phenylamino)-dihydro-furan-2-one (3.62):**

3-Benzoyloxy-4-hydroxymethyl azetididin-2-one (**3.54**) (3.13 g, 10 mmol) was dissolved in methanolic HCl (20%, 20 mL) and the reaction mixture was stirred for 12 h at room temperature. After the reaction was over (TLC) methanol was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. It was then extracted with ethyl acetate (3 x 50 mL) and the combined organic extract was washed with saturated brine solution (15 mL). It was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get thick oil, which was

quickly purified by flash column chromatography using acetone/petroleum ether (15:85) as an eluent to furnish **3.62** (1.94 g, 62%) as a white solid.

- MP** : 113-114 °C.  
 **$[\alpha]_D^{25}$**  : +46 (*c* 1.0, CHCl<sub>3</sub>).  
**IR (CHCl<sub>3</sub>)** : 3373, 3519, 1785 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** : δ<sub>H</sub> 3.77 (s, 3H), 3.99 (bs, 1H), 3.96 (d, *J* = 6.3 Hz, 1H), 4.12 (dd, *J* = 6.3, 6.6 Hz, 1H), 4.14 (d, *J* = 6.6 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.66 (dd, *J* = 3.3, 6.6 Hz, 1H), 5.0 (d, *J* = 11.9 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.27-7.38 (m, 5H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>) (75.48 MHz)** : δ<sub>C</sub> 55.2, 56.7, 70.0, 72.0, 114.6, 115.0, 127.8, 127.9, 128.1, 136.3, 139.2, 152.9, 173.1.  
**MS (m/z)** : 314 (M+1).  
**Analysis** : Calculated: C, 68.99; H, 6.11; N, 4.47.  
(C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>) Observed: C, 68.83; H, 5.96; N, 4.39.

**(3*R*,4*R*)3-Benzyloxy-4-[(*tert*-butoxycarbonyl)-4-methoxy-phenylamino]-dihydro-furan-2-one (3.62):**

Boc<sub>2</sub>O (0.74 mL, 3.2 mmol) and DMAP (0.013 g, 0.1 mmol) were added to a solution of aziridino-γ-lactone **3.61** (0.5 g, 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C, and the reaction mixture was stirred for 12 h. Then, CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added, and it was washed with a saturated solution of NaHCO<sub>3</sub> (10 mL), and brine (5 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography by acetone/petroleum ether (10:80) as an eluent to furnish **3.62** (0.5 g, 68%) as oil.

- $[\alpha]_D^{25}$**  : +28 (*c* 1.0, CHCl<sub>3</sub>).  
**IR (CHCl<sub>3</sub>)** : 3448, 1764 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** : δ<sub>H</sub> 1.45 (s, 9H), 3.78 (s, 3H), 3.91 (d, *J* = 3.6 Hz, 1H), 4.32-4.41 (m, 3H), 4.45-4.65 (m, 2H), 4.74 (d, *J* = 11.9, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.26-7.36 (m, 7H).

**<sup>13</sup>C NMR** :  $\delta_C$  27.7, 55.4, 58.7, 63.7, 72.6, 75.6, 83.2, 114.5, 124.6, 124.8,  
(**CDCl<sub>3</sub>**) 127.8, 128.1, 128.5, 129.1, 136.6, 157.5, 173.1.

(75.48 MHz)

**MS (m/z)** : 414 (M+1).

**Analysis** : Calculated: C, 66.81; H, 6.58; N, 3.39.

(**C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub>**) Observed: C, 66.54; H, 6.34; N, 3.20.

**(3R,4S)-3-Benzoyloxy-4-(tert-butyl-dimethylsilyloxy)methylazetidin-2-one (3.64):**

To a mixture of azetidin-2-one **3.55** (0.73 g, 3.5 mmol) and imidazole (0.6 g, 8.8 mmol) in anhydrous DMF (1.2 mL) was added *tert*-butyldimethylsilyl chloride (0.63 g, 4.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. After completion of reaction (TLC), the reaction mixture was poured on the water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were successively washed with water (3 x 5 mL) and brine (10 mL). It was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to afford crude product, which was purified by column chromatography using ethyl acetate/petroleum ether (20:80) as an eluent to furnish **3.64** (1.02 g, 90%) as a colorless oil.

**$[\alpha]_D^{25}$**  : +0.51 (*c* 1.0, CHCl<sub>3</sub>).

**IR (Neat)** : 3259, 1762 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_H$  0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 3.70-3.82 (m, 3H),  
(**CDCl<sub>3</sub>**) 4.67 (d, *J* = 11.9 Hz, 1H), 4.71-4.74 (m, 1H), 4.81 (d, *J* = 11.9  
(200 MHz) Hz, 1H), 6.12 (bs, 1H), 7.26-7.35 (m, 5H).

**<sup>13</sup>C NMR** :  $\delta_C$  -5.4, 18.2, 25.8, 55.7, 62.8, 73.1, 82, 127.9, 128.3, 128.4,  
(**CDCl<sub>3</sub>**) 137.0, 168.7.

(50.32 MHz)

**MS (m/z)** : 322 (M+1).

**Analysis** : Calculated: C, 63.51; H, 8.47; N, 4.36.

(**C<sub>17</sub>H<sub>27</sub>NO<sub>3</sub>Si**) Observed: C, 63.40; H, 8.41; N, 4.22.

**(3R,4S)-3-Benzoyloxy-1-(tert-butoxycarbonyl)-4-(tert-butylidimethylsilyloxy)methylazetidin-2-one (3.65):**

Boc<sub>2</sub>O (1.35 mL, 5.9 mmol) and DMAP (0.04 g, 0.3 mmol) were added to a solution of azetidin-2-one **3.64** (0.950 g, 2.9 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C, and the mixture was stirred for 2.5 h. Then, CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added, and the mixture was washed with a saturated solution of NaHCO<sub>3</sub> (20 mL), and saturated solution of brine (10 mL). Organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography by ethyl acetate/petroleum ether (12:88) as an eluent to furnished title β-lactam **3.65** (1.03 g, 83%) as a colourless oil.

**[α]<sup>25</sup><sub>D</sub>** : +50.78 (*c* 1.5, CHCl<sub>3</sub>).

**IR (Neat)** : 1811, 1718 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>)** : δ<sub>H</sub> 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.51 (s, 9H), 3.97-4.03 (m, 2H), 4.04-4.09 (m, 1H), 4.69 (d, *J* = 5.2 Hz, 1H), 4.77 (s, 2H), 7.31-7.36 (m, 5H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>)** : δ<sub>C</sub> -5.6, -5.5, 18.2, 25.7, 28, 58.2, 63.1, 73.3, 80.3, 83.3, 127.9, 128.2, 128.4, 136.8, 148, 164.9.  
(50.32 MHz)

**MS (m/z)** : 422 (M+1).

**Analysis** : Calculated: C, 62.67; H, 8.37; N, 3.32.  
(C<sub>22</sub>H<sub>35</sub>NO<sub>5</sub>Si) Observed: C, 62.49; H, 8.29; N, 3.24.

**(2S,3R)-3-Benzoyloxy-2-(tert-butoxycarbonylamino)-1-(tert-butylidimethylsilyloxy)octadecane-4-one (3.66):**

*n*-Tetradecyl magnesium bromide (1 M in THF 2.2 mL, 2.2 mmol) was added to a solution of β-lactam **3.65** (0.84 g, 2 mmol) in THF (5 mL) at -78 °C (acetone-CO<sub>2</sub> bath). The reaction mixture was stirred at -40 °C (acetonitrile-CO<sub>2</sub> bath) for 1 h. After completion of reaction (TLC), a saturated solution of NH<sub>4</sub>Cl (4 mL) was poured in to mixture and then extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine (10 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed in *vacuo* yielding the product. Purification by flash column chromatography

with ethyl acetate/ petroleum ether (1:99) gave  $\beta$ -amino ketone **3.66** (0.804 g, 65%) as oil.

- $[\alpha]_D^{25}$  : -4.00 (*c* 1.0, CHCl<sub>3</sub>).
- IR (CHCl<sub>3</sub>) : 3436, 1718, 1706 cm<sup>-1</sup>.
- <sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz) :  $\delta_H$  0.05 (s, 3H), 0.07 (s, 3H), 0.85-0.89 (m, 12H), 1.20-1.30 (m, 22H), 1.39 (s, 9H), 1.55 (t, *J* = 6.8 Hz, 2H), 2.48 (dd, *J* = 6.8, 14.4 Hz, 2H), 3.51-3.69 (m, 2H), 4.05-4.18 (m, 1H), 4.26 (d, *J* = 2.9 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 9.6 Hz, 1H), 7.29-7.39 (m, 5H).
- <sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz) :  $\delta_C$  -5.5, -5.4, 14.1, 18.1, 22.6, 23.4, 25.8, 28.2, 29.2, 29.3, 29.4, 29.6, 31.9, 39.1, 53.1, 61.4, 73.0, 81.3, 127.9, 128.1, 128.4, 137.4, 155.2, 210.3.
- MS (*m/z*) : 620 (M+1).
- Analysis : Calculated: C, 69.74; H, 10.57; N, 2.26.  
(C<sub>36</sub>H<sub>65</sub>NO<sub>5</sub>Si) Observed: C, 69.61; H, 10.48; N, 2.12.

**(2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxyoctadecane-4-one (3.67):**

A mixture of  $\beta$ -amino ketone **3.66** (0.62 g, 1 mmol), ammonium formate (0.189 g, 3 mmol) and 10% Pd/C (0.07 g) in methanol (10 mL) was refluxed for 1 h. The reaction mixture was filtered through a small pad of celite and washed with ethyl acetate (2 x 10 mL). The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with water (2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> to get crude product, which was purified by flash column chromatography using ethyl acetate/petroleum ether (2:98) as an eluent to afford **13.67** (0.45 g, 85%) as oil.

- $[\alpha]_D^{25}$  : -24 (*c* 1.0, CHCl<sub>3</sub>).
- IR (CHCl<sub>3</sub>) : 3442, 1712 cm<sup>-1</sup>.
- <sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz) :  $\delta_H$  0.09 (s, 3H), 0.10 (s, 3H), 0.79-0.97 (m, 13H), 1.20-1.35 (m, 23H), 1.39 (s, 9H), 2.41-2.62 (m, 2H), 3.61-3.73 (m, 3H), 4.10-4.25 (m, 1H), 4.30-4.50 (m, 1H), 4.56-4.65 (m, 1H).

**<sup>13</sup>C NMR** :  $\delta_C$  -5.5, -5.4, 14.1, 18.2, 22.7, 23.6, 25.8, 28.2, 29.1, 29.3, 29.4,  
(**CDCl<sub>3</sub>**) 29.5, 29.6, 31.9, 37.7, 53.1, 62.3, 74.7, 79.7, 155.2, 211.5.  
(50.32 MHz)

**MS (m/z)** : 530 (M+1).

**Analysis** : Calculated: C, 65.74; H, 11.22; N, 2.64.

(C<sub>29</sub>H<sub>59</sub>NO<sub>5</sub>Si) Observed: C, 65.61; H, 11.18; N, 2.52.

**(2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3bis(*tert*-butyldimethylsilyloxy)octadecane-4-one (3.68):**

To a mixture of hydroxyl compound **3.67** (0.3 g, 0.56 mmol) and imidazole (0.096 g, 1.4 mmol) in anhydrous DMF (1 mL) was added *tert*-butyldimethylsilyl chloride (0.102 g, 0.068 mmol) at 35 °C. The reaction mixture was stirred at same temperature for 12 h. After completion of reaction (TLC), the reaction mixture was poured on water (3 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were successively washed with water (3 x 5 mL) and saturated brine (8 mL). It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to get crude product, which was purified by column chromatography by ethyl acetate/petroleum ether (1:99) as an eluent to furnish **3.68** (0.26 g, 73%) as a colorless oil.

**[ $\alpha$ ]<sub>D</sub><sup>25</sup>** : -9 (*c* 1.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 3436, 1715 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta_H$  0.01 (s, 3H), 0.04 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s,  
(**CDCl<sub>3</sub>**) 9H), 0.94 (s, 9H), 1.20-1.27 (m, 22H), 1.41 (s, 9H), 1.45-1.61  
(500 MHz) (m, 5H), 2.42-2.53 (m, 2H), 3.51 (t, *J* = 8.5, 1H), 3.62-3.67 (m,  
1H), 3.70 (bs, 1H), 4.42-4.44 (m, 1H), 4.90 (d, *J* = 9.1, 1H).

**<sup>13</sup>C NMR** :  $\delta_C$  -5.4, -5.3, -4.7, 14.1, 18.2, 18.3, 22.7, 23.5, 25.8, 28.3, 29.2,  
(**CDCl<sub>3</sub>**) 29.4, 29.5, 29.6, 31.9, 38.6, 54.2, 61.0, 75.7, 77.2, 79.5, 155.2,  
(125 MHz) 211.3.

**MS (m/z)** : 654 (M+1).

**Analysis** : Calculated: C, 65.26; H, 11.42; N, 2.17.

(C<sub>35</sub>H<sub>73</sub>NO<sub>5</sub>Si<sub>2</sub>) Observed: Found: C, 65.14; H, 11.28; N, 2.10.

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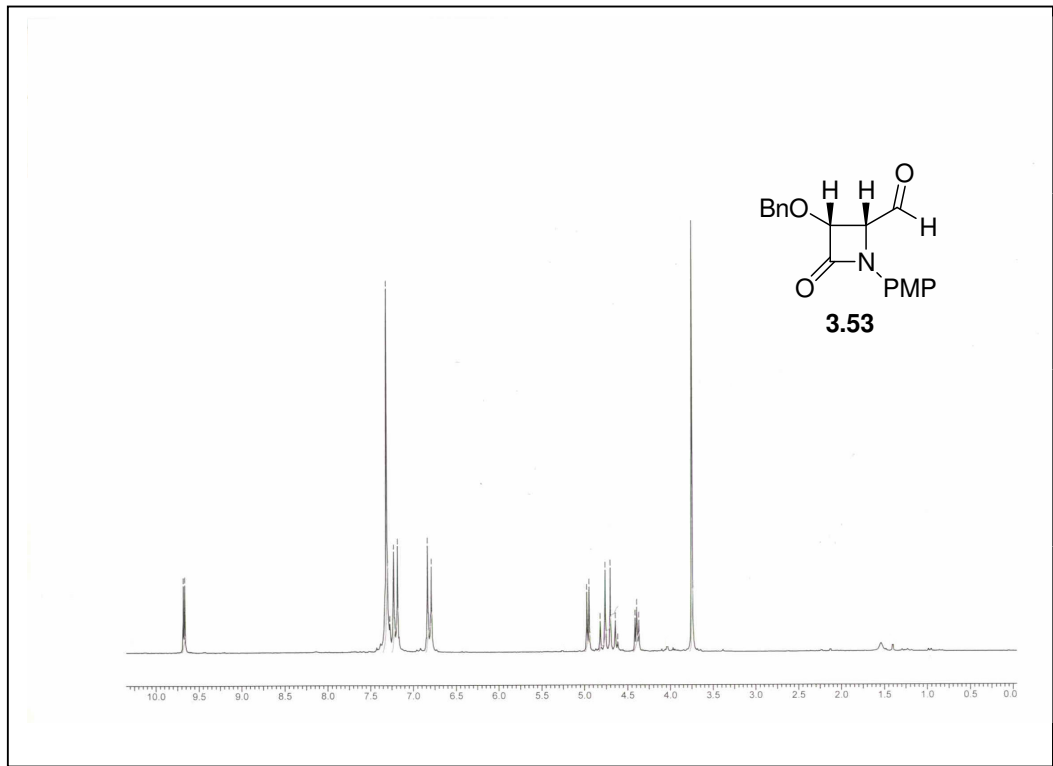
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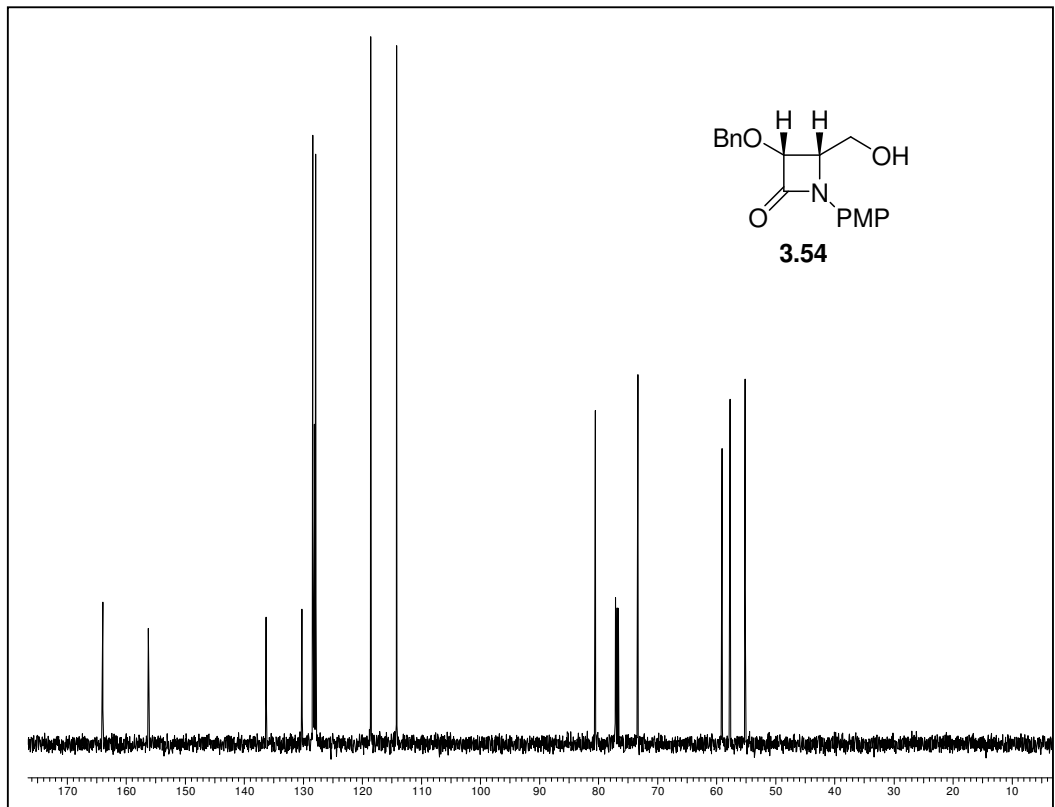
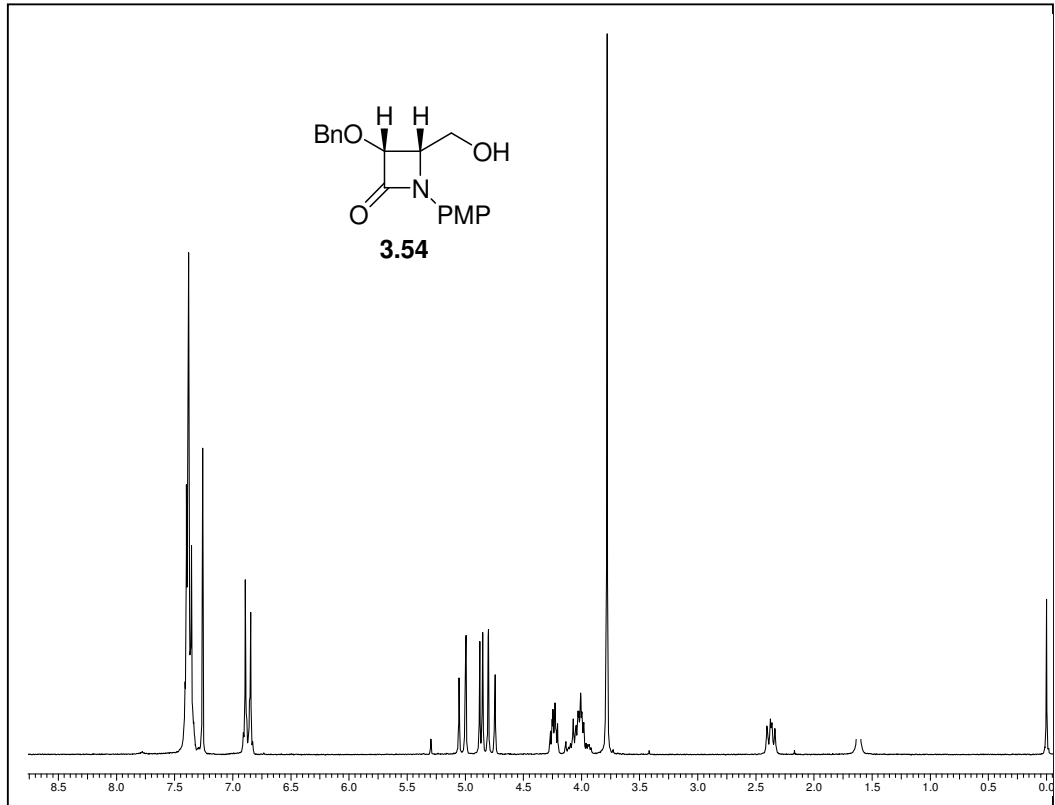
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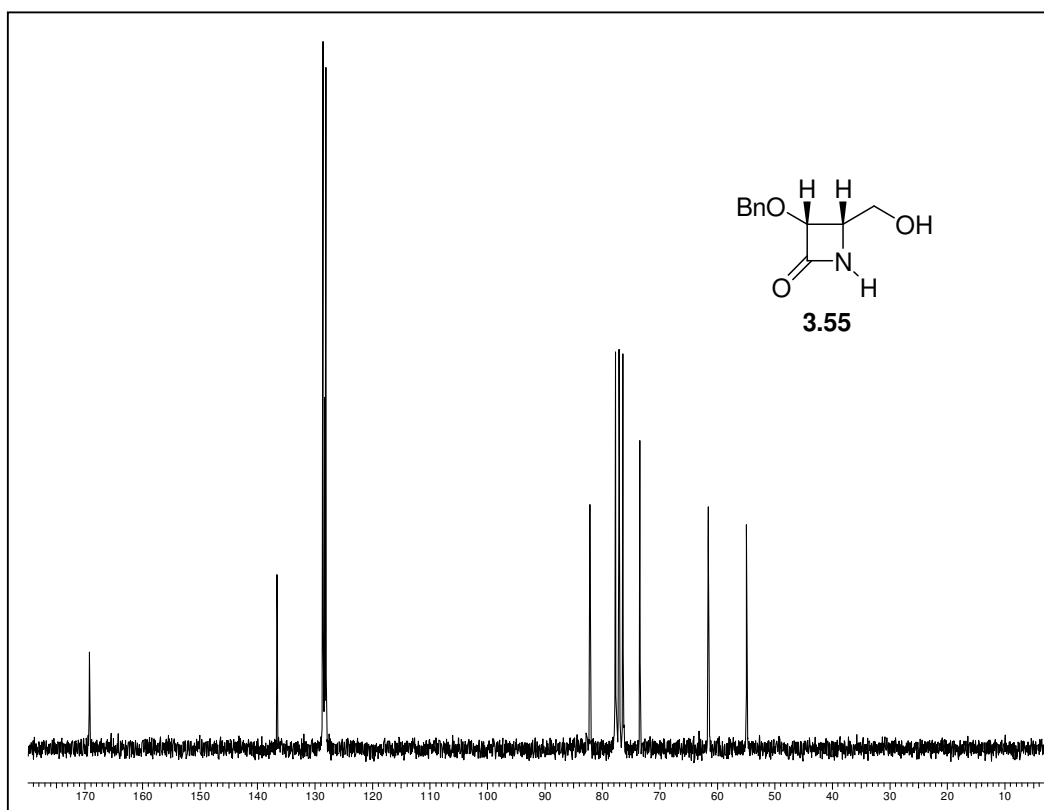
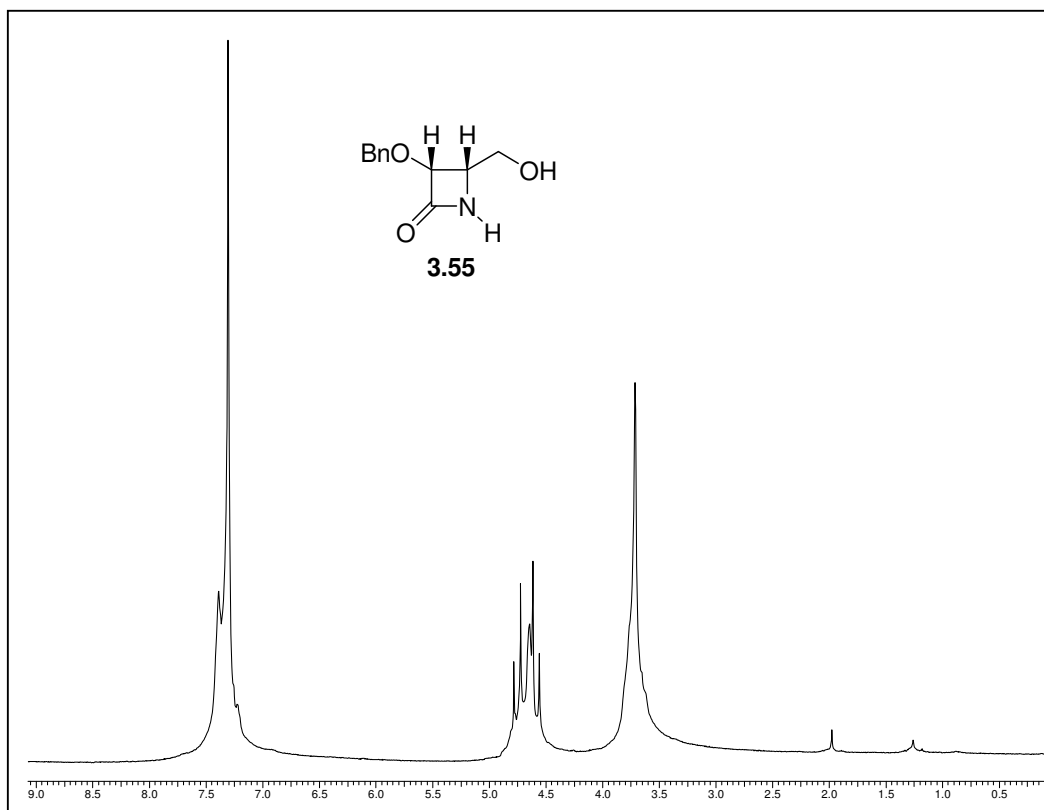
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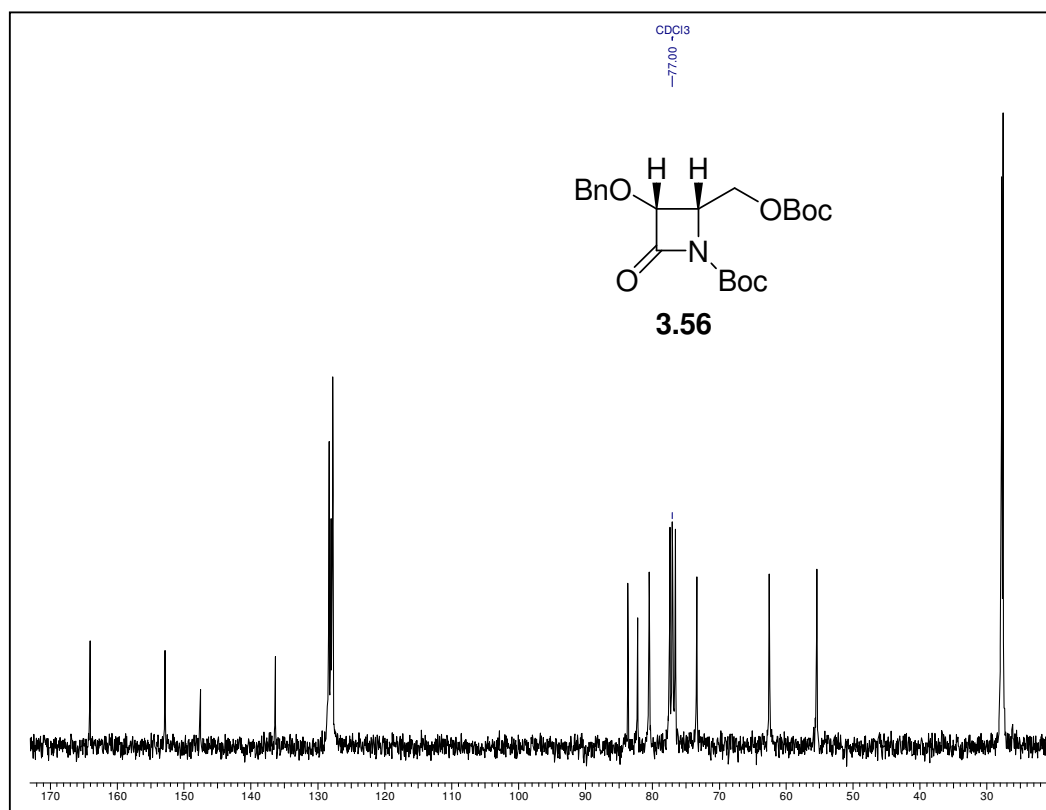
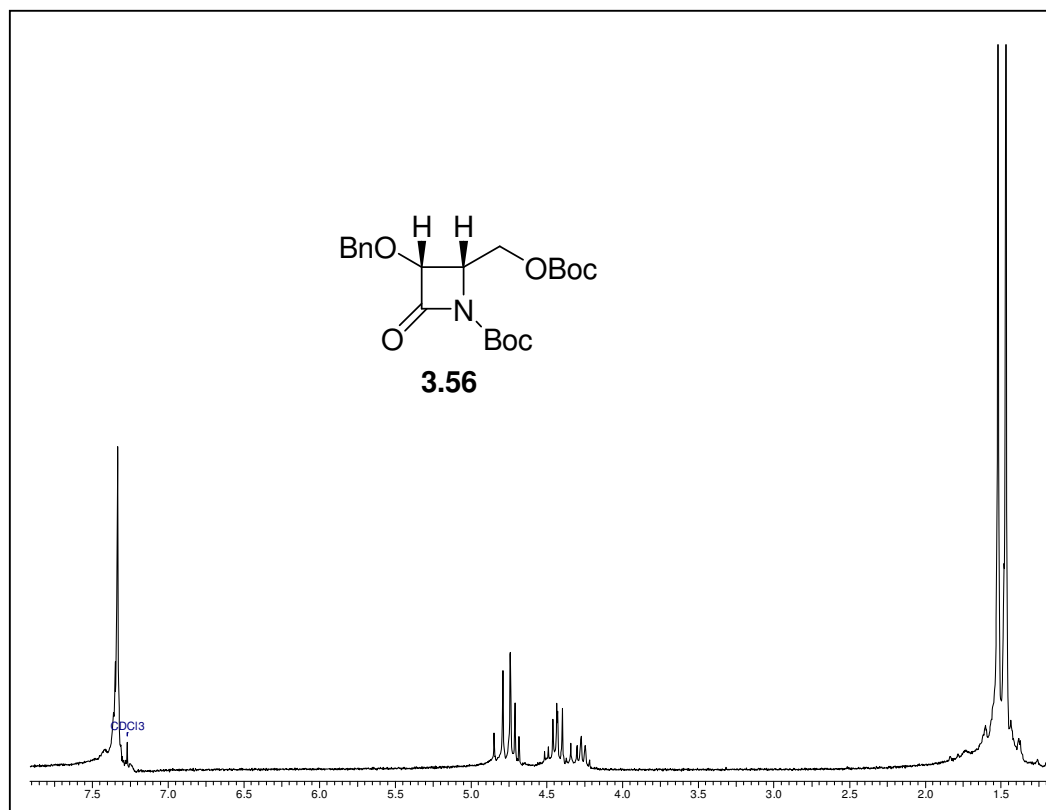
Chapter 3

**Spectra**

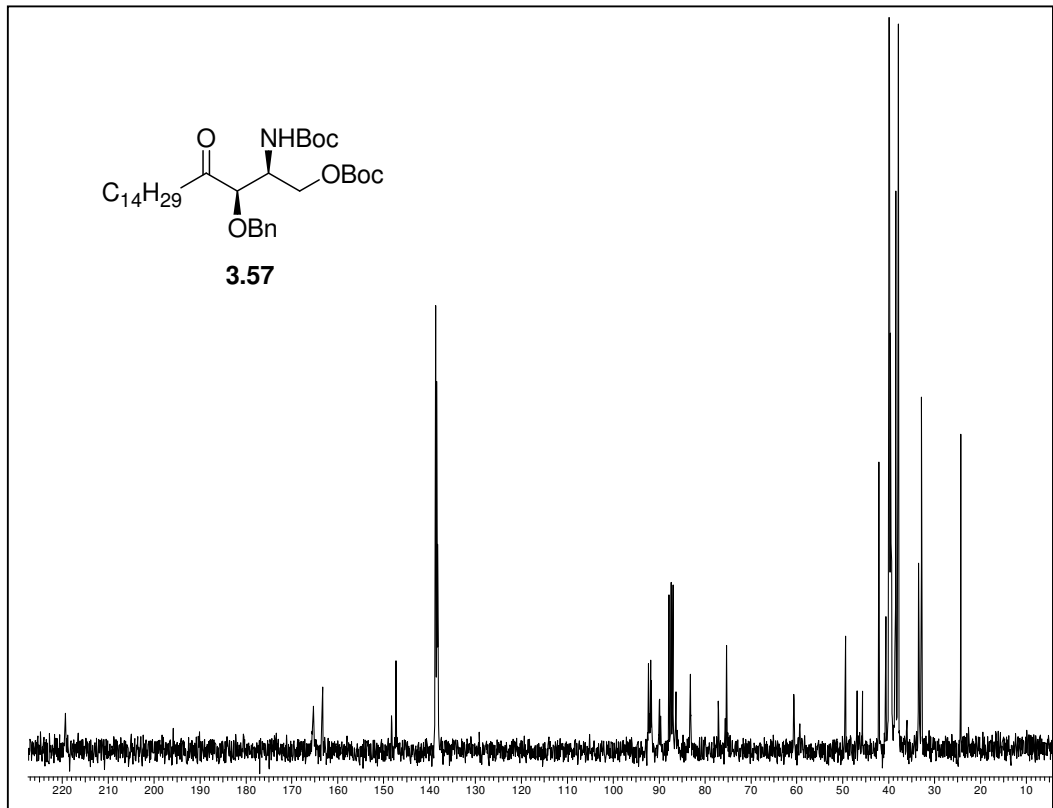
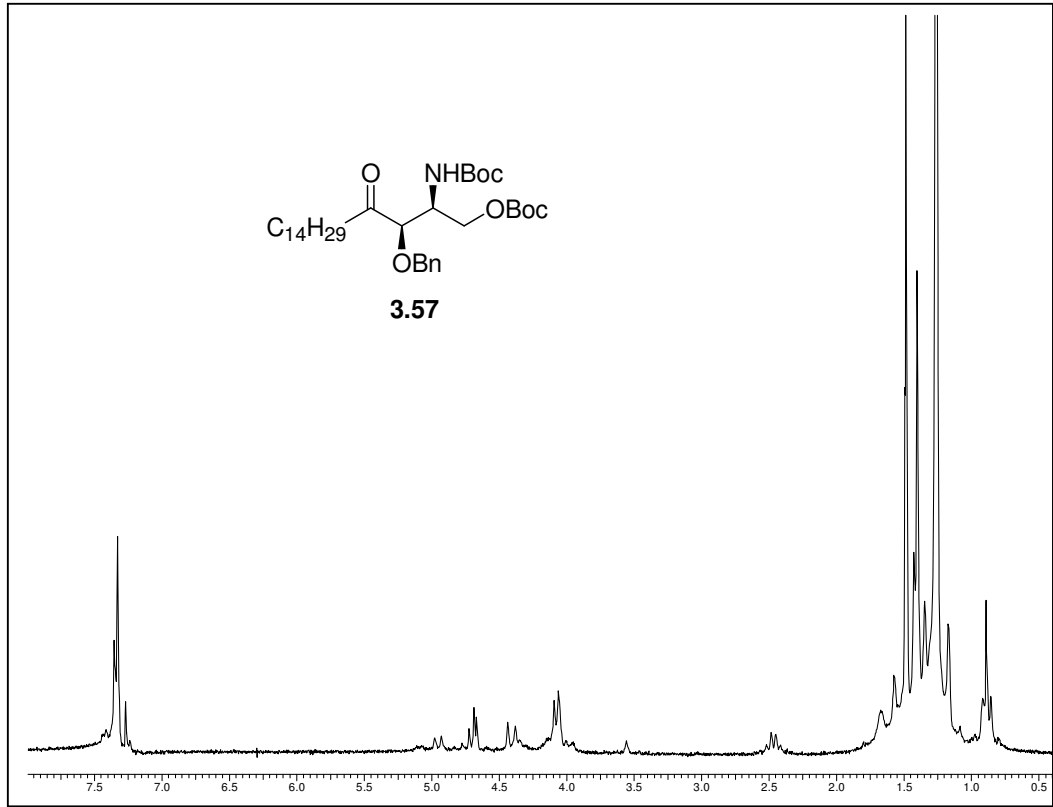


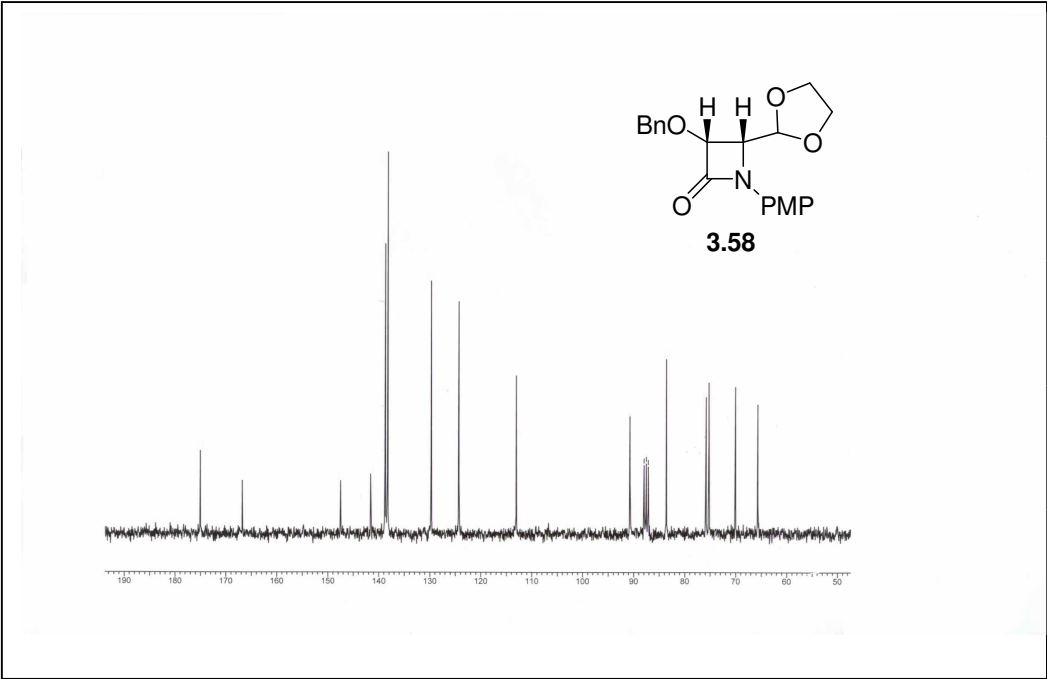
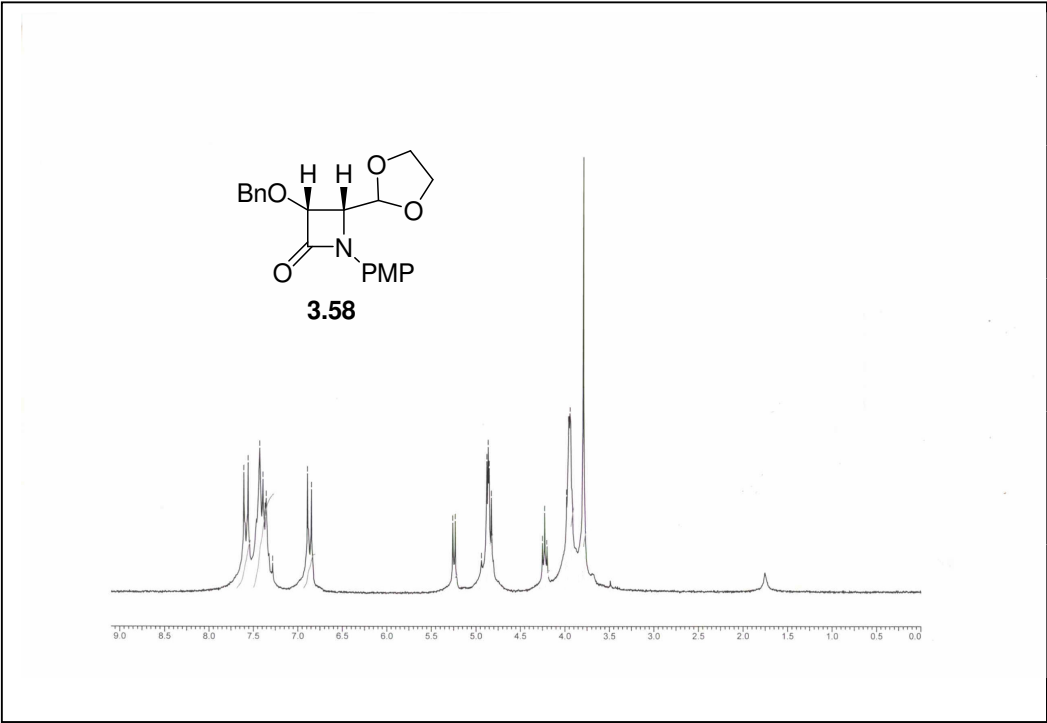


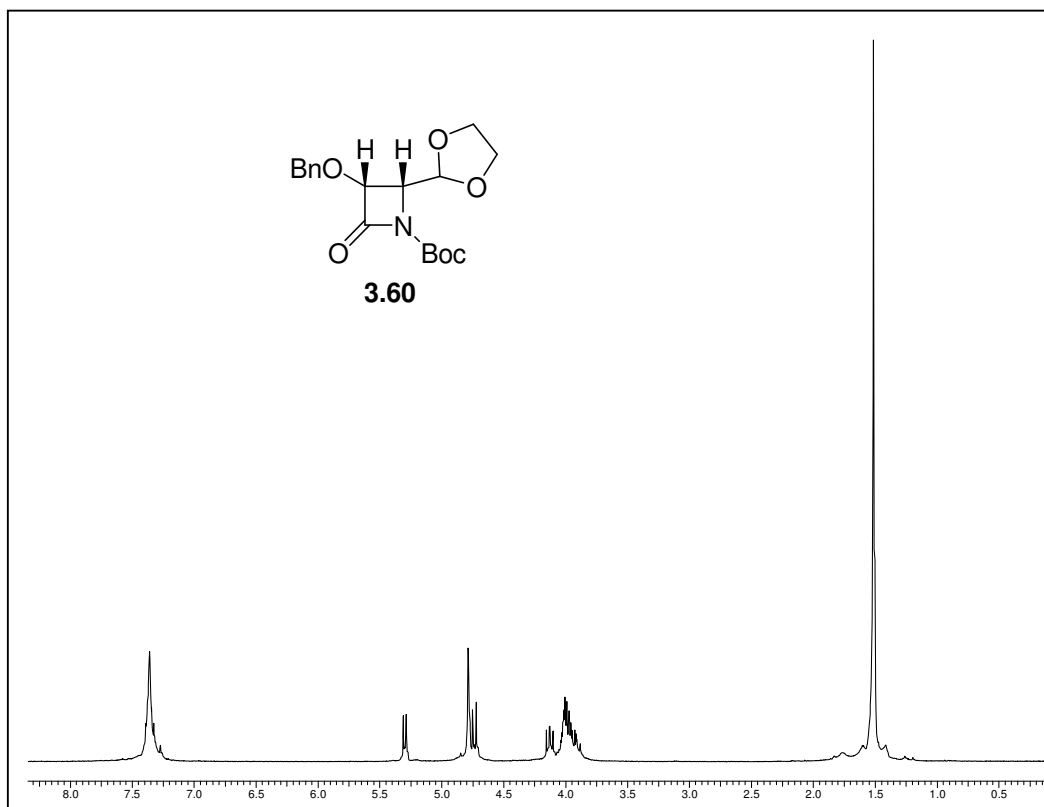
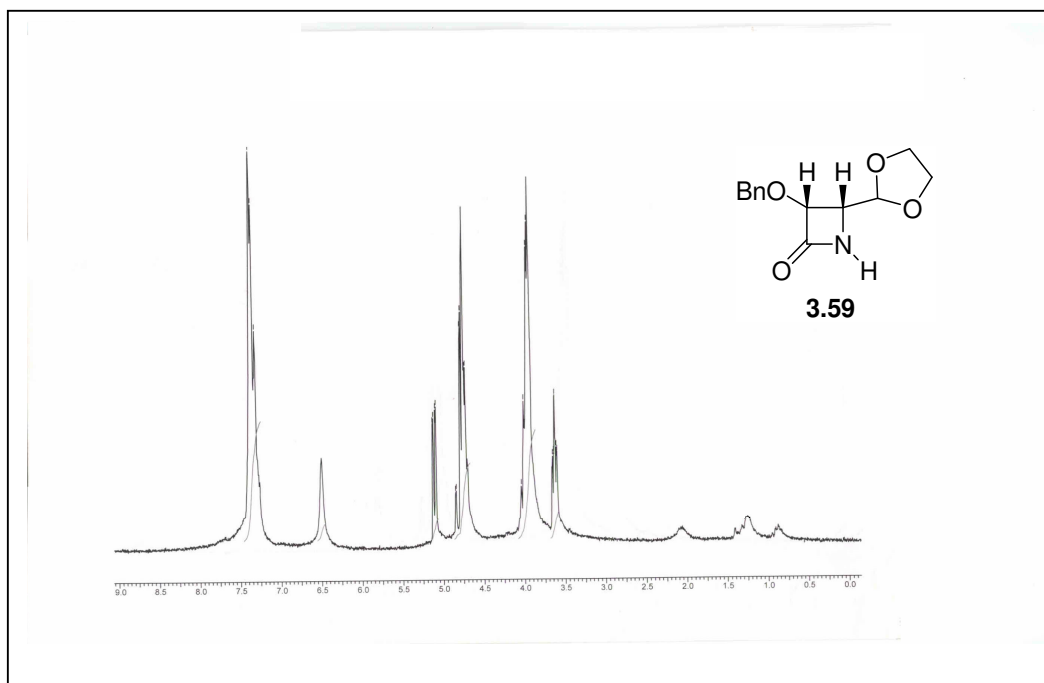


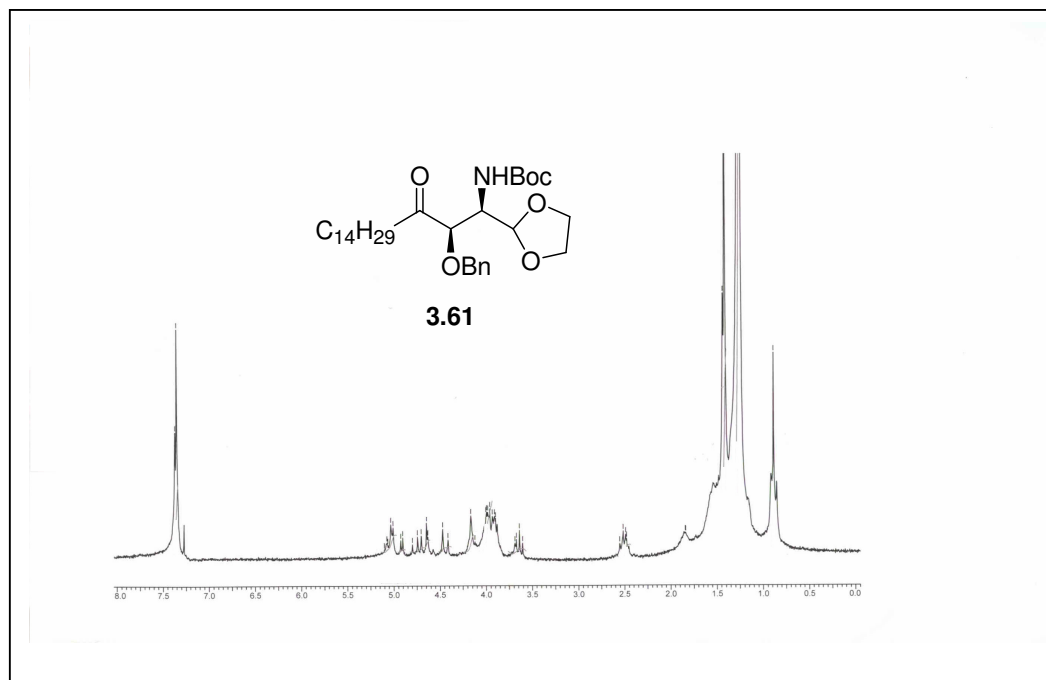
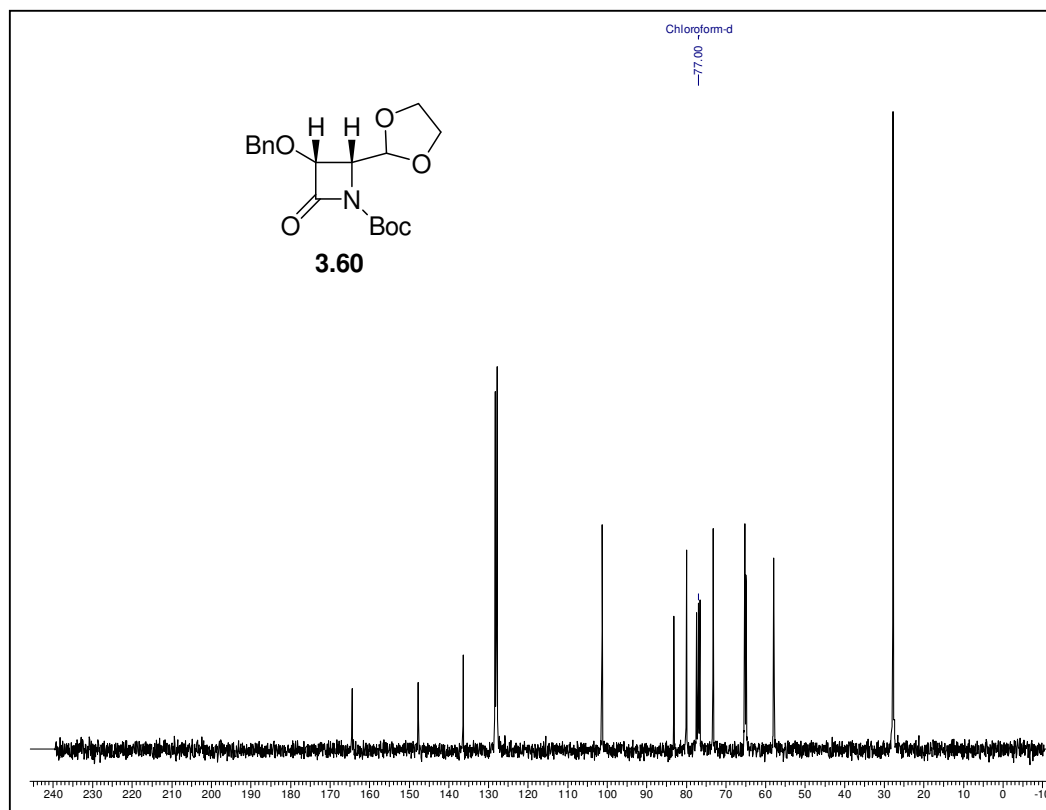


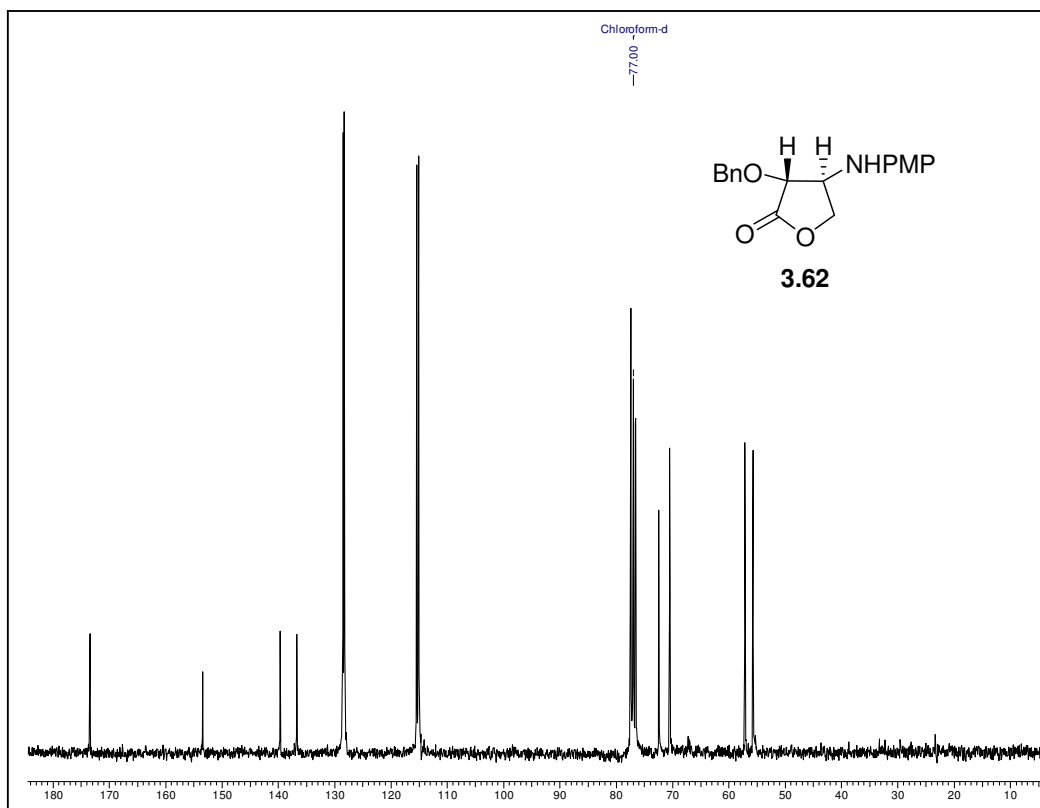
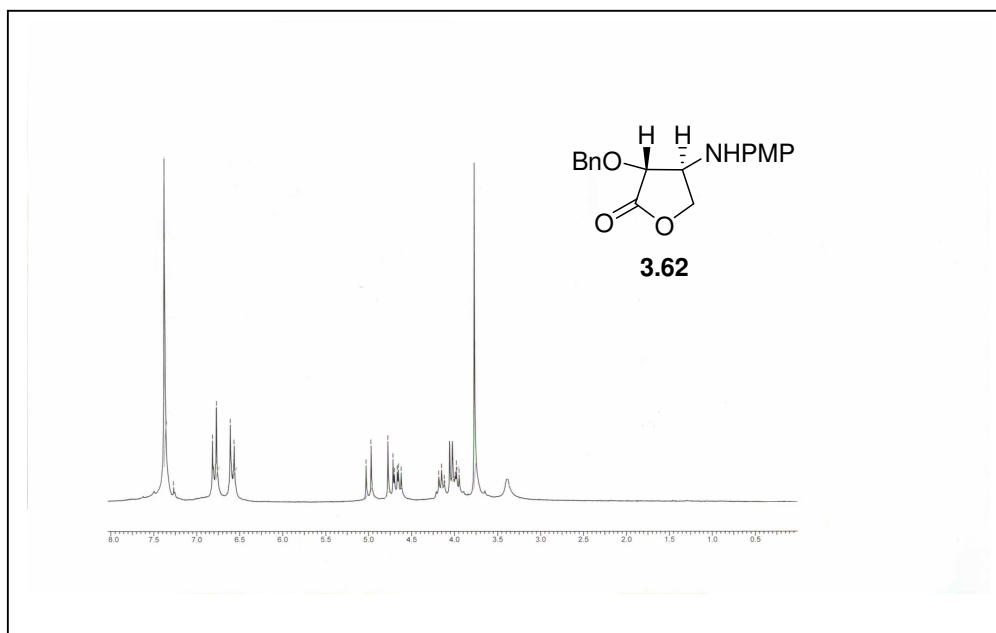


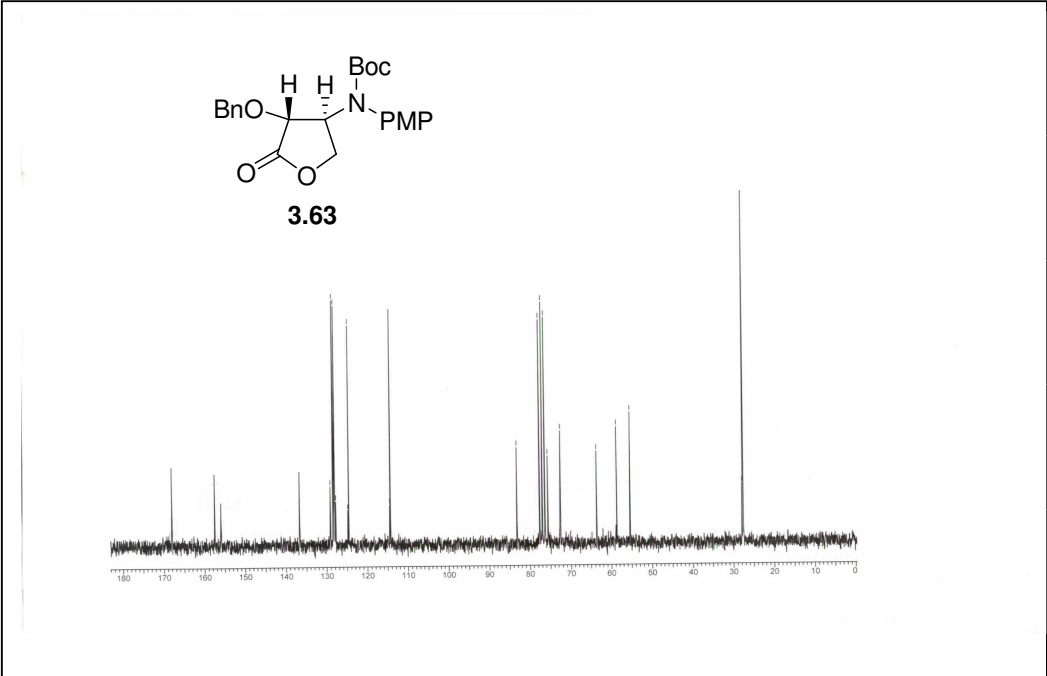
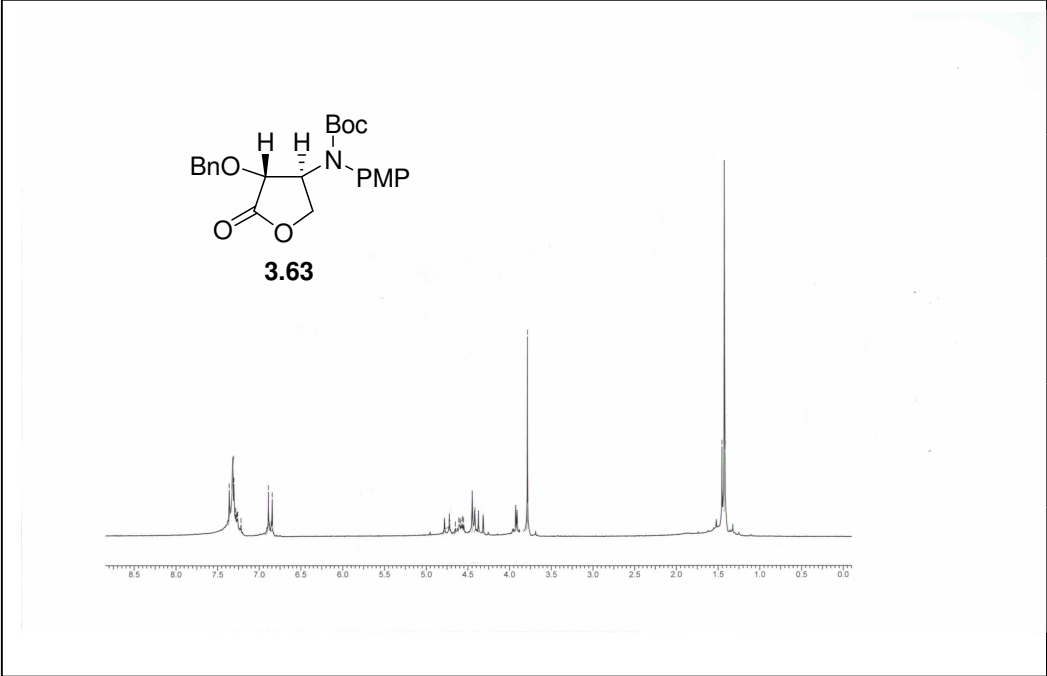


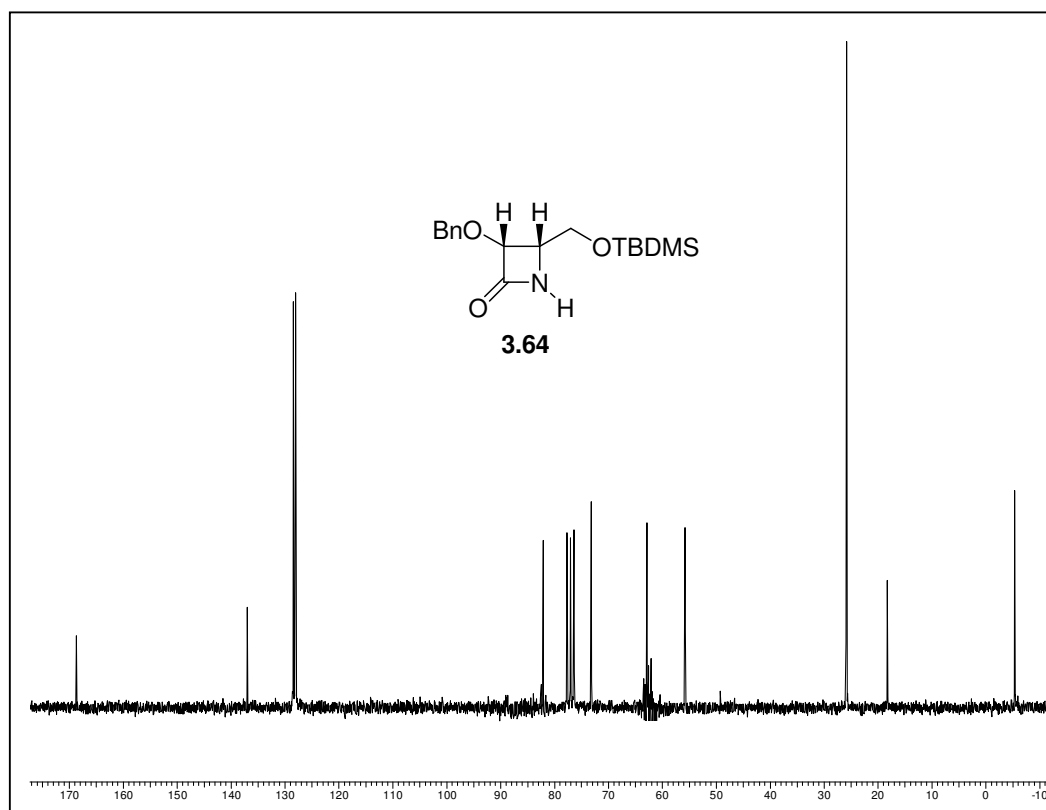
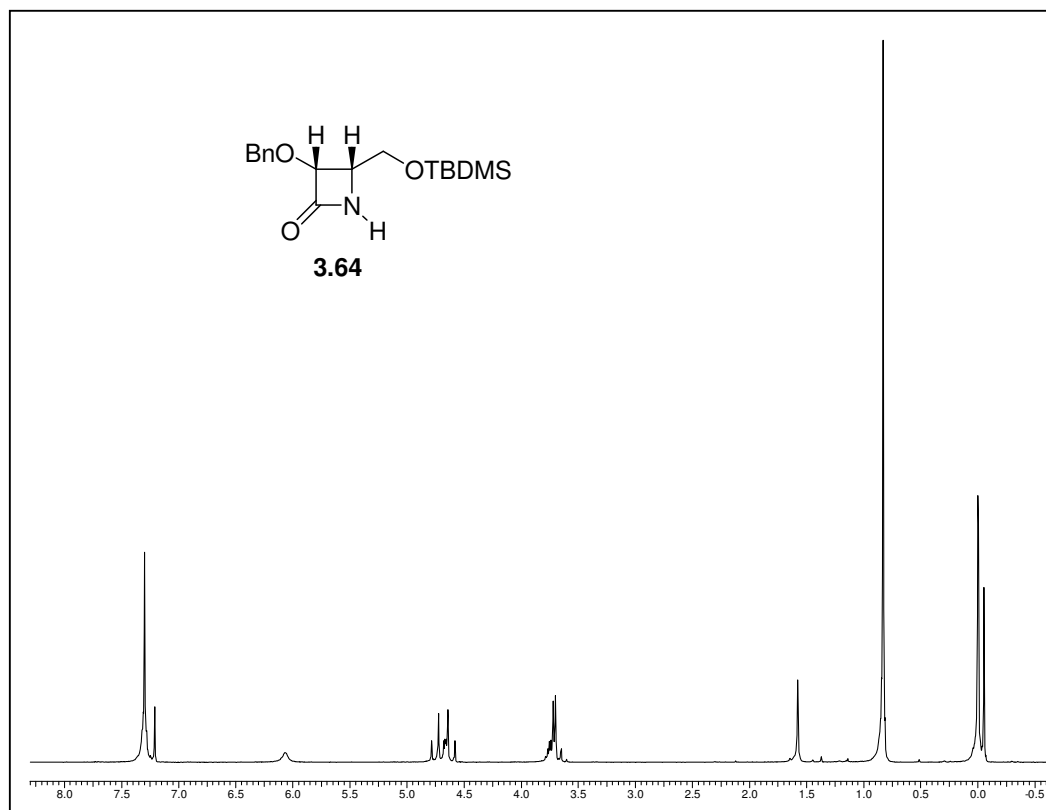


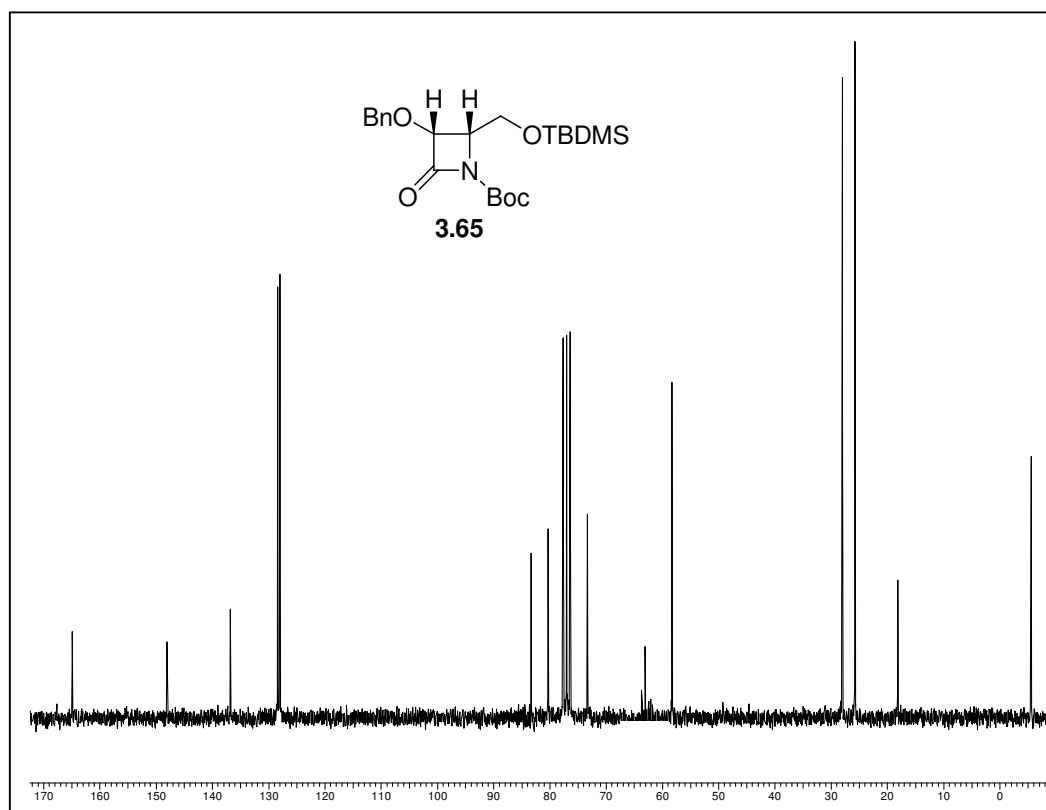
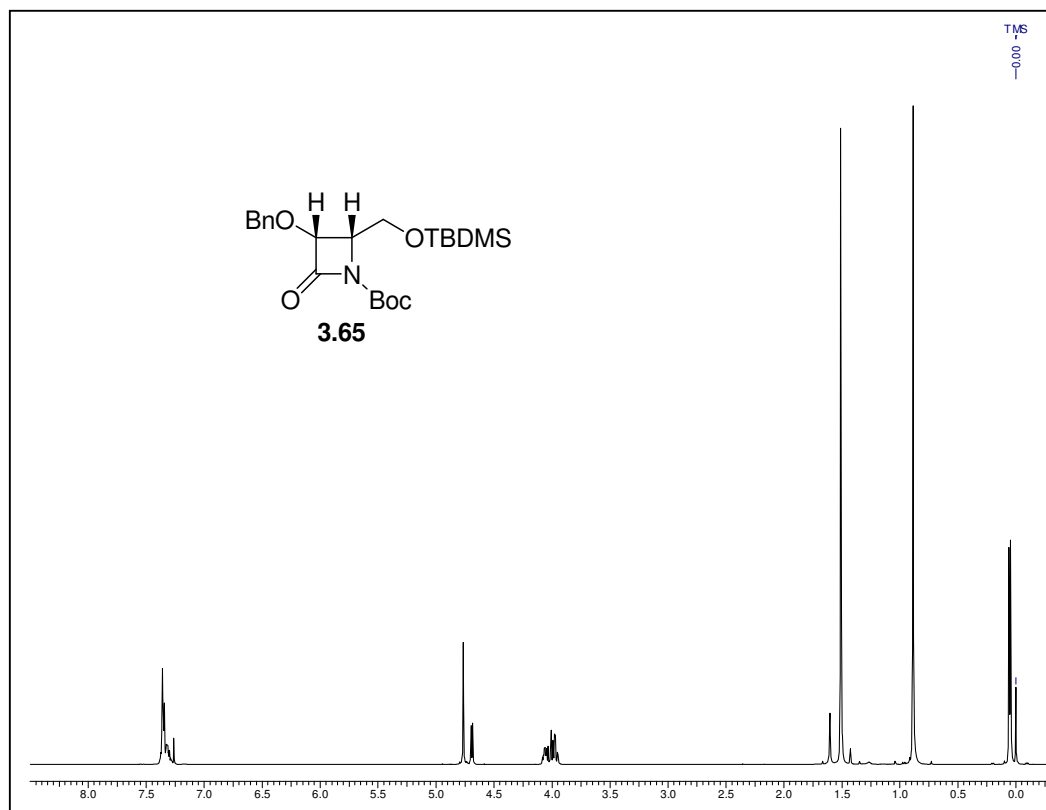




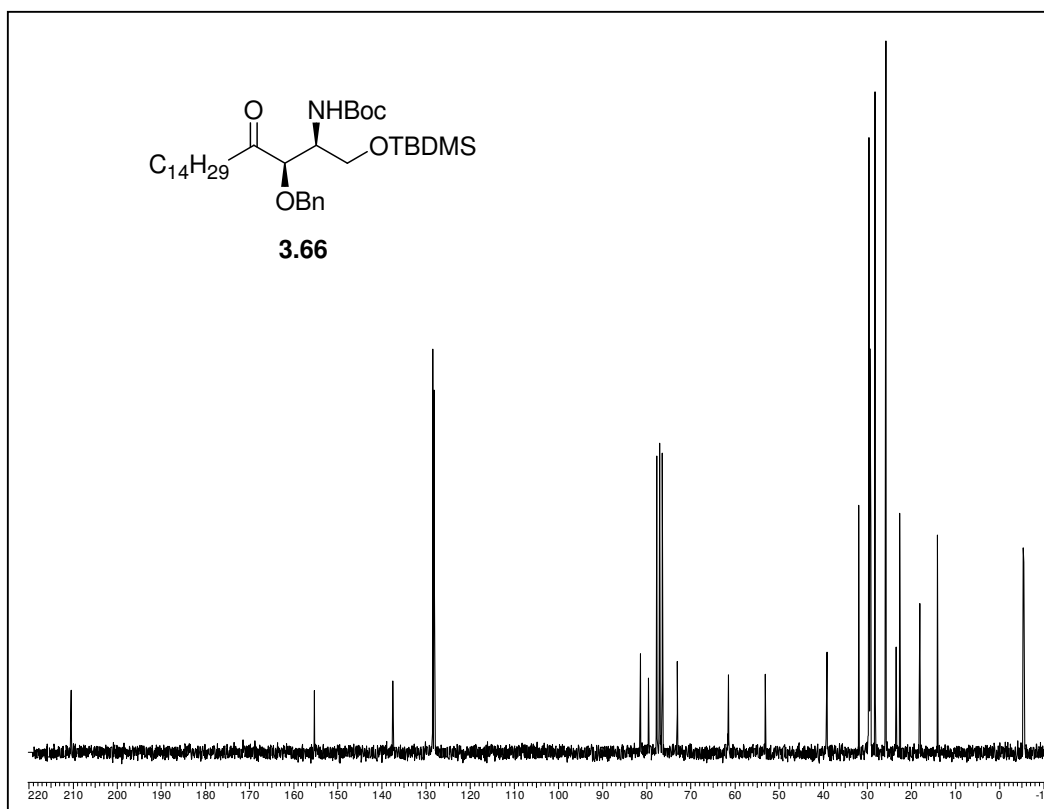
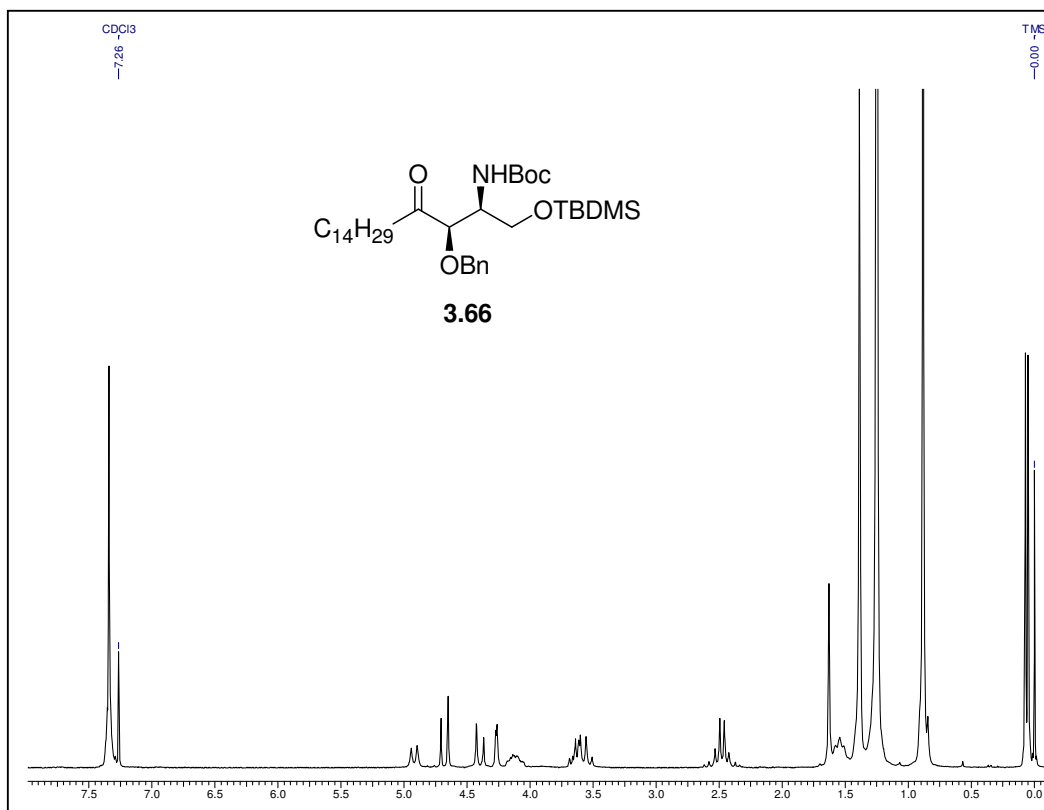


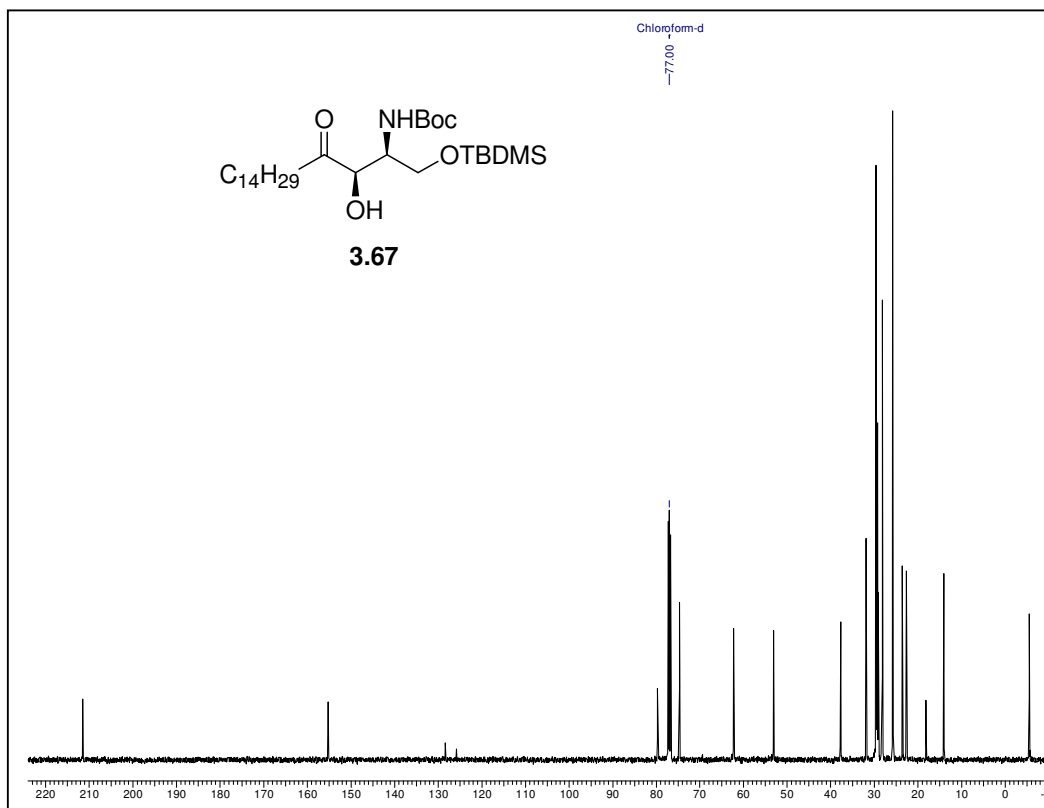
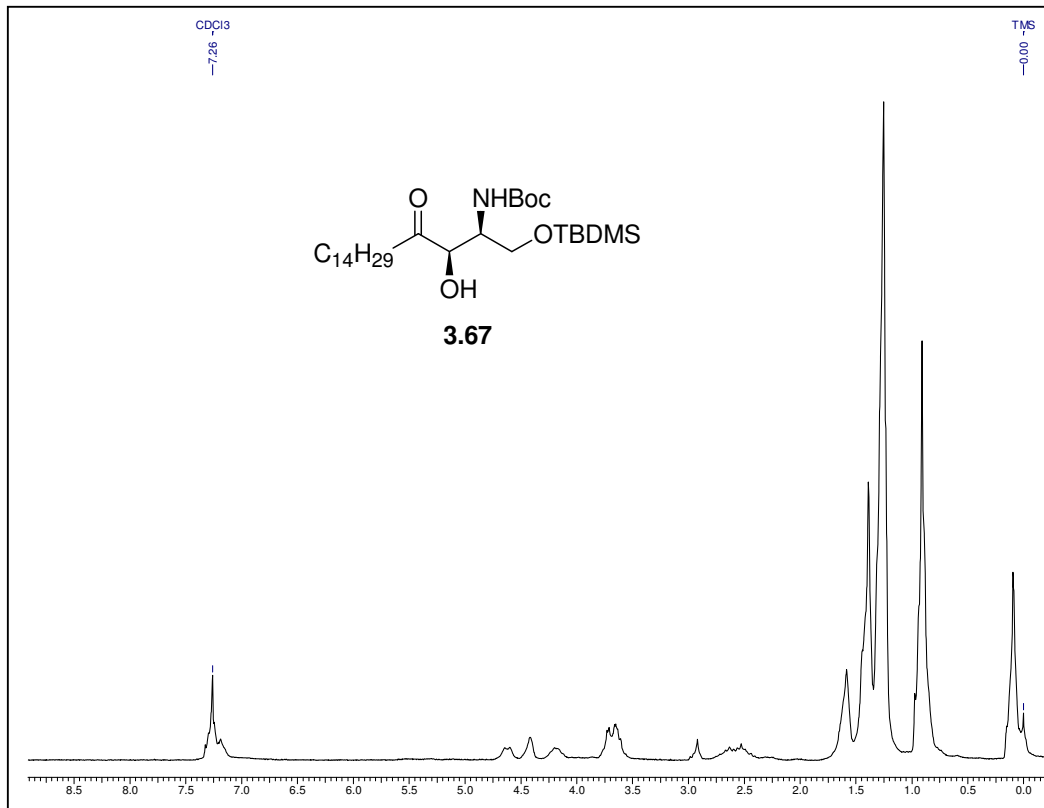


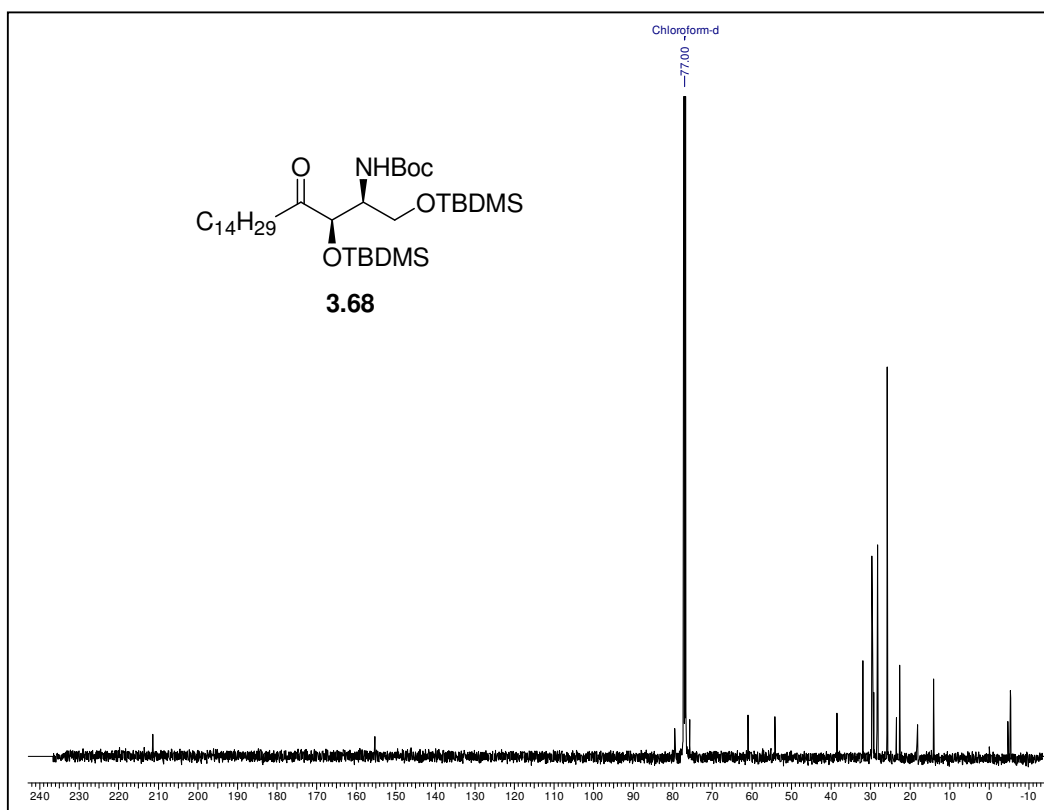
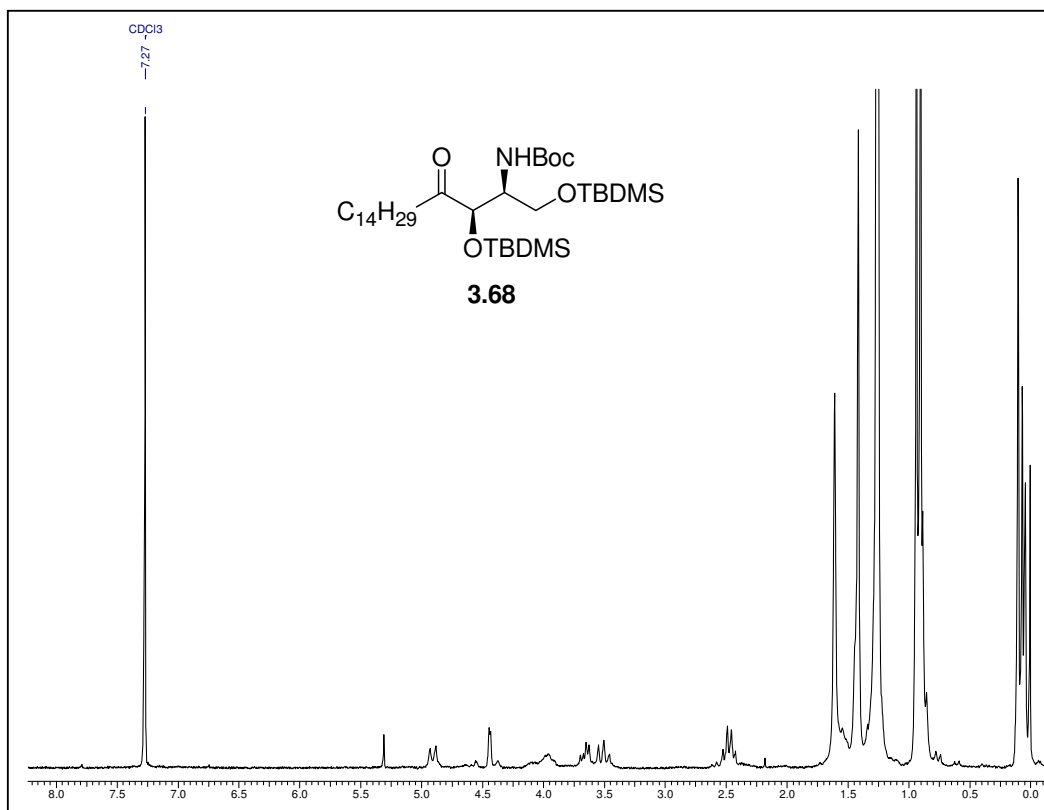












**CHAPTER 4**

**AN EFFICIENT SYNTHESIS  
OF (4R,5S) AND (4S,5R)-EPI  
CYTOXAZONE FROM  
3-HYDROXAZETIDIN-2-ONE.**

*Freedom is not worth having if it does not include the freedom to make mistakes.*

-Mahatma Gandhi

## 4.1: Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(-)-**1a**, generic name cytoxazone],<sup>1</sup> which was shown to possess high cytokine modulator activity by acting on the Th2 cells.<sup>2</sup> Because of these biological properties, several total syntheses of (-)-**4.1a** and its *trans*-diastereoisomer ((+)-*epi*-cytoxazone (**4.1b**) (Figure 4.1) have been reported.<sup>3, 7-17</sup>

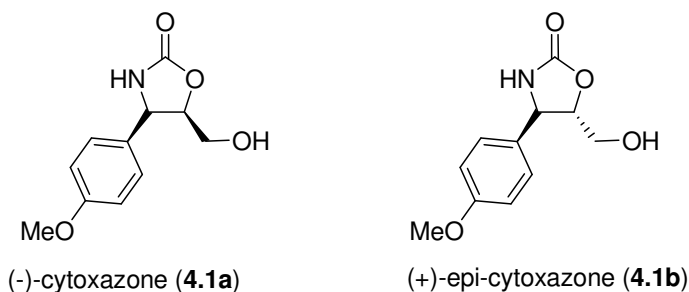


Figure 4.1

Prompted by the first positive biological results, many researchers have also reported the preparation of *cis*- and *trans* isocytoxazones **4.2a,b**, structural isomers of cytoxazone **4.1a** and its *trans* epimer **4.1b** (Figure 4.2).<sup>3</sup>

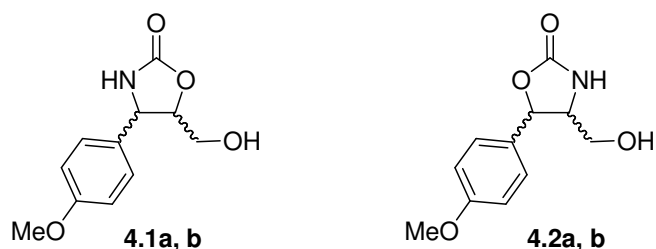


Figure 4.2: Structural isomers of Cytoxazone

### 4.1a: The Pharmacology of Cytoxazone

It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of CD4<sup>+</sup> T cells.<sup>4</sup> The Th1 cell subset produces predominantly IL-2, GM-CSF, INF- $\gamma$ , and TNF- $\beta$ , (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for B cell growth and differentiation to Ig secretion. The imbalance of cytokine production by CD4<sup>+</sup> T cells leads to a wide variety of immunological disorders, i.e. allergy, progressive lymphoproliferation, and severe immunodeficiency.<sup>5</sup> Skin and lung biopsies from allergic patients indicate that the

pivotal cells in the allergic site are the Th2 cells.<sup>6</sup> Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases.

In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine production in Th2 cells, it was found that cytoxazone (**4.1a**) containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces* sp. Cytoxazone (**4.1a**) shows a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.<sup>1</sup>

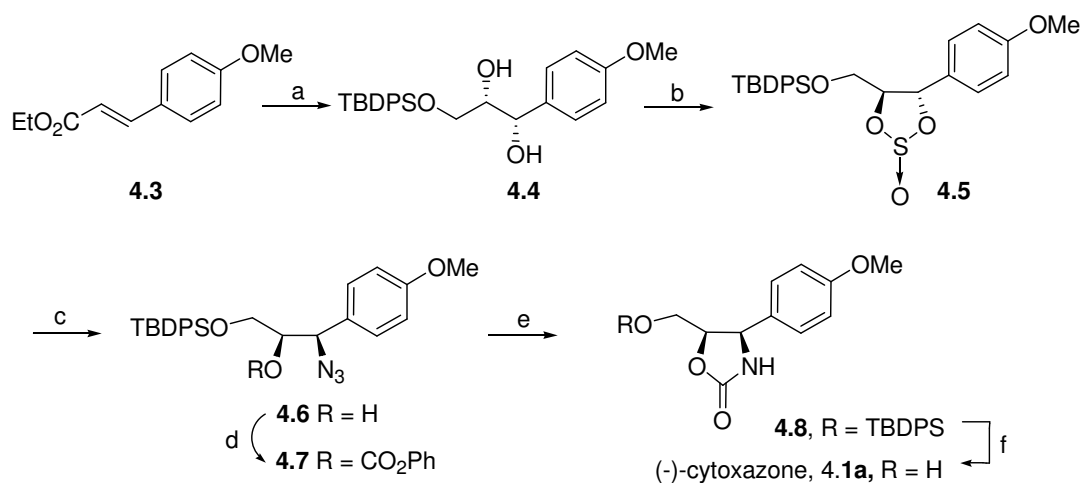
## 4.2: Background for the present work

Literature search revealed that there are several reports available for the synthesis of cytoxazone (**4.1a**)<sup>7-17</sup> involving resolution, chemo-enzymatic or enantioselective syntheses, which are described below.

### Nakata's approach:

Nakata *et al.* have achieved the synthesis of (-)-cytoxazone (**4.1a**) using Sharpless asymmetric dihydroxylation of ester **4.3**. The cyclic sulfite **4.5** was afforded from ethyl *p*-methoxycinnamate (**4.3**) by the Sharpless catalytic asymmetric dihydroxylation followed by treatment with SOCl<sub>2</sub> in 99 % yield and 97 % ee.

Scheme 1

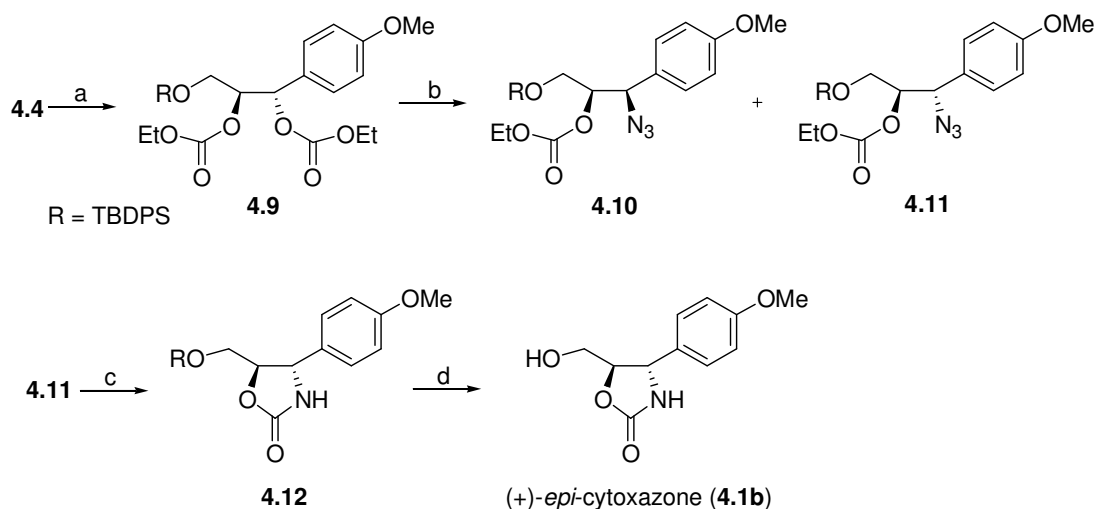


*Reagents and conditions:* a) i) AD-mix-a, t-BuOH: H<sub>2</sub>O (1:1), 25 °C, 93 %, 99% ee., ii) NaBH<sub>4</sub>, THF, 0 °C, 66%; ii) TBDPSCI, imidazole, DMF, 0 °C, 99%; b) SOCl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 99%; c) LiN<sub>3</sub>, DMF, 70 °C, 74 %; d) ClCO<sub>2</sub>Ph, Py, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 96%; e) PPh<sub>3</sub>, THF/ H<sub>2</sub>O, 50 °C, 90%; f) n-Bu<sub>4</sub>NF, THF, 0 °C, 89% ee, 96%.

The cyclic sulfite **4.5** was then opened using  $\text{LiN}_3$  and the alcohol obtained was protected as the corresponding carbonate **4.7**. Intramolecular cyclization of carbonate **4.7** with  $\text{PPh}_3$  followed by the deprotection of TBDPS group gave (-)-cytoxazone (**4.1a**) in 89% ee and 96% yield (Scheme 4.1).<sup>7</sup>

The same group has achieved the synthesis of (+)-*epi*-cytoxazone (**4.1b**) from the common intermediate **4.4** using an efficient one-step method for the stereoselective azidation. Thus, (4*S*,5*S*)-diethylcarbonate (**4.9**), prepared from diol **4.4**, was treated with  $\text{TMSN}_3$  (6 eq.) in the presence of  $\text{TMSOTf}$  to afford a 6:1 mixture of the desired  $\alpha$ -azide **4.11** and its  $\beta$ -isomer **4.10**. The  $\alpha$ -azide **4.11** was then treated with  $\text{PPh}_3$  in  $\text{THF}/\text{H}_2\text{O}$  to give 2-oxazolidinone **4.12**, which was converted to 4-*epi*-cytoxazone (**4.1b**) in 99% yield using tetrabutylammonium fluoride (Scheme 4.2).

Scheme 4.2



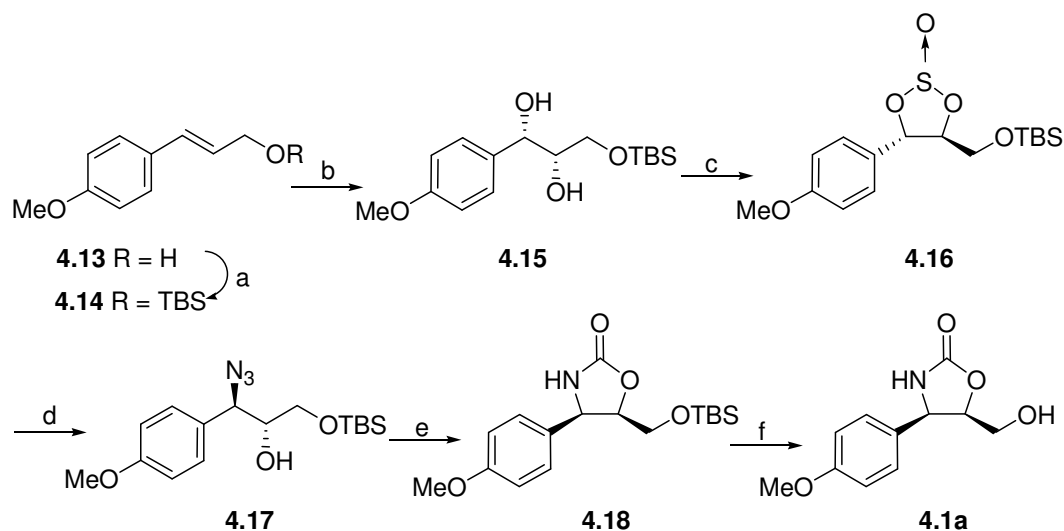
*Reagents and conditions:* a)  $\text{ClCO}_2\text{Et}$ , Pyridine,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 92%; b)  $\text{TMSN}_3$ ,  $\text{TMSOTf}$ ,  $\text{MeCN}$ , -43 °C, 99%; c)  $\text{PPh}_3$ ,  $\text{THF}/\text{H}_2\text{O}$ , 50 °C, 100%; d)  $n\text{-Bu}_4\text{NF}$ ,  $\text{THF}$ , 0 °C, 99%.

### Mori's approach:

Mori *et al.* have synthesized (-)-cytoxazone (**4.1a**) employing the Sharpless asymmetric dihydroxylation as the key reaction. Thus, silyl ether **4.14** was subjected to asymmetric dihydroxylation to give diol **4.15** in 99% yield, which was further converted to the corresponding azido alcohol **4.17** via cyclic sulfite **4.16**. Azido alcohol **4.17** was converted to (-)-cytoxazone (**4.1a**) in 3 steps of (i) reduction of azide

to amine (ii) formation of oxazolidinone (iii) deprotection of silyl protection (Scheme 4.3).<sup>8</sup>

Scheme 4.3

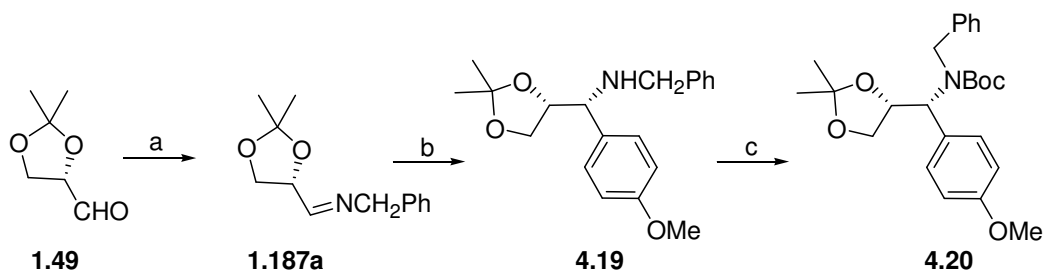


*Reagents and conditions:* a) TBSCl, imidazole, DMF, 97%; b) (DHQD)<sub>2</sub>-PHAL, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, <sup>t</sup>BuOH/H<sub>2</sub>O, 99%; c) SOCl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 88%; d) LiN<sub>3</sub>, DMF, 100 °C, then H<sub>2</sub>O at 0 °C, 61%; e) i) HCO<sub>2</sub>NH<sub>4</sub>, Pd/C, MeOH, 50 °C, 87%; ii) CO(OEt)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, 66%; f) TBAF, THF, 89%.

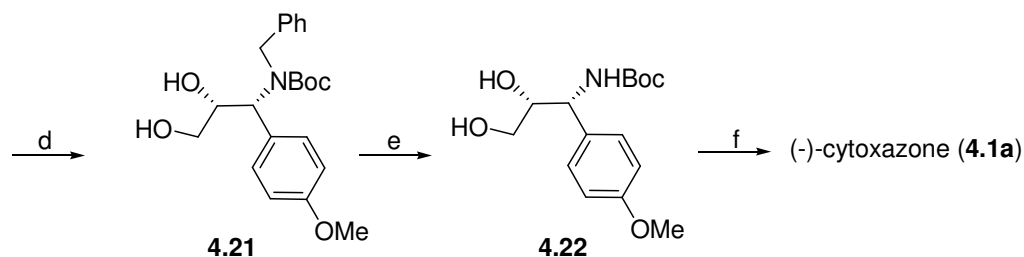
### Rao's approach:

Rao *et al.* have achieved the synthesis of (-)-cytoxazone (**4.1a**) via chiral pool approach starting from aldehyde **1.49**. Grignard addition of *p*-methoxyphenylmagnesium bromide provided *N*-benzylimine **1.187a** derived from (*S*)-2,3-*O*-isopropylidene glyceraldehyde **1.49** gave the acetonide protected aminoalcohol **4.19** which was further protected as its carbamate. Reductive removal of the benzyl protection in the carbamate **4.21** followed by intramolecular cyclization afforded (-)-cytoxazone (**4.1a**) (Scheme 4.4).<sup>9</sup>

Scheme 4.4





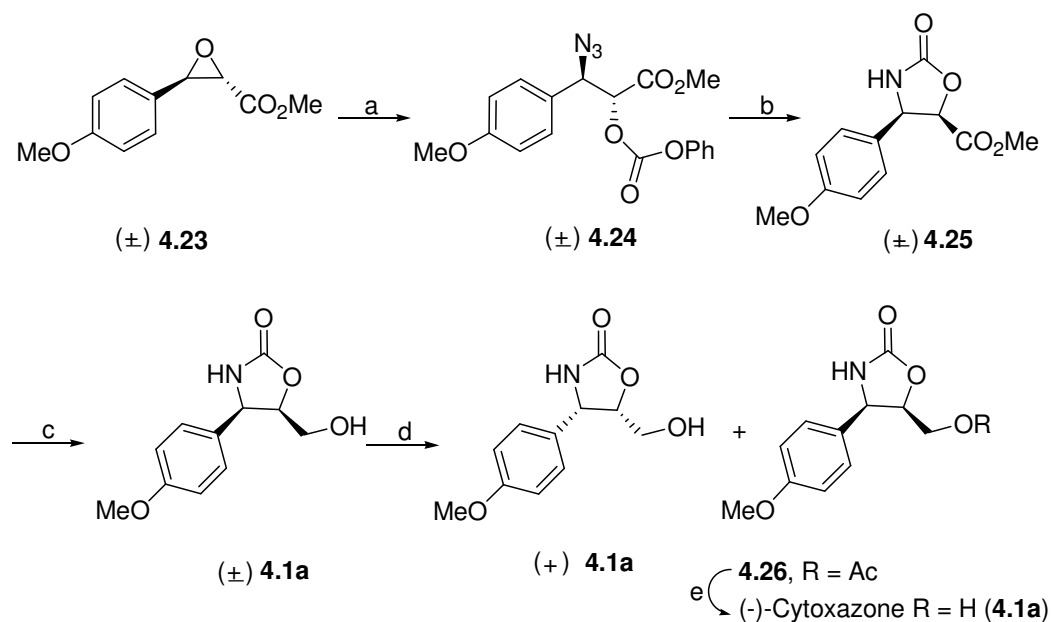


*Reagents and conditions:* a) PhCH<sub>2</sub>NH<sub>2</sub>, dry ether, 0 °C; b) 4-methoxyphenyl magnesium bromide, dry ether; c) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, dry ethanol; d) PTSA (cat), MeOH; e) Pd/C (cat), conc.HCl (a drop), EtOH; f) NaH, dry THF.

### Sunjic's approach:

In this approach, synthesis of (-)-cytoxazone (**4.1a**) was achieved starting from the glycidic ester **4.23** using enzymatic kinetic resolution. Nucleophilic ring opening of the epoxide **4.23** with NaN<sub>3</sub>, followed by protection of the alcohol and intramolecular cyclization gave ester **4.25**. Reduction of the ester **4.25** and the subsequent kinetic resolution of racemic **4.1a** using *Penicillium camemberti* lipase (PcamL) afforded (-)-cytoxazone (**4.1a**) in 33% overall yield and 88.2% ee (Scheme 4.5).<sup>10</sup>

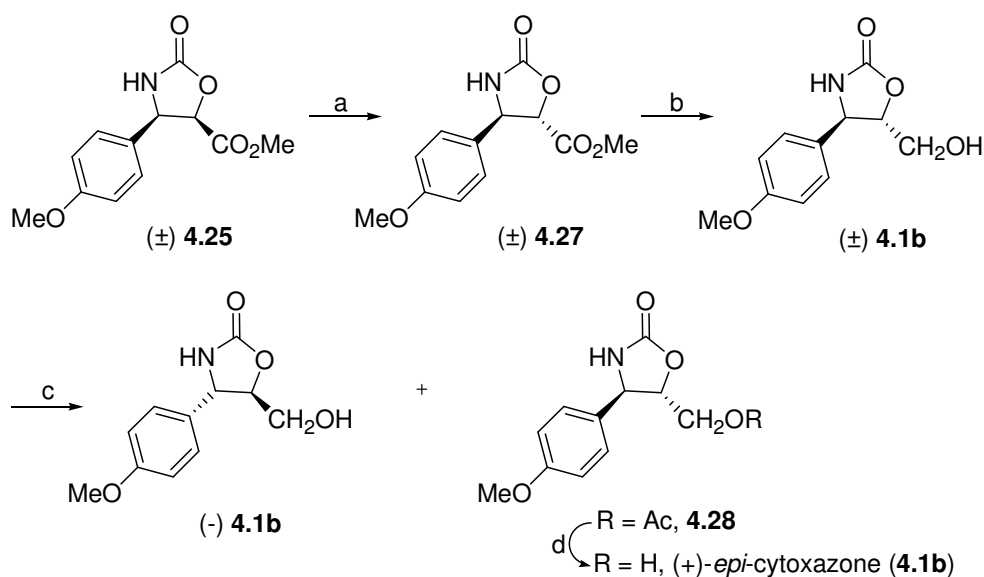
**Scheme 4.5**



*Reagents and conditions:* a) aq NaN<sub>3</sub>, dioxane, 50 °C, 3 h, 56%; b) ClCO<sub>2</sub>Ph, CH<sub>2</sub>Cl<sub>2</sub>, -5 °C, 1 h, 100%; c) i) Ph<sub>3</sub>P, aq THF, 50 °C, 1.5 h, 88%, ii) NaBH<sub>4</sub>, CaCl<sub>2</sub>, absolute EtOH, 25 °C, 20 min, 79%; d) PcamL, vinyl acetate, 30 °C; e) KOH, MeOH, 25 °C, 1 h.

Also, ( $\pm$ )-*epi*-cytoxazone ( $\pm$ )-**4.1b** was synthesized from the common intermediate, oxazolidinone ( $\pm$ )-**4.25**. Epimerization at C-5 in oxazolidinone ( $\pm$ )-**4.25** using potassium hydroxide followed by esterification with methyl iodide gave ester **4.27**. Reduction of ester **4.27** with calcium chloride/sodium borohydride and the subsequent kinetic resolution using CAL in SOL-Gel-AK afforded (+)-*epi*-cytoxazone **4.1b** in 49% overall yield and 87.3% ee (Scheme 4.6).

**Scheme 4.6**

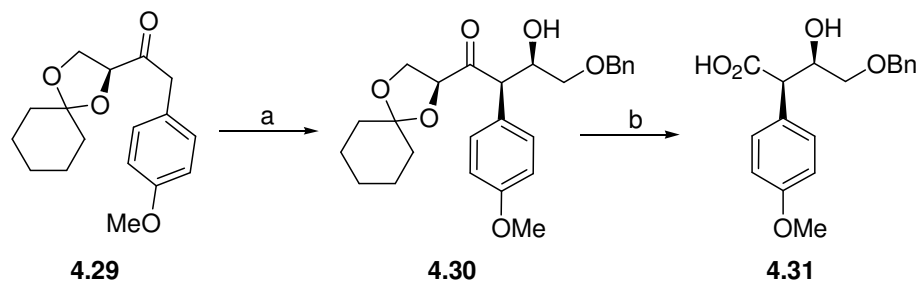


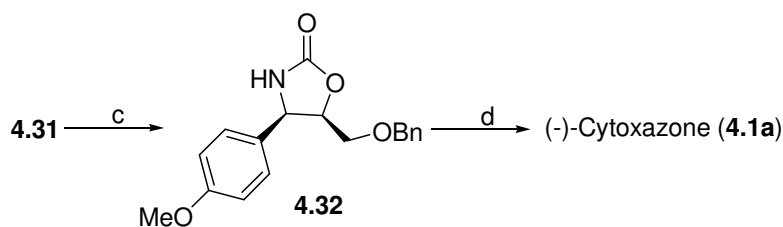
*Reagents and conditions:* a) i) KOH, EtOH, reflux, 1 h, ii) MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 16 h, 46%; b) NaBH<sub>4</sub>, CaCl<sub>2</sub>, absolute EtOH, 25 °C, 20 min., 82%; c) CAL in SOL-Gel-AK, vinyl acetate, 30 °C; d) KOH, MeOH, 25 °C, 1 h.

### Carda's approach:

The key steps in Carda's approach are *syn*-stereoselective aldol reaction and Curtius rearrangement. Aldol reaction of ketone **4.29** with benzyl protected glycolic aldehyde furnished the expected *syn-syn* aldol adduct **4.30** in 79% yield.

**Scheme 4.7**



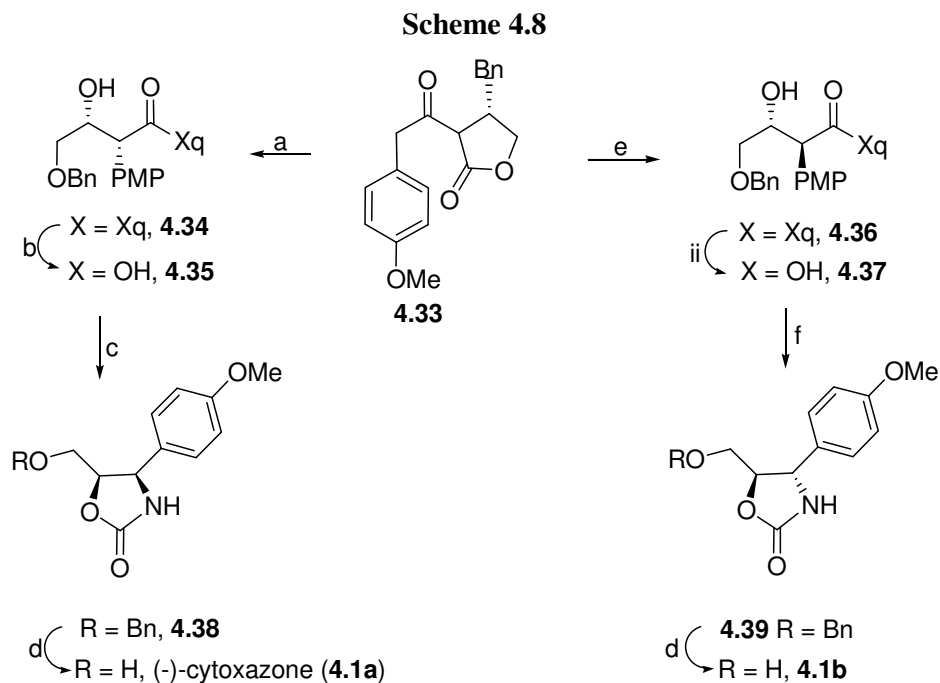


*Reagents and conditions:* a)  $\text{Chx}_2\text{BCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Et}_2\text{O}$ ,  $\text{BnOCH}_2\text{CHO}$ ,  $-78\text{ }^\circ\text{C}$ – $25\text{ }^\circ\text{C}$ , 79%; b)  $\text{H}_5\text{IO}_6$ ,  $\text{Et}_2\text{O}$ - $\text{EtOAc}$ , 70%; c)  $\text{Et}_3\text{N}$ , 4 Å MS, DPPA, toluene, reflux, 12 h; d)  $\text{EtOH}$ , cat.  $\text{Pd}(\text{OH})_2$ ,  $\text{H}_2$  (500 psi), 24 h, 78%.

Oxidative cleavage of the acetonide ring in alcohol **4.30** gave  $\beta$ -hydroxy acid **4.31** which was subjected to Curtius rearrangement to give the corresponding oxazolidinone **4.32**. Debenzylation by hydrogenolysis of **4.32** afforded (-)-Cytosaxone (**4.1a**) (Scheme 4.7).<sup>11</sup>

#### Carter's approach:

Carter *et al.* have made use of the Evan's aldol approach as the key reaction for the synthesis of (-)-cytosaxone (**4.1a**) as well as (+)-*epi*-cytosaxone (**4.1b**). The reaction of dibutylboron enolate of **4.33** with the benzyloxyacetaldehyde provided the aldol **4.34** in good syn-diaselectivity.



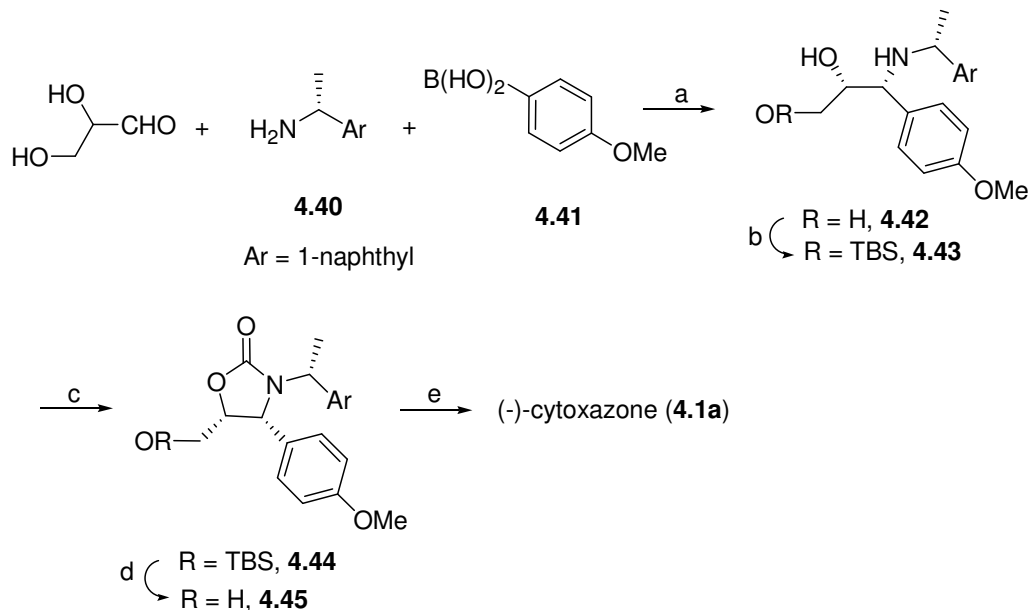
*Reagents and conditions:* a)  $\text{Bu}_2\text{BOTf}$ ,  $i\text{-Pr}_2\text{EtN}$ ,  $-78\text{ }^\circ\text{C}$ , 20 min.,  $\text{BnOCH}_2\text{CHO}$ ,  $-78\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$ , 1.5 h, 51%; b) 4:1  $\text{THF}:\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{LiOH}$ ,  $0\text{ }^\circ\text{C}$ , 1 h;  $\text{NaHSO}_3$ ; c)  $(\text{PhO})_2\text{PON}_3$ ,  $\text{PhCH}_3$ ,  $23\text{ }^\circ\text{C}$ , 40 min.,  $110\text{ }^\circ\text{C}$ , 3 h, 77%; d)  $\text{H}_2$  (1 atm),  $\text{Pd}(\text{OH})_2$ ,  $\text{MeOH}$ ,  $23\text{ }^\circ\text{C}$ , 24 h, 84%; e)  $\text{Bu}_2\text{BOTf}$ ,  $i\text{-Pr}_2\text{EtN}$ ,  $0\text{ }^\circ\text{C}$ , 30 min.; add  $\text{BnOCH}_2\text{CHO}$  precomplexed 0.5 equiv  $\text{SnCl}_4$ ,  $-78\text{ }^\circ\text{C}$ , 3 h, 64%. f)  $(\text{PhO})_2\text{PON}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $23\text{ }^\circ\text{C}$ , 40 min.;  $45\text{ }^\circ\text{C}$ , 12 h, 61%.

Removal of the chiral auxiliary from **4.34** provided the acid **4.35** which was transformed into the oxazolidinone **4.38** in a one-pot 3 step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Ether **4.38** was debenzylated using Pearlman's catalyst to provide (-)-cytoxazone (**4.1a**). The synthesis of (+)-*epi*-cytoxazone required the use of an *anti*-selective aldol product **4.36** which was obtained by the addition of a pre-complexed solution of benzyloxyacetaldehyde and 0.5 equiv. of SnCl<sub>4</sub> to the dibutylboryl enolate of **4.33**. The same sequence of reactions was used to synthesize (+)-*epi*-cytoxazone (**4.1b**) starting from aldol product **4.36** (Scheme 4.8).<sup>12</sup>

#### Sugiyama's approach:

Sugiyama *et al.* have synthesized (-)-cytoxazone **4.1a** using the Petasis three-component coupling reaction of DL-glyceraldehyde, 4-methoxyphenylboronic acid (**4.41**) and (*R*)-1-(1-naphthyl)ethylamine (**4.40**), followed by formation of an oxazolidin-2-one ring. Separation of the diastereomers by column chromatography and the acidic removal of 1-naphthylethyl group produced (-)-cytoxazone (**4.1a**) in 13 % overall yield (Scheme 4.9).<sup>13</sup>

Scheme 4.9

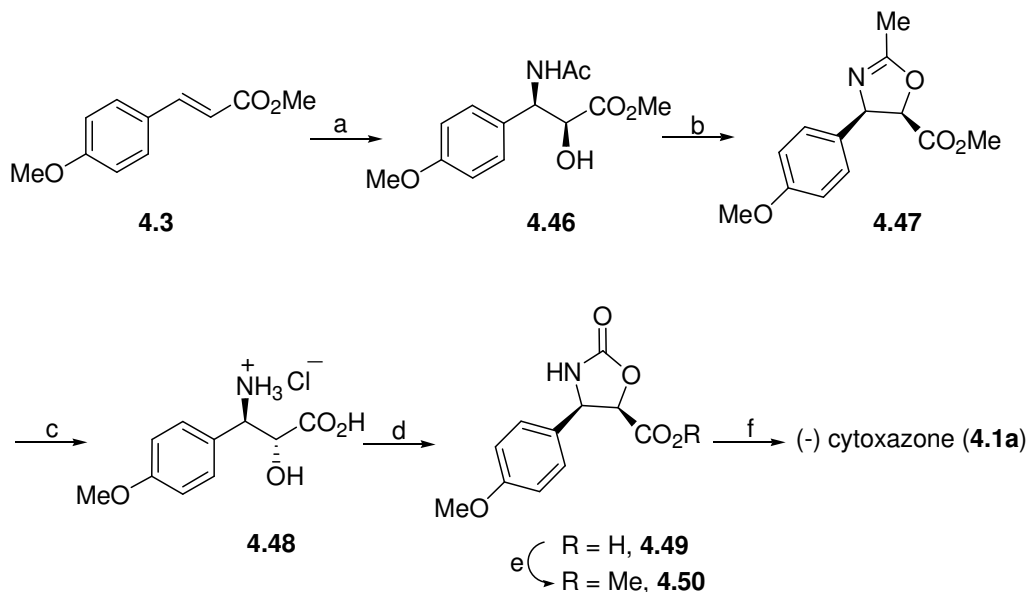


*Reagents and conditions:* a) EtOH, reflux, 3 days, 50%. b) TBDMSCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 5 h. c) DSC, Et<sub>3</sub>N, MeCN, 25 °C, 6 h, 66%. d) TBAF, THF, 25 °C, 63 h and SiO<sub>2</sub> column chromatographic separation 59%. e) MsOH, anisole, MeNO<sub>2</sub>, 50 °C, 6 h.

### Saicic's approach:

Saicic's approach was based on the Sharpless asymmetric aminohydroxylation reaction, starting from methyl *p*-methoxycinnamate, in six steps and 31% overall yield (Scheme 4.10).<sup>14</sup>

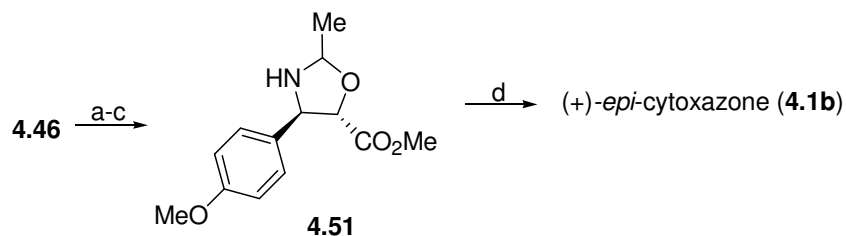
Scheme 4.10



*Reagents and conditions:* a)  $K_2[OsO_2(OH)_4]$  (4 mol %), BrNHAc, (DHQD)<sub>2</sub>PHAL (1 mol%), LiOH, H<sub>2</sub>O, *t*-BuOH, 4 °C, 20 h, 72%; b) Tf<sub>2</sub>O, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 80%; c) 12% HCl, 25 °C, 1.5 h; d) ClCO<sub>2</sub>CCl<sub>3</sub>, NaOH, H<sub>2</sub>O, 0 °C; e) CH<sub>2</sub>N<sub>2</sub>, THF, 72%; e) NaBH<sub>4</sub>, THF, 0 °C, 75%.

The required *anti*-aminoalcohol **4.48** was synthesized using Sharpless asymmetric aminohydroxylation and subsequent inversion of configuration in amidoalcohol **4.46** via an oxazoline **4.47**. Submission of amidoalcohol **4.46** to the sequence of reactions already described for cytoxazone *i.e.* hydrolysis, cyclization and esterification, gave the methyl ester **4.51**, which on reduction with sodium borohydride gave (+)-*epi*-cytoxazone (**4.1b**) (Scheme 4.11).<sup>14</sup>

Scheme 4.11

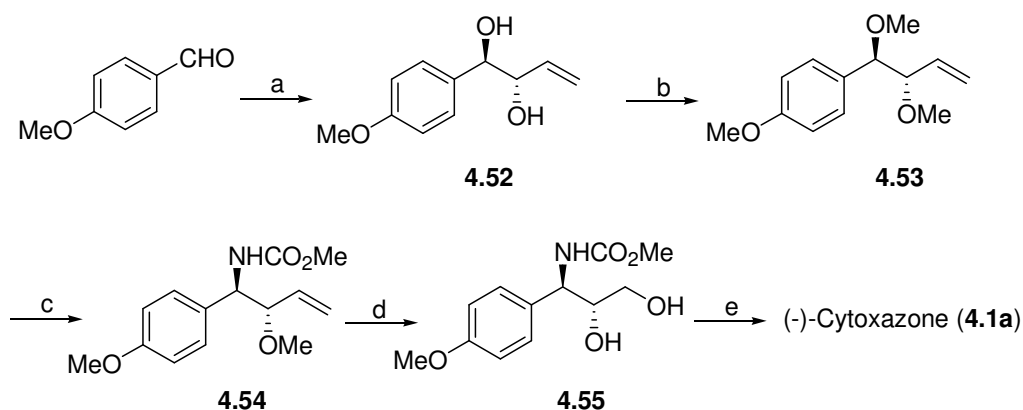


*Reagents and conditions:* a) 10% HCl, reflux, 4 h; b) ClCO<sub>2</sub>CCl<sub>3</sub>, NaOH, H<sub>2</sub>O, 0 °C; c) CH<sub>2</sub>N<sub>2</sub>, THF, 63%; d) NaBH<sub>4</sub>, THF, 0 °C, 80%.

### Jung's approach:

Jung *et al.* have made use of the regio- and diastereoselective introduction of a *N*-protected amine group in to the intermediate **4.53** with chlorosulfonyl isocyanate (CSI) to obtain *anti*-1,2-aminoalcohol **4.54**. Thus the treatment of compound **4.53** with CSI in the presence of sodium carbonate in dry toluene at  $-78\text{ }^{\circ}\text{C}$ , followed by the reduction of the *N*-chlorosulfonyl group furnished the desired *anti*-1,2-amino alcohol **4.54** with a high diastereoselectivity (27:1). Ozonolysis of the double bond and intramolecular cyclization of **4.55** using NaH finally gave (-)-cytoxazone (**4.1a**) in 95% yield (Scheme 4.12).<sup>15</sup>

Scheme 4.12

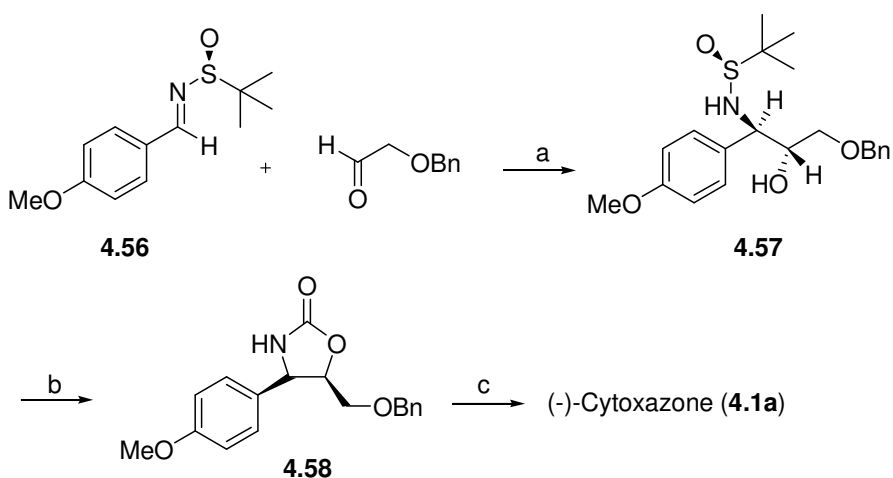


*Reagents and conditions:* a) i) B-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheyl borane,  $\text{Et}_2\text{O}$ ,  $-78\text{ }^{\circ}\text{C}$ , ii)  $\text{H}_2\text{O}_2$ , KF,  $\text{KHCO}_3$ , THF-MeOH,  $25\text{ }^{\circ}\text{C}$ , 52%; b) MeI, NaH, THF,  $0\text{ }^{\circ}\text{C}$ , 96%; c) i) chlorosulfonyl isocyanate,  $\text{Na}_2\text{CO}_3$ , toluene,  $-78\text{ }^{\circ}\text{C}$ , ii)  $\text{Na}_2\text{SO}_3$ , KOH,  $25\text{ }^{\circ}\text{C}$ , 95% (dr = 27:1); d) i)  $\text{O}_3$ ,  $-78\text{ }^{\circ}\text{C}$  then  $\text{NaBH}_4$ ,  $0\text{ }^{\circ}\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ -MeOH, 94%, ii)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^{\circ}\text{C}$ , 80%; e) NaH, THF,  $0\text{ }^{\circ}\text{C}$ , 95%.

### Bentley's approach:

Bentley *et al.* have made use of stereoselective cross-coupling of phenyl imine auxiliary **4.56** and aldehyde in presence of samarium iodide to obtain the corresponding aminoalcohol **4.57**. Removal of chiral auxiliary and cyclization using triphosgene gave **4.58**, which on debenzylation afforded (-)-cytoxazone (**4.1a**) (Scheme 4.13).<sup>16</sup>

### Scheme 4.13

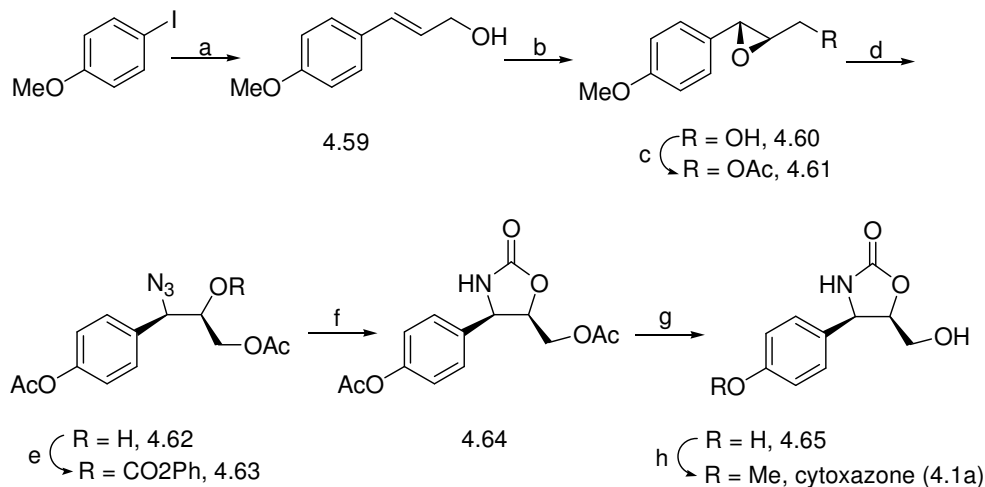


Reagents and conditions: a)  $\text{Sml}_2$ , tBuOH, THF,  $-78\text{ }^\circ\text{C}$ , 83%; b) i) HCl, MeOH,  $25\text{ }^\circ\text{C}$ , ii) triphosgene,  $\text{Et}_3\text{N}$ , DCM,  $25\text{ }^\circ\text{C}$ , 85%; c)  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{H}_2$ , MeOH, 86%.

### Sudalai's approach:

Sudalai *et al.* have developed a simple method for the enantioselective synthesis of (-)-cytoxazone (**4.1a**) using Sharpless asymmetric epoxidation as the key step. Thus, asymmetric epoxidation of allyl alcohol **4.59** gave chiral epoxide **4.60**, which was further acylated to give acetate **4.61**. The nucleophilic opening of the epoxide **4.61** at the benzylic position with  $\text{NaN}_3$  gave azido alcohol **4.62** in 88% yield.

### Scheme 4.14

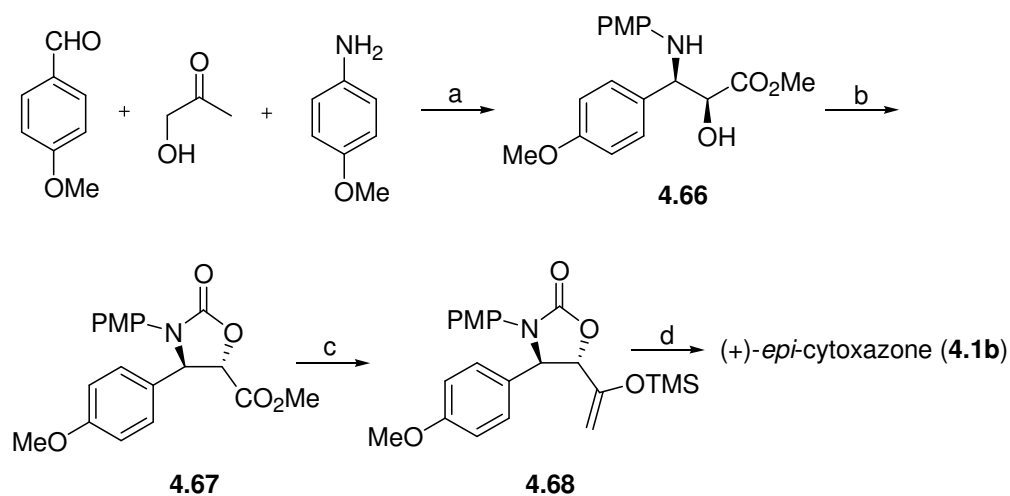


Reagents and conditions: a) allyl alcohol,  $\text{AgOAc}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ , DMF,  $70\text{ }^\circ\text{C}$ , 16 h, 81%; b) anhyd. 5.4 M TBHP in  $\text{CH}_2\text{Cl}_2$ , 4Å molecular sieves,  $\text{Ti}(\text{OiPr})_4$ , (+)-DIPT,  $\text{CH}_2\text{Cl}_2$ ,  $-20\text{ }^\circ\text{C}$ , 20 h, 78%; c)  $\text{AcCl}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $25\text{ }^\circ\text{C}$ , 87%; d)  $\text{NaN}_3$ ,  $\text{NH}_4\text{Cl}$ , THF/ $\text{H}_2\text{O}$  (2:1),  $50\text{ }^\circ\text{C}$ , 3 h, 79%; e)  $\text{PhOCOCl}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ,  $-5$  to  $25\text{ }^\circ\text{C}$ , 1 h, 93%; f)  $\text{PPh}_3$ , THF/ $\text{H}_2\text{O}$ ,  $50\text{ }^\circ\text{C}$ , 2 h, 87%; g) aq  $\text{NaHCO}_3$ , MeOH, reflux, 1 h; h)  $\text{NaH}$ , MeI, THF,  $0$ - $25\text{ }^\circ\text{C}$ , 3 h, 69%, 83% ee.

Protection of the alcohol followed by reductive cyclization with  $\text{PPh}_3$  gave oxazolidinone **4.64**, which was directly subjected to methylation with methyl iodide in the presence of  $\text{NaH}$  to afford (-)-cytoxazone (**4.1a**) in 65% yield and 83% ee (Scheme 4.14).<sup>17a</sup>

The same group has achieved the synthesis of (+)-*epi*-cytoxazone (**4.1b**) using L-proline catalyzed asymmetric Mannich reaction. Thus, key intermediate *syn*-amino alcohol **4.66** was obtained from L-proline catalyzed asymmetric Mannich reaction of 4-methoxybenzaldehyde, hydroxyacetone and *p*-anisidine in 76% yield with *syn/anti* ratio 2:1. Amino alcohol **4.66** was then protected with triphosgene to give oxazolidinone **4.67** in 82% yield. *In situ* generated silyl enol ether **4.68** was subjected to ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN furnished (+)-*epi*-cytoxazone (**4.1b**) in 59% yield and 81% ee (Scheme 4.15).<sup>17a</sup>

**Scheme 4.15**



*Reagents and conditions:* a) *p*-anisidine, hydroxyacetone, L-proline, DMSO, 25 °C, 24 h, 76%; b) triphosgene,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , -10 to 25 °C, 82%; c) Li-HMDS, TMSCl, THF, -78 °C. d) i)  $\text{O}_3$ ,  $\text{PPh}_3$ ,  $\text{CH}_2\text{Cl}_2$ , -78 °C, ii)  $\text{NaBH}_4$ , MeOH, 25 °C, iii) CAN,  $\text{CH}_3\text{CN}$ , 5 h, 59% (in three steps), 81% ee.

### 4.3: Present Work

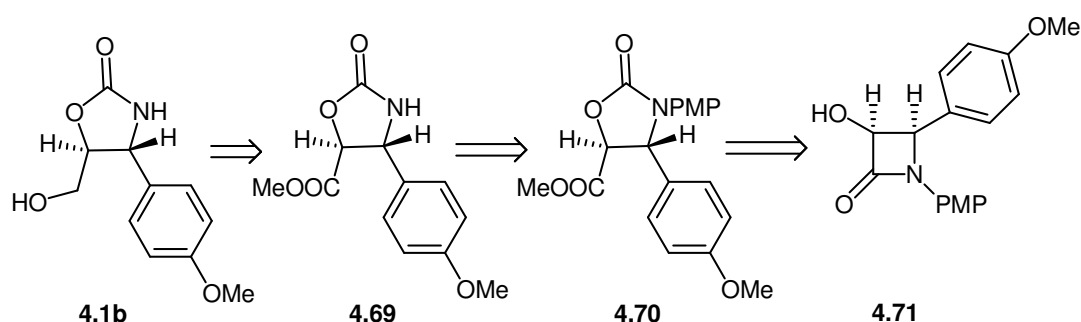
Literature search revealed that several methods such as classical resolution, chemo-enzymatic or enantioselective synthesis have been reported for the synthesis of (-)-cytoxazone (**4.1a**) and its epimer (+)-*epi*-cytoxazone (**4.1b**).<sup>3, 7-17</sup> However, these methods suffer from many disadvantages such as low over all yields, the need for



separation of diastereomers and the use of expensive chiral reagents. The synthetic precursors of (-)-cytoxazone (**4.1a**) and (+)-*epi*-cytoxazone (**4.1b**) are 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years.<sup>18</sup> In this context, a more practical method for the synthesis of (-)-cytoxazone (**4.1a**) and (+)-*epi*-cytoxazone (**4.1b**) is highly desirable.

Looking structural similarity of previously synthesized compound **2.73** (Chapter 2, Scheme 2.17) and *epi*-cytoxazone and our experience in  $\beta$ -lactams chemistry inspired us to design retrosynthetic strategy of *epi*-cytoxazone (Scheme 4.16).

**Scheme 4.16**



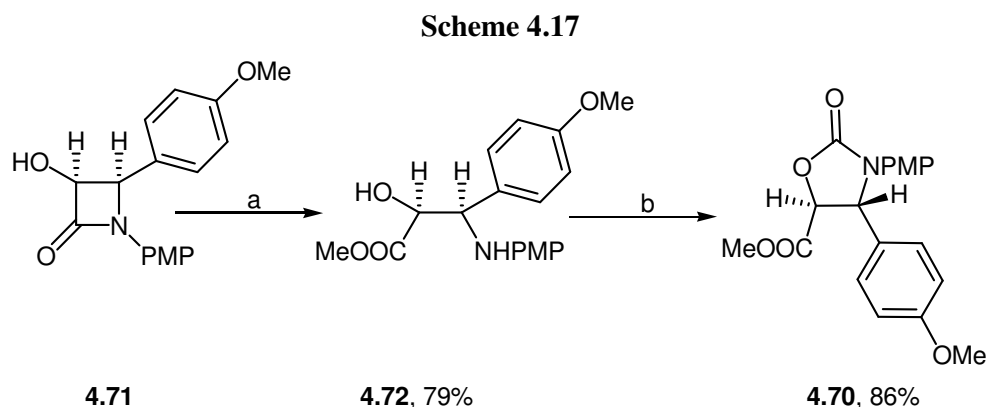
3-Hydroxyazetidin-2-one **4.71** on acid catalyzed ring opening, would give cyclic carbamate ester **4.70**, which on reduction with sodium borohydride would provide the target molecule.

#### 4.4: Result and discussion

During the course of our research work in the area of asymmetric synthesis and transformations of  $\beta$ -lactams we have developed very good method for asymmetric synthesis of 3-hydroxyazetidin-2-ones using ephedrine derived recyclable chiral auxiliary.<sup>19a</sup>

Initially we established the reaction conditions with racemic 3-hydroxyazetidin-2-one **4.71**, which was easily obtained by the hydrolysis of the corresponding 3-acetoxyazetidin-2-one in very good yield.<sup>20</sup> 3-Acetoxyazetidin-2-one was prepared by well established Staudinger's ketene-imine cycloaddition reaction. The ketene was generated *in situ* from acetoxyacetyl chloride and the imine prepared by the reaction of *p*-anisidine with *p*-methoxybenzaldehyde.

3-Hydroxy- $\beta$ -lactam **4.71** on treatment with methanolic HCl (20%) at room temperature furnished  $\beta$ -amino methyl ester **4.72** in 79% yield as thick oil (Scheme 4.17).

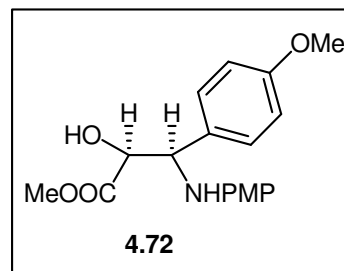


*Reagents and conditions:* a) H<sup>+</sup>/ MeOH (20%), rt, 48 h; b) (CCl<sub>3</sub>)<sub>2</sub>CO, Et<sub>3</sub>N, THF, 8 h.

3-Hydroxy-1,4-bis(4-methoxyphenyl)azetidin-2-one (**4.71**) was dissolved in methanolic HCl (20%) and the reaction mixture was stirred for 48 h at room temperature. After extractive work up with ethyl acetate, solvent was removed under reduced pressure afforded crude product, which was quickly purified by flash column chromatography to furnish **4.72** as thick oil. The structure of **4.72** was established by spectral and analytical data.

IR spectrum of **4.72** showed a broad band at 3387 cm<sup>-1</sup> which is for the hydroxyl group and the sharp peak at 1739 cm<sup>-1</sup> was attributed to the ester carbonyl group.

The <sup>1</sup>H NMR spectrum of **4.72** showed a broad singlet of two protons at 3.31 ppm which is for the hydroxy and amino proton. The two sharp singlets corresponding to the methoxy group appeared at 3.68 ppm and 3.69 ppm while; sharp singlet at 3.61 ppm was attributed for methyl ester. The  $\alpha$ -keto and  $\beta$ -keto protons appeared as two doublets at 4.43 ppm and 4.72 ppm with  $J = 3.3$  Hz respectively. The ortho protons of the *p*-methoxy phenyl group appeared as two doublets at 6.50 ppm and 6.61 ppm with  $J = 9.1$  Hz and the remaining aromatic protons also displayed two doublets at 6.77 ppm and 7.26 ppm with  $J = 8.7$  Hz. The strong absorption band at 1739 cm<sup>-1</sup> for ester carbonyl group in IR and singlet at 3.61



ppm in  $^1\text{H}$  NMR spectrum clearly indicates the nucleophilic opening of azetidinone ring.

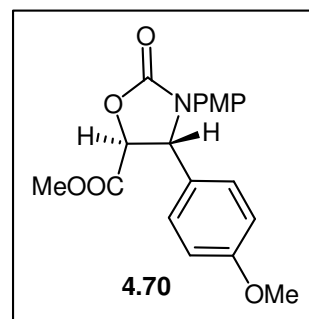
The  $^{13}\text{C}$  NMR spectrum of **4.72** showed the peak at 52.81 ppm which was attributed to the methyl carbon in the ester group. The methoxy carbons on aromatic part appeared at 55.1 ppm and 55.6 ppm. The  $\alpha$ -keto and  $\beta$ -keto carbons displayed two peaks at 74.6 ppm and 59.8 ppm respectively. The quaternary carbons of aromatic ring (*para* to methoxy) appeared at 131.0 and 140.1 while, other quaternary carbons bearing the methoxy group showed peaks at 152.4 ppm and 158.9 ppm. The remaining aromatic carbons appeared at 113.9, 114.7, 115.6 and 128.1 ppm. The peak at 173.3 ppm was assigned for the ester carbonyl carbon. The compound gave satisfactory elemental analysis data and mass spectrum showed a peak at  $m/z$  332 ( $M+1$ ).

The  $\beta$ -amino methyl ester **4.72** on treatment with triphosgene in the presence of triethyl amine in anhydrous THF gave the oxazolidinone **4.70** in excellent yield. To a cooled solution of **4.72**,  $\text{Et}_3\text{N}$  in dry THF, triphosgene was added at once. The reaction mixture was then allowed to warm up to room temperature. After completion of reaction solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography to furnish **4.70** as thick oil. The structure of **4.70** was established by spectral and analytical data.

IR spectrum of **4.70** showed a broad peak at  $1766\text{ cm}^{-1}$  in which ester carbonyl and oxazolidinone carbonyl groups were merged.

The  $^1\text{H}$  NMR spectrum of **4.70** revealed that one of the *trans* disposed oxazolidinone ring protons, appeared as a doublet at 4.76 ppm with  $J = 4.6$  Hz while, other proton appeared as doublet at 5.29 with  $J = 4.6$  Hz. The methoxy protons resonated at 3.78 ppm and 3.89 ppm respectively while, the ester methyl protons appeared at 3.73 ppm. The *ortho* protons of the *p*-methoxy phenyl group appeared as two doublets at 6.79 ppm and 6.88 ppm with  $J = 9.1$  Hz and the remaining aromatic protons also displayed two doublets at 7.24 ppm and 7.25 ppm with  $J = 8.1$  Hz.

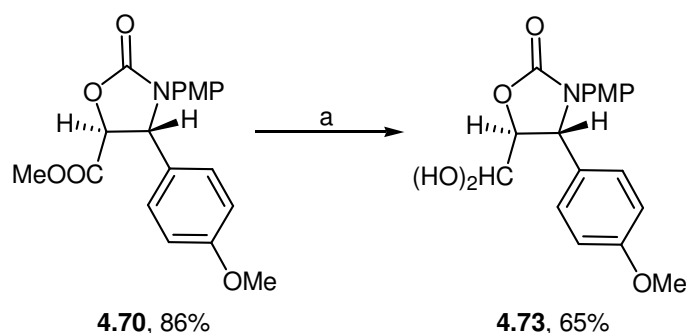
The  $^{13}\text{C}$  NMR spectrum of **4.70** showed the peak at 53.1 ppm which was attributed for the methyl carbon in the ester group. The methoxy carbons on aromatic



part appeared at 55.2 ppm and 55.3 ppm. The oxazolidinone C-3 and C-4 carbons displayed two peaks at 77.7 and 63.7 ppm respectively. The quaternary carbons of aromatic ring (*para* to methoxy) appeared at 129.3 and 154.4 while, other quaternary carbons bearing the methoxy group showed peaks at 157.1 ppm and 157.2 ppm. The remaining aromatic carbons appeared at 114.2, 114.7, 123.3 and 127.7 ppm. The peaks at 160.1 ppm and 168.2 ppm were assigned for the ester carbonyl carbon and oxazolidinone carbonyl carbon respectively. The compound gave satisfactory elemental analysis data and mass spectrum showed a peak at  $m/z$  358 (M+1).

The reduction of ester group was attempted by the known procedure using  $\text{CaCl}_2$  and  $\text{NaBH}_4$  to get corresponding hydroxyl methylene compound but reaction yielded hemiacetal product **4.73** in 65% yield as a white solid instead of complete reduced product (Scheme 4.18). The structure of hemiacetal **4.73** was established by spectral and analytical data.

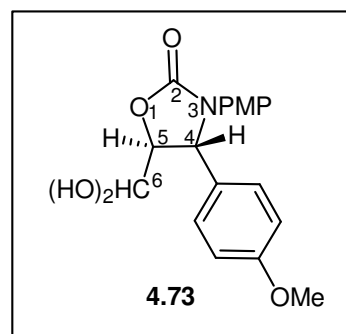
**Scheme 4.18**



*Reagent and conditions:* a)  $\text{NaBH}_4$ ,  $\text{CaCl}_2$ , EtOH, 0 °C-rt, 3 h.

IR spectrum of **4.73** showed a broad peak at  $3315\text{ cm}^{-1}$  corresponding to hydroxyl group and sharp peak at  $1730\text{ cm}^{-1}$  which was attributed to oxazolidinone carbonyl group.

The  $^1\text{H}$  NMR spectrum of **4.73** showed a broad singlet at 2.50 ppm corresponding to hydroxyl protons. The sharp singlets corresponding to the methoxy protons appeared at 3.66 ppm and 3.69 ppm. The oxazolidinone ring proton (C-5) resonated as doublet of doublet at 4.06 ppm with  $J = 3.7$  and  $4.3$  Hz while, the other ring proton (C-4) resonated as



doublet at 5.33 ppm with  $J = 4.3$  Hz. The hemiacetal proton displayed a doublet at 5.04 ppm with  $J = 3.7$  Hz. The *ortho* protons of the *p*-methoxy phenyl group appeared as two doublets at 6.75 ppm and 6.81 ppm with  $J = 9.1$  Hz and the remaining aromatic protons also displayed two doublets at 7.20 ppm and 7.27 ppm with  $J = 8.7$  Hz.

The  $^{13}\text{C}$  NMR spectrum of **4.73** showed the peaks at 54.7 ppm and 54.8 ppm corresponding for methoxy carbons on aromatic part. The oxazolidinone C-4 and C-5 carbons displayed two peaks at 88.4 and 59.1 ppm respectively. The hemiacetal carbon appeared at 82.0 ppm. The quaternary carbons of aromatic ring were appeared at 130.0, 131.6, 154.8 and 155.9 ppm. The remaining aromatic carbons appeared at 113.5, 114.0, 122.6 and 127.5 ppm. The peak at 158.7 ppm was assigned for oxazolidinone carbonyl carbon. The absence of any signal corresponding to methylene carbon in DEPT experiment confirms the formation of hemiacetal compound.

The bond connectivity and stereo alignment of protons present in compound **4.73** were confirmed by using 2D NMR spectroscopy. In the COSY spectrum the proton H-4 shows connectivity with proton H-5. The proton H-5 shows cross peak with proton H-6 which indicate that these two are connected to each other (Figure 4.3).

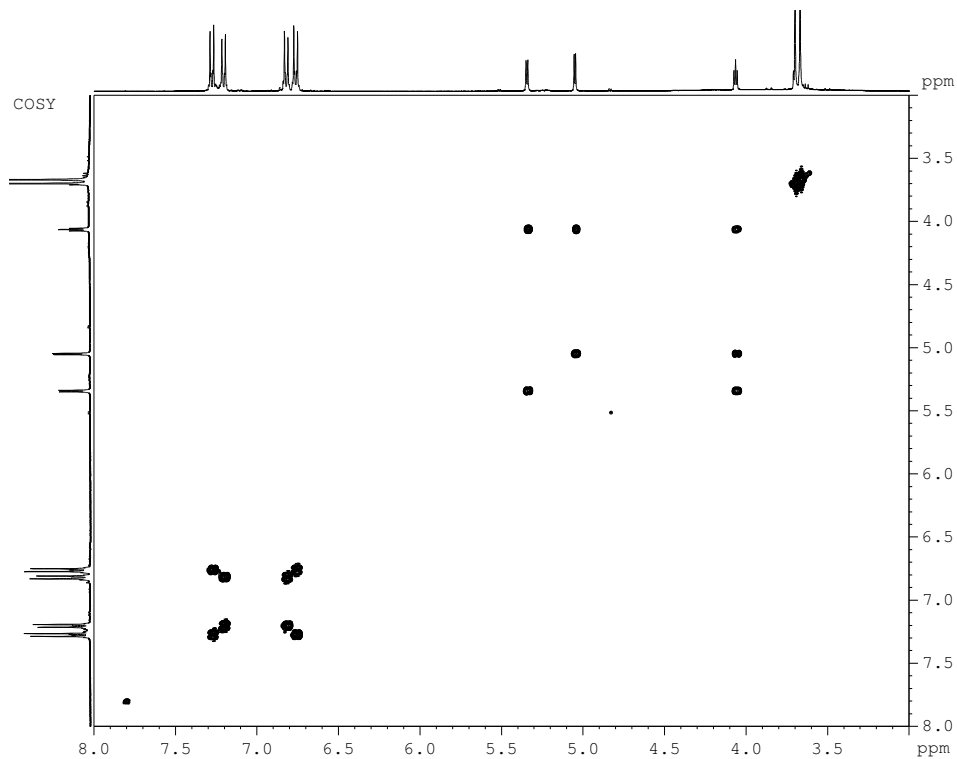
Proton	ppm	$^1\text{H}$ - $^1\text{H}$ connectivity
H-4	5.34 (dd)	H-5
H-5	4.06 (t)	H-4, H-6
H-6	5.05 (d)	H-5

In  $^1\text{H}$  NMR peak at 5.05 ppm corresponding to the integration of one proton, this shows that ester was not reduced to corresponding alcohol.

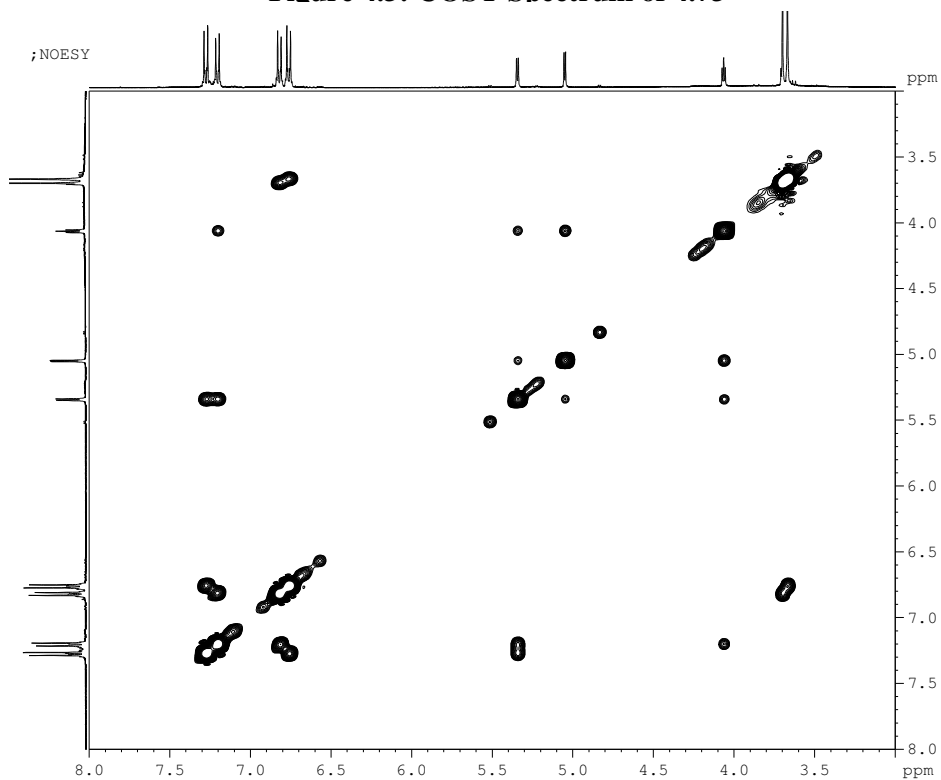
The stereo alignment of H-4 and H-5 was already known to be *trans*, which was further confirmed by NOESY spectrum. In NOESY spectrum proton H-4 and H-5 does not show cross peak this indicate that they have *trans* relationship with each other while, proton H-6 which is newly formed in compound **4.73** shows cross peak with H-5 indicating their *cis* relationship (Figure 4.4).

The compound **4.73** gave satisfactory elemental analysis data and mass spectrum showed a peak at  $m/z$  346 (M+1).

Various reactions were carried out on compound **4.73** by changing solvent for reaction such as MeOH, THF for complete reduction of ester. However, all our



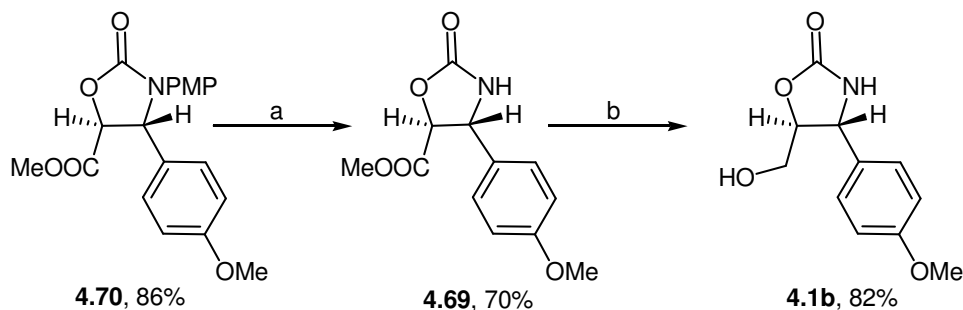
**Figure 4.3: COSY Spectrum of 4.73**



**Figure 4.4: NOESY Spectrum of 4.73**

attempts proved to be failed. Therefore, the selective removal of the *N*-PMP group was successfully achieved using ceric ammonium nitrate (CAN) in CH<sub>3</sub>CN-H<sub>2</sub>O (1:1.2) to get crude product, which was purified by flash column chromatography to furnish **4.69** as a white solid in 70% yield (Scheme 4.19).

**Scheme 4.19**

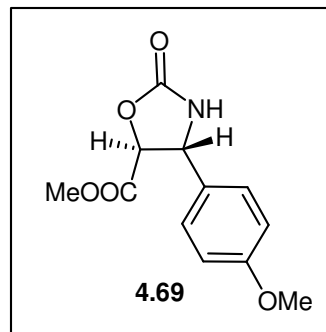


*Reagents and conditions:* a) CAN, CH<sub>3</sub>CN - H<sub>2</sub>O, 45min; b) NaBH<sub>4</sub>, CaCl<sub>2</sub>, absolute EtOH, rt, 2 h.

The structure of **4.69** was established by spectral and analytical data.

IR spectrum of **4.69** showed a broad peak at 1764 cm<sup>-1</sup> in which ester carbonyl and oxazolidinone carbonyl groups were merged.

The <sup>1</sup>H NMR spectrum of **4.69** revealed that one of the *trans* disposed oxazolidinone ring protons appeared as a doublet at 4.75 ppm with *J* = 5.2 Hz while, other proton appeared as doublet at 4.93 with *J* = 5.2 Hz. The methoxy protons resonated at 3.87 ppm while, the ester methyl protons appeared at 3.83 ppm. The broad singlet at 5.99 ppm was attributed for NH proton. The protons of the *p*-methoxy phenyl group appeared as two doublets at 6.94 ppm and 7.30 ppm with *J* = 8.6 Hz.



The <sup>13</sup>C NMR spectrum of **4.69** showed the peak at 52.9 ppm which was attributed to the methyl carbon in the ester group. The methoxy carbon on aromatic part appeared at 55.2 ppm. The oxazolidinone C-4 and C-5 carbons displayed two peaks at 80.3 and 58.6 ppm respectively. The quaternary carbons of aromatic ring appeared at 130.8 and 158.0. The remaining aromatic carbons appeared at 114.4, 127.1 ppm. The peaks at 159.9 ppm and 168.8 ppm were assigned to the ester carbonyl carbon and oxazolidinone carbonyl carbon respectively.

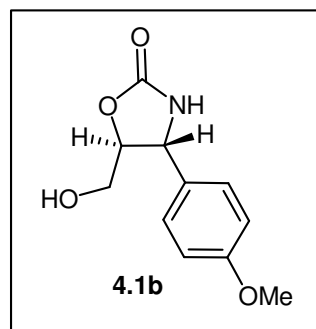
The compound **4.69** gave satisfactory elemental analysis data and mass spectrum showed a peak at  $m/z$  252 ( $M+1$ ). The spectral and physical data were in agreement with that of the reported compound.<sup>10</sup>

The reduction of ester group was achieved by the known procedure using  $\text{CaCl}_2$  and  $\text{NaBH}_4$  to get *epi*-cytoxazone **4.1b** in 82 % yield (Scheme 4.19).

Oxazolidinone **4.69** was dissolved in absolute EtOH,  $\text{CaCl}_2$  and  $\text{NaBH}_4$  was added, and reaction mixture was stirred for 2 h at room temperature. The excess of reagent was destroyed by adding saturated  $\text{NH}_4\text{Cl}$  and ethanol was evaporated. The crude product was purified by flash column chromatography to give pure **4.1b** as a white solid. The structure was established by comparing the spectral data with that of the reported *epi*-cytoxazone.<sup>21</sup>

IR spectrum of **4.1b** showed a broad peak at  $3244\text{ cm}^{-1}$  corresponding to hydroxyl group and sharp peak at  $1724\text{ cm}^{-1}$  which was attributed to oxazolidinone carbonyl group.

The  $^1\text{H}$  NMR spectrum of **4.1b** showed a multiplet of two protons at 3.49-3.66 ppm in which one of the protons from hydroxy methylene group and hydroxyl proton were merged while, other hydroxy methylene proton appeared as doublet of doublet at 4.13 ppm with  $J = 9.9$  and  $3.8$  Hz. The sharp singlet at 3.75 ppm was attributed to the methoxy protons. The C-4 proton resonated as doublet at 4.61 ppm with  $J = 6.3$  Hz while, C-5 proton appeared as a multiplet between 5.18-5.24 ppm. The aromatic proton appeared as two doublets at 6.95 ppm and 7.25 ppm with  $J = 8.8$  Hz. The  $\text{NH}$  proton appeared as broad singlet at 8.05 ppm.



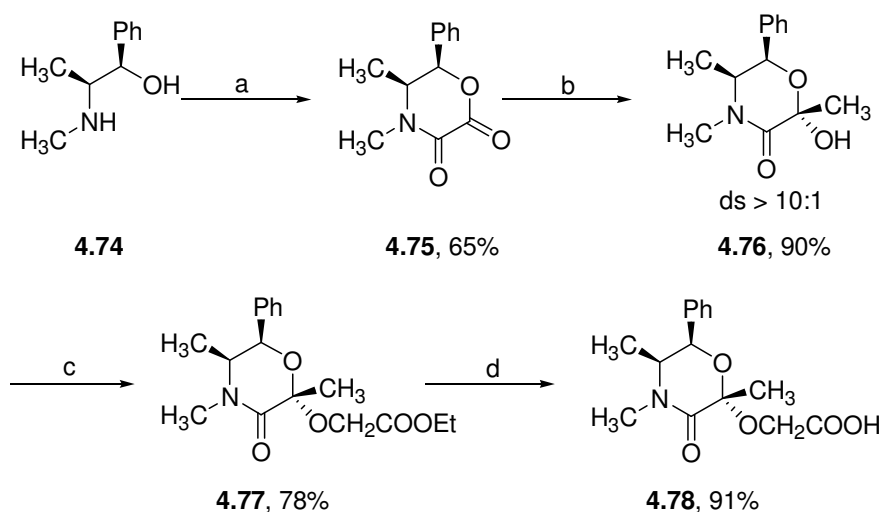
The  $^{13}\text{C}$  NMR spectrum of **4.1b** showed the peak at 55.2 ppm corresponding to the methoxy carbon. The oxazolidinone C-4 and C-5 carbons displayed two peaks at 56.2 and 61.0 ppm respectively. The hydroxy methylene carbon appeared at 84.2 ppm. The quaternary carbons of aromatic ring appeared at 132.9 and 158.2 ppm. The remaining aromatic carbons appeared at 114.2 and 127.5 ppm. The peak at 159.1 ppm was assigned for oxazolidinone carbonyl carbon. The compound gave satisfactory elemental analysis data and mass spectrum showed a peak at  $m/z$  224 ( $M+1$ ).



After establishing the reaction conditions for the synthesis of racemic *epi*-cytoxazone, the same synthetic protocol was used for the synthesis of enantiomerically pure *epi*-cytoxazone starting from enantiomerically pure 3-hydroxyazetid-2-one. Asymmetric synthesis of 3-hydroxyazetid-2-ones was achieved by using ephedrine derived recyclable chiral auxiliary.<sup>19a</sup>

The hemiketal **4.76** was easily prepared by reacting (-)-ephedrine **4.74** with oxalyl chloride followed by addition of Grignard reagent to the corresponding lactone **4.75**. The resulting hemiketal **4.76** was then alkylated with ethyl bromoacetate followed by hydrolysis of the corresponding ester to afford the chiral acid **4.78** as a white solid (Scheme 4.20).

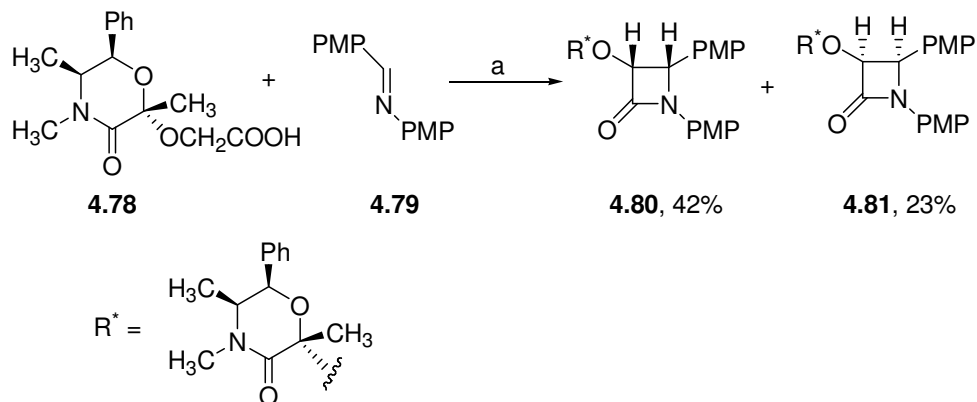
**Scheme 4.20**



*Reagents and conditions:* a)  $(\text{COCl})_2$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; b)  $\text{CH}_3\text{MgI}$ , ether, 1 h; c)  $\text{NaH}$ ,  $\text{BrCH}_2\text{CO}_2\text{Et}$ ,  $\text{THF}+\text{DMF}$  (1:1),  $70^\circ\text{C}$ , 16 h; d) aq.  $\text{NaOH}$ ,  $\text{THF}$ ,  $0^\circ\text{C}$  to rt, 6 h.

The chiral acid **4.78** derived from ephedrine was then subjected to Staudinger reaction with imine **4.79** in presence of triphosgene as an acid activator. Triphosgene converts acid to acid chloride *in situ* in presence of triethyl amine which then reacts with imine to give  $\beta$ -lactams (Scheme 4.21).

### Scheme 4.21

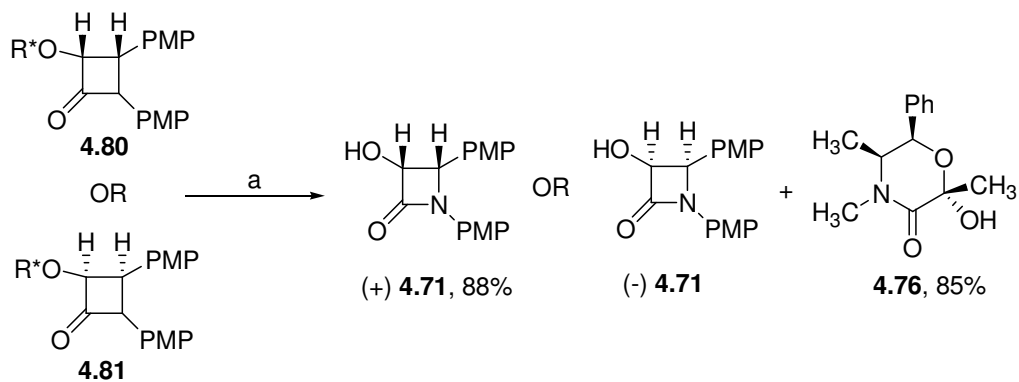


*Reagents and conditions:* a) triphosgene, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 12 h.

The chiral auxiliary could be effectively cleaved by refluxing the pure diastereomer **4.80** in a mixture of THF and water (4:1) using PTSA (excess) for 12 h.

The cleavage of chiral auxiliary from **4.80** gave enantiomerically pure (+)-3-hydroxy-β-lactam **4.71** in excellent yield along with the recovery of chiral auxiliary **4.76** in pure form. The chiral auxiliary was separated from the β-lactam simply by column chromatography in pure form, which was recycled. There was no loss in optical activity of the recovered auxiliary as it showed the same optical rotation as that of starting hemiketal **4.76** (Scheme 4.22). The structure of (+)-3-hydroxy-β-lactam **4.71** was established by spectral and analytical data.

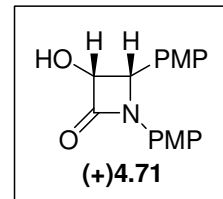
### Scheme 4.22



*Reagents and conditions:* a) PTSA, THF/H<sub>2</sub>O, reflux, 12 h.

IR spectrum of (+) **4.71** showed a broad band at  $3310\text{ cm}^{-1}$  which was for the hydroxyl group and the sharp peak at  $1728\text{ cm}^{-1}$  was attributed to the  $\beta$ -lactam carbonyl.

The  $^1\text{H}$  NMR spectrum of (+) **4.71** showed a broad singlet at 3.04 ppm which was for the hydroxy proton. The two sharp singlets corresponding to the methoxy protons appeared at 3.75 ppm and 3.79 ppm. The C-3  $\beta$ -lactam proton appeared as a doublet at 5.21 ppm with  $J = 5.4$  Hz and the C-4  $\beta$ -lactam as a doublet at 5.15 ppm with  $J = 5.4$



Hz. The *ortho* protons of the *p*-methoxy phenyl group appeared as two doublets at 6.79 ppm and 6.92 ppm with  $J = 8.8$  Hz and the remaining aromatic protons appeared as a multiplet in the range 7.10-7.40 ppm. This compound showed the molecular ion peak at 300 (M+1) and gave satisfactory elemental analysis. The optical rotation for **4.71**  $\{[\alpha]_{25}^D = +179.1 (c\ 2.2, \text{CHCl}_3)\}$  matched with that reported in the literature<sup>19c</sup>  $\{[\alpha]_{25}^D = +181.9 (c\ 2.2, \text{CHCl}_3)\}$  and the sign of the optical rotation confirmed the stereochemistry of the  $\beta$ -lactam ring which is *3R, 4S*.

In a similar way, the cleavage of chiral auxiliary from **4.81** gave enantiomerically pure 3-hydroxy- $\beta$ -lactam (-) **4.71** in excellent yield along with the recovery of chiral auxiliary **4.76** in optically pure form (Scheme 4.22).

These optically active 3-hydroxy- $\beta$ -lactams were used for synthesis of optically active *epi*-cytoxazone. The specific rotation of (+)-*epi*-cytoxazone was in agreement with the reported value  $[\alpha]_{25}^D +28.3 (c\ 1, \text{MeOH}; \{\text{Lit.}^{21} [\alpha]_{25}^D +28.6 (c\ 1, \text{MeOH})\})$ . The spectral data of (+)-*epi*-cytoxazone (**1b**) matched very well with that of the reported values.<sup>53</sup> The other enantiomer of *epi*-cytoxazone was also synthesized following same protocol using enantiomeric (*3R,4S*)-3-hydroxy azetidin-2-one.

While this work was going on, Turos *et al.*<sup>17b</sup> synthesized cytoxazone starting from azetidin-2-one. They have used (*S*)-methyl-(4-methoxy) benzyl amine as a chiral pool for synthesis of azetidin-2-one, which was separated and used for distereoselective synthesis of cytoxazone and its isomers.

## 4.5: Conclusion

Synthesis of racemic as well as (*4R,5S*) and (*4S,5R*)-*epi*-cytoxazone has been achieved in four synthetic high yielding steps from the corresponding azetidin-2-one. Acid catalyzed intramolecular azetidinone ring opening followed by the formation of oxazolidinone ring using triphosgene, is the key step in this synthesis.

## 4.6: Experimental

### (2*S*,3*R*)Methyl-2-hydroxy-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)propanoate (4.72):

3-Hydroxy-1,4-bis(4-methoxyphenyl)azetidin-2-one (**4.71**) (1 g, 3.33 mmol) was dissolved in methanolic HCl (20%, 10 mL) and the reaction mixture was stirred for 48 h at room temperature. After the reaction was over (TLC), methanol was removed under reduced pressure and saturated sodium bicarbonate solution was added to the residue. The resulting mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic extract was washed with saturated brine solution (10 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get crude product, which was quickly purified by flash column chromatography using acetone/petroleum ether (15:85) as an eluent to furnish **4.72** (0.87, 79%) as a thick oil.

$[\alpha]_D^{25}$  : -4.70 (*c* 1.7, CHCl<sub>3</sub>).

IR (CHCl<sub>3</sub>) : 3500, 3388, 1739 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz) : δ<sub>H</sub> 3.31 (bs, 2H), 3.61 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 4.44 (d, *J* = 3.3 Hz, 1H), 4.72 (d, *J* = 3.3 Hz, 1H), 6.5 (d, *J* = 9.1 Hz, 2H), 6.61 (d, *J* = 9.1 Hz, 2H), 6.77 (d, *J* = 8.7 Hz 2H), 7.21 (d, *J* = 8.7 Hz 2H).

<sup>13</sup>C NMR (CHCl<sub>3</sub>) (125 MHz) : δ<sub>C</sub> 52.8, 55.1, 55.6, 59.8, 74.6, 113.9, 114.7, 115.6, 128.1, 131, 140.1, 152.4, 158.9, 173.3.

MS (*m/z*) : 332 (*M*+1).

Analysis : Calculated: C, 65.23; H, 6.39; N, 4.23.

(C<sub>18</sub>H<sub>21</sub>NO<sub>5</sub>) Observed: C, 65.16; H, 6.21; N, 4.17.

#### Data for enantiomer of 4.72:

$[\alpha]_D^{25}$  : +4.72 (*c* 1.7, CHCl<sub>3</sub>).

Analysis : Calculated: C, 65.23; H, 6.39; N, 4.23.

(C<sub>18</sub>H<sub>21</sub>NO<sub>5</sub>) Observed: C, 65.01; H, 6.19; N, 4.02.

### (4*R*,5*S*)Methyl 3,4-bis(4-methoxyphenyl)-2-oxo-1,3-oxazolidine-5-carboxylate (4.70):

To a cooled (-10 °C to -15 °C) solution of **4.72** (0.6 g, 1.81 mmol), Et<sub>3</sub>N (1.4 ml, 9.06 mmol) in dry THF (10 mL), triphosgene (0.65 g, 2.17 mmol) was added at

once. The reaction mixture was then allowed to warm up to room temperature. After completion of reaction as indicated by TLC (8 h), THF was removed under reduced pressure and residue was dissolved in ethyl acetate (50 mL), washed with saturated solution of NaHCO<sub>3</sub> (10 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography using acetone/petroleum ether (12:88) as an eluent to furnish **4.70** (0.56 g, 86%) as a thick oil.

$[\alpha]_D^{25}$  : -5.0 (*c* 1.7, CHCl<sub>3</sub>).

IR (CHCl<sub>3</sub>) : 1766 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz) : δ<sub>H</sub> 3.73 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 4.76 (d, *J* = 4.6 Hz, 1H), 5.29 (d, *J* = 4.6 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H).

<sup>13</sup>C NMR (CHCl<sub>3</sub>) (125 MHz) : δ<sub>C</sub> 53.1, 55.2, 55.3, 63.7, 77.7, 114.2, 114.7, 123.3, 127.7, 129.2, 129.3, 154.4, 157.1, 160.1, 168.8.

MS (*m/z*) : 358 (*M*+1).

Analysis : Calculated: C, 63.84; H, 5.36; N, 3.92.  
(C<sub>19</sub>H<sub>19</sub>NO<sub>6</sub>) Observed: C, 63.69; H, 5.29; N, 3.78.

#### Data for enantiomer of **3.70**:

$[\alpha]_D^{25}$  : -5.02 (*c* 1.7, CHCl<sub>3</sub>).

Analysis : Calculated: C, 63.84; H, 5.36; N, 3.92.  
(C<sub>19</sub>H<sub>19</sub>NO<sub>6</sub>) Observed: C, 63.63; H, 5.14; N, 3.69.

#### **5-Dihydroxymethyl-3,4-bis-(4-methoxy-phenyl)-oxazolidin-2-one (4.73):**

To a cooled solution of **4.70** (0.27 g 0.76 mmol) and calcium chloride (0.17 g, 1.52 mmol) in absolute ethanol (5 mL) at 0 °C was added NaBH<sub>4</sub> (0.04 g, 1.1 mmol) portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 3 h. After completion of reaction (TLC) water (3 mL) was added carefully and the reaction mixture was further stirred for 1 h. Ethanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with saturated brine solution (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced

pressure gave the crude product, which was purified by column chromatography using acetone/petroleum ether (30:70) to afford alcohol **4.73** (0.17 g, 65%) as a white solid.

<b>MP</b>	: 132-133 °C.
<b>IR (Nujol)</b>	: 3315, 1730 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub> +DMSO-<i>d</i><sub>6</sub>) (400 MHz)</b>	: δ <sub>H</sub> 2.50 (bs, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 4.06 (dd, <i>J</i> = 3.7, 4.3 Hz, 1H), 5.04 (d, <i>J</i> = 3.5 Hz, 1H), 5.33 (d, <i>J</i> = 4.3 Hz), 6.75 (d, <i>J</i> = 9.1, 2H), 6.81 (d, <i>J</i> = 9.1 Hz, 2H), 7.20 (d, <i>J</i> = 8.7 Hz, 2H), 7.27 (d, <i>J</i> = 8.7 Hz, 2H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub> +DMSO-<i>d</i><sub>6</sub>) (100.61 MHz)</b>	: δ <sub>C</sub> 54.7, 54.8, 59.2, 82.2, 88.5, 113.5, 113.9, 122.6, 127.5, 130.0, 131.6, 154.8, 155.9, 158.7.
<b>MS (m/z)</b>	: 346 (M+1).
<b>Analysis (C<sub>18</sub>H<sub>19</sub>NO<sub>6</sub>)</b>	: Calculated: C, 62.60; H, 5.55; N, 4.06. Observed: C, 62.42; H, 5.72; N, 4.21.

**(4*R*,5*S*)Methyl 4-(4-methoxyphenyl)-2-oxo-1,3-oxazolidine-5-carboxylate (4.69):**

A solution of (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> (1.38 g, 2.52 mmol) in water (10 mL) was added drop wise to a solution of methyl 3,4-bis(4-methoxyphenyl)-2-oxo-1,3-oxazolidine-5-carboxylate (**4.70**) (0.3 g, 0.84 mmol) in acetonitrile (12 mL) at 0 °C. The mixture was stirred at this temperature for 45 min. Water (2 mL) was added, and mixture was extracted with ethyl acetate (3 x 20 mL) and washed with saturated solution of NaHCO<sub>3</sub> (2 x 5 mL). The aqueous layer of NaHCO<sub>3</sub> was extracted again with ethyl acetate (1 x 15 mL), and combined organic extracts were washed with NaHSO<sub>3</sub> (40%) (3 x 20 mL) and saturated solution of NaCl (10 mL). It was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to get crude product, which was purified by flash column chromatography using acetone/petroleum ether (15:85) as an eluent to furnish **4.69** (0.15 g, 70%) as a white solid.

<b>MP</b>	: 92-94 °C.
<b>[α]<sub>D</sub><sup>25</sup></b>	: +86.5 ( <i>c</i> 1.5, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 3270, 1760, 1710 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>)</b>	: δ <sub>H</sub> 3.82 (s, 3H), 3.87 (s, 3H), 4.75 (d, <i>J</i> = 5.2 Hz, 1H), 4.93 (d, <i>J</i> = 5.2 Hz, 1H), 6.0 (bs, 1H), 6.94 (d, <i>J</i> = 8.6 Hz, 2H), 7.29 (d,

(200 MHz)  $J = 8.6$  Hz, 2H).  
 $^{13}\text{C}$  NMR :  $\delta_{\text{C}}$  52.9, 55.2, 58.6, 80.3, 114.4, 127.1, 130.8, 157.9, 159.9,  
( $\text{CDCl}_3$ ) 168.8.  
(125 MHz)  
MS (m/z) : 252 (M+1).  
Analysis : Calculated: C, 57.35; H, 5.22; N, 5.58.  
( $\text{C}_{12}\text{H}_{13}\text{NO}_5$ ) Observed: C, 57.28; H, 5.12; N, 5.32.

**Data for enantiomer of 4.69:**

Yield : 68%  
MP : 93-95 °C.  
 $[\alpha]_{\text{D}}^{25}$  : -85.8 ( $c$  1.5,  $\text{CHCl}_3$ ).  
Analysis : Calculated: C, 57.35; H, 5.22; N, 5.58.  
( $\text{C}_{12}\text{H}_{13}\text{NO}_5$ ) Observed: C, 57.23; H, 5.01; N, 5.41.

**(4*R*,5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (4.1b):**

To a cooled solution of **4.69** (0.15 g 0.6 mmol) and calcium chloride (0.14 g, 1.2 mmol) in absolute ethanol (5 mL) at 0 °C was added  $\text{NaBH}_4$  (0.03 g, 0.9 mmol) portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 2 h. After completion of reaction (TLC) water (3 mL) was added carefully and the reaction mixture was further stirred for 1 h. Ethanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with saturated brine solution (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography using acetone/petroleum ether (40:60) to afford alcohol **4.1b** (0.10 g, 82%) as a white solid.

MP : 160-161 °C.  
 $[\alpha]_{\text{D}}^{25}$  : +28.3 ( $c$  1, MeOH); {Lit.<sup>21</sup>  $[\alpha]_{\text{D}}^{25}$  +28.6 ( $c$  1, MeOH)}.  
IR ( $\text{CHCl}_3$ ) : 3244, 1724  $\text{cm}^{-1}$ .  
 $^1\text{H}$  NMR :  $\delta_{\text{H}}$  3.49-3.66 (m, 2H), 3.75 (s, 3H), 4.13 (dd,  $J = 9.9, 3.8$  Hz,  
(DMSO- $d_6$ ) 1H), 4.61 (d,  $J = 6.3$ , 1H), 5.18-5.24 (m, 1H), 6.95 (d,  $J = 8.8$   
(200 MHz) Hz, 2H), 7.25 (d,  $J = 8.8$  Hz, 2H), 8.05 (bs, 1H).  
 $^{13}\text{C}$  NMR :  $\delta_{\text{C}}$  55.2, 56.2, 61.0, 83.2, 114.2, 127.5, 132.9, 158.2, 159.1.  
(DMSO- $d_6$ )  
(200 MHz)

**MS (m/z)** : 224 (M+1).

**Analysis** : Calculated: C, 59.19; H, 5.87; N, 6.27.

(C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>) Observed: C, 59.01; H, 5.59; N, 6.01.

**(4*S*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (enantiomer of 4.1b):**

**Yield** : 81%

**MP** : 158-160 °C.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> : -28.1 (*c* 1, MeOH).

**Analysis** : Calculated: C, 59.19; H, 5.87; N, 6.27.

(C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>) Observed: C, 59.04; H, 5.62; N, 5.98.

**(5*S*,6*R*)-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (4.75):**

To a stirred suspension of ephedrine hydrochloride **4.74** (2 g, 9.9 mmol) and DMAP (60 mg, 0.49 mmol) in dichloromethane (200 mL) at 0 °C was added triethyl amine (5.5 mL, 39.6 mmol). The mixture was stirred for 10 minutes and a solution of oxalyl chloride (1.3 mL, 14.9 mmol) in dichloromethane (100 mL) was added dropwise over a period of 4 h at 0 °C. The mixture was further stirred at 0 °C for 1 h and ice was added. The mixture was warmed to ambient temperature and the biphasic mixture was separated. The dichloromethane layer was washed with water (70 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate/pet ether (75:25) as an eluent to furnish **4.75** (1.42 g, 65%) as a white solid.

**MP** : 182-183 °C.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> : -184.3 (*c* 0.8, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 1771, 1693 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** :  $\delta$ <sub>H</sub> 1.12 (d, *J* = 6.8 Hz, 3H), 3.19 (s, 3H), 3.66-3.77 (dq, *J* = 2.9, 6.8 Hz, 1H), 5.90 (d, *J* = 2.9 Hz, 1H), 7.28-7.50 (m, 5H).

(CDCl<sub>3</sub>)  
(200 MHz)

**<sup>13</sup>C NMR** :  $\delta$ <sub>C</sub> 11.8, 33.2, 58.1, 79.3, 125.3, 128.0, 128.6, 133.8, 153.0, 156.4.

(CDCl<sub>3</sub>)  
(50.32 MHz)

**MS (m/z)** : 220 (M+1).

**Analysis** : Calculated: C, 65.74; H, 5.97; N, 6.38.

(C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>) Observed: C, 65.45; H, 6.09; N, 6.36.



**(2*S*,5*S*,6*R*)-2-Hydroxy-2,4,5-trimethyl-6-phenyl-morpholin-3-one (4.76):**

To a suspension of dione **4.75** (0.219 g, 1 mmol) in anhydrous ether at  $-20\text{ }^{\circ}\text{C}$  was added the methyl magnesium iodide (5 mL, 1M solution in ether, 5 mmol) and the mixture was stirred at  $-20\text{ }^{\circ}\text{C}$  for 1 h. Saturated aqueous  $\text{NH}_4\text{Cl}$  was added and the reaction mixture was warmed up to ambient temperature. The precipitated solid was dissolved in water and the solution was extracted in ethyl acetate (3 x 20 mL) and washed with brine solution (10 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum to give crude methyl hemiketals **4.76** (de = 85%,  $^1\text{H}$  NMR). The crude compound upon purification by flash column chromatography using ethyl acetate/petroleum ether (60:40) gave **4.76** (0.22 g, 90%, de > 95%).

<b>MP</b>	: 79-80 $^{\circ}\text{C}$ .
<b><math>[\alpha]_{\text{D}}^{25}</math></b>	: $-107.4$ (c 1.1, $\text{CHCl}_3$ ).
<b>IR (<math>\text{CHCl}_3</math>)</b>	: 3340, 1635 $\text{cm}^{-1}$ .
<b><math>^1\text{H}</math> NMR</b> ( $\text{CDCl}_3$ ) (200 MHz)	: $\delta_{\text{H}}$ 0.93 (d, $J = 6.5$ Hz, 3H), 1.71 (s, 3H), 2.99 (s, 3H), 3.43 (dq, $J = 2.9, 6.5$ Hz, 1H), 4.58 (bs, 1H), 5.47 (d, $J = 2.9$ Hz, 1H), 7.23-7.36 (m, 5H).
<b><math>^{13}\text{C}</math> NMR</b> ( $\text{CDCl}_3$ ) (50.32 MHz)	: $\delta_{\text{C}}$ 11.9, 26.3, 33.5, 59.2, 71.2, 95.9, 125.6, 127.4, 128.1, 137.4, 168.7.
<b>MS (m/z)</b>	: 235 (M+1).
<b>Analysis</b> ( $\text{C}_{13}\text{H}_{17}\text{NO}_3$ )	: Calculated: C, 66.36; H, 7.28; N, 5.05. Observed: C, 66.38; H, 7.43, N, 5.97.

**(2*S*,5*S*,6*R*)Ethyl[(2,4,6-trimethyl-3-oxo-6-phenylmorpholin-2yl)oxy]acetate (4.77):**

To a suspension of sodium hydride (0.11 g, 4.5 mmol) in DMF (2 mL) and THF (2 mL) at  $0\text{ }^{\circ}\text{C}$  was added methyl hemiketal solution **4.76** (0.71 g, 3 mmol) dropwise in DMF (2 mL) and THF (2 mL) and the resulting solution was stirred at  $0\text{ }^{\circ}\text{C}$  for 10 min. Ethyl bromoacetate (0.33 mL, 3 mmol) was then added dropwise and the resulting solution was heated at  $70\text{ }^{\circ}\text{C}$  for 16 h. Ice was added to the reaction mixture. Ethyl acetate (15 mL) and water (15 mL) were added and organic layer was separated. Organic layer was washed with water (3 x 15 mL), brine (3 x 15 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue upon

purification by column chromatography ethyl acetate/petroleum ether (50:50) furnished **4.77** (0.75 g, 78%) as a white solid.

<b>MP</b>	: 87-89 °C.
$[\alpha]_D^{25}$	: -80.7 ( <i>c</i> 1.1, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 1753, 1659 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)</b>	: δ <sub>H</sub> 0.96 (d, <i>J</i> = 6.3 Hz, 3H), 1.11 (t, <i>J</i> = 7.3 Hz, 3H), 1.67 (s, 3H), 3.04 (s, 3H), 3.43-3.53 (dq, <i>J</i> = 2.9, 6.3 Hz, 1H), 3.90-4.04 (q, <i>J</i> = 7.3 Hz, 2H), 4.18 (s, 2H), 5.62 (d, <i>J</i> = 2.9 Hz, 1H), 7.20-7.47 (m, 5H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)</b>	: δ <sub>C</sub> 12.2, 13.9, 21.4, 33.6, 59.0, 59.8, 60.7, 71.2, 99.3, 125.5, 127.5, 128.2, 137.0, 165.8, 169.8.
<b>MS (m/z)</b>	: 322 (M+1).
<b>Analysis (C<sub>17</sub>H<sub>23</sub>NO<sub>5</sub>)</b>	: Calculated: C, 63.53; H, 7.21; N, 4.36. Observed: C, 63.80; H, 7.50; N, 4.69.

**(2*S*,5*S*,6*R*)-[(2,4,6-trimethyl-3-oxo-6-phenylmorpholin-2yl)oxy]acetic acid (4.78):**

To the solution of **4.77** (0.96 g, 3 mmol) in THF (9 mL) was added aqueous NaOH (1M, 9 mL) and stirred at ambient temperature for 5-6 h. THF was removed under reduced pressure. Aqueous layer was acidified with conc. HCl dropwise and extracted with ethyl acetate (3 x 15 mL). The combined organic layer were washed with brine solution (2 x 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to furnish **4.78** (0.80 g, 91%) as a white solid.

<b>MP</b>	: 98-100 °C.
$[\alpha]_D^{25}$	: -64.9 ( <i>c</i> 0.9, CHCl <sub>3</sub> ).
<b>IR (CHCl<sub>3</sub>)</b>	: 3418, 1738, 1651 cm <sup>-1</sup> .
<b><sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)</b>	: δ <sub>H</sub> 0.98 (d, <i>J</i> = 6.3 Hz, 3H), 1.68 (s, 3H), 3.05 (s, 3H), 3.44-3.60 (dq, <i>J</i> = 2.9, 6.4 Hz, 1H), 4.12 (d, <i>J</i> = 16.6 Hz, 1H), 4.30 (d, <i>J</i> = 16.6 Hz, 1H), 5.46 (d, <i>J</i> = 2.9 Hz, 1H), 6.40-6.70 (bs, 1H), 7.10-7.50 (m, 5H).
<b><sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)</b>	: δ <sub>C</sub> 11.7, 20.9, 33.4, 58.6, 58.8, 70.7, 98.7, 125.0, 127.2, 127.9, 136.3, 166.1, 172.1.
<b>MS (m/z)</b>	: 294 (M+1).

**Analysis** : Calculated: C, 61.42; H, 6.53; N, 4.78.

(C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>) Observed: C, 61.70; H, 6.72; N, 4.99.

**Procedure for preparation of 4.80 & 4.81:**

To the solution of carboxylic acid **4.78** (0.32 g, 0.76 mmol) in dry dichloromethane (6 mL) was added triethylamine (0.91 mL, 6.45 mmol) and imine **4.79** (0.25 g, 1 mmol) at -5 °C. To this was added triphosgene (0.23 g, 0.76 mmol) solution in dichloromethane (6 mL) dropwise over a period of 15 minutes. The reaction mixture was then allowed to warm-up to ambient temperature at which it was stirred for 12 h. The reaction mixture was then diluted with dichloromethane and washed successively with water, saturated NaHCO<sub>3</sub>, brine solution, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford β-lactams (mixture of diastereomers) which on purification by flash column chromatography gave **4.80** (0.21 g, 42%) as a gum and **4.81** (0.12 g, 23%) as a white solid. Both the diastereomers could be easily separated by flash column chromatography.

**(3R,4S,2'S,5'S,6'R)-1,4-Di-(4-methoxyphenyl)-3-[(2',4',5'-trimethyl-3'-oxo-6'-phenylmorpholin-2'-yl)oxy]azetid-2-one (4.80):**

[α]<sub>D</sub><sup>25</sup> : -78.5 (c 1.3, CHCl<sub>3</sub>).

**IR** (CHCl<sub>3</sub>) : 1747, 1649 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** : δ<sub>H</sub> 0.84 (d, *J* = 6.4 Hz, 3H), 1.72 (s, 3H), 2.91 (s, 3H), 3.16-3.32 (dq, *J* = 2.9, 6.4 Hz, 1H), 3.71 (s, 3H), 3.80 (s, 3H), 4.63 (200 MHz) (d, *J* = 2.9 Hz, 1H), 4.95 (d, *J* = 5.3 Hz, 1H), 5.33 (d, *J* = 5.3 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.02-7.60 (m, 9H).

**<sup>13</sup>C NMR** : δ<sub>C</sub> 12.2, 23.4, 33.5, 55.3, 55.4, 59.0, 62.0, 71.0, 75.9, 100.0, (CDCl<sub>3</sub>) 113.9, 114.4, 118.8, 125.6, 125.8, 127.7, 128.4, 129.8, 131.0, (50.32 MHz) 137.2, 156.3, 159.9, 164.5, 165.3.

**MS** (*m/z*) : 517 (M+1).

**Analysis** : Calculated: C, 69.75; H, 6.24; N, 5.42.

(C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>) Observed: C, 69.98; H, 6.49; N, 5.71.

**(3S,4R,2'S,5'S,6'R)-1,4-Di-(4-methoxyphenyl)-3-[(2',4',5'-trimethyl-3'-oxo-6'-phenylmorpholin-2'-yl)oxy]azetid-2-one (4.81):**

**MP** : 207-208 °C.

[α]<sub>D</sub><sup>25</sup> : -170.9 (c 2.0, CHCl<sub>3</sub>).

**IR (CHCl<sub>3</sub>)** : 1747, 1649 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** : δ<sub>H</sub> 0.80 (d, *J* = 6.4 Hz, 3H), 1.49 (s, 3H), 2.90 (s, 3H), 2.96-3.11 (dq, *J* = 2.9, 6.4 Hz, 1H), 3.72 (s, 3H), 3.84 (s, 3H), 4.57 (d, *J* = 2.9 Hz, 1H), 5.12 (d, *J* = 4.9 Hz, 1H), 5.55 (d, *J* = 4.9 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.06-7.45 (m, 9H).  
**<sup>13</sup>C NMR (CDCl<sub>3</sub>) (50.32 MHz)** : δ<sub>C</sub> 12.1, 22.5, 33.4, 55.2, 55.3, 59.0, 62.6, 70.7, 77.6, 98.6, 113.6, 114.2, 118.7, 125.4, 126.1, 127.5, 128.2, 129.9, 130.7, 137.0, 156.1, 159.6, 163.9, 165.5.  
**MS (m/z)** : 517 (M+1).  
**Analysis (C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>)** : Calculated: C, 69.75; H, 6.24; N, 5.42. Observed: C, 69.96; H, 6.48; N, 5.70.

**(3*R*,4*S*)-1,4-Di-(4-methoxyphenyl)-3-hydroxyazetidin-2-one (4.71):**

To a stirred solution of **4.80** (1 g, 2 mmol) in a mixture of THF (15 mL) and water (4 mL) was added PTSA (3.7 g, 20 mmol) and refluxed for 12 h. THF was then removed under reduced pressure and reaction mixture was then diluted with water (5 mL). Solid NaHCO<sub>3</sub> was added to the reaction mixture till basic pH and extracted with dichloromethane (3 x 10 mL). The combined organic layer were washed with brine (2 x 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and residue on purification by column chromatography using ethyl acetate/petroleum ether (50:50) gave **4.71** (0.51 g, 88 %) as a white solid and chiral auxiliary **4.76** (0.39 g, 85 %).

**MP** : 132-133 °C.  
**[α]<sub>D</sub><sup>25</sup>** : +179.1 (*c* 2.2, CHCl<sub>3</sub>), {Lit<sup>19c</sup> [α]<sub>25</sub><sup>D</sup> = +181.9 (*c* 2.2, CHCl<sub>3</sub>)}.  
**IR (CHCl<sub>3</sub>)** : 3310, 1728 cm<sup>-1</sup>.  
**<sup>1</sup>H NMR (CDCl<sub>3</sub>) (200 MHz)** : δ<sub>H</sub> 3.04 (bs, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 5.15 (d, *J* = 5.3 Hz, 1H), 5.21 (d, *J* = 5.3 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.10-7.40 (m, 4H).  
**<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) (75.78 MHz)** : δ<sub>C</sub> 55.0, 55.1, 61.7, 76.7, 113.6, 114.3, 118.2, 126.5, 129.3, 130.7, 155.5, 159.0, 166.4.  
**MS (m/z)** : 300 (M+1).  
**Analysis** : Calculated: C, 68.22; H, 5.73; N, 4.68.

(C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>)            Observed: C, 68.32; H, 5.80; N, 4.61.

**Data for enantiomer of 4.71:**

**Yield**                    : 89%

**MP**                        : 130-131 °C.

**[α]<sup>25</sup><sub>D</sub>**                    : -180.1 (*c* 2.2, CHCl<sub>3</sub>), {Lit<sup>19c</sup> [α]<sup>D</sup><sub>25</sub> = -181.9 (*c* 2.2, CHCl<sub>3</sub>)}.

## 4.7: References

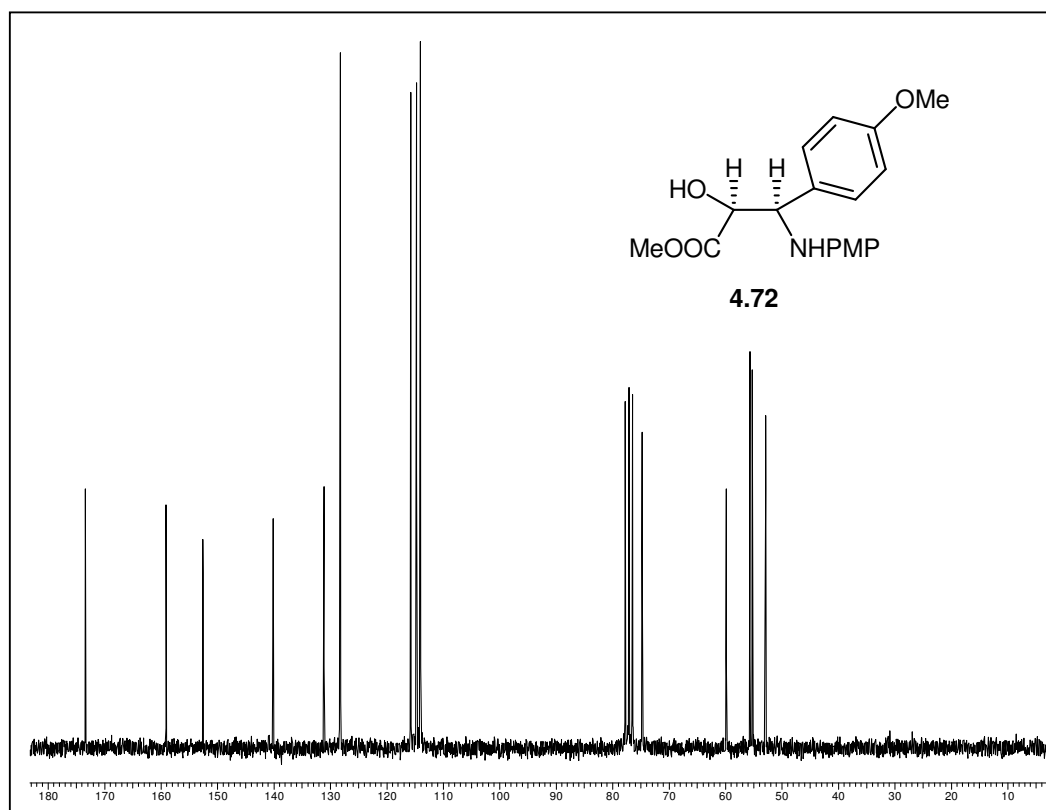
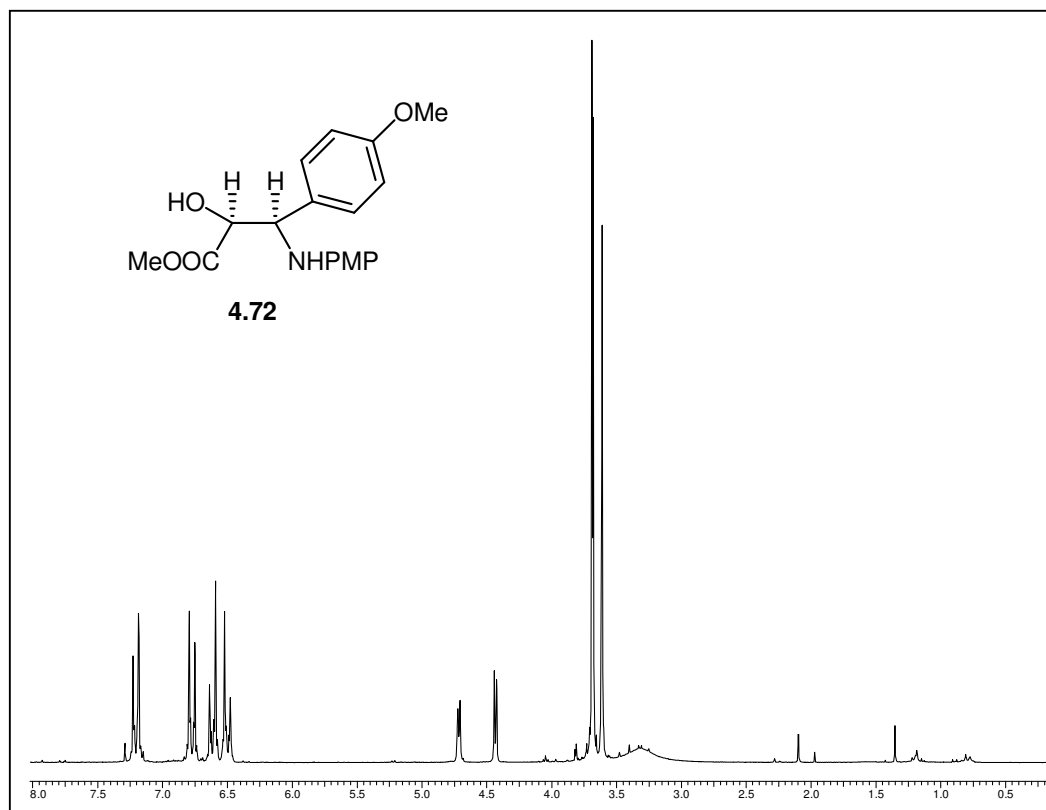
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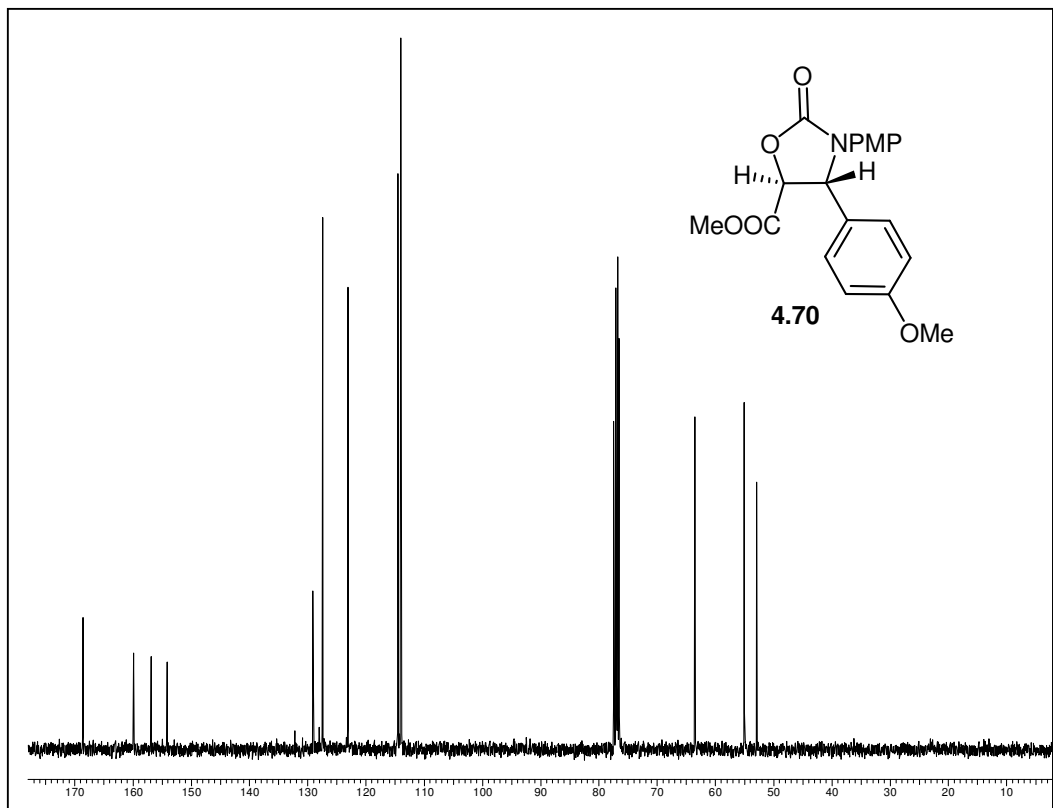
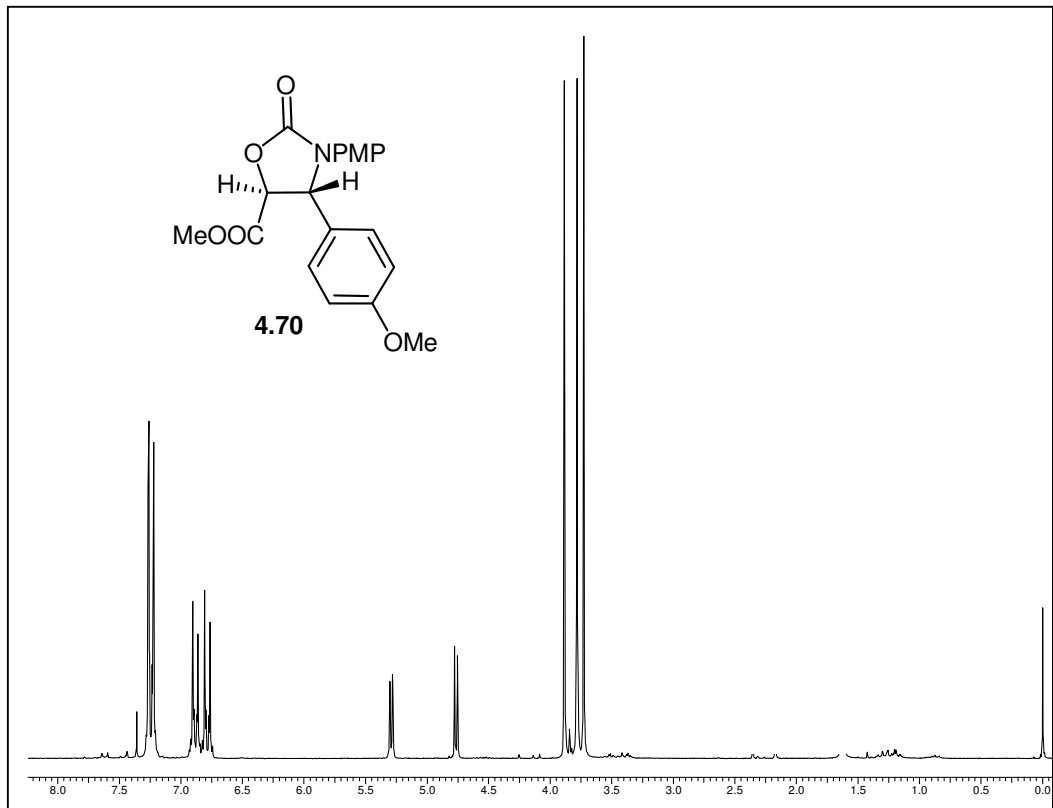
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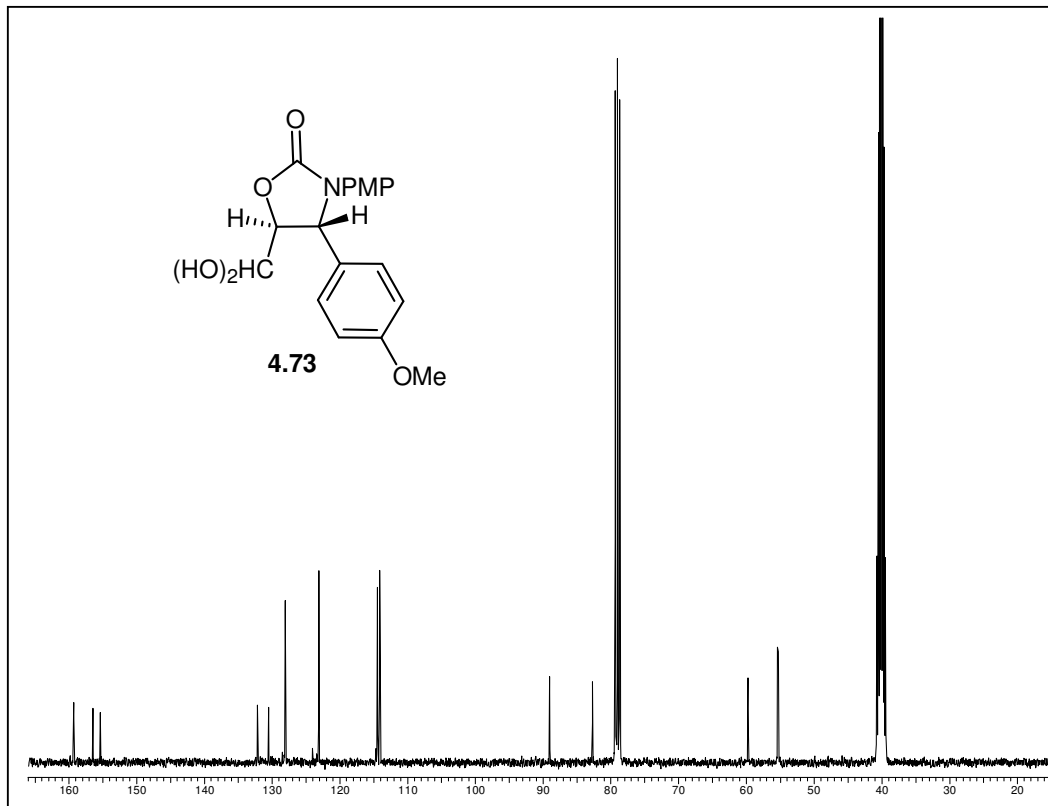
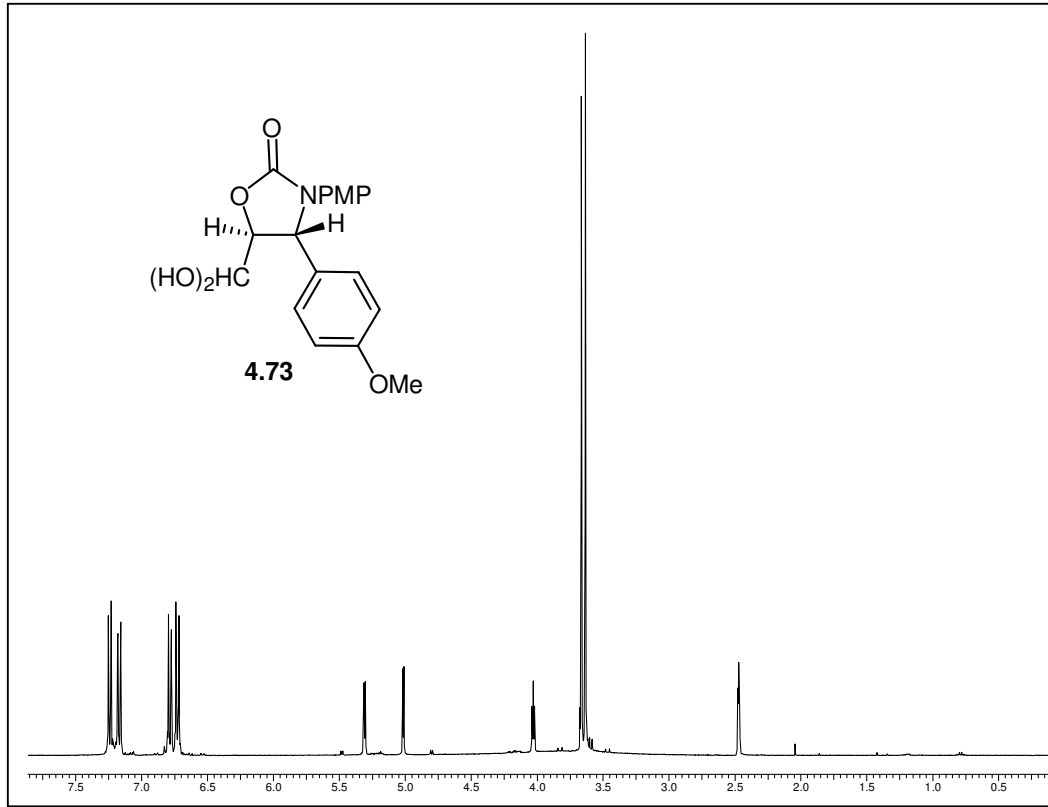
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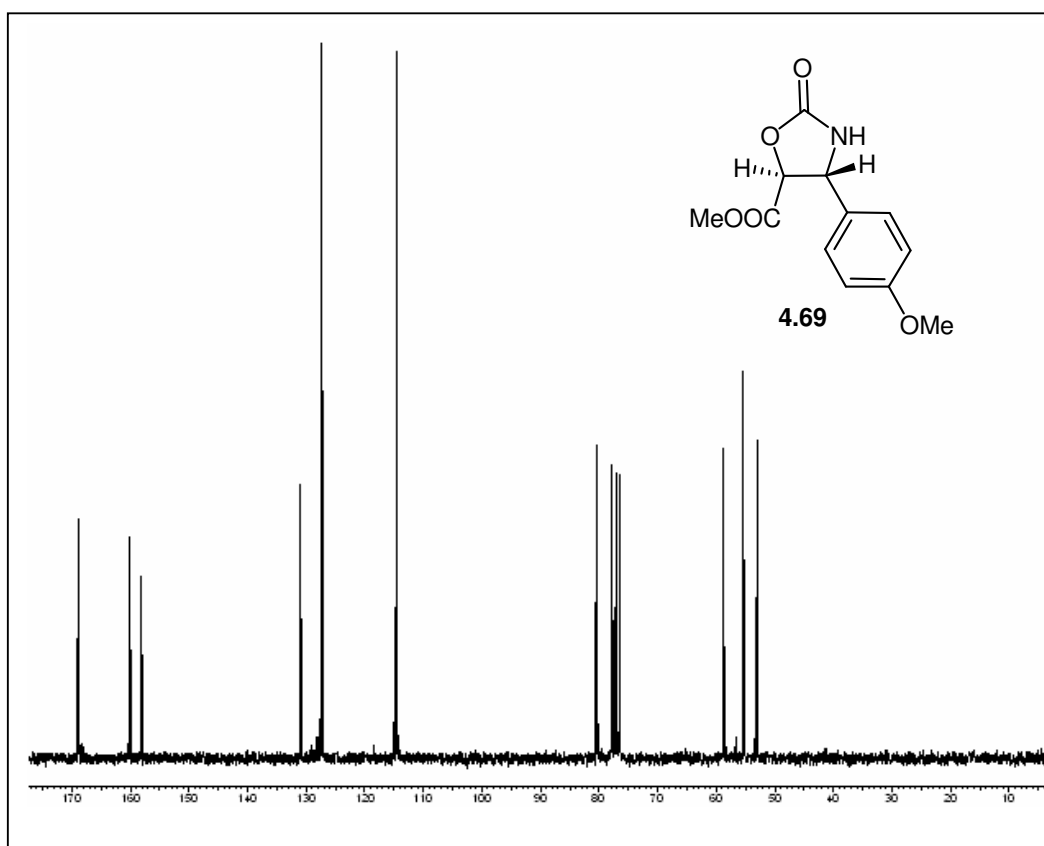
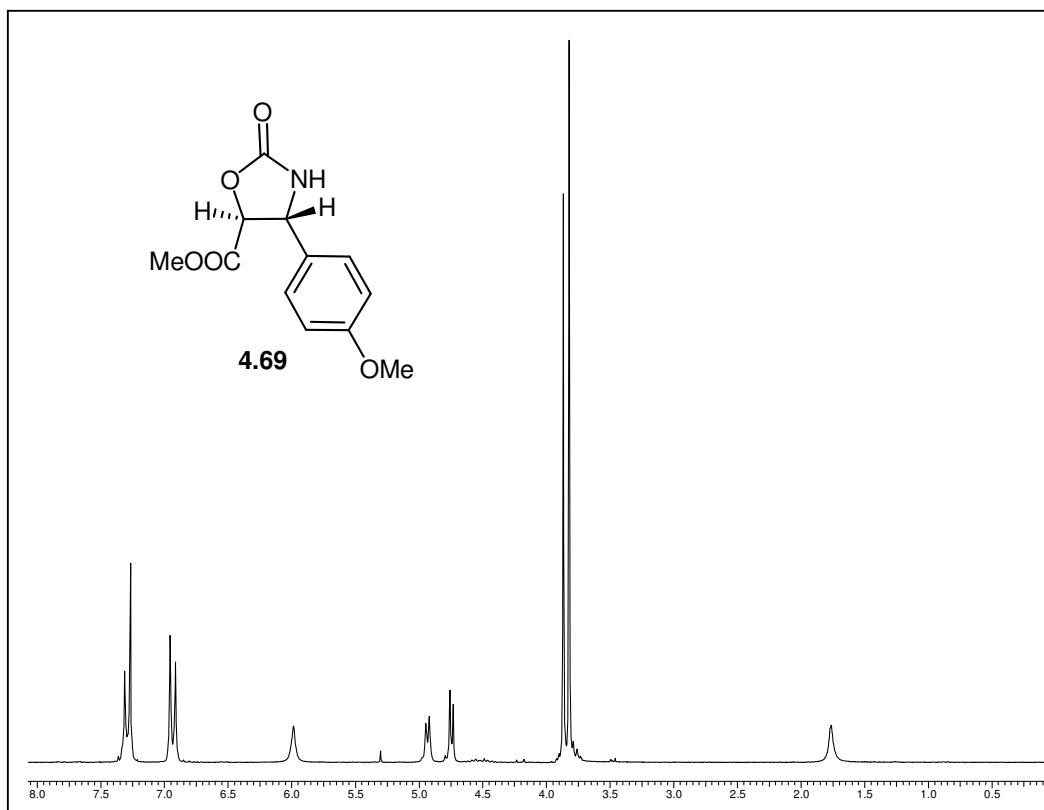
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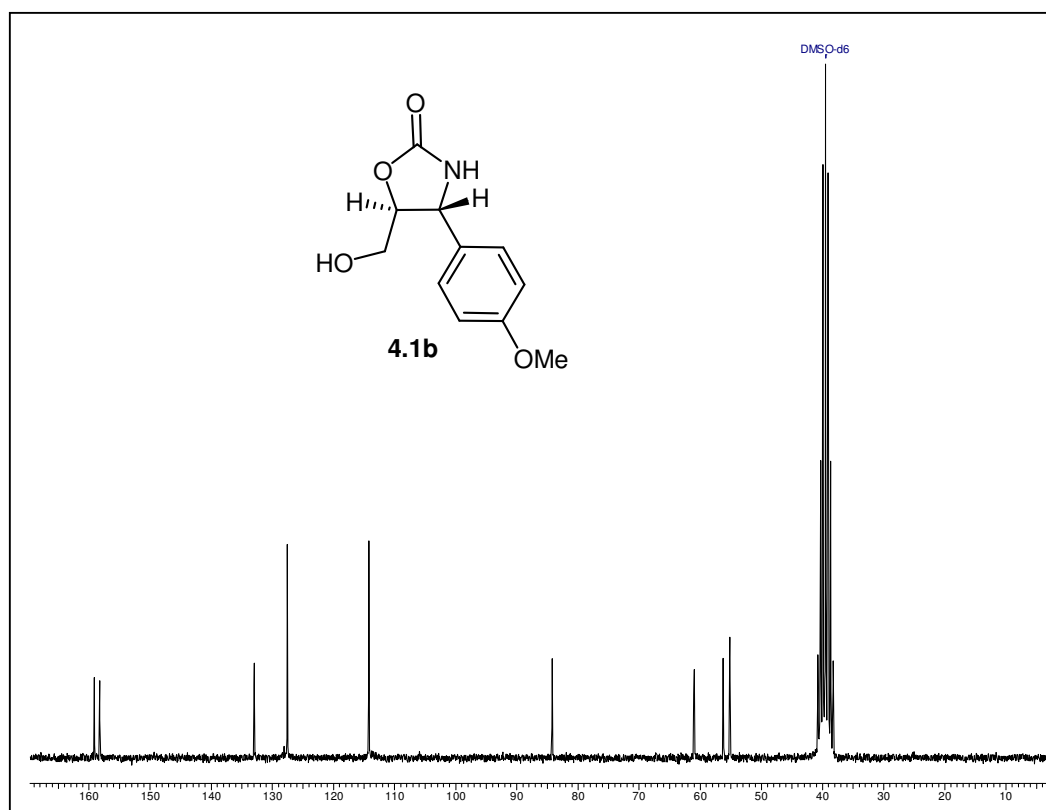
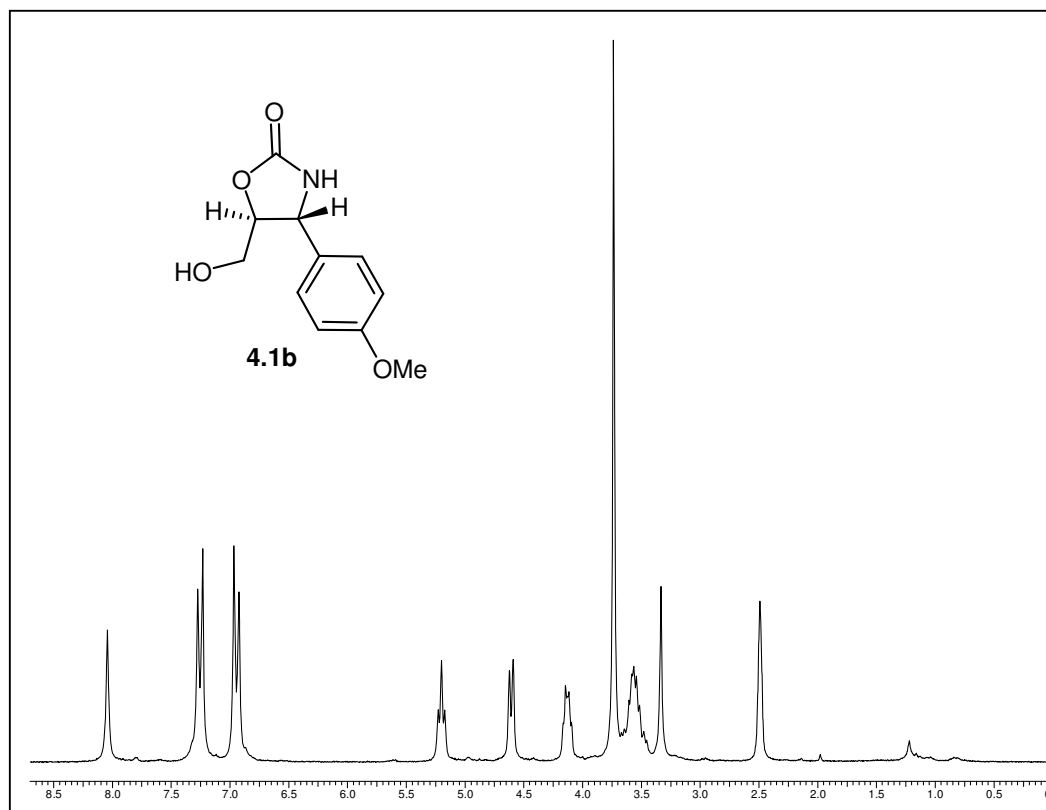


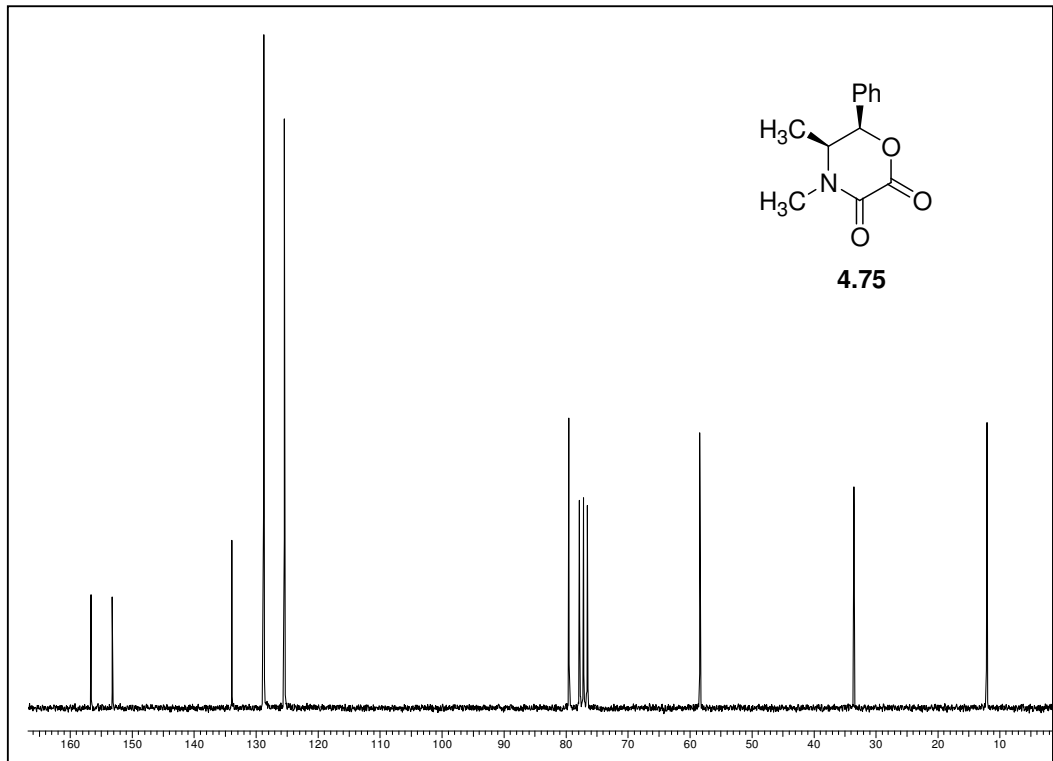
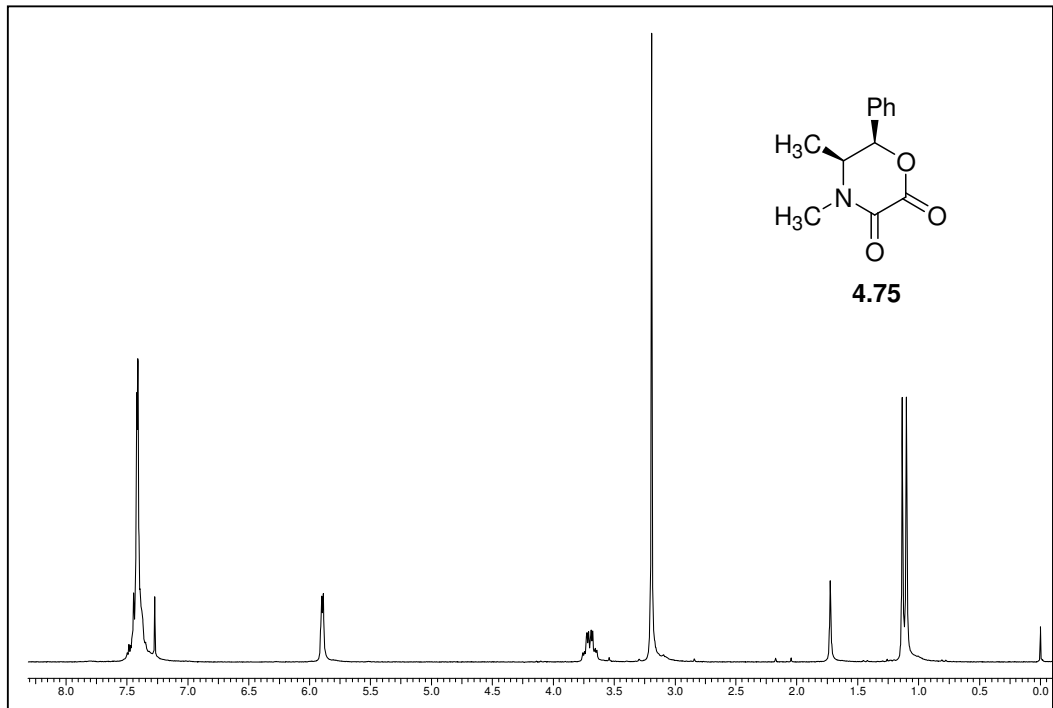


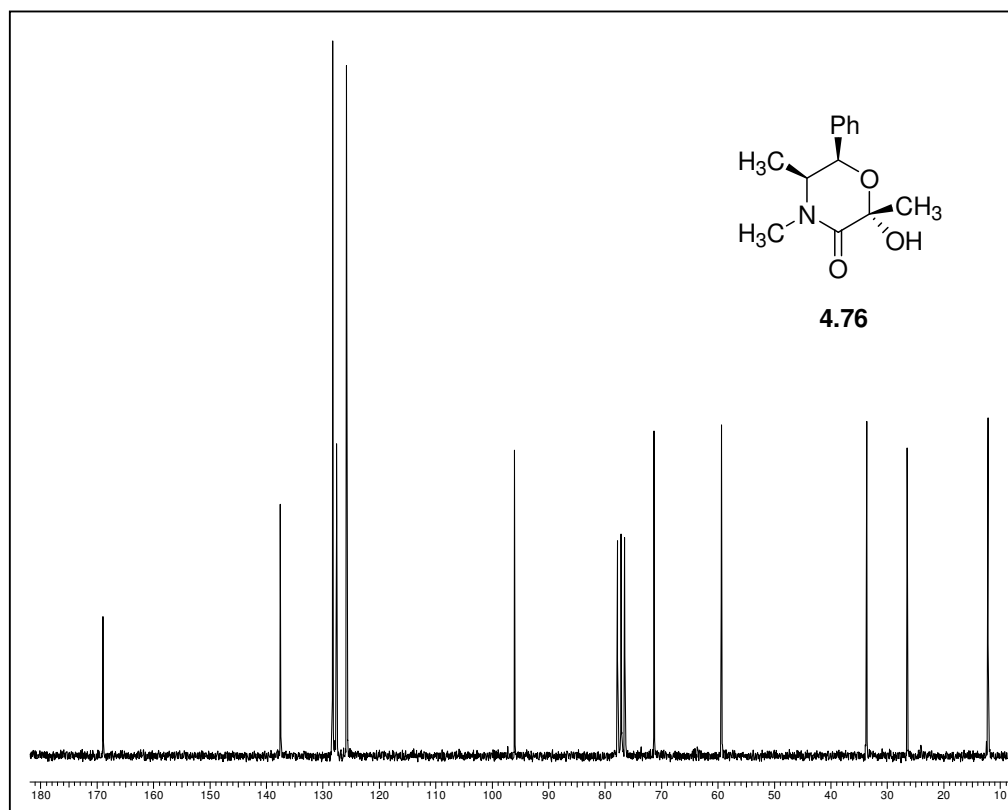
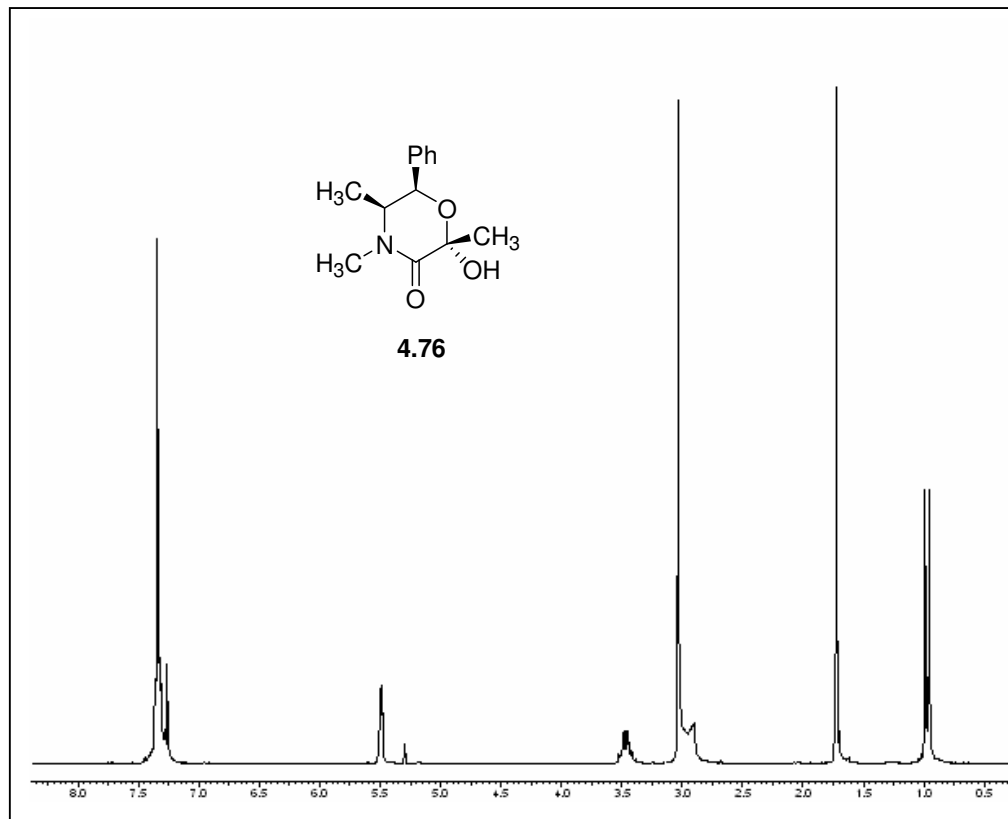


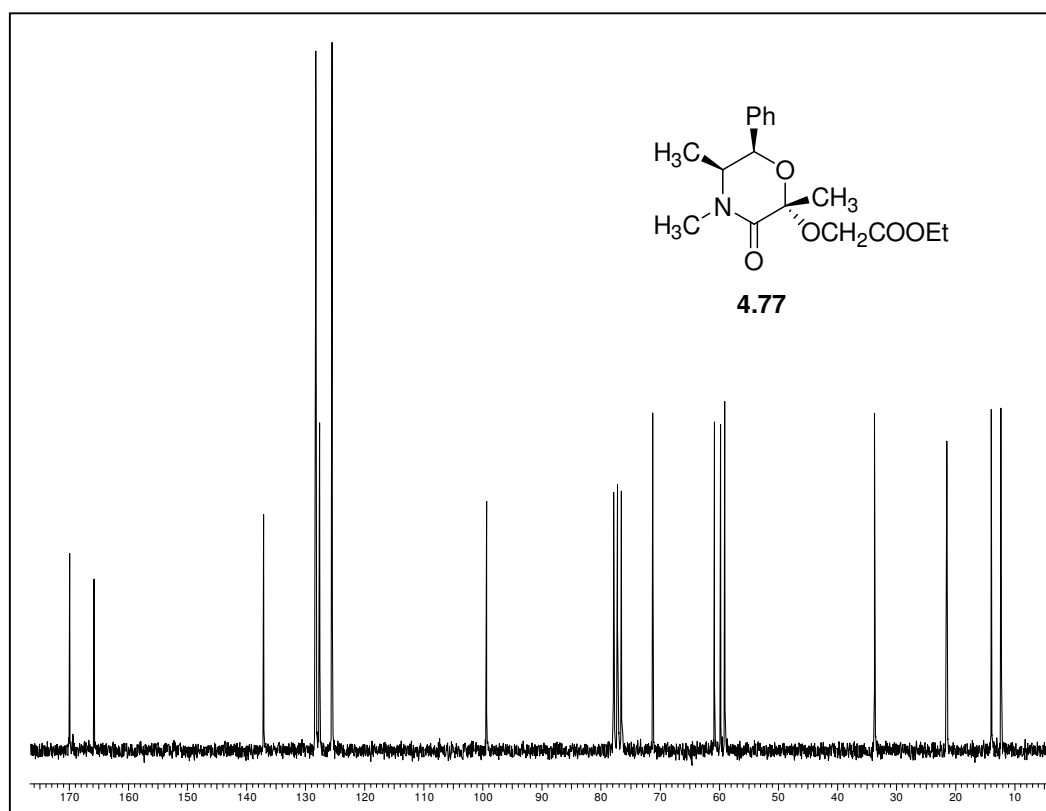
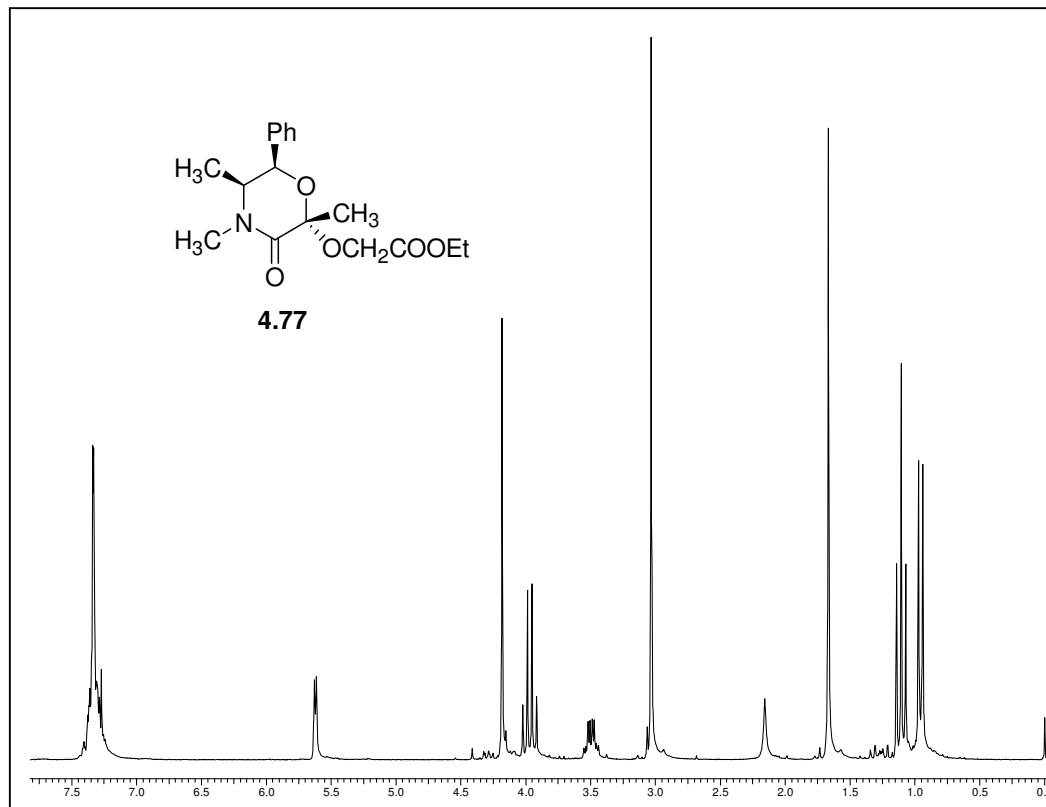




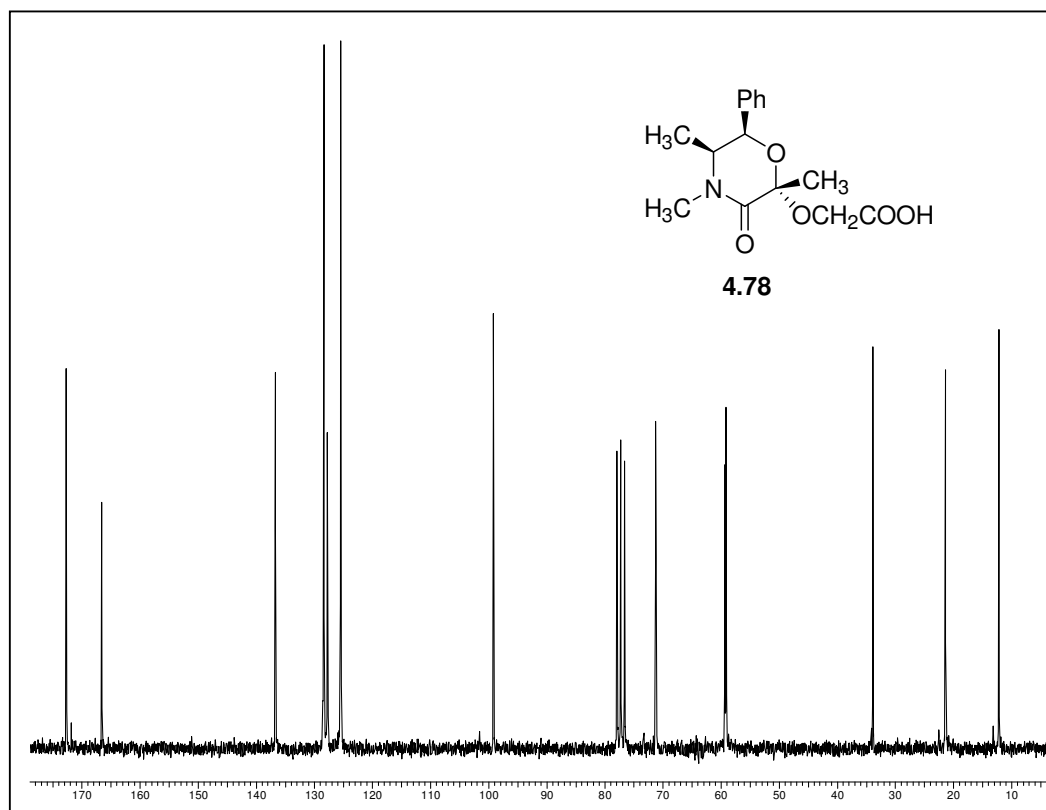
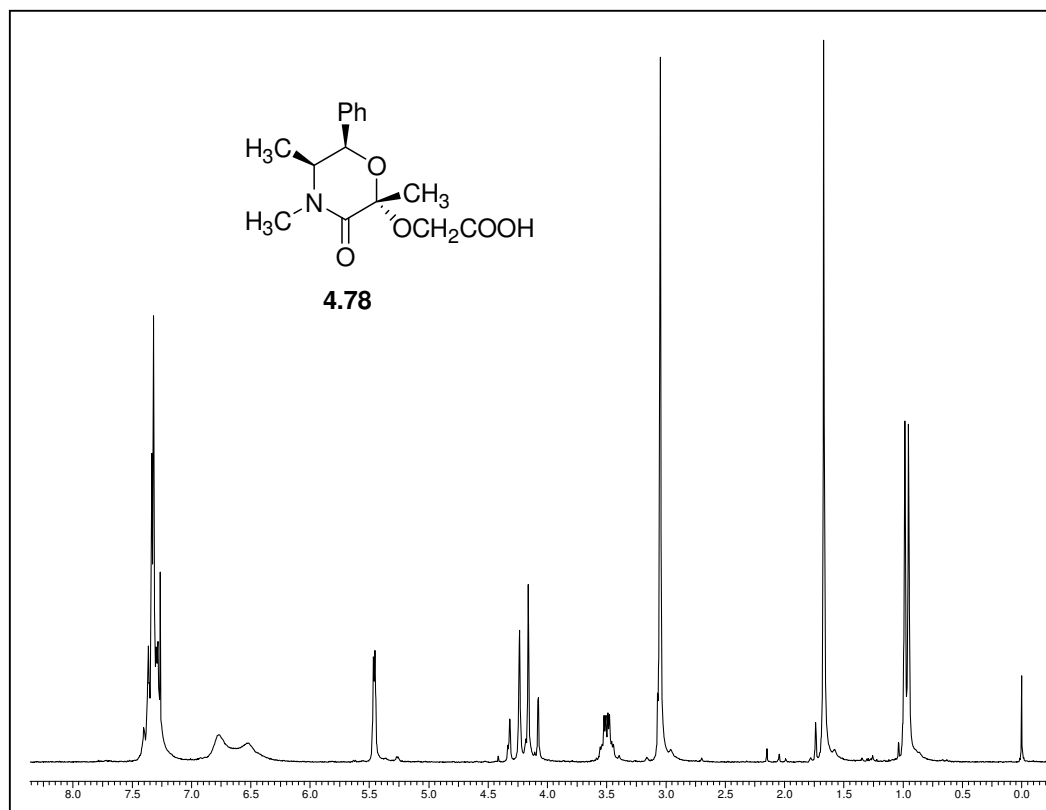


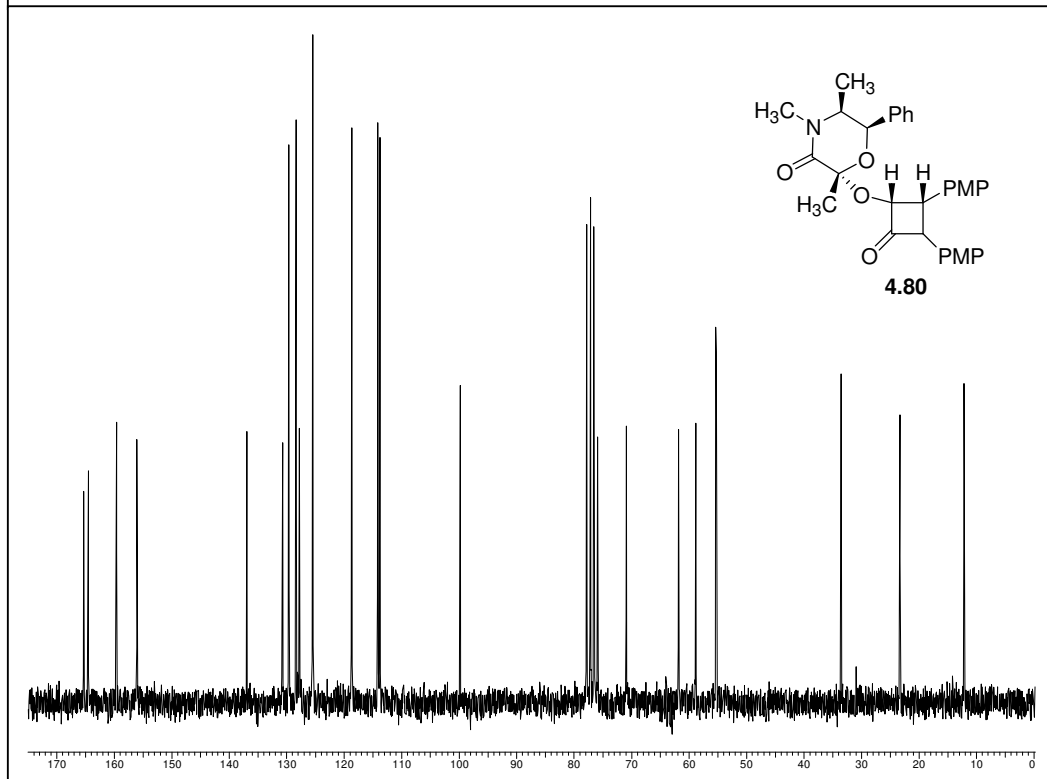
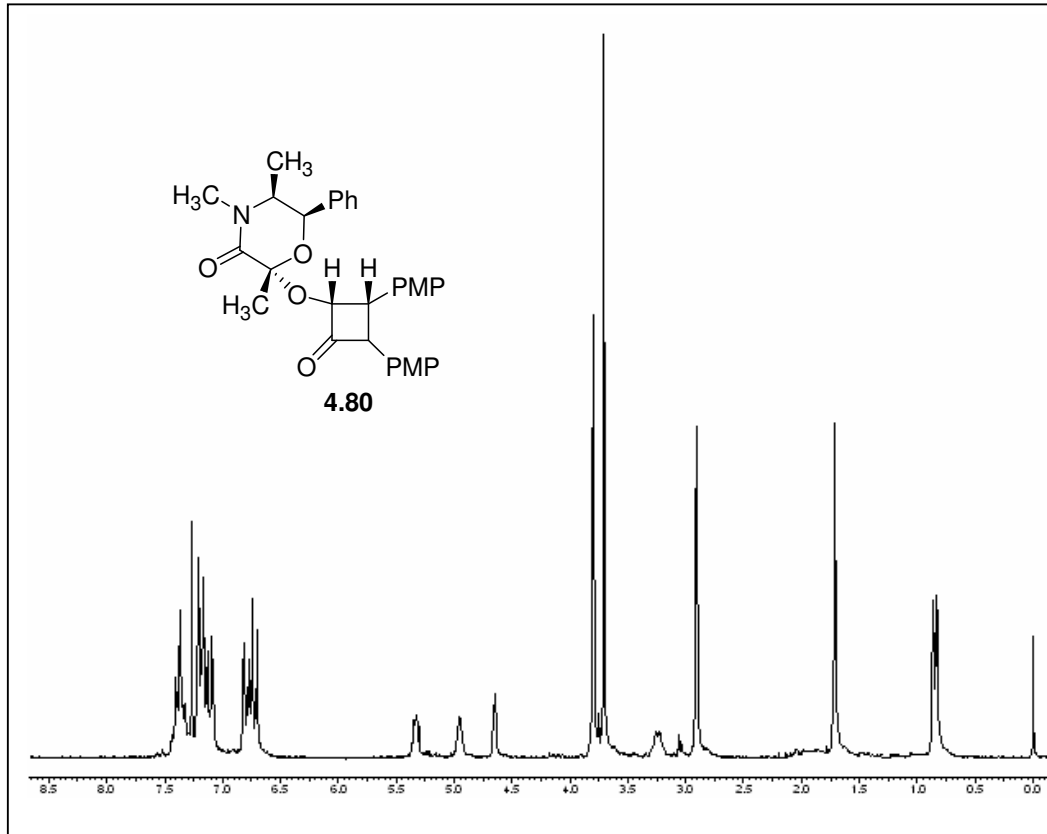


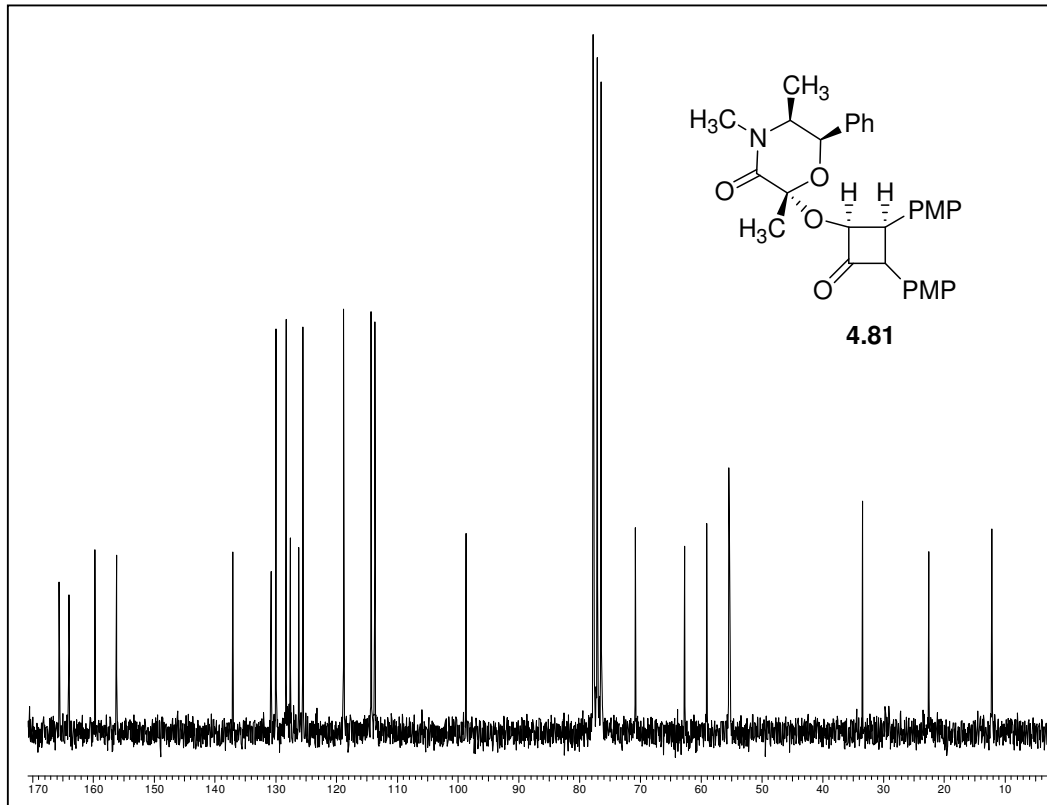
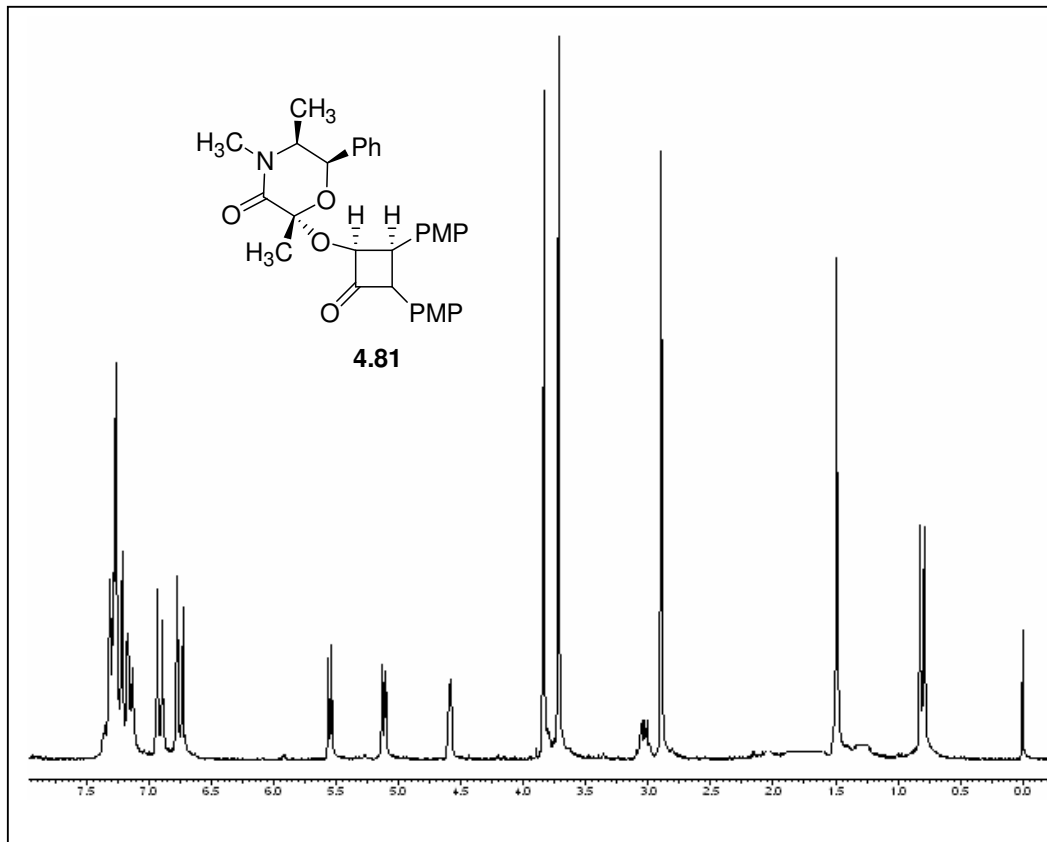


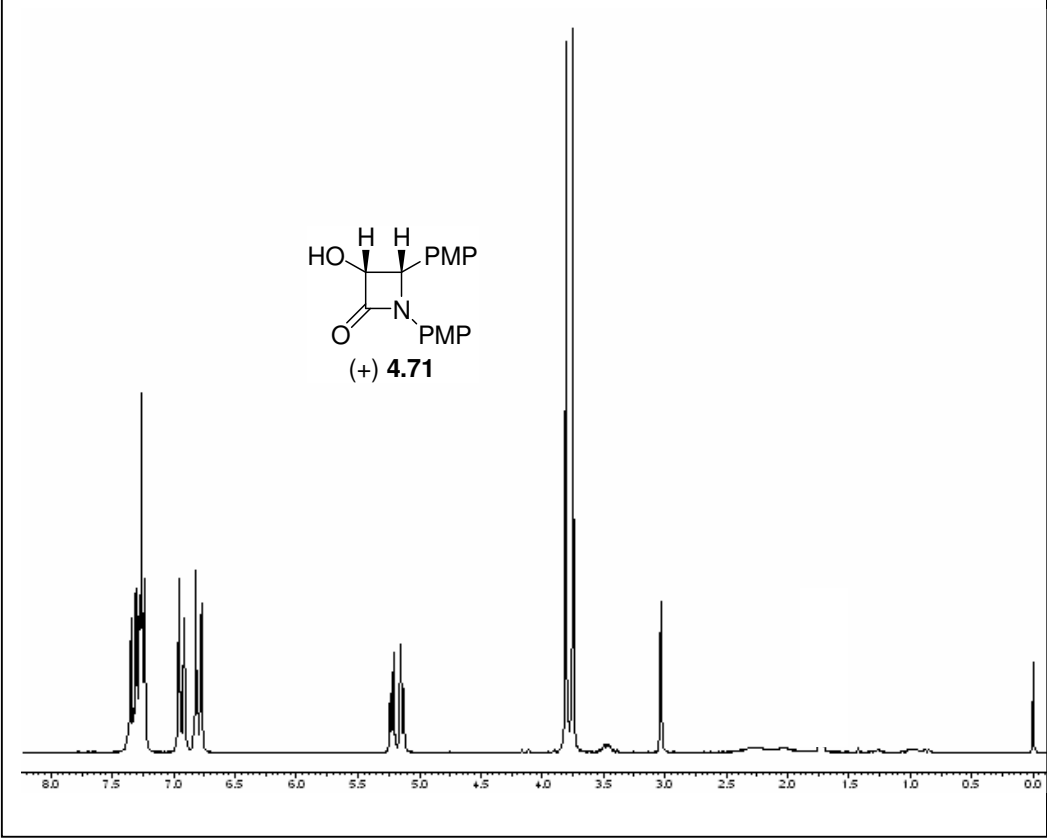












## List of publications

1. An Efficient Synthesis of 2,3-Aziridino- $\gamma$ -lactones from Azetidin-2-ones  
**Ajaykumar S. Kale**, Deshmukh A. R. A. S. *Synlett* **2005**, *15*, 2370-2372.
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**Ajaykumar S. Kale**, P. S. Sakle, V. K. Gumaste, A. R. A. S. Deshmukh *Synthesis*, **2007**, *17*, 2631-2636.
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5. A general route to synthesis of 2,3-Aziridino- $\gamma$ -lactones from Azetidin-2-ones  
**Ajaykumar S. Kale**, Deshmukh A. R. A. S. (manuscript under preparation).

## **Erratum**

