STUDIES ON THE SYNTHESIS OF AZETIDIN-2-ONES AND THEIR APPLICATION IN THE SYNTHESIS OF BIOLOGICALLY IMPORTANT COMPOUNDS

BY

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DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

RESEARCH GUIDE

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STUDIES ON THE SYNTHESIS OF AZETIDIN-2-ONES AND THEIR APPLICATION IN THE SYNTHESIS OF BIOLOGICALLY IMPORTANT COMPOUNDS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

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BY

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PUNE 411 008, INDIA

Dedicated to my Family

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Studies on the Synthesis of Azetidin-2-ones and their Application in the Synthesis of Biologically Important Compounds**" which is being submitted to the University of Pune for the award of **Doctor of Philosophy in Chemistry** by **Mr. Pinak M. Chincholkar** 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 on the Synthesis of Azetidin-2-ones and their Application in the Synthesis of Biologically Important Compounds**" 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.

Date:
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Pinak M. Chincholkar
Research Student

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Finally, I thank the almighty for carrying me safely through everything.

(Pinak M. Chincholkar)

Contents

Spectra

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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 (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 (δ, 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. $CDCl_3$ was used as the solvent unless otherwise mentioned.

4. ^{13}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_{254} (Merck) and glass plates coated with silica gel F_{254}.

10. Silica Gel used for column chromatography was 60-120 mesh, 100-200 mesh or 230-400 mesh size.

11. ^{1}H NMR and ^{13}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}C NMR spectra and then the assignment of the peaks in ^{13}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 P_2O_5 and stored over 4Å 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 [$(CH_3)_2C(CN)N=NC(CH_3)_2CN$]
Ar	Aryl
Bn	Benzyl
Boc	*t*-Butoxy carbonyl
CAN	Ceric ammonium nitrate
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Disiobutylaluminium hydride
DMAP	*N*,*N*'-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	Dichloroethane or ethylene dichloride
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
h	Hour(s)
Hz	Hertz
LAH	Lithium aluminium hydride
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	*p*-Methoxyphenyl
PTSA or TSOH	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
TBDMS	*t*-Butyldimethylsilyl
TBDMSCl	*t*-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Abstract of the thesis

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

Name of candidate: **Pinak Mohan Chincholkar**

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

Synopsis of thesis entitled: **Studies on the synthesis of azetidin-2-ones and their application in the synthesis of biologically important compounds.**

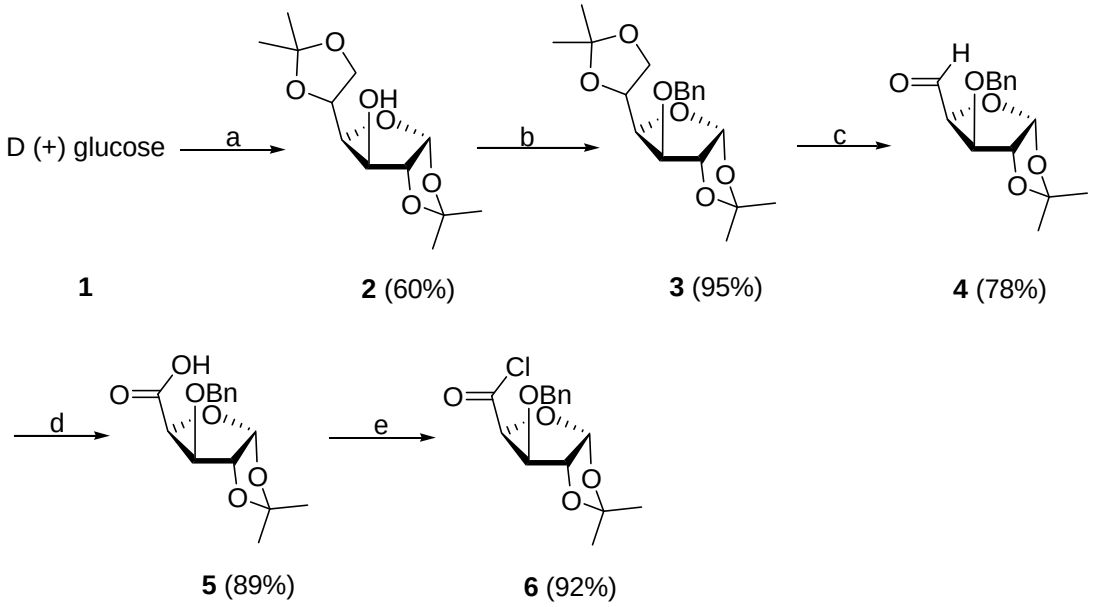
Chapter 1

Stereoselective synthesis of spiro azetidin-2-ones using D-(+)-glucose derived chiral pool

β-Lactams being a structural motif in most widely used antibiotics, have occupied a pivotal position in medicinal chemistry for almost a century now. With the microorganisms retaliating the traditional antibiotics *via* β-lactamase enzymes, the need for novel antibiotics prevails making synthesis of newer β-lactams ever more important. Besides their use as antibiotics, β-lactams are increasingly being used as synthons for biologically important molecules. Apart from this, the recent literature has seen a spurt in the number of other diverse applications of the β-lactams. They have been shown to increase the expression of glutamate transporters through gene activation. β-lactams have also been found to act as cholesterol acyl transferase inhibitors, thrombin inhibitors, human cytomegalovirus protease inhibitors, matrix metalloprotease inhibitors, human leucocyte elastase, cysteine protease and apoptosis inductors. Thus, owing to their ever growing applications, synthesis of β-lactams remains a field of incessant activity. We have been involved in the stereoselective synthesis of a variety of β-lactams using different naturally available chiral starting materials. This chapter deals with the stereoselective synthesis of spirocyclic β-lactams starting from D-(+)-glucose. Spiro β-lactams have attracted attention of synthetic as well as medicinal chemists, as they have been shown to be β-turn mimetics and precursors for α,α-disubstituted β-amino acids. The spiro β-lactam moiety also forms a part of the chartellins, a family of marine natural products. Spiro β-lactams have also been found to act as poliovirus and human rhinovirus 3C-proteinases inhibitors. They have also found application as cholesterol absorption inhibitors.

We planned to synthesize the chiral acid chloride **6** from D-(+)-glucose **1** (Scheme-1). Accordingly, starting with D-(+)-glucose **1** chiral aldehyde **4** was synthesized using a reported sequence of reactions. Aldehyde **4** was then subjected to oxidation using $AgNO_3$

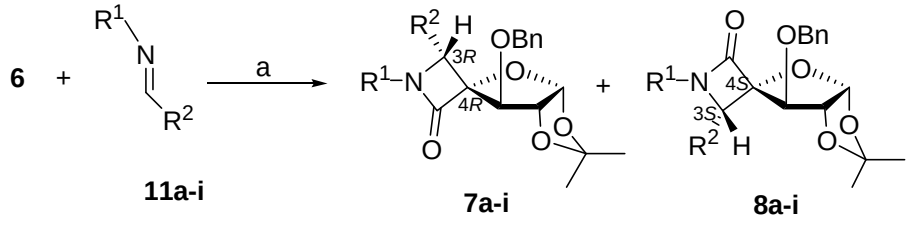
in KOH to obtain chiral acid **5** which was then converted to acid chloride **6** with oxalyl chloride in DCM under reflux conditions.



Reagents and conditions: a) dry acetone, anhydrous $CuSO_4$, conc. H_2SO_4, rt, 48h. b) NaH, BnBr, dry DMF, 0 °C-rt, 3h. c) 75% CH_3COOH, 70 °C, 3h. ii) silica gel, 0.65 M aq.$NaIO_4$, DCM, rt, 2h. d) $AgNO_3$, aq. KOH, HCl, rt, 1h. e) $(COCl)_2$, dry DCM, reflux, 4h.

Scheme 1

This acid chloride was used as a chiral ketene precursor in Staudinger reaction (Scheme-2) with various imines **11a-i** to get diastereomeric mixture of spiro β-lactams **7a-i & 8a-i** in varying diastereomeric ratios (Table-1). The formation of only two products out of theoretically possible four products indicated a high level of diastereoselectivity.



Reagents and conditions: a) Et_3N, dry DCM, -40 °C-rt, 15h.

Scheme 2

Table 1. Synthesis of spiro-β-lactams **7a-i** & **8a-i**

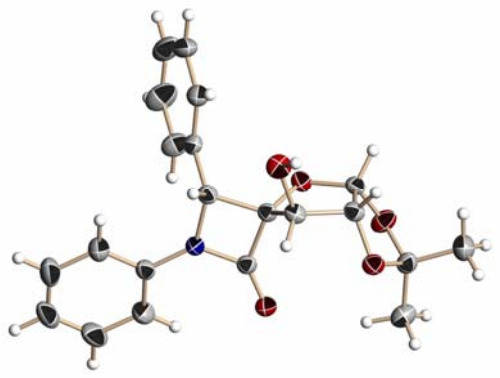
7&8	R^1	R^2	Yield (%)[a]	Isomers[b] 7:8
a	PMP	PMP[c]	65	70:30
b	PMP	Ph	62	68:32
c	Ph	PMP	71	72:28
d	Ph	Ph	62	70:30
e	4-Cl-Ph	Ph	59	65:35
f	Ph	Styryl	69	71:39
g	PMP	Styryl	67	68:32
h	4-Me-Ph	Ph	72	64:36
i	Ph	*p*-Tolyl	70	64:36

[a] isolated yields of diastereomeric mixture.

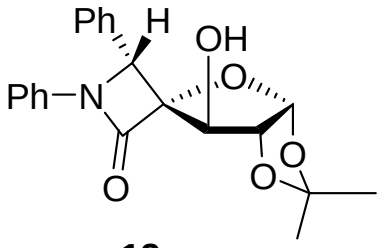
[b]Ratio of diastereomers was determined by ^{1}H NMR.

[c] PMP = *p*-Methoxyphenyl.

Stereochemistry was assigned to spiro- β-lactams with the help of NOESY experiments and single crystal X-ray analysis. The NOESY experiments which exhibited some crucial interactions provided conclusive evidence about stereochemistry of the spiro- β-lactams which was further confirmed by single crystal X-ray diffraction analysis of one of the spiro- β-lactam derivatives. As none of the spiro- β-lactams yielded good crystals, one of the lactams **7c** was debenzylated to obtain compound **12c** which was crystallized and used for X-ray analysis. From these studies, the major isomer **7** was found to have absolute configuration (3*R*,4*R*) and the minor **8** was found to be (3*S*,4*S*) at the newly generated chiral centers.



ORTEP Diagram of compound **12c**



12c

We found that among the two factors that govern stereoselectivity, *viz*, steric and torquoelectronic, the torquoelectronic effect exerted stronger influence in the reaction delivering products which were obtained by attack of imine taking place from more hindered side of the ketene.

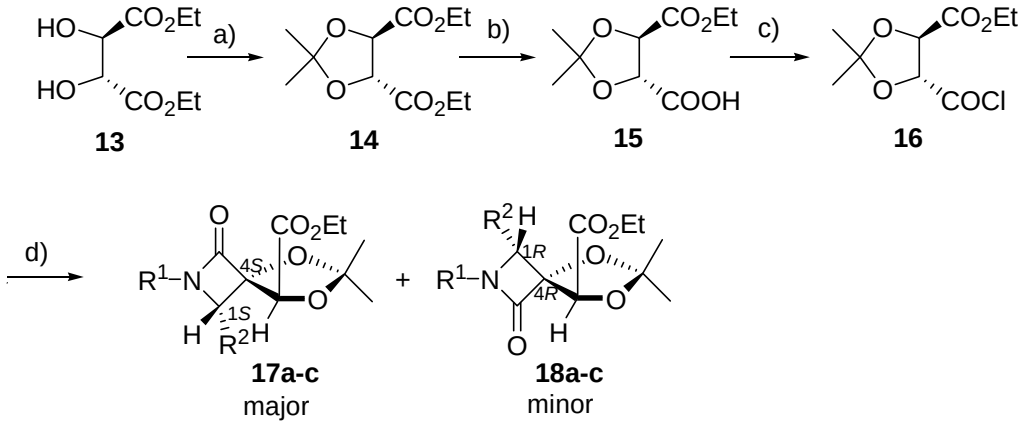
In conclusion, we have developed a method for stereoselective synthesis of spiro-β-lactams from a D-(+)-glucose derived chiral pool. Although, theoretically four diastereomers are possible the reaction yielded only two diastereomers stereoselectively in good to moderate yields. The stereochemical outcome of the reaction was in accordance with the torquoelectronic model.

Chapter 2

Stereoselective synthesis of spiro azetidin-2-ones from L-(+)-diethyl tartrate derived chiral pool and their transformation into enantiopure azetidin-2,3-diones and 3-hydroxy-azetidin-2-ones

The results acquired and inferences drawn from the use of D-(+)-glucose in synthesizing spiro azetidin-2-one motivated us to extend the work further using different chiral starting materials. We wanted to synthesize spiro-β-lactams which could further be transformed into more useful products. We envisaged that spiro-β-lactams derived from L-(+)-diethyl tartrate could be converted into important synthetic intermediates azetidin-2,3-diones. L-(+)-diethyl tartrate, apart from being an efficient chiral ligand, has also been used as a chiral pool for a variety of synthetic intermediates and natural products. It has also been used for stereoselective synthesis of substituted β-lactams. We decided to use it for stereoselective synthesis of spiro-β-lactams. Accordingly, L-(+)-diethyl tartrate **13** was

protected as its acetonide **14** using a reported procedure (Scheme-3). Partial hydrolysis of the symmetrical diester **14** using NaOH in THF-water mixture yielded the mono acid **15**. On refluxing acid **15** with oxalyl chloride in DCM we got acid chloride **16** which was used as a chiral ketene precursor in Staudinger reaction with different imines **11a-c** to obtain spiro-β-lactams as a diastereomeric mixture **17a-c & 18a-c** in good yield. From our experience of glucose derived spiro-β-lactams we could predict the stereochemical outcome of the Staudinger reaction. The structures of actual products **17a-c** and **18a-c** were found be according to our expectations as confirmed by single crystal X-ray analysis.



a, R^1 = PMP, R^2 = PMP (70%)
b, R^1 = PMP, R^2 = Ph (72%)
c, R^1 = Ph, R^2 = PMP (70%)

Reagents and conditions: a) 2,2-dimethoxy propane,benzene, PTSA, reflux, 5h. b) NaOH,THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) R^1-N=CH-R^2(**11a-c**), Et_3N, DCM, -40 °C-rt, 15h.

Scheme-3

One of the major diastereomers **17a** could be crystallized to get good crystals. Its X-ray diffraction analysis revealed that the newly generated stereocenters had absolute configuration (1*S*,4*S*). The absolute stereochemistry of the minor diastereomer was confirmed at the latter stages of the scheme.

With spiro-β-lactams in hand, we proceeded further with their transformation into enantiopure azetidin-2,3-diones. Azetidin-2,3-diones are very useful starting materials for a variety of other β-lactam and non β-lactam intermediates (Figure 1). They have been shown to be promising building blocks and precursors for highly functionalized β-

lactams including Sch-48461 and Sch-58235 which display an important cholesterol absorption inhibitory activity.

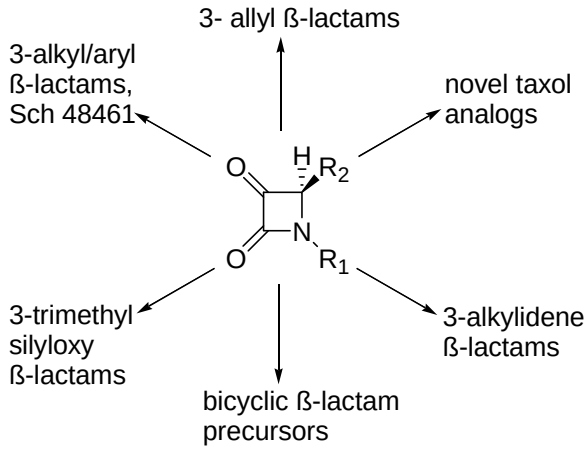
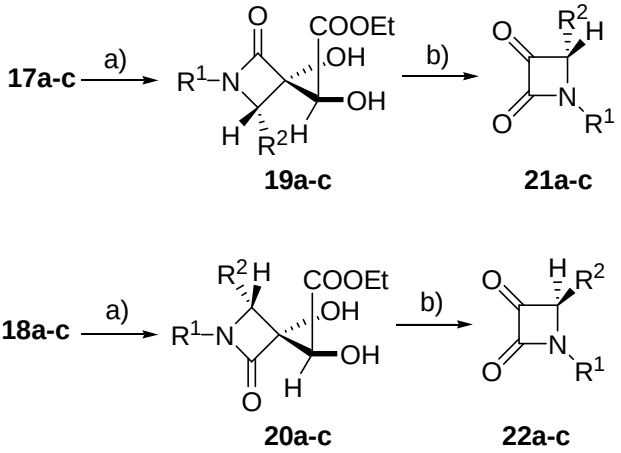


Figure 1 Applications of azetidine-2,3-diones in synthesis.

The transformation of spiro-β-lactams into azetidin-2,3-diones started with deprotection of acetonide moiety in the spiro-β-lactams. On subjecting spiro-β-lactams **17a-c** and **18a-c** to acetonide cleavage with $FeCl_3$ in DCM, diols **19a-c** and **20a-c** respectively, were obtained in very good yields (Scheme-4).



Reagents and conditions: a) $FeCl_3$, DCM, rt, 2h.
b) $NaIO_4$, acetone-water, rt, 6-8h.

Scheme-4

One of the minor diastereomers, gratifyingly crystallized well which enabled us to deduce the absolute configuration of the minor diastereomer with the help of X-ray

diffraction analysis. Diol **20b** on X-ray analysis revealed the absolute configuration at both the chiral centers on the β-lactam ring to be *R*. Thus, the minor diastereomers of spiro-β-lactams **18a-c** were assigned configuration (1*R*,4*R*). Diols **19a-c & 20a-c** were then subjected to oxidative cleavage using $NaIO_4$ in acetone-water mixture to furnish azetidin-2,3-diones **21a-c** and **22a-c** in excellent yields.

Table 2: Synthesis of azetidine-2,3-diones **21a-c** and **22a-c.**

Entry No.	β-lactam	Diones	Yield[a] (%)	$[\alpha]^{26}_{D}$ ($CHCl_3$)
1	**17a**	**21a**	74	+ 53.3 (*c* 0.9)
2	**17b**	**21b**	78	+ 123.0 (*c* 2.0)
3	**17c**	**21c**	81	+ 80.0 (*c* 0.8)
4	**18a**	**22a**	77	- 54.6 (*c* 1.5)
5	**18b**	**22b**	74	- 123.6 (*c* 1.1)
6	**18c**	**22c**	75	- 79.2 (*c* 5.3)

[a] Isolated overall yields from spiro-β-lactams **17a-c** and **18a-c**.

We further planned to reduce azetidin-2,3-diones to 3-hydroxy-azetidin-2-ones. 3-hydroxy-β-lactams are known in the literature to be another class of important intermediates for β-lactam as well as non β-lactam products. One particular 3-hydroxy-β-lactam has been used in the synthesis of phenyl isoserine side chain of taxol. 3-hydroxy-β-lactams have also been used as starting materials for the synthesis of all four isomers of cytoxazone, an important natural product.

Reduction of azetidin-2,3-diones using $NaBH_4$ proceeds stereoselectively, with the reducing agent attacking from the opposite side of the substituent on the C-4 of the lactam ring. We subjected diones **21a-c** and **22a-c** to reduction using $NaBH_4$ at 0 °C. The reaction proceeded cleanly to furnish exclusively *cis* 3-hydroxy-azetidin-2-ones (**23a-c &24a-c**) in excellent yields (Scheme-5).

21a-c **23a-c**

23a, R^1 = PMP, R^2 = PMP (92%)
23b, R^1 = PMP, R^2 = Ph (90%)
23c, R^1 = Ph, R^2 = PMP (90%)

22a-c **24a-c**

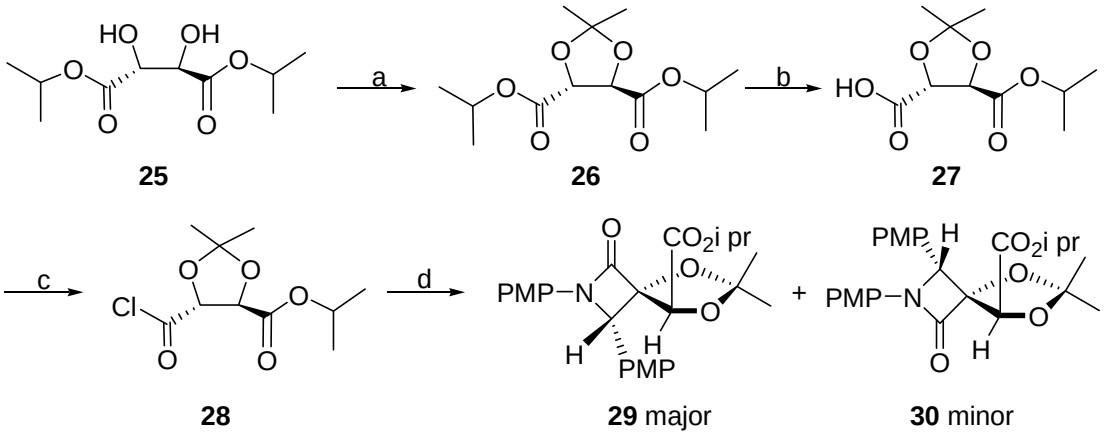
24a, R^1 = PMP, R^2 = PMP (92%)
24b, R^1 = PMP, R^2 = Ph (87%)
24c, R^1 = Ph, R^2 = PMP (89%)

Scheme-5

In conclusion, stereoselective synthesis of spiro-azetidin-2-ones was achieved from L-(+)-diethyl tartrate derived chiral pool. These spiro-β-lactams were transformed into useful synthetic intermediates azetidin-2,3-diones in an efficient process. Further, these azetidin-2,3-diones were reduced to 3-hydroxy-azetidin-2-ones which are of high synthetic value.

Effect of change in the ester moiety on diastereoselectivity.

After using L-(+)-diethyl tartrate as a chiral starting material for synthesis of spiro-β-lactams, we were interested in checking the effect of differing ester substituents in the ketene on the stereoselectivity of the spiro-β-lactam formation reaction. We thus started with L-(+)-diisopropyl tartrate **25** by protecting it as an acetonide **26** (Scheme-6). Partial hydrolysis of **26** yielded mono acid **27** which was refluxed with oxalyl chloride in DCM yielded acid chloride **28**.



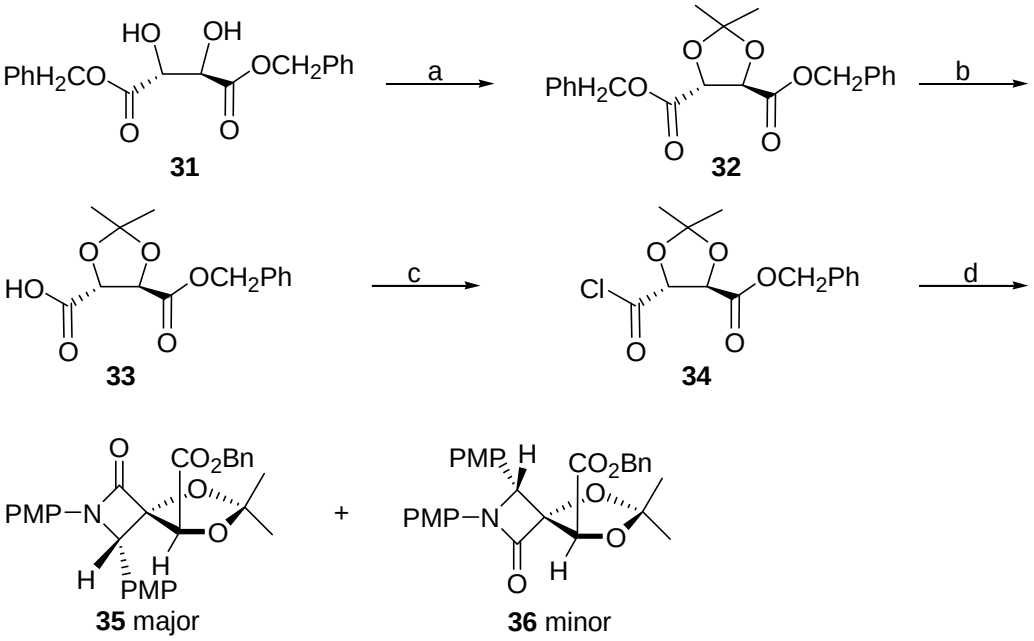
Reagents and conditions: a) 2,2-dimethoxy propane,benzene, PTSA, reflux, 5h.b) NaOH, THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) PMP-N=CH-PMP (**11a**), Et_3N, DCM, -40 °C-rt, 15h.

Scheme-6

Acid chloride **28** was used in Staudinger cycloaddition reaction with imine **11a** at -40 °C which furnished spiro-β-lactams **29** and **30** in a diastereomeric ratio of 65:35 (Table 3). We also intended to find out whether lowering the temperature was having any effect on the selectivity. When same reaction was carried out at -78 °C, products **29** and **30** obtained in diastereomeric ratio of 67:33.

We then attempted similar synthesis of spiro-β-lactams starting with L-(+)-dibenzyl tartrate **31** (Scheme 7). It was protected as acetonide **32** and partial hydrolysis of

compound **32** yielded mono acid **33**. Acid **33** was refluxed with oxalyl chloride in DCM to obtain acid chloride **34** which was used in Staudinger reaction with imine **11a** at -40°C to obtain diastereomeric mixture of spiro-β-lactams **35** and **36** in 64:36 ratio.

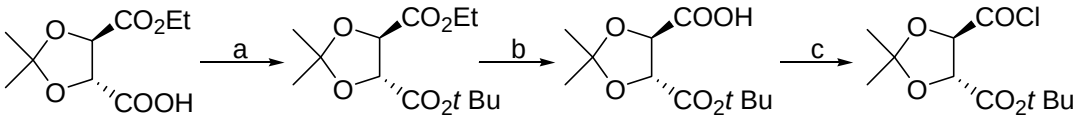


Reagents and conditions: a) 2,2-dimethoxy propane,benzene, PTSA, reflux, 5h.b) NaOH, THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) PMP-N=CH-PMP (**11a**), Et_3N, DCM, -40°-rt, 15h.

Scheme-7

The reaction when carried out at -78 °C yielded mixture of **35** and **36** in a diastereomeric ratio of 65:35.

Finally, we planned similar synthesis of spiro-β-lactams with a tertiary butyl ester. As tertiary butyl esters are stubborn to basic hydrolysis and controlled acidic hydrolysis is difficult, we had to devise an indirect route to acid chloride having a tertiary butyl ester as an α substituent. We started off with acid **15** by esterifying it with $(Boc)_2O$ and DMAP in *t*-BuOH which afforded mixed ethyl, tertiary butyl ester **37** which was then selectively hydrolysed with NaOH (Scheme-8). The hydrolysis reaction yielded acid **38** leaving the tertiary butyl ester untouched.

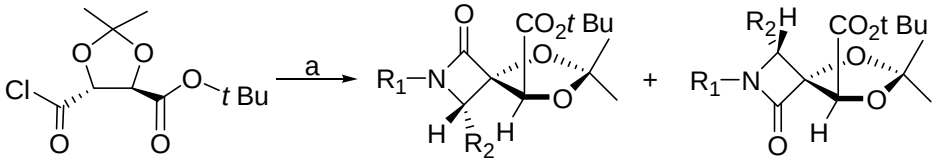


15 **37** **38** **39**

Reagents and conditions: a) $(BOC)_2O$, *t*-BuOH, DMAP, 8h. b) NaOH,THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h.

Scheme-8

Acid **38** was then as usual converted to acid chloride with oxalyl chloride to obtain acid chloride **39** which was subjected to Staudinger reaction with imine **11a** at -40 °C which afforded diastereomeric mixture of spiro-β-lactams **40** and **41** in 65:35 ratio (Scheme-9).



39 **40** major **41** minor

Reagents and conditions: a) PMP-N=CH-PMP (**11a**), Et_3N, DCM, 15h.

Scheme-9

When the Staudinger cycloaddition was carried out at -78 °C the reaction afforded diastereomeric mixture of compounds **40** and **41** in the ratio of 67:33.

For sake of comparison we also carried out Staudinger cycloaddition reaction of acid chloride **16** with imine **11a** at -78 °C which furnished diastereomeric mixture of spiro-β-lactams **17a** and **18a** in a ratio of 62:38.

Table-3: Synthesis of substituted spiro-β-lactams from different L-(+)-tartaric acid esters

Entry No.	Starting Acid chloride	Products	Temperature °C	Diastereo-selectivity
1	**16**	**17a, 18a**	-40	60:40
2	**16**	**17a, 18a**	-78	62:38
3	**28**	**29, 30**	-40	65:35
4	**28**	**29, 30**	-78	67:33
5	**34**	**35, 36**	-40	64:36
6	**34**	**35, 36**	-78	65:35
7	**39**	**40, 41**	-40	65:35
8	**39**	**40, 41**	-78	67:33

In conclusion, stereoselective synthesis of spiro-β-lactams was achieved starting from different L-(+)-tartaric acid esters. The changes in ester group substituents on the ketene as well as change in temperature had little effect on the diastereoselectivity.

Chapter 3

An efficient formal synthesis of (*S*)-dapoxetine from enantiopure 3-Hydroxy azetidin-2-one

(*S*)-Dapoxetine (Figure 2) is one of the most preferred prescriptions against mental disorders like depression and bulimia. It is a selective serotonin reuptake inhibitor (SSRI) type of drug. Moreover, recently concluded phase 3 clinical trials have shown it to be effective against premature ejaculation which is a sexual disorder in men. Almost 30% of men worldwide are suffering from this problem.

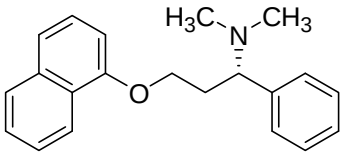
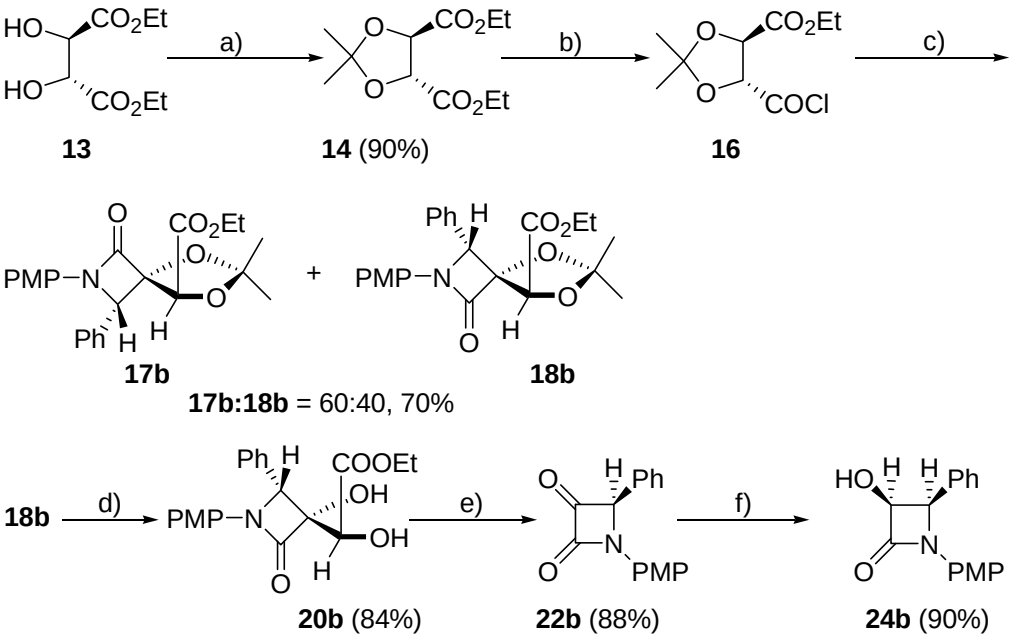


Figure 2 Dapoxetine

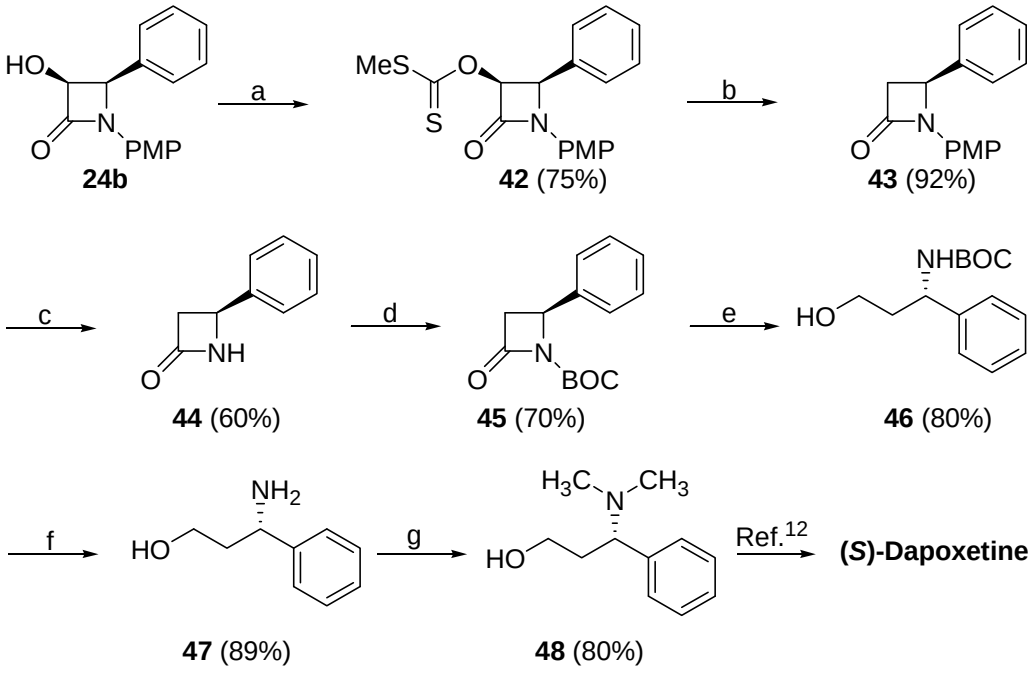
We envisioned that intermediate (*S*)-3-dimethylamino-3-phenyl-propan-1-ol **48** can be synthesized from a suitably substituted 3-hydroxy β-lactam. The required 3-hydroxy β-lactam **24b** was synthesized by reduction of appropriate azetidin-2,3-dione **22b** which in turn was obtained from L-(+)-diethyl tartrate **13** (Scheme-10).

3-hydroxy β-lactam **24b** was then converted to its xanthate **42** which was then reduced with Bu_3SnH in toluene at reflux temperature in presence of catalytic AIBN to obtain deoxygenated β-lactam **43** (Scheme 11). Compound **43** on oxidative removal of PMP group on the lactam nitrogen yielded compound **44** which was then protected as its Boc derivative **45**. Compound **45** was subjected to LAH reduction which yielded alcohol **46**. Compound **46** was deprotected with TFA in DCM to furnish amino alcohol **47**. Amino alcohol **47** was bis-methylated using sodium cyanoborohydride to obtain intermediate (*S*)-3-dimethylamino-3-phenyl-propan-1-ol **48**. As elaboration of **48** to (*S*)-dapoxetine is known, synthesis of intermediate **48** constitutes a formal synthesis of (*S*)-dapoxetine.



Reagents and conditions:a) 2,2-dimethoxy propane benzene, PTSA, reflux, 5h. b) i) NaOH, THF-H_2O, rt, 4-6h. ii) $(COCl)_2$, DCM, reflux, 5h c) PMP-N=CH-Ph, Et_3N, DCM, -40°-rt, 15h. d) $FeCl_3$, DCM, rt, 2h. e) $NaIO_4$, acetone-water, rt, 6-8h. f) $NaBH_4$, MeOH, 0°C, 2h.

Scheme-10



Reagents and conditions: a) NaH, CS_2, CH_3I, THF, 0°-rt, 6h. b) Bu_3SnH, AIBN, toluene, reflux, 3-4h.c) CAN, CH_3CN-H_2O, 0°C, 1h. d) $(BOC)_2O$, DMAP, DCM, 0°-rt, 6h. e) LAH, THF, 0°-rt,4h. f) TFA, DCM, 0°-rt, 2h. g) HCHO, $NaBH_3CN$, CH_3COOH, CH_3CN, rt, 2h.

Scheme-11

Chapter 4

Section A: Stereoselective synthesis of cholesterol absorption inhibitor Sch 48461 from enantiopure azetidin-2,3-dione

β-lactams, apart from their traditional antibiotic activity, recently have been proven to be useful in other similar applications. Thus, its medicinal value only continues to increase. One such important and new application is the use of some *trans*-β-lactams as cholesterol absorption inhibitors. Sch 48461 (Figure 3) is one such *trans*-β-lactam exhibiting good cholesterol absorption inhibitory activity.

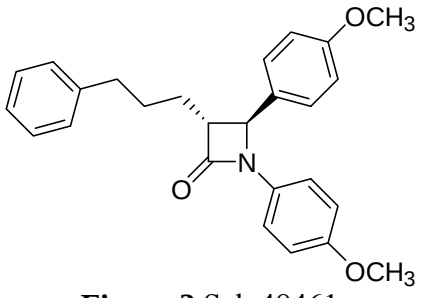
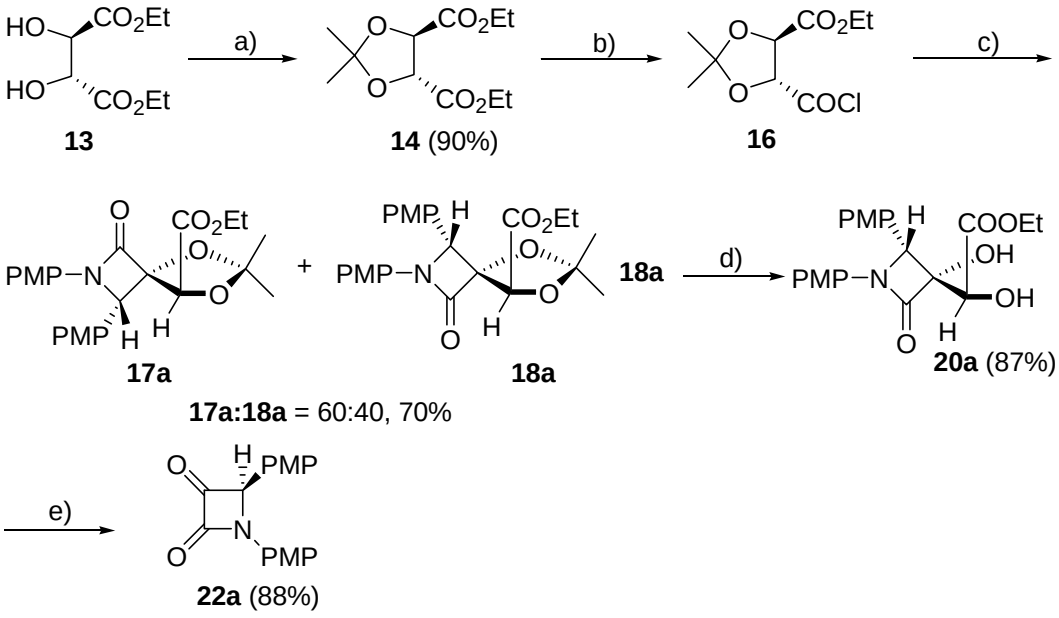


Figure 3 Sch 48461

Till date only a few reports of stereoselective synthesis of Sch 48461 exist in the literature. We have been using the β-lactam synthon method for naturally occurring and medicinally important molecules. As a part of the same we have devised a methodology for 3-alkyl/aryl β-lactams from azetidin-2,3-diones. Using that method we synthesized Sch 48461 in racemic form. We planned to apply the same method to enantiopure azetidin-2,3-diones for the stereoselective synthesis of Sch 48461.

We synthesized the requisite azetidin-2,3-dione **22a** from L-(+)-diethyl tartrate (**13**) (Scheme-12). Phenyl magnesium bromide was generated from 3-phenyl bromo propane in THF and its addition on dione **22a** proceeded with complete stereoselectivity to yield substituted 3-hydroxy β-lactam **49** (Scheme-13). Compound **49** was converted to its xanthate **50** which was reduced using *n*-tributyl tin hydride and catalytic AIBN in refluxing toluene to furnish compound **51**. *Cis* lactam **51** was isomerized to *trans* lactam to get Sch 48461 using potassium *tert* butoxide in THF.



13 **14** (90%) **16**

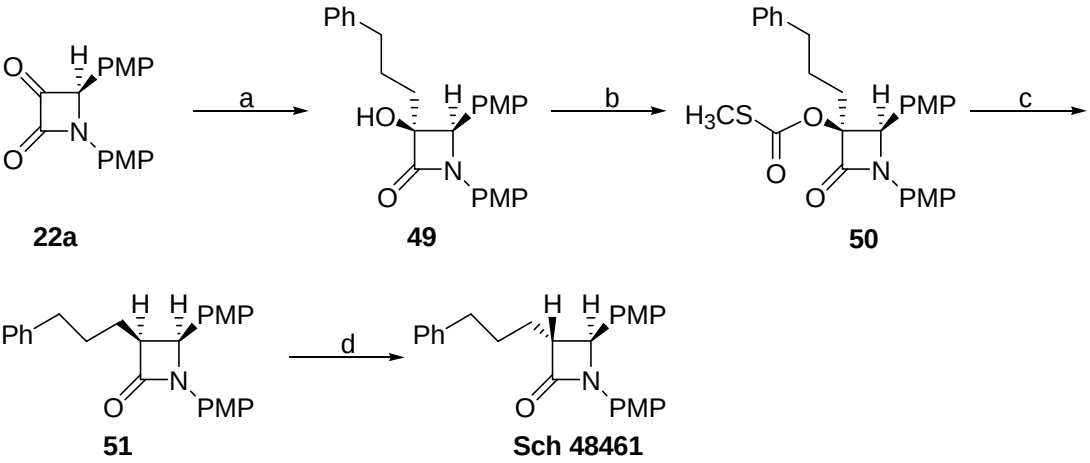
17a **18a** **20a** (87%)

17a:18a = 60:40, 70%

22a (88%)

Reagents and conditions:a) 2,2-dimethoxy propane benzene, PTSA, reflux, 5h.b) i) NaOH, THF-H_2O, rt, 4-6h. ii) $(COCl)_2$, DCM, reflux, 5h c) PMP-N=CH-PMP **11a**, Et_3N, DCM, -40°-rt, 15h. d) $FeCl_3$, DCM, rt, 2h. e) $NaIO_4$, acetone-water, rt, 6-8h.

Scheme-12



22a **49** **50**

51 **Sch 48461**

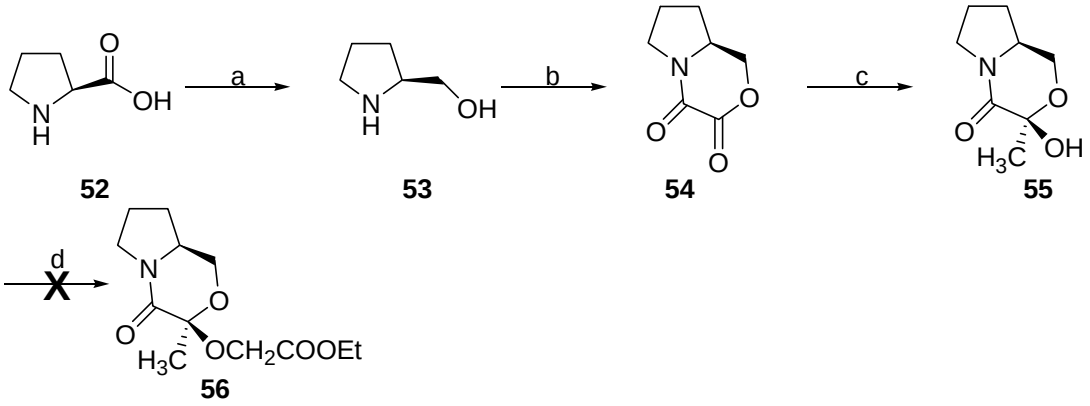
Reagents and conditions: a) $Ph(CH_2)_3MgBr$, THF, 0 °C-rt, 6h. b) NaH, CS_2, CH_3I THF, 0 °C-rt, 3h. c) Bu_3SnH, AIBN, toluene, reflux, 3h. d) KO^{t}Bu, THF, 0 °C, 2h.

Scheme-13

Section B: Studies toward L-(+)-proline derived chiral auxiliary for diastereoselective synthesis of azetidin-2-ones.

We have been involved in the diastereoselective synthesis of β-lactams using different chiral starting materials like, D-(+)-glucose, ephedrine etc. As a part of the same research program, our group has reported a methodology for diastereoselective synthesis β-lactams from an ephedrine derived chiral auxiliary and its subsequent conversion into

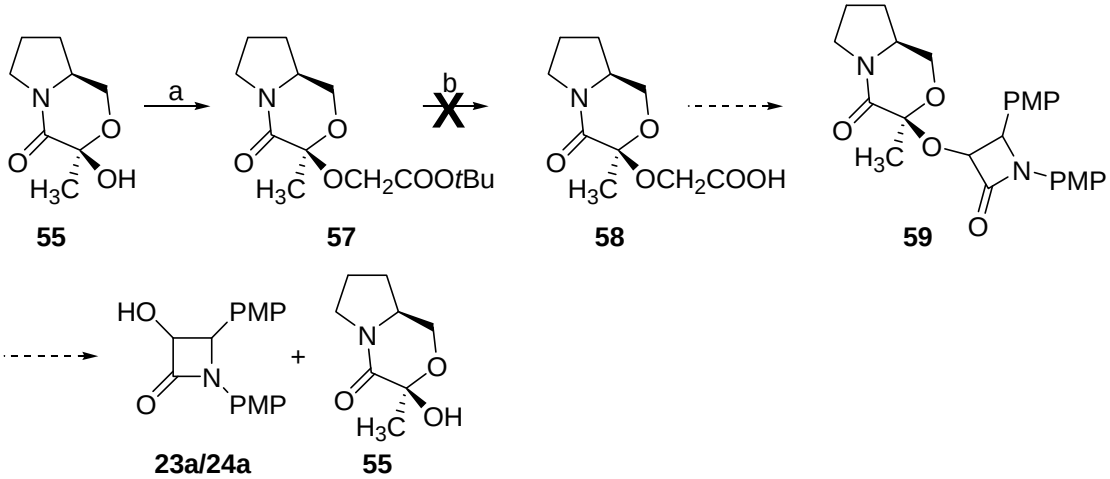
synthetically useful 3-hydroxy-β-lactams. Along same lines we envisioned a diastereoselective synthesis of β-lactams using proline derived chiral auxiliary. Starting with L-(+)-proline **52**, we reduced it using LAH to obtain prolinol **53** (Scheme-14).



Reagents and conditions: a) LAH, THF, reflux, 3h. b) $(COCl)_2$, DCM, Et_3N, DMAP, 0 °C, 4h. c) CH_3MgI, ether, -20 °C, 2h, d) NaH, $BrCH_2COOEt$, THF-DMF, 70 °C and various other conditions

Scheme-14

Prolinol **53** was then cyclized with oxalyl chloride to get dione **54**. Addition of CH_3MgI on **54** provided alcohol **55**. All attempts to alkylate **55** with ethyl bromoacetate to get compound **56** proved to be unsuccessful. Thus we changed our route slightly. We alkylated **55** with tertiary butyl bromoacetate (Scheme-15).



Reagents and conditions: a) $BrCH_2COOtBu$, aq. NaOH, C_6H_6, Bu_4NHSO_4. b) *p*TSA, C_6H_6.

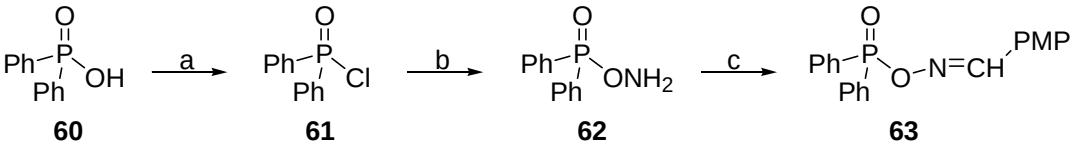
Scheme-15

Alkylation proceeded cleanly to furnish ester **57**. However, our attempts to hydrolyse **57** using acidic medium proved futile. We had planned to use the acid **58** resulting from

hydrolysis of **57**, in a Staudinger reaction to generate β-lactam **59** which on acid treatment would have yielded 3-hydroxy β-lactam and the regenerated chiral auxiliary **55**, hopefully in a reusable form.

Section C: Studies towards synthesis of some novel phosphorus containing azetidin-2-ones from diphenyl phosphinic acid derived imines.

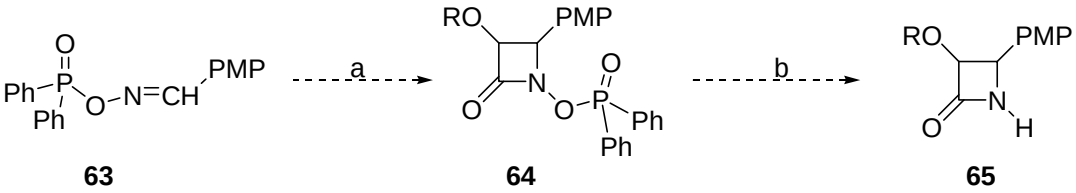
β-Lactam antibiotics are almost a century old now, and yet, the interest of medicinal and synthetic chemists exists in discovery of newer β-lactams, in quest of better antibiotic activity. In a similar search we were aiming at the synthesis of novel β-lactams. Thus, we planned to synthesize some phosphorus containing β-lactams. We started with diphenyl phosphinic acid (**60**) by converting it into diphenyl phosphinic chloride (**61**) with thionyl chloride in refluxing benzene (Scheme-16).



Reagents and conditions: a) $SOCl_2$, C_6H_6, reflux, 2h. b) $NH_2OH.HCl$, aq. NaOH,dioxane, 0 °C, 1h. c) *p*-anisaldehyde, anh. $MgSO_4$, DCM, rt, 20h.

Scheme-16

Compound **61** on reacting with hydroxylamine provided *O*-(diphenylphosphinyl) hydroxylamine **62** which was then reacted with *p*-anisaldehyde and anhydrous $MgSO_4$ in DCM to obtain imine **63**. We then used imine **63** in a Staudinger reaction with suitable acid chloride in an attempt to get β-lactam **64** (Scheme-17), but all our attempts to synthesize β-lactam met failure. It is known that *O*-(diphenylphosphinyl) hydroxylamine is a reagent used for electrophilic amination. Thus, we had envisioned that, very similarly sodium borohydride may attack the lactam **64** derived from *O*-(diphenylphosphinyl) hydroxylamine to yield *N*-unsubstituted β-lactam **65**.



Reagents and conditions: a) $ROCH_2COCl$, Et_3N, DCM, 0-rt. b) $NaBH_4$, MeOH.

Scheme-17

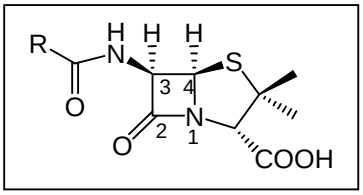
CHAPTER 1

STEREOSELECTIVE SYNTHESIS OF SPIRO AZETIDIN-2-ONES USING D-(+)-GLUCOSE DERIVED CHIRAL POOL.

This work has been published in *Tetrahedron* **2007**, *63*, 9179-9187.

1.1: Introduction

Azetidin-2-one (β-lactam), a four membered cyclic amide, is a part structure of many biologically important antibiotics. The unique structural feature and chemotherapeutic properties of β-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 β-lactam ring was reported way back in 1907 by Staudinger,[1] β-lactam as a class acquired immense importance only after the discovery of penicillin by Fleming in 1928.[2] It was actually Prof. R. B Woodward who first proposed the structure of penicillin based on a β-lactam ring, which was indeed later confirmed and unambiguously proved the presence of 4-membered amide ring by X-ray crystallography.[3] The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.



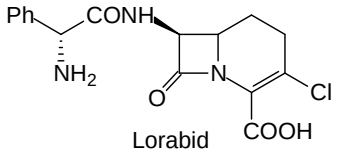
Azetidin-2-one

(β-Lactam ring)

Figure 1

Until 1970, penicillin and cephalosporins[4] were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7-α-methoxycephalosporins[5] from "*Streptomyces*" in 1971 stimulated the search for novel antibiotics. The β-lactam antibiotics can be classified into several groups based on their structures (Figure 3).

Carbacephems,[6] 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).



Lorabid

Figure 2

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

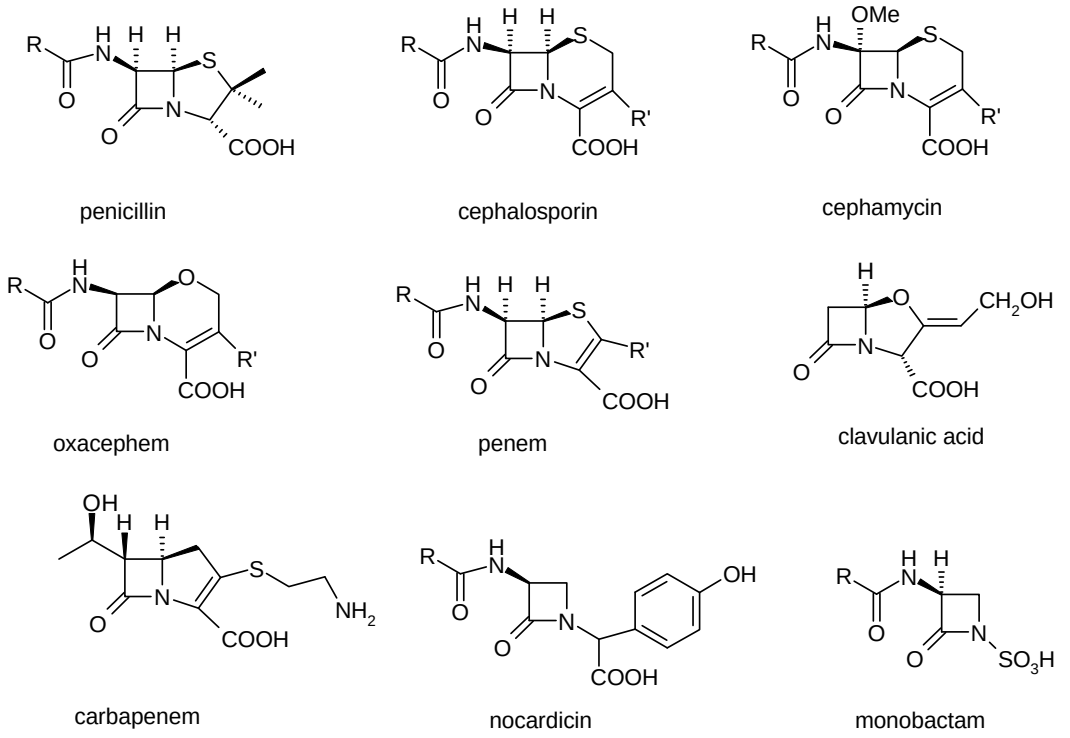


Figure 3. Classification of β-lactam antibiotics based on core structure

Tricyclic β-lactam antibiotics called trinems[7] (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.

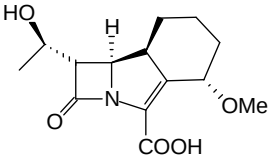


Figure 4

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

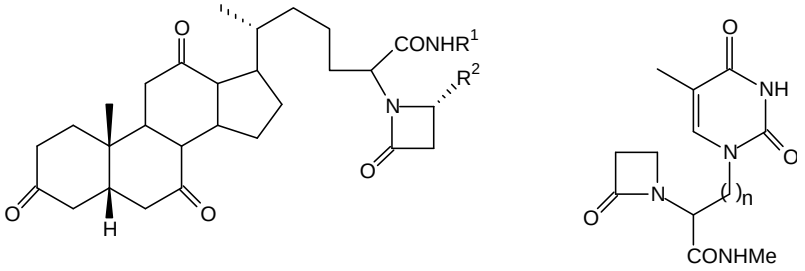


Figure 5

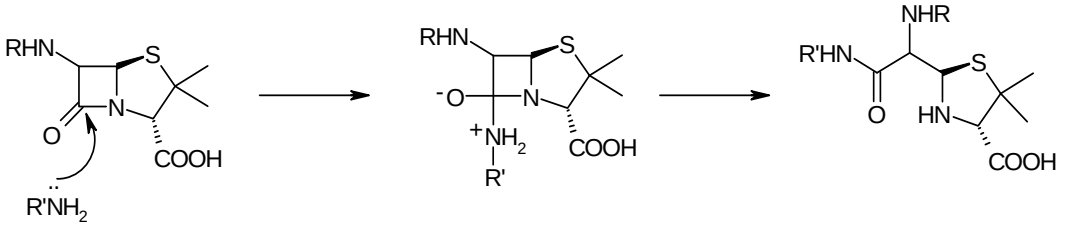
Apart from their antibacterial activities, β-lactams also show other biological activities that include cholesterol absorption inhibition[10] and human leukocyte elastase (HLE).[11]

Mode of action of penicillin:

The biological activity of these antibiotics is mainly due to the presence of β-lactam ring. The SAR (structure activity relationship) studies[12] 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.[13]

Biological activity of penicillin:[14]

Scheme 1.01

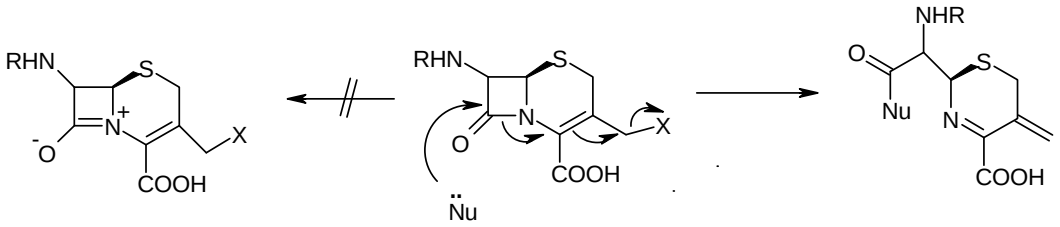


The schematic representation of this phenomenon in the case of penicillin and cephalosporin is shown in Scheme 1.01, 1.02. Penicillin and cephalosporin are entering

into human body and it binds with transpeptidases, which are responsible for cell wall growth synthesis. Then this will disturb the peptidoglycan structure and acylation of active site of enzyme weaken the cell wall synthesis and destroys the bacteria.

Biological activity of cephalosporin:[15]

Scheme 1.02

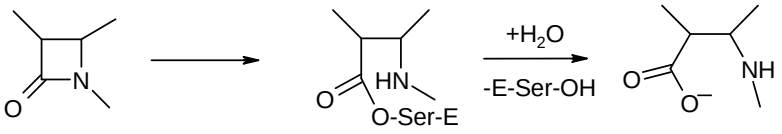


β-lactamases and β-lactamase inhibitors:

β-lactamases[16] are bacterial enzymes mainly responsible for the resistance against β-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 β-lactam ring and release the cleaved, inactive antibiotics as amino acids.

There are four different classes of β-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.[16] 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 1.03



The problem of bacterial resistance to commercial antibiotics has opened a gateway to develop novel β-lactam antibiotics as β-lactamase inhibitors.[17-18] These β-lactamase inhibitors are compounds which are structural variants of natural antibiotics with a modified β-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 β-lactamase with the β-lactam antibiotics and thereby safeguarding the antibiotic activity of the β-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 β-lactamase inhibitors.

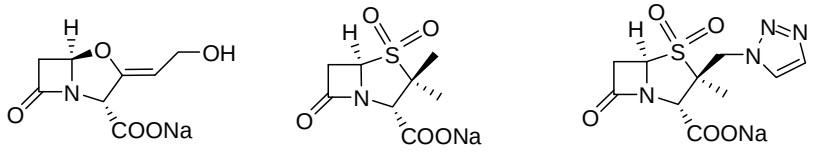


Figure 6

Temocillin, Formidacillin[18] and tricyclic tribactams[19] are other examples of effective β-lactamase inhibitors.

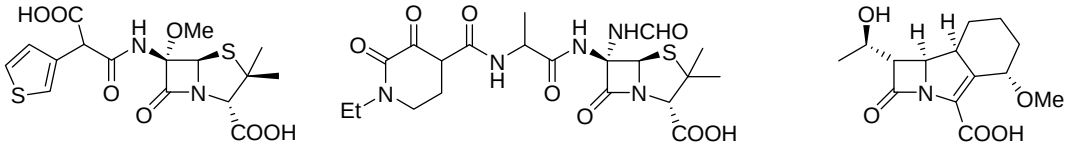


Figure 7

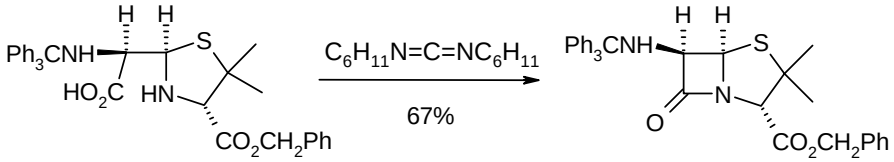
Methods for constructing β-lactam ring:

There are several approaches available to construct these β-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 β-amino acids. This method has been used in the landmark synthesis of penicillin by Sheehan et al. using dicyclohexylcarbodiimide as a condensing agent.[20]

Scheme 1.04

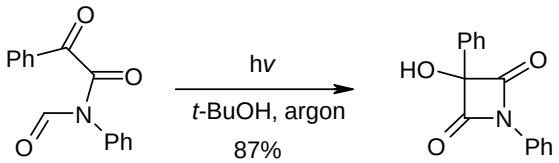


Triphenylphosphine-pyridine disulfide, methanesulfonyl chloride in combination with base and Grignard reagent (RMgX) can also be used instead of DCC to form the amide bond from β-amino acids.

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-β-lactam.[21]

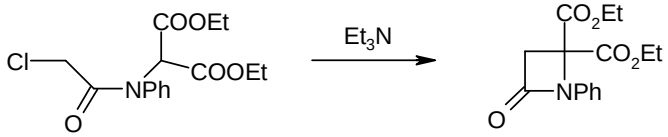
Scheme 1.05



Formation of C3-C4 bond:

The simplest method for the formation of C3-C4 bond is to generate the 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.[22]

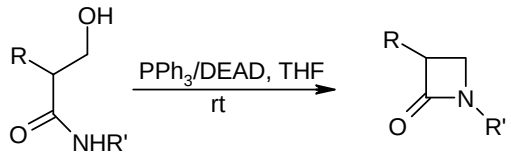
Scheme 1.06



Formation of C4-N1 bond:

This methodology involves an S_N2 displacement of a good leaving group attached at β-carbon amide by an intramolecular amide nitrogen under basic conditions. Miller has reported the synthesis of β-lactams by the cyclization of β-hydroxy amides under Mitsunobu reaction conditions.[23]

Scheme-1.07



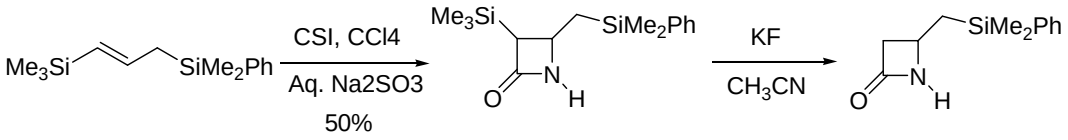
Multiple bond forming reactions:

Olefin-isocyanate cycloaddition reaction:

The addition of chlorosulfonyl isocyanate to olefins is a well-known method for the construction of β-lactams.[24] Colvin et al.[25] have reported the addition of

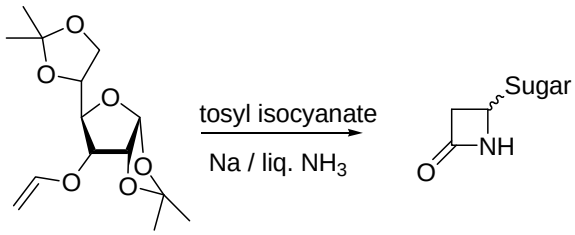
chlorosulfonyl isocyante to various allyl and allenyl silanes to give functionalized β-lactams, which were then converted into synthetically important 3-unsubstituted *NH*-β-lactams by removal of the chlorosulfonyl group followed by silyl deprotection (Scheme 1.08).

Scheme 1.08



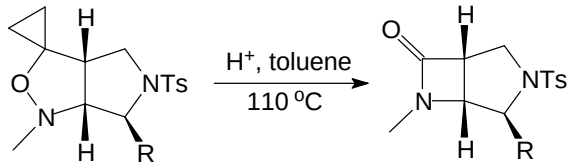
Chmielewski and co-workers have used this cycloaddition reaction between tosyl isocyanate and sugar derived vinyl ethers to obtain good diastereoselectivities in β-lactam formation (Scheme 1.09).[26]

Scheme 1.09



Cordero et al.[27] have reported that spirocyclopropane isoxazolidines undergo ring contraction to yield β-lactams on heating in the presence of protic acid (Scheme 1.10).

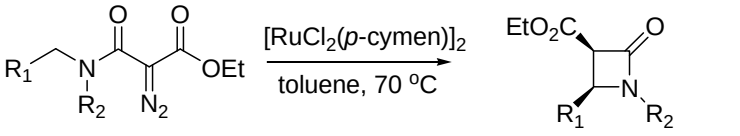
Scheme 1.10



R = Me, *iso*-propyl

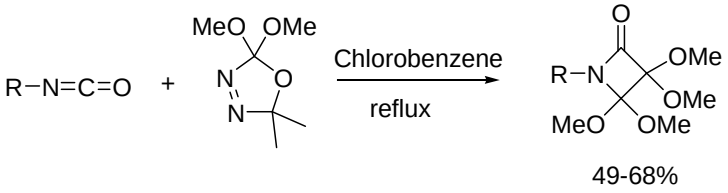
Wing et al.[28a] have developed an operationally simple Ru-catalyzed stereoselective intramolecular carbenoid C-H insertion reaction for the β-lactam formations in excellent yields with *cis*-stereoselectivity (Scheme 1.11).

Scheme 1.11



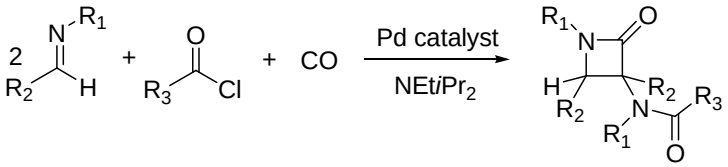
Rigby et al.[28b] have reported a highly substituted β-lactam ring formation *via* a reaction between dimethoxycarebene with selected isocyanates. This reaction offers a new entry into β-lactams and the potential for rapid access into variety of highly functionalized species (Scheme 1.12).

Scheme 1.12



Recently, Arndtsen et al.[28c] have developed a new palladium-catalyzed synthesis of 3-amido-substituted β-lactams. This is multicomponent approach, which involved the one-pot coupling of four components, imines, carbon monoxide and acid chloride (Scheme 1.13).

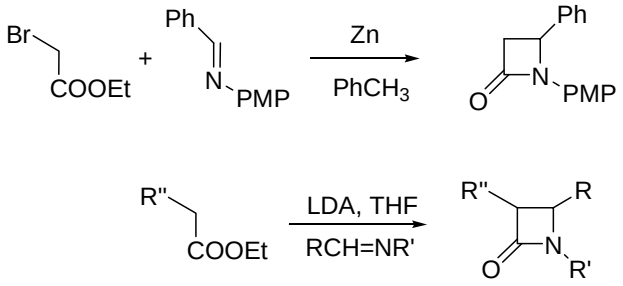
Scheme 1.13



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 β-lactams. Other metal enolates have also been used in enolate-imine cycloaddition to achieve diastereoselective synthesis of β-lactams (Scheme 1.14).[29]

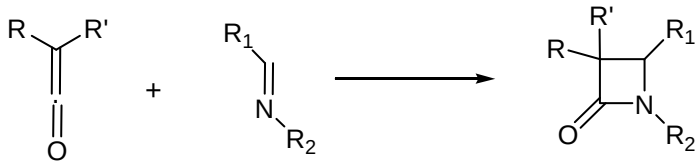
Scheme 1.14



Staudinger reaction:

The first synthesis of a β-lactam was achieved by Staudinger[1] 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 β-lactam rings (Scheme 1.15).

Scheme 1.15



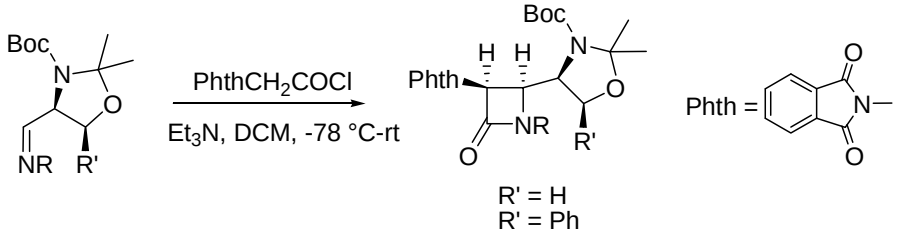
Asymmetric synthesis of β-lactams using Staudinger reaction:

Better understanding of the mechanistic aspects of the β-lactams biological activity, their inhibition and the chemical exploitation of β-lactams as synthetic intermediates in organic chemistry have led to profound development in this field. In this regard, the accessibility of enantiopure β-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 1.16).[30]

Scheme 1.16



The most common approaches in the Staudinger reaction involve the use of α-oxyaldehyde derived imines, sugar derived imines and α, β-epoxyimines.[31]

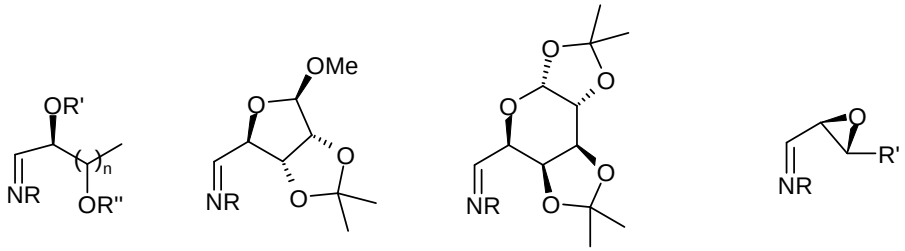
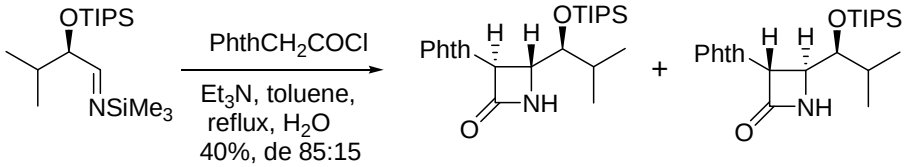


Figure 8

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 1.17).[32]

Scheme 1.17



Carbohydrate derived chiral imines:

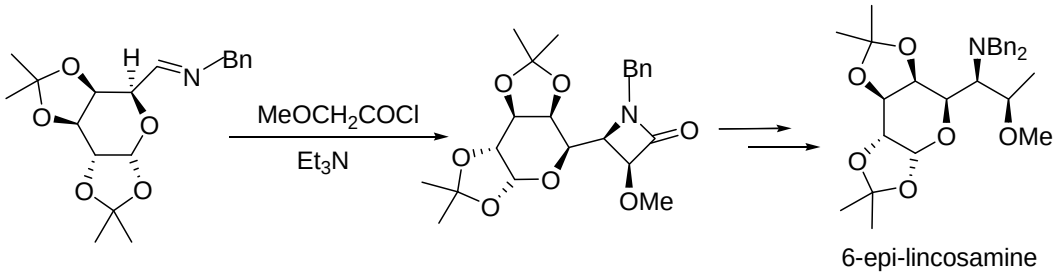
Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[33] The use of carbohydrates in the

asymmetric synthesis of β-lactams has become well established and considerable amount of work has been done on sugar derived imines for β-lactam ring construction.

Bose and Manhas[34] 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 β-lactams as chiral synthons rather than as a chiral pool and have utilized the carbohydrate skeleton for the synthesis of important natural products.

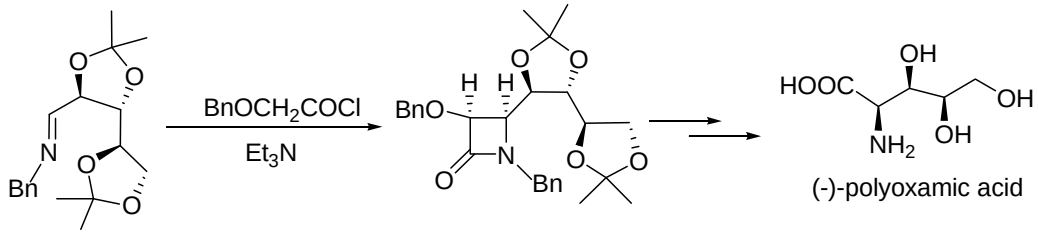
A single *cis*-diastereomer was obtained from the reaction of D-galactopyranose derived chiral imine and methoxy-ketene. On further synthetic transformation this isomer was converted into 6-*epi*-lincosamine (Scheme 1.18).[35]

Scheme 1.18



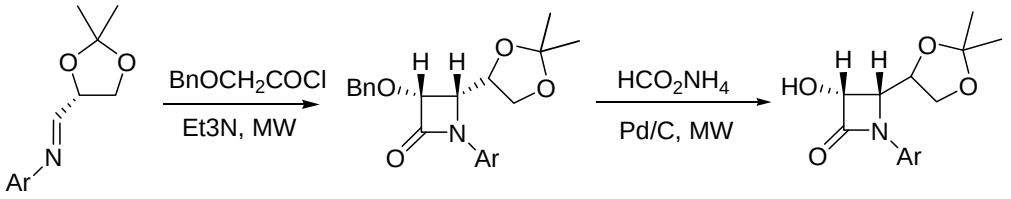
Similarly, the cycloaddition reaction of benzyloxyketene with the imine provided *cis*-β-lactams with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, an antipode of natural (+)-polyoxamic acid (Scheme 1.19).[36]

Scheme 1.19



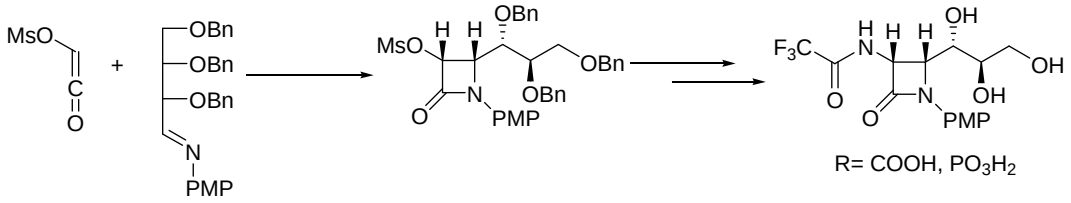
Bose and Manhas have recently reported the enantiospecific synthesis of α-hydroxy-β-lactams using Schiff's bases derived from D-glyceraldehyde under microwave irradiation (Scheme 1.20).[37]

Scheme 1.20



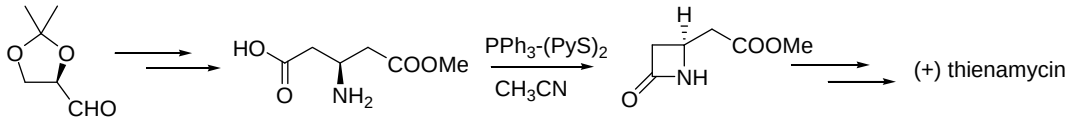
Recently, Stortz et al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-mannonic acid derivatives (Scheme 1.21).[38]

Scheme 1.21



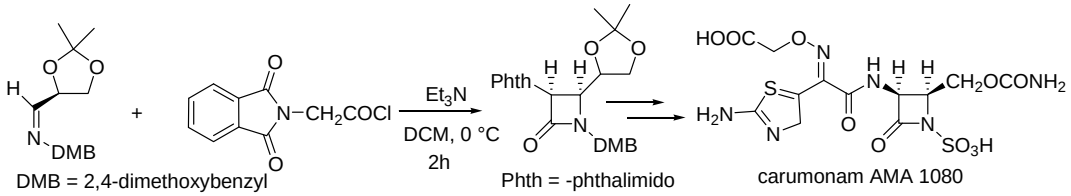
The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into a β-amino ester, which on cyclization with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubstituted β-lactam. This β-lactam has been converted into (+)-thienamycin antibiotic in several steps (Scheme 1.22).[39]

Scheme 1.22



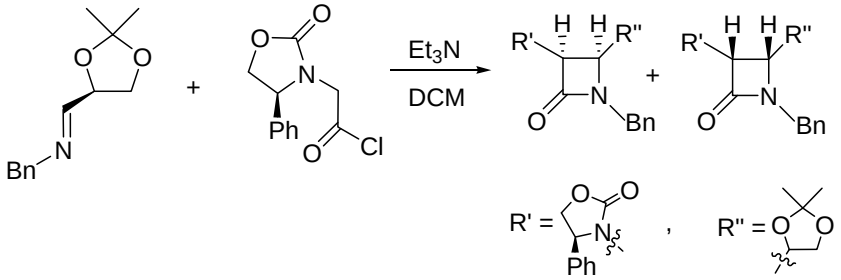
The imine derived from L-(-)-glyceraldehyde and 2,4-dimethoxybenzylamine underwent Staudinger reaction with phthalimidoacetyl chloride to afford the corresponding 3-Phth substituted β-lactam, which is a key intermediate in the synthesis of carumonam antibiotics (Scheme 1.23).[40]

Scheme 1.23



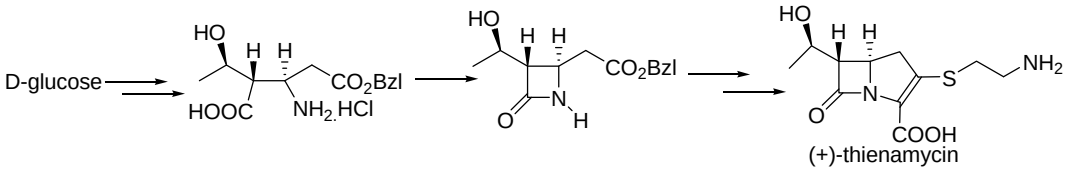
Palomo et al. have treated the imine derived from L-(-)-glyceraldehyde and benzylamine with oxazolidinone derived acid chloride to give *cis*-β-lactams in good yield with 40:60 diastereomeric ratio (Scheme 1.24).[41]

Scheme 1.24



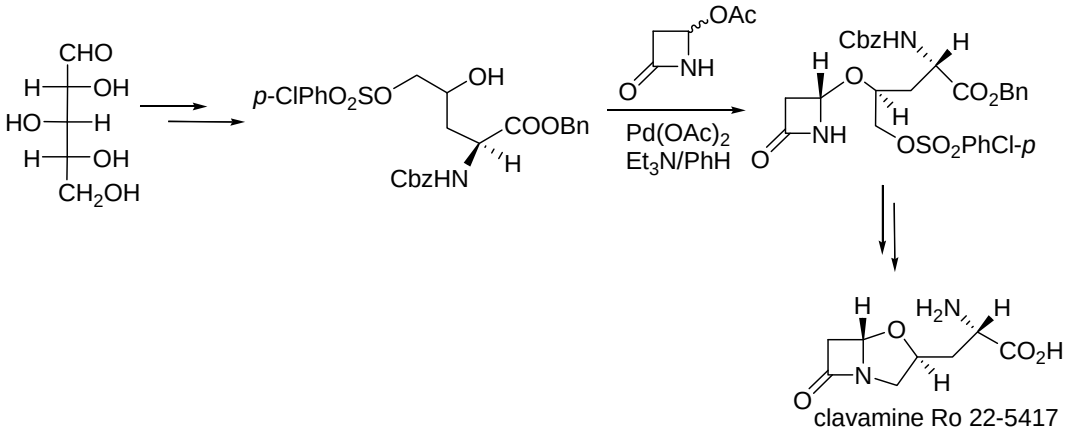
The β-amino acid derived from D-glucose, on cyclization in the presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotic in several steps (Scheme 1.25).[42]

Scheme 1.25



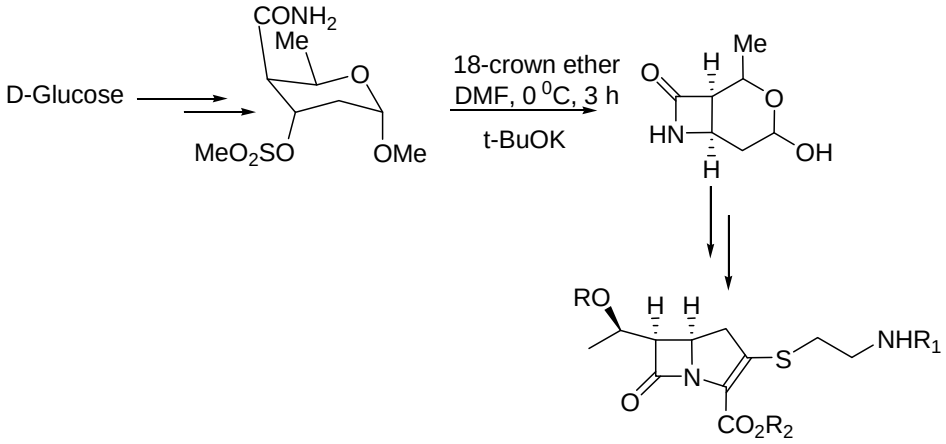
A chiral amino alcohol derived from D-xylose was coupled with racemic 4-acetyloxy-*N*-unsubstiuted-β-lactam in the presence of palladium acetate/ Et_3N to give diastereomeric 70:30 mixture of β-lactams in 65% yield. The major isomer has been converted to the antibiotic clavamine Ro 22-5417 (Scheme 1.26).[43]

Scheme 1.26



The amide derived from D-glucose has been cyclized in the presence of potassium *tert*-butoxide, to give bicyclic β-lactams in 45% yield. This bicyclic β-lactam has been transformed into 6-*epi*thienamycin in a multi-step process (Scheme 1.27).[44]

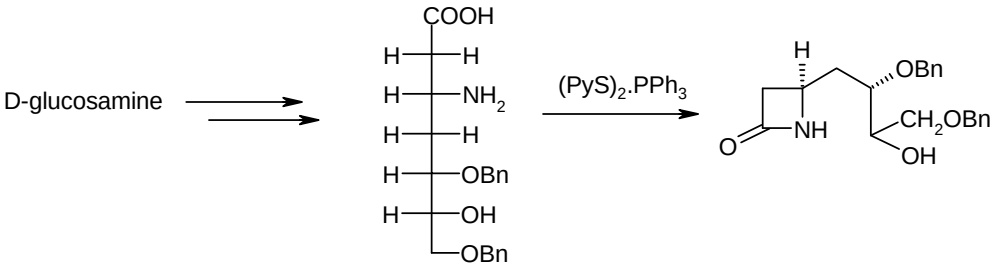
Scheme 1.27



6-epithienamycin

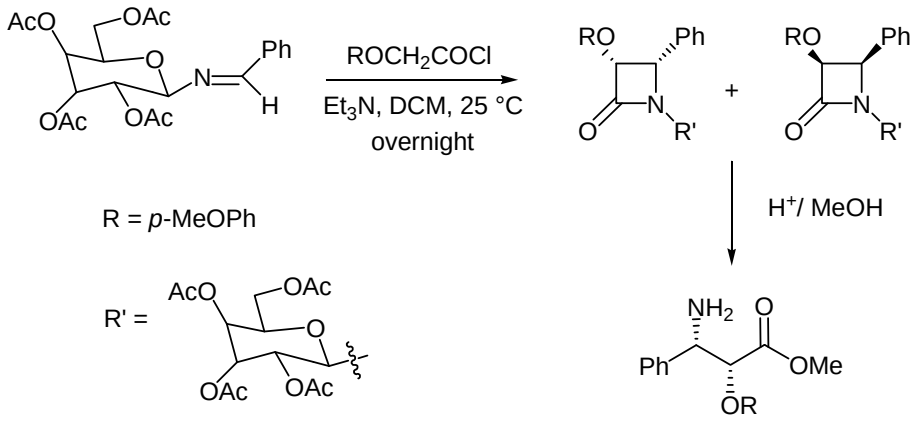
The β-amino acid derived from D-glucosamine has been cyclized to *N*-unsubstituted β-lactam in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. This *N*-unsubstituted β-lactam serves as an intermediate for the synthesis of (+)-thienamycin antibiotic (Scheme 1.28).[45]

Scheme 1.28



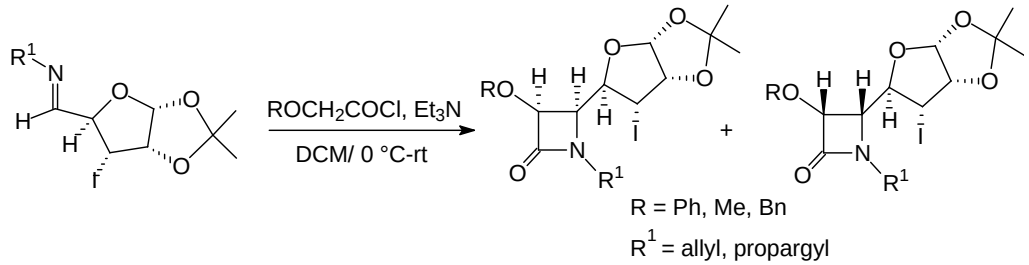
Georg et al. have used the chiral imine derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactose amine for diastereoselective synthesis of β-lactams. They obtained a 60:40 diastereomeric mixture of β-lactams in 90% yield. The α-isomer is transformed to β-amino ester, which is used as a building block for the synthesis of side chain of anticancer agent taxol (Scheme 1.29).[46]

Scheme 1.29



Recently Jayanthi et al.[47] have utilized D-glucose derived imine as a chiral template for the synthesis of azetidin-2-ones. There is no diastereoselectivity in this reaction, however, both the diastereomers can be separated (Scheme 1.30).

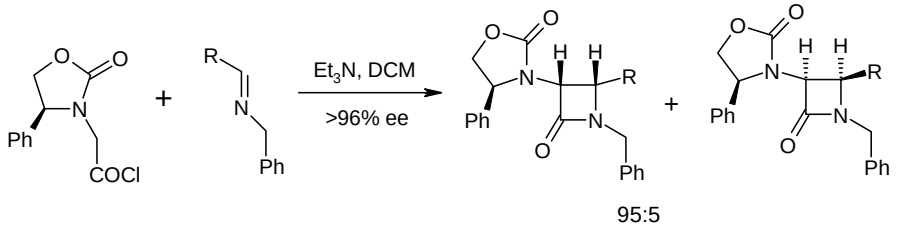
Scheme 1.30



Chiral Ketenes:

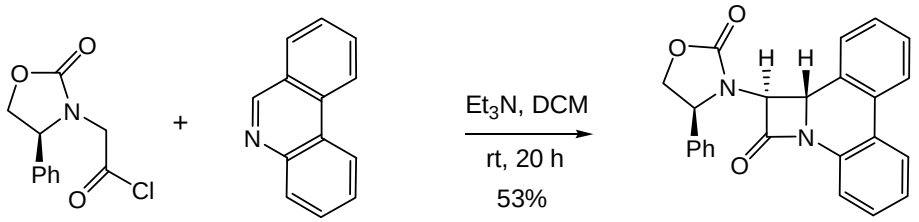
Chiral ketenes have also been used in the Staudinger reaction. However, in most of the cases poor diastereoselectivity has been observed. The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides and triethylamine, with achiral imines afforded optically active β-lactams with high levels of asymmetric induction, typically greater than 96% ee (Scheme 1.31).[48]

Scheme 1.31



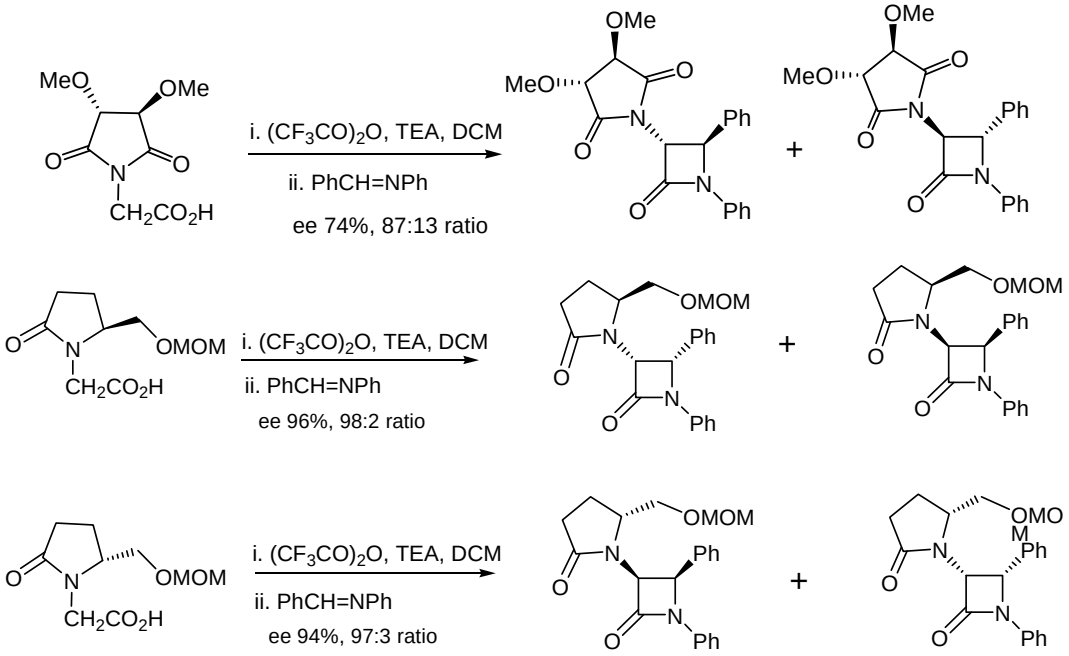
Recently, phenanthridine has been reported to give exclusively *trans* β-lactam with Evans-Sjogren chiral ketene (Scheme 1.32).[49]

Scheme 1.32



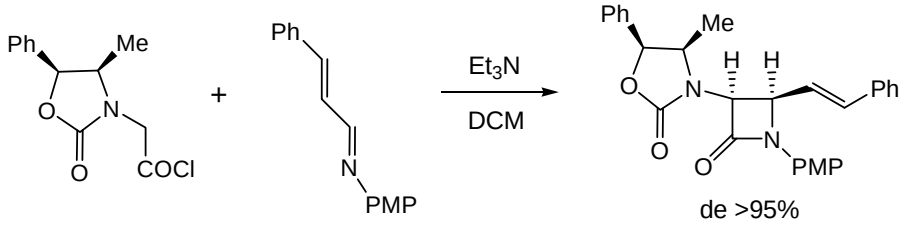
Ikota, in a series of papers, has reported a highly stereoselective β-lactam formation by asymmetric cyclo-condensation employing chiral heterocycles derived from L-(+)-tartaric acid, (*S*)-glutamic acid and (*S*)-serine as ketene precursors.

Scheme 1.33



Ikota used these acids in the presence of trifluoroacetic anhydride and a base to achieve high levels of diastereoselectivity (Scheme 1.33).[50a-b]

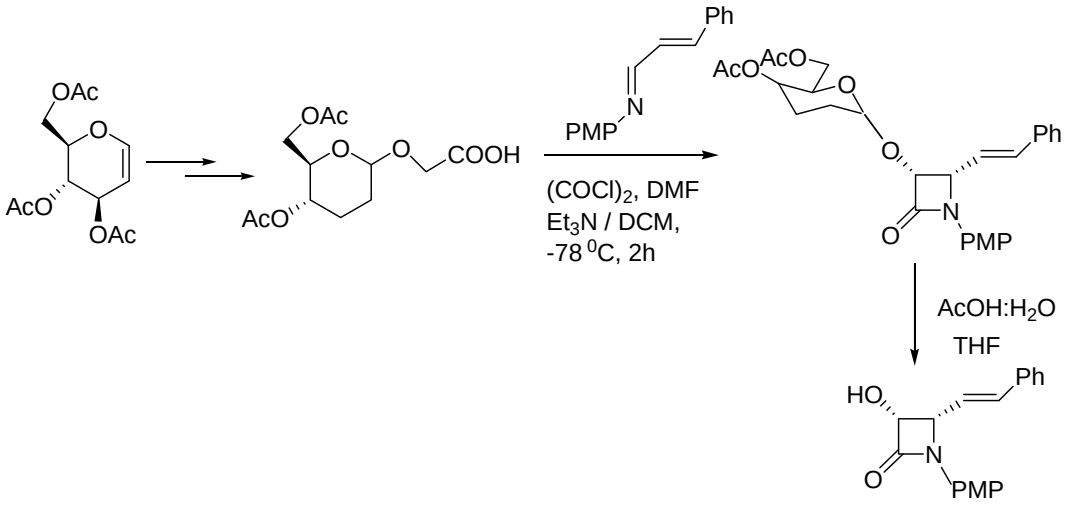
Scheme 1.34



Cooper et al. used a norephedrine derived oxazolidinone derivative as the chiral ketene precursor and achieved >95% diastereoselectivity in the β-lactam formation (Scheme 1.34).[51]

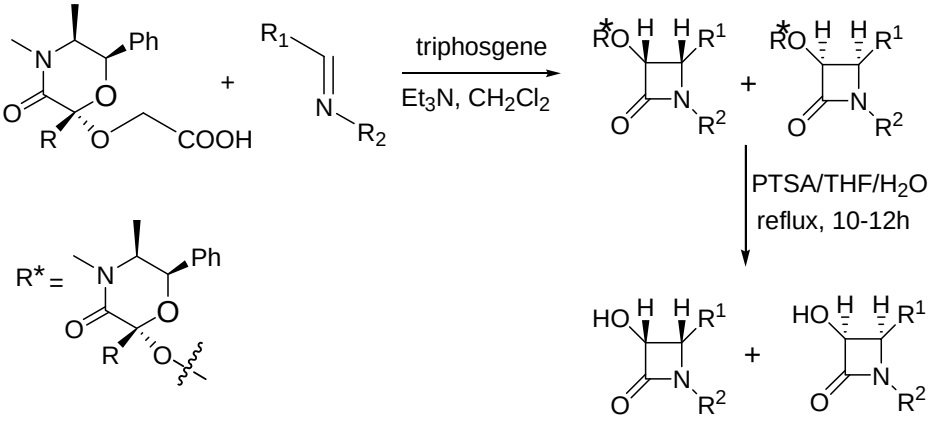
Borer et al. have employed tri-*O*-acetyl-D-glucal derived chiral acid as ketene precursor for diastereoselective synthesis of β-lactams and obtained a diastereoselectivity of 70:30 in this reaction. The sugar moiety was deprotected upon treatment with acetic acid/water to generate 3-hydroxy-β-lactam, which may be used in the synthesis of taxol side chain (Scheme 1.35).[50c]

Scheme 1.35



Shinkre et al. have reported the 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* β-lactams in good yields.

Scheme 1.36



The chiral auxiliary, ephedrine, was removed under acidic hydrolysis and furnished both the enantiomers of 3-hydroxy-4-aryl β-lactams. One of these hydroxy β-

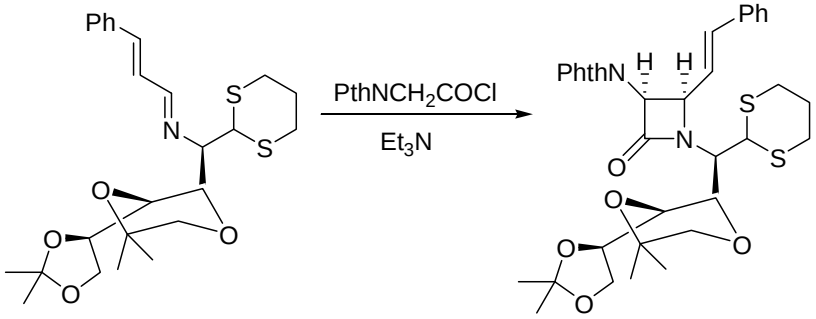
lactams (β isomer) is an advanced intermediate for the synthesis of taxol side chain (Scheme 1.36).[50d]

Chiral Amines:

Asymmetric Staudinger reaction using imines derived from achiral aldehydes and chiral amines often result in poor diastereoselectivity in β-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.

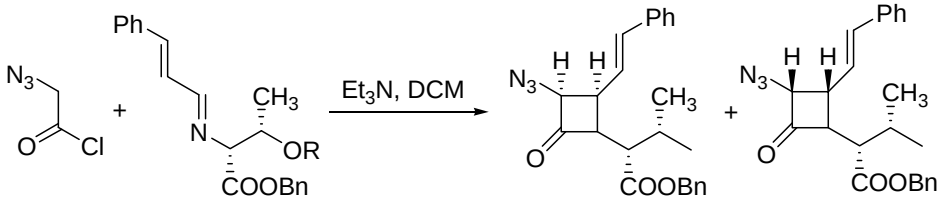
Asymmetric Staudinger reaction using imines derived from D-Glucosamine[52] and cinnamaldehyde have resulted in diastereospecific formation of single *cis* β-lactam (Scheme 1.37).

Scheme 1.37



D-Threonine has also been used as chiral auxiliary in the Staudinger reaction. In this case the diastereoselectivity was dependent on the bulkiness of the substituents (Scheme 1.38).[53]

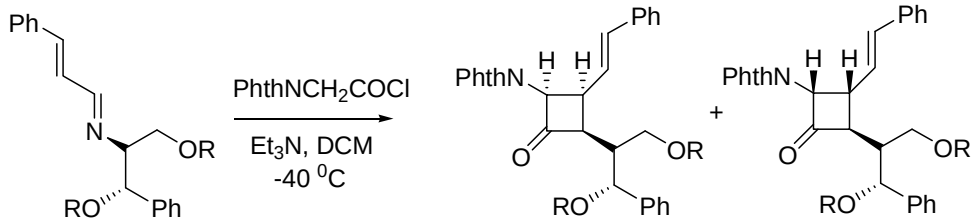
Scheme 1.38



R = TBDMS (ratio 90:10)
R = H (ratio 1:1)
R = $SiPh_3$ (ratio 95:5)

Gunda[54] has used a chiral imine derived from (1*S*, 2*S*)-2-amino-1-phenyl-1,3-propanediol in the ketene-imine cycloaddition reaction and here too, the hydroxy protecting group dictated the diastereoselectivity (Scheme 1.39).

Scheme 1.39

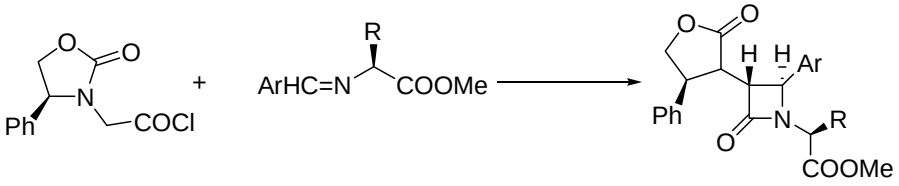


R = TBDMS (ratio 90:10)

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*)-α-amino acid esters[55] (Scheme 1.40).

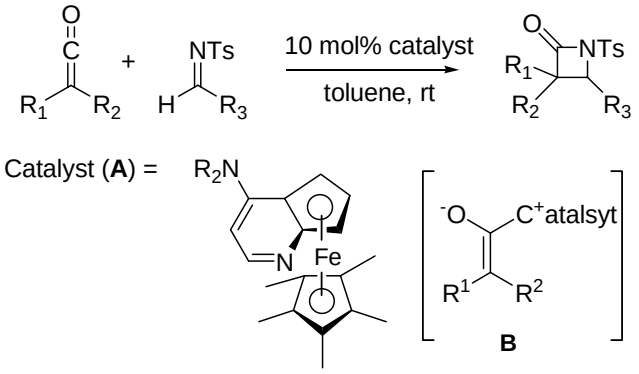
Scheme 1.40



Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu[56] have reported a highly enantioselective synthesis of β-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 1.41). The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka[57] has observed.

Scheme 1.41



Mechanism of Staudinger reaction:

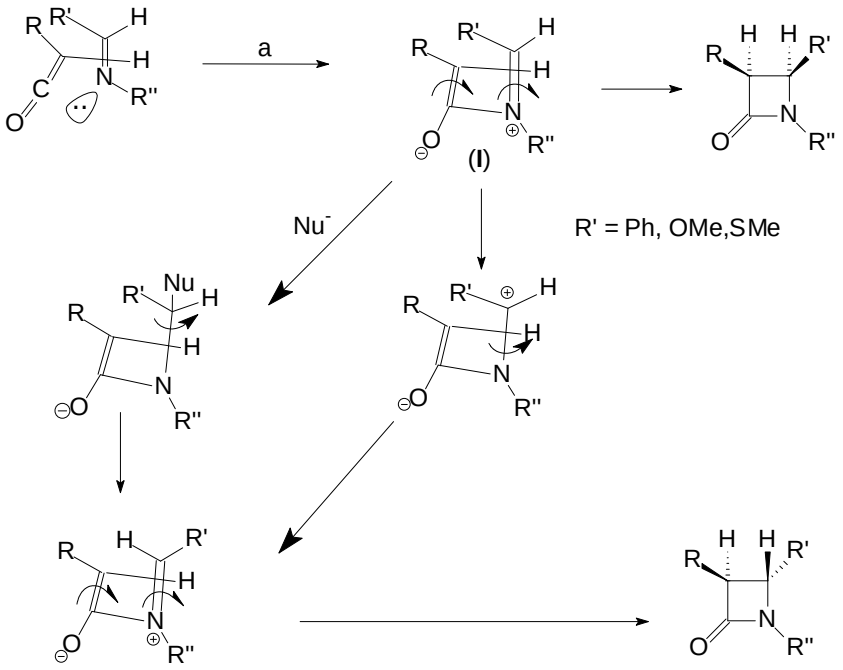
Although the ketene-imine cycloaddition (Staudinger reaction) has been known for a century, the mechanism and the stereochemical course of this reaction are still obscure. Recent efforts in this aspect have resulted in a series of papers by various groups.[58] Based on these results, a two-step zwitterionic 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.[59] That the zwitterion intermediate was indeed formed from a ketene precursor was proved by results from Lynch's group[60] wherein, treatment of the acid chloride with diisopropylamine in an FT-IR cell displayed a strong band at 2120 cm^{-1}, 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).[61] 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. [51]

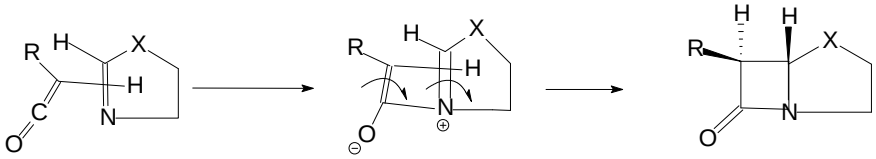
It is further believed that the attack of the imine occurs from the less hindered side of the ketene while forming the zwitterionic intermediate (I). Rotation of the imine into the plane of the ketene followed by a *con*-rotatory ring closure produces the thermodynamically less stable β-lactam in which 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.

Scheme 1.42



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* β-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 1.43



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* β-lactam since the imine substituents are held in *syn* geometry and the same has been observed in most cases (Scheme 1.43).

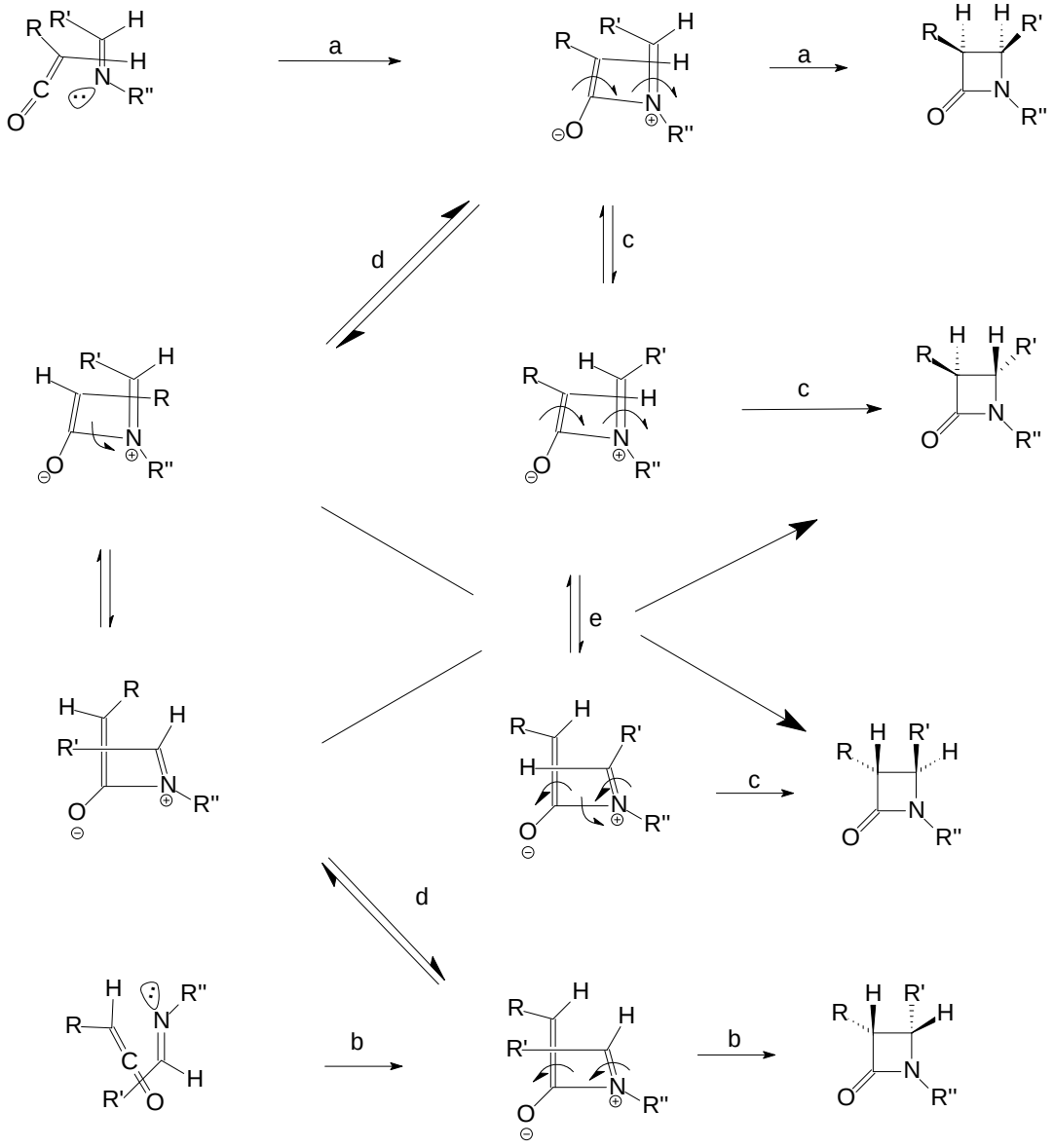
Asymmetric Induction:

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 β-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.

The formation of the thermodynamically more stable *trans* β-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 β-lactams are then accessible from any single zwitterion by isomerization followed by rotation about the C-N single bond (*path e*).

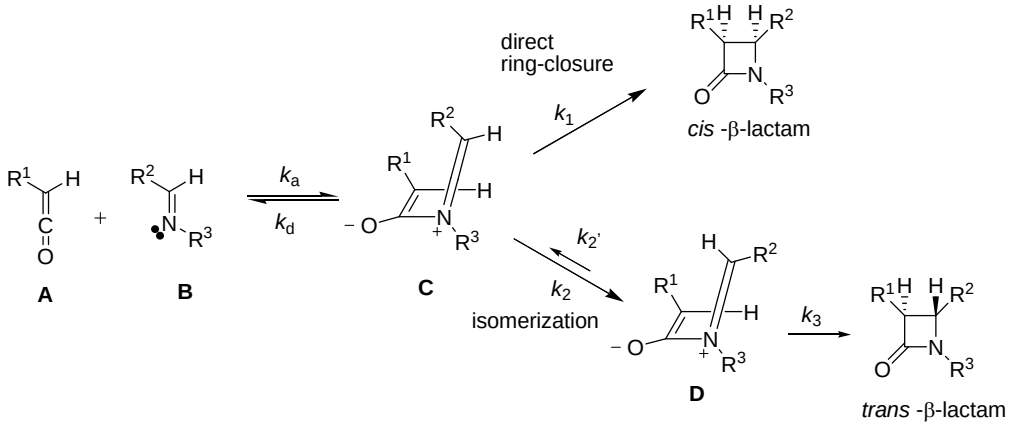
Scheme 1.44



Recently, Xu et al. [62] 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 β-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*-β-lactam formation while reverse substituents lower the ring closure (decrease k_1), leading to a preference for *trans*-β-lactam (Scheme 1.45).

Scheme 1.45



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 β-lactam products depends upon k_1/k_2 ratio and the electronic effect of the substituents is a key factor in deciding the stereoselectivity.

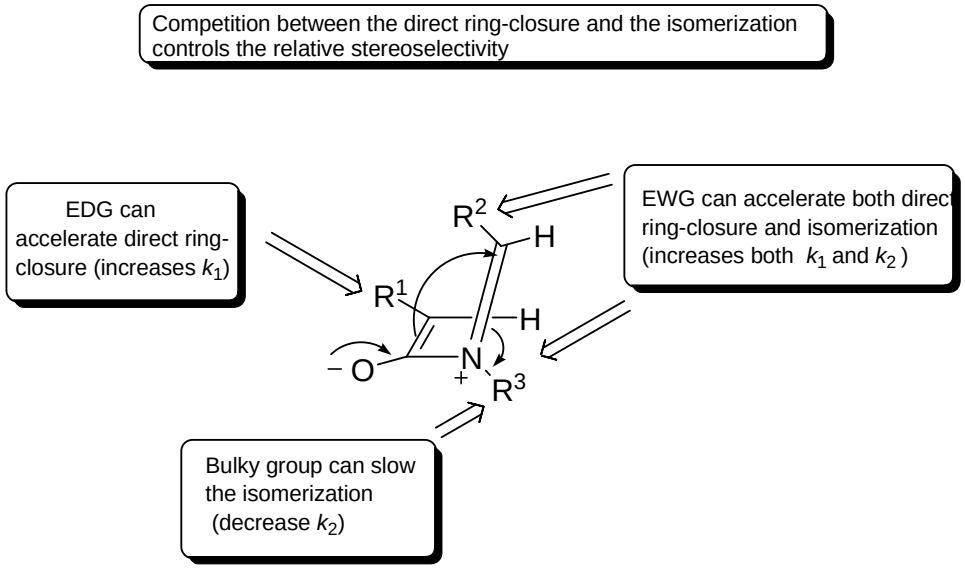


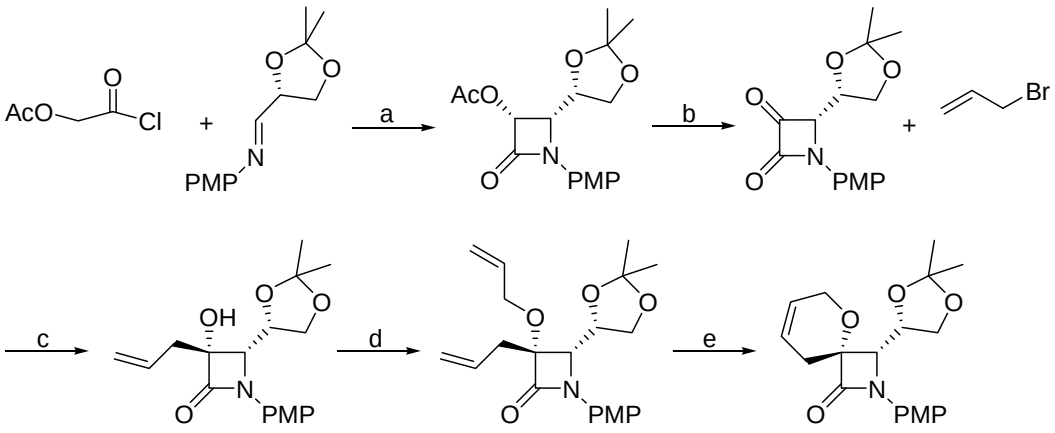
Figure 9

1.2: Background for the present work

β-Lactams being a structural motif in most widely used antibiotics,[63] have occupied a pivotal position in medicinal chemistry for almost a century now. Besides their use as antibiotics, β-lactams are increasingly being used as synthons for biologically important molecules.[64] Apart from this; recent literature has seen a spurt in the number of other diverse applications of the β-lactams. They have been shown to increase the expression of glutamate transporters through gene activation.[65] β-lactams have also been found to act as cholesterol acyl transferase inhibitors,[66] thrombin inhibitors,[67] human cytomegalovirus protease inhibitors,[68] matrix metalloprotease inhibitors,[69] human leucocyte elastase,[70] cysteine protease[71] and apoptosis inductors.[72] In particular, spirocyclic β-lactams have attracted attention as they have been shown to be β-turn mimetics[73] and precursors for α,α-disubstituted β-amino acids.[74] The spiro β-lactam moiety forms a part of the chartellins, a family of marine natural products.[75] Spiro β-lactams have also been found to act as poliovirus and human rhinovirus 3C-proteinases inhibitors.[76] They have also found application as cholesterol absorption inhibitors.[77]

Alcaide *et al.*[78] have reported a metal assisted synthesis of spirocyclic β-lactams wherein a D-glyceraldehyde derived imine was treated with acetoxy acetyl chloride to get β-lactam which on transesterification and oxidation yielded enantiopure azetidin-2,3-diones which on further allylations and subsequent Grubbs metathesis reaction yielded spiro-β-lactams (Scheme 1.46).

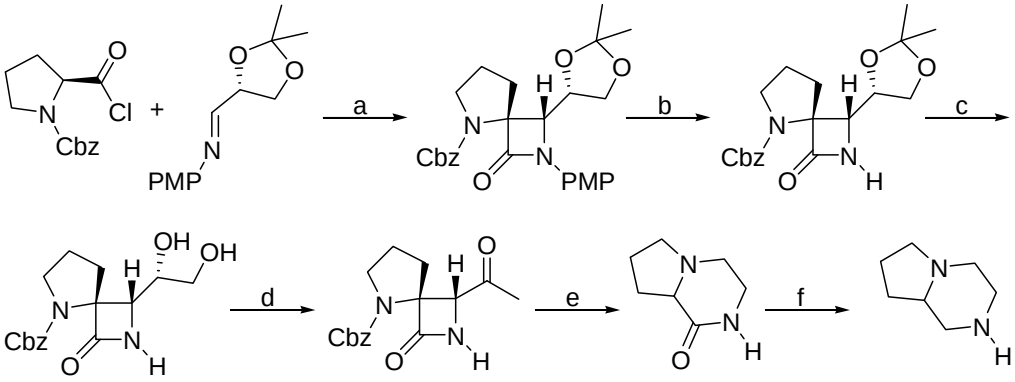
Scheme 1.46



Reagents and conditions: a) Et_3N, DCM, 0 °C-rt 12h; b) i) Na_2CO_3, $NaHCO_3$, MeOH, overnight; ii) $(COCl)_2$, DMSO, -78 °C; c) In/NH_4Cl, THF/H_2O; d) allyl bromide (1.6 eq), TBAI (cat) NaOH (aq. 50%)-DCM (1:1), rt, 16h; e) Grubbs catalyst (5%), toluene, reflux.

Gonzalez *et al.*[79] have reported a stereoselective synthesis of spiro-β-lactams using a proline derived ketene and D-glyceraldehyde derived imine (Scheme 1.47). These spiro-β-lactams were further transformed into 1,4-diazabicyclo[4,3,0] nonanes. The method has also been used for the synthesis of conformationally restricted σ-receptor ligands.

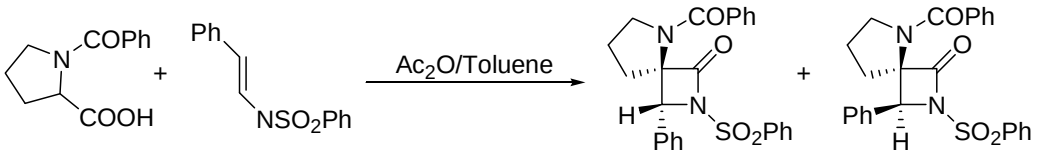
Scheme 1.47



Reagents and conditions: a) Et_3N, DCM, -78 °C-rt; b) CAN, CH_3CN-H_2O, 0 °C, 1h; c) PTSA, THF-H_2O; d) $NaIO_4$, MeOH-H_2O; e) H_2/Pd-C; f) LAH, THF

In another report on the stereoselective synthesis of spiro-β-lactams La Rosa *et al.*[80] describe the use of benzene sulfonamide derived imine to obtain *N*-phenylsulfonyl substituted spiro-β-lactams using acetic anhydride as a dehydrating agent yielding a diastereomeric mixture with 3:1 ratio (Scheme 1.48).

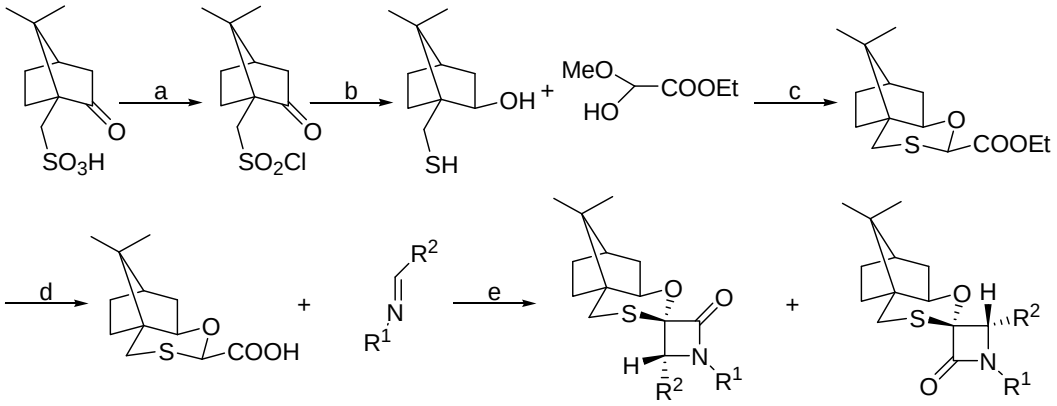
Scheme 1.48



3:1

Krishnaswamy *et al.*[81] from our lab have developed a stereoselective synthesis of spiro-β-lactams from a (1*S*)-(+)-10-camphor sulfonic acid derived chiral acid using triphosgene as an acid activator (Scheme 1.49). The *exo*-thiol derived from camphor sulfonic acid on cyclization with ethyl glyoxalate followed by hydrolysis yielded the required chiral acid which on Staudinger cycloaddition reaction with imine afforded spiro-β-lactams.

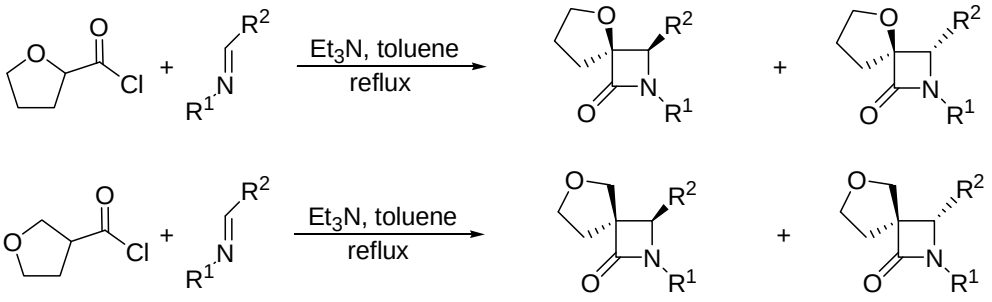
Scheme 1.49



Reagents and conditions: a) $SOCl_2$, reflux, 4h; b) LAH, ether, -78 °C - rt, 3h, reflux, 8h; c) $BF_3.Et_2O$, DCM, 0 °C, 30 min; d) MeOH-KOH, rt, 5h; e) Et_3N, triphosgene, DCM, 0 °C - rt, 12h.

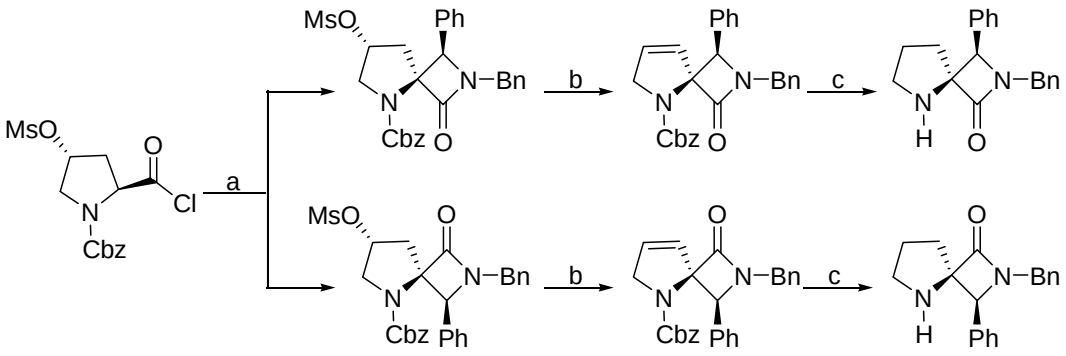
Gonzalez *et al*.[82] have reported synthesis of spiro-β-lactams from tetrahydrofuroyl chloride derived ketene (Scheme 1.50). They have studied different unsymmetrical ketenes and the electronic effects operating in each of them. The theoretical study accompanying this work points towards a strong torquoelectronic effect playing a major role in governing the stereochemistry of final spiro-β-lactams.

Scheme 1.50



In another example of stereoselective synthesis of spiro-β-lactams Thiruvazhi *et al*.[83] have reported use of a 4-hydroxy proline derived chiral ketene (Scheme 1.51). They have used the chirality of *C*-4 of 4-hydroxy proline to introduce asymmetry in the resultant spiro-β-lactams. After formation of spiro-β-lactams, chiral center at *C*-4 was destroyed to obtain proline derived spiro-β-lactams. They have attributed the stereochemical results to the steric effect of bulky *N*-Cbz group.

Scheme 1.51



Reagents and conditions: a) PhCH=NBn, Et_3N, DCM, rt, 14h; b) K_2CO_3, MeOH, rt, 16h, 70 °C, 3h; c) H_2, 10% Pd-C, EtOH.

1.3: Present work

This chapter deals with the stereoselective synthesis of spiro-β-lactams from a D-(+)-glucose derived chiral ketene, generated *in situ* from the corresponding acid chloride using triethyl amine, *via* a Staudinger cycloaddition reaction with different imines.

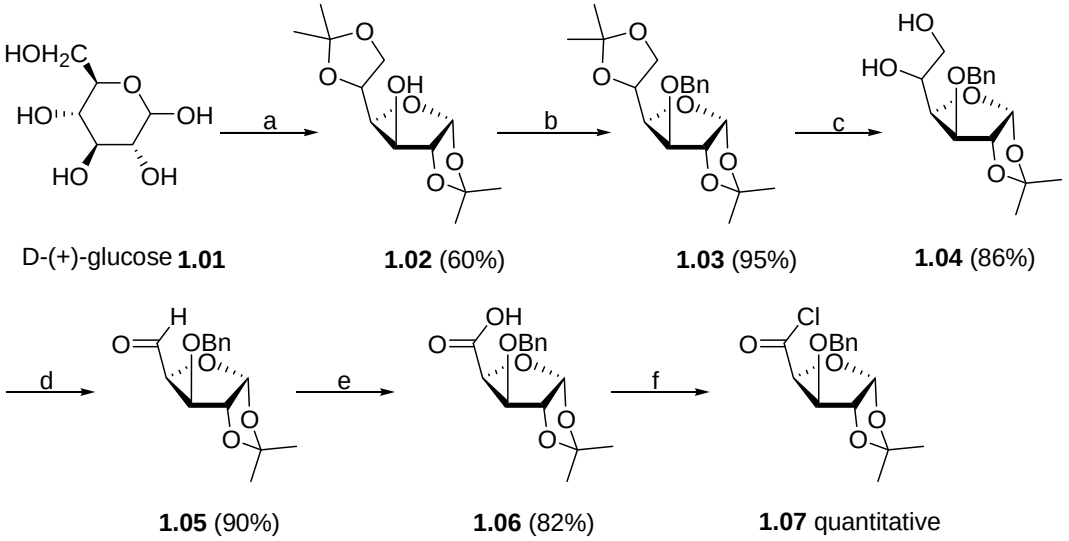
D-(+)-glucose is a widely used naturally available enantiopure starting material. Its widespread use is mainly due to its easy availability, inexpensiveness and the plethora of chemical transformations it can be subjected to. Apart from D-(+)-glucose, carbohydrates, as a class of compounds has been a popular choice as an enantiopure starting material for the stereoselective synthesis of β-lactams.[84] We too, have been involved in the use of D-(+)-glucose as a starting material for synthesis of various functionalized β-lactams.[85] However, there are no reports available in the literature on the use of D-(+)-glucose, or for that matter any other carbohydrate in the synthesis of spiro-β-lactams. We were thus interested in the synthesis of spiro-β-lactams, starting from D-(+)-glucose and the stereochemical implications of the same.

1.4: Results and Discussion

We started our synthesis of spiro-β-lactams with D-(+)-glucose. D-(+)-glucose (**1.01**) on reaction with dry acetone, anhydrous copper sulphate and concentrated sulfuric acid following a reported procedure[86] gave glucose diacetonide (**1.02**) in nearly 60% yield (Scheme 1.52). The hydroxy group of glucose diacetonide was then protected as its benzyl ether using sodium hydride and benzyl bromide in DMF to obtain compound **1.03** in good yield. Compound **1.03** was then converted to diol **1.04** by selectively cleaving one of the acetonide groups using 0.8 % H_2SO_4 in MeOH. Diol **1.04**

was then subjected to oxidative glycolic cleavage using sodium periodate supported on silica gel.[87] The reaction proceeded cleanly to afford the corresponding aldehyde **1.05** in excellent yield. The aldehyde **1.05** was then oxidized to acid **1.06** in very good yield, using mild conditions in form of silver oxide which was generated *in situ* from silver nitrate and aq. NaOH. Carboxylic acid **1.06** on a simple reflux with oxalyl chloride in anhydrous DCM yielded corresponding acid chloride **1.07**.

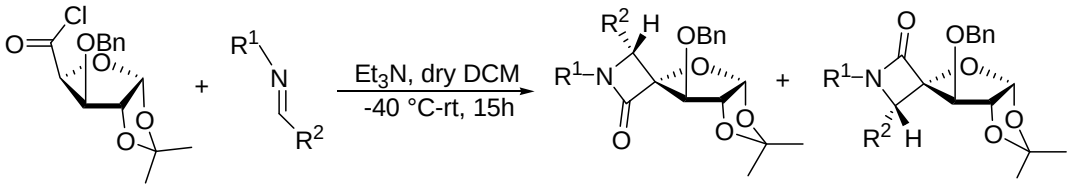
Scheme 1.52



Reagents and conditions: a) dry acetone, anhydrous $CuSO_4$, conc. H_2SO_4, rt, 48 h.b) NaH, BnBr, dry DMF, 0 °C- rt, 3 h. c) 0.8% H_2SO_4, MeOH, rt, 24 h. d) silica gel, 0.65 M aq.$NaIO_4$, DCM, rt, 2 h. e) $AgNO_3$, aq. KOH, HCl, rt, 1h. f) $(COCl)_2$, dry DCM, reflux, 4 h.

Having prepared the required acid chloride **1.07** the stage was set for the synthesis of glucose derived spiro-β-lactams. The acid chloride **1.07** was then used as ketene precursor in Staudinger cycloaddition reaction with various imines (**1.08a-i**) and triethyl amine as base to get a diastereomeric mixture of spiro-β-lactams **1.09a-i** and **1.10a-i** (Scheme 1.53, Table 1). The diastereomeric ratio of **1.09:1.10** varied over a small range with the average being around 70:30. Both the diastereomers in each case could be successfully separated with the help of careful flash column chromatography.

Scheme 1.53



1.07 **1.08a-i** **1.09a-i** **1.10a-i**

	R^1	R^2
a	PMP	PMP
b	Ph	PMP
c	Ph	Ph
d	PMP	Ph
e	4-Cl-Ph	Ph
f	Ph	styryl
g	PMP	styryl
h	4-Me-Ph	Ph
i	Ph	*p*-tolyl

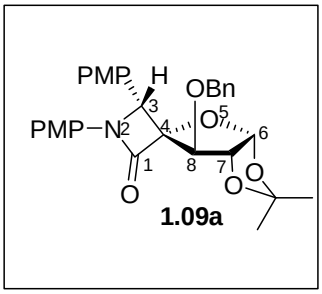
Table 1. Synthesis of spiro-β-lactams **1.09a-i** & **1.10a-i**

1.09& 1.10	**R^1**	**R^2**	**Yield (%)[a]**	**Isomers[b] 1.09:1.10**
a	PMP	PMP[c]	71	70:30
b	Ph	PMP	65	72:28
c	Ph	Ph	62	70:30
d	PMP	Ph	62	68:32
e	4-Cl-Ph	Ph	59	65:35
f	Ph	Styryl	69	71:29
g	PMP	Styryl	67	68:32
h	4-Me-Ph	Ph	72	64:36
i	Ph	*p*-Tolyl	70	64:36

[a] Isolated yields of diastereomeric mixture.
[b]Ratio of diastereomers was determined by ^{1}H NMR.
[c] PMP = *p*-Methoxyphenyl.

Compound **1.09a** from the series of major diastereomers is chosen as a representative for characterization and spectral discussion. The IR spectrum of **1.09a** showed an intense band at 1759 cm^{-1} characteristic of a β-lactam. In ^{1}H NMR, the two

acetonide methyl groups appeared as a singlet at 1.35 and 1.73 ppm whereas the methyl groups from the two PMP moieties resonated as two singlets at 3.75 and 3.79 ppm. The proton on the carbon atom of the glucose ring bearing the benzyloxy group appeared as a doublet at 4.47 ppm (J = 1.2 Hz). One of the protons from the methylene group of the benzyloxy group and the proton attached to C-7 of the glucose ring resonated together as a multiplet between 4.62-4.68. The other proton from the methylene group appeared at 4.83 ppm as a doublet (J = 11.6 Hz). The sole proton on the lactam ring (C3-H) appeared as a singlet at 5.39 ppm. The proton C6-H flanked by two adjoining oxygen atoms appeared deshielded at 5.50 ppm as a doublet (J = 4.1 Hz). The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.79 and 6.87 ppm (J = 9.1, 8.7 Hz). The remaining nine aromatic protons clustered together as a multiplet at 7.22-7.36 ppm.

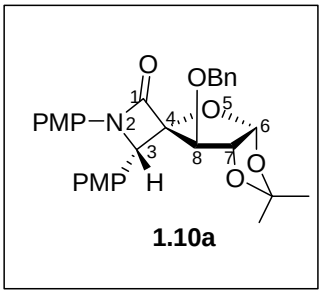


1.09a

In ^{13}C NMR spectrum, the two acetonide carbons appeared at 26.9 and 27.0 ppm. The two methoxy carbons appeared at 55.2 and 55.4 ppm. The C-3 carbon resonated at 61.9. The methylene carbon from the benzyloxy moiety was seen at 72.7 which was confirmed by ^{13}C DEPT experiment. The carbons C-7 and C-8 from the glucose portion appeared at 83.2 and 83.9 ppm. The spiranic carbon appeared at 95.3 ppm. The anomeric carbon C-6 was seen at 105.3 ppm. The quaternary carbon from the acetonide moiety appeared at 113.9 ppm. A total of ten peaks for aromatic carbon atoms were seen in the region 114.2-136.9 ppm. The quaternary carbons with the methoxy substituents in both the PMP rings appeared at 156.2 and 159.6 ppm. The carbonyl carbon of the β-lactam appeared at 163.6 ppm.

The structure was further supported by the mass spectrum which displayed a peak at m/z 518 corresponding to M+1.

Among the series of minor isomers **1.10a-i**, **1.10a** is chosen as a representative compound for characterization and spectral discussion. The IR spectrum of **1.10a** showed an intense band at 1753 cm^{-1} characteristic of the lactam carbonyl. In ^{1}H NMR, the two acetonide methyl groups appeared as a singlet at 1.03 and 1.23 ppm whereas the methyl groups from the two PMP moieties resonated as two singlets at 3.72 and 3.75 ppm. The carbon atom C-8 of the glucose ring bearing the benzyloxy group appeared as a

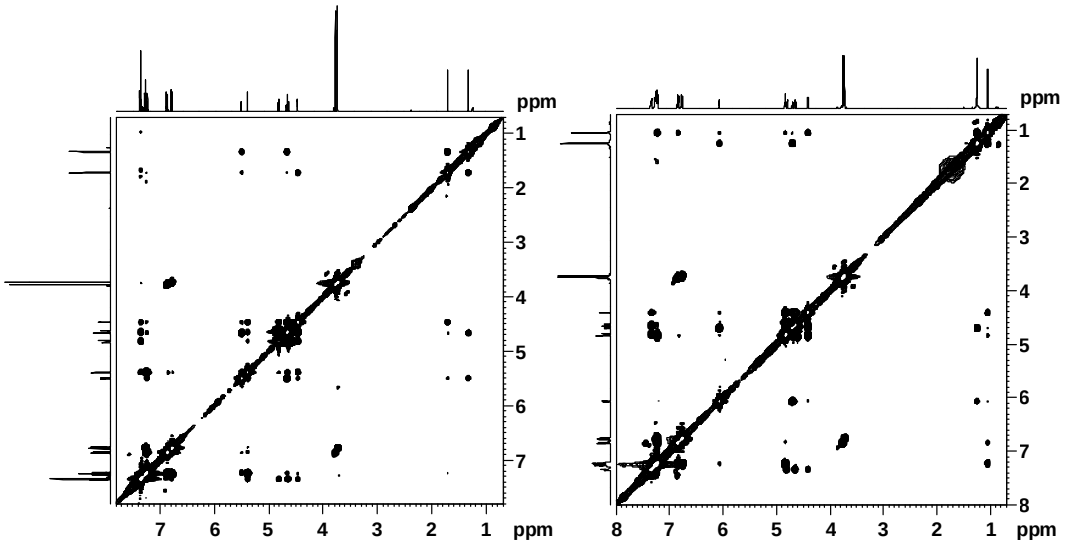


1.10a

doublet at 4.40 ppm (J = 1.2 Hz). One of the protons from the methylene group of the benzyloxy group and the proton attached to C-7 of the glucose ring resonated together as a multiplet between 4.60-4.70. The other proton from the methylene group appeared at 4.81 ppm as a doublet (J = 12.4 Hz). The sole proton on the lactam ring (C3-H) appeared as a singlet at 4.82 ppm. The proton C6-H flanked by two adjoining oxygen atoms appeared deshielded at 6.06 ppm as a doublet (J = 4.0 Hz). The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.76 and 6.83 ppm (J = 9.1, 8.7 Hz). The remaining nine aromatic protons clustered together as a multiplet at 7.19-7.36 ppm.

In the ^{13}C NMR spectrum, the two acetonide carbons appeared at 26.3 and 26.7 ppm. The two methoxy carbons appeared at 55.0 and 55.3 ppm. The C-3 carbon resonated at 66.5. The methylene carbon from the benzyloxy moiety was seen at 72.4 which was confirmed by ^{13}C DEPT experiment. The carbons C-7 and C-8 from the glucose portion appeared at 83.9 and 85.4 ppm. The spiranic carbon appeared at 94.7 ppm. The anomeric carbon C-6 was seen at 106.2 ppm. The quaternary carbon from the acetonide moiety appeared at 113.7 ppm. A total of ten peaks for aromatic carbon atoms were seen in the region 113.8-137.0 ppm. The quaternary carbons with the methoxy substituents in both the PMP rings appeared at 156.2 and 159.9 ppm. The carbonyl carbon of the β-lactam appeared at 163.3 ppm. The structure was further supported by the mass spectrum which displayed a peak at m/z 518 corresponding to M+1.

To find out the absolute configurations of newly formed chiral centers we further carried out NOE experiments on one of major and minor isomers respectively. The NOE experiments carried out on major diastereomer **1.09a** and minor isomer **1.10a** revealed different interactions, with the help of which stereochemistry was elucidated. In major diastereomer **1.09a**, the only proton on the β-lactam ring (C3-H) showed NOE interactions with C8-H and the *ortho* protons of the aromatic ring (C3-PMP) on the C-3 carbon (Figure 10 and Figure 12).



Major isomer **1.09a** Minor isomer **1.10a**

Figure 10 NOE spectra for **1.09a** (major) and **1.10a** (minor) isomers.

In the minor diastereomer **1.10a**, too the only proton on the β-lactam ring (C3-H) showed NOE interactions with C8-H and the *ortho* protons of the aromatic ring (C3-PMP) on the C-3 carbon (Figure 10 and Figure 12). Apart from these interactions, another interaction was observed in **1.10a** which distinguished it from **1.09a**. In compound **1.10a**, proton C3-H showed interaction with one of the methyl groups of the acetonide moiety, which was not observed in case of compound **1.09a** (Figure 11 and Figure 12). This indicated the fact that, if the plane of furanose ring is considered as a plane of reference then, in compound **1.10a** the C3-H proton of the lactam ring has to be below the plane of reference to show such an interaction with the acetonide methyl protons.

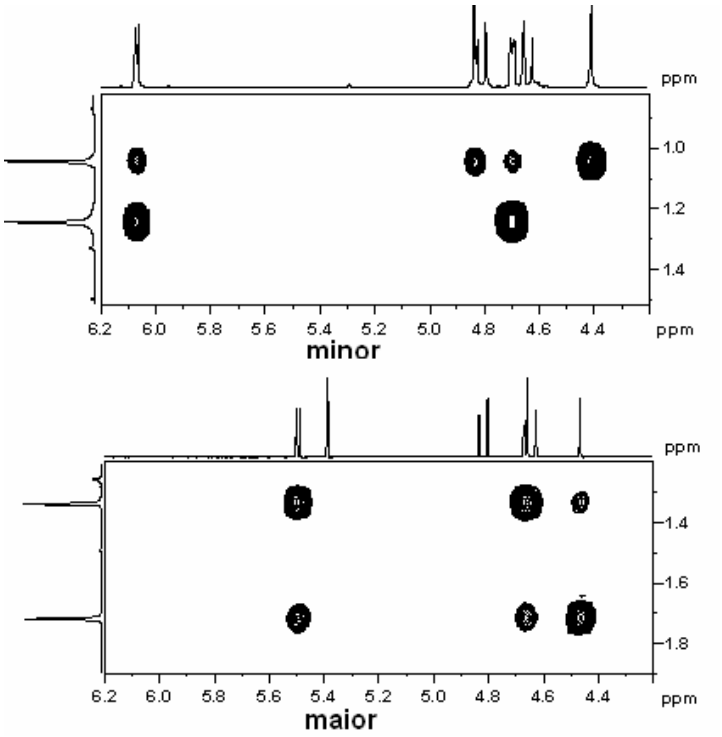
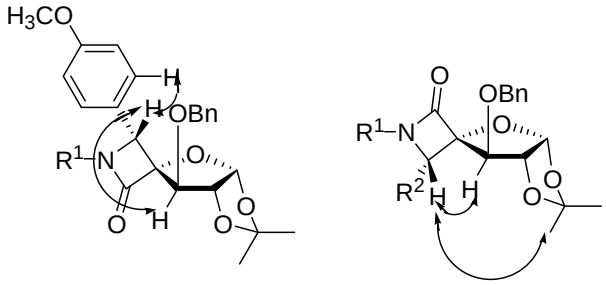


Figure 11 2D NOE spectra showing interaction of C3-H with acetonide group in minor isomer **1.10a** (above) and absence of this interaction in major isomer **1.09a** (below).



1.09a, R^1 = PMP **1.10a**, R^1, R^2 = PMP

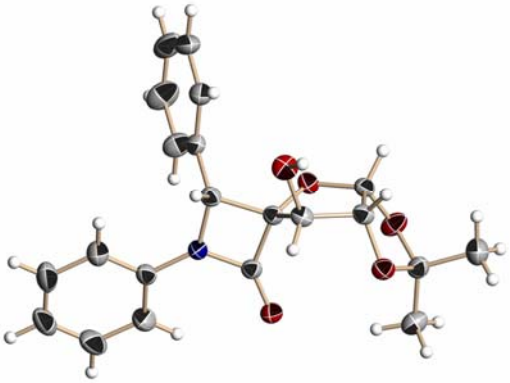
Figure 12 NOE Interactions in major isomer **1.09a** and minor isomer **1.10a**

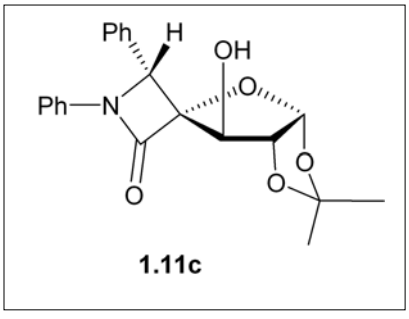
Thus, based on the interactions observed in the NOE experiments, structures **1.09a** (3*R*, 4*R*) and **1.10a** (3*S*, 4*S*) were assigned to the major and minor isomers respectively.

Furthermore, we tried to debenzylation on some of the spiro-β-lactams. Gratifyingly we could get good crystals after C8-O-debenzylation of one of the major isomers **1.09c**. A single crystal X-ray diffraction analysis of debenzylated product **1.11c** (Fig. 13) confirmed the stereochemistry inferred by NOE experiments.

X-ray diffractable crystals of **1.11c** were obtained by crystallization from ethyl acetate and pet. ether. Single crystal X-ray structure determination of $C_{21}H_{21}NO_5$, was carried out using Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo K_α= 0.71073Å) radiation at room temperature. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.3° and with three different settings of φ (0°, 90° and 180°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data collection was monitored by Bruker's SMART program (*Bruker (1998). SMART. Version 5.0. Bruker AXS Inc., Madison, Wisconsin, USA*). All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs (Bruker. *SAINT* (V6.45a). Bruker AXS Inc. Madison.Wisconsin, USA, 2004). SHELX-97 was used for structure solution and full matrix least squares refinement on F^2 (G. M. Sheldrick, *SHELXS97, SHELXL97*: University of Göttingen, Germany. **1997**). Hydrogen atoms were included in the refinement as per the riding model. ORTEP diagram was generated using ORTEP-32 (M. N. Burnett, C. K. Johnson, ORTEPIII. Report ORNL-6895. Oak-Ridge National Laboratory, Oak Ridge, Tennessee, USA, 1996).

Crystal data for **1.11c**: $C_{21}H_{21}NO_5$, M= 367.39, crystal size, 0.17 x 0.16 x 0.11mm^3, T = 297(2) K, crystal system, orthorhombic, space group $P2_12_12_1$; a = 5.7972(5), b = 10.6478(10), c = 30.579(3) Å, v = *1887.6(3)* Å^3, Z = 4, F(000) = 776, d calc [g cm^{-3}] = 1.293, μ [mm^{-1}] = 0.093, absorption correction, multi-scan, T_{min} = 0.9846; T_{max} = 0.9898; 16685 reflection collected, 3317 unique reflections, 2957 observed reflections, 247 refined parameters, R_1 [$I>2\sigma(I)$] = 0.0352, WR_2 = 0.0769 (all data R = 0.0411, $wR2$ = 0.0794), goodness of fit, 1.098, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})= 0.130, -0.102.





1.11c

Figure 13 ORTEP Diagram of compound **1.11c**

Mechanism of spiro-β-lactam formation:

Although the ketene-imine Staudinger cycloaddition is over a century old now, its mechanism and stereochemical course still remain unclear. Studies conducted till date on this topic favour a two step zwitterionic mechanism over a concerted (2+2) cycloaddition. The factors controlling steric course in formation of spiro-β-lactams are even less explored. There are sporadic reports on the study of mechanism of spiro-β-lactam formation using Staudinger cycloaddition in the literature, in which prominently two schools of thought *viz* steric effect and torquoelectronic effect are evident explaining the stereochemical results.

In a report on proline derived spiro-β-lactams,[83] the observed stereochemistry of the β-lactams is ascribed to attack of imine taking place from the less hindered side of ketene. In that case the steric bulk on the nitrogen diverts the attack of the imine towards the less hindered side of the ketene. In another study of the Staudinger reaction of ketenes derived from 2 and 3 tetrahydrofuroyl chloride,[82] the torquoelectronic effect has been invoked to explain the differences in stereochemical outcome. The oxygen atom of the 2-tetrahydrofuroyl chloride derived ketene prefers an outward position in the ring closure step, thereby repelling the attack of imine towards the opposite side of the ketene. Although this ketene exhibits torquoelectronic effects, the two sides of the ketene are not much differentiated sterically.

In this context, it is interesting to imagine a case wherein the steric and torquoelectronic factors counter each other. Our present study makes a case in point. Considering the starting imine to be having *E* configuration, and the approach towards the ketene to be from two different sides, four products are possible. Figure 14 shows the approach of the imine from all possible directions. In case of pathway 1 and pathway 2 the imine attacks from the opposite side of the furanose oxygen delivering two products **1.09** (3*R*, 4*R*), **1.10**(3*S*, 4*S*) *via* a con-rotatory ring closure (Figure 14). Pathways 3 and 4 represent an attack of the imine from the side of the furanose oxygen giving rise to compounds **1.09'** (3*S*,4*R*) and **1.10'** (3*R*,4*S*). With the C-8 bearing a benzyloxy group, steric factors state that attack of the imine should take place from the opposite side (Figure 14) resulting in formation of compounds **1.09'** (3*S*,4*R*) and **1.10'** (3*R*,4*S*). Whereas with the torquoelectronic factors governing the course of reaction, attack should happen from opposite side of the furanose oxygen (pathways 1&2), delivering compounds **1.09** (3*R*,

4*R*) and **1.10** (3*S*, 4*S*). In pathway 1, after the initial attack of the imine resulting in formation of a zwitterionic

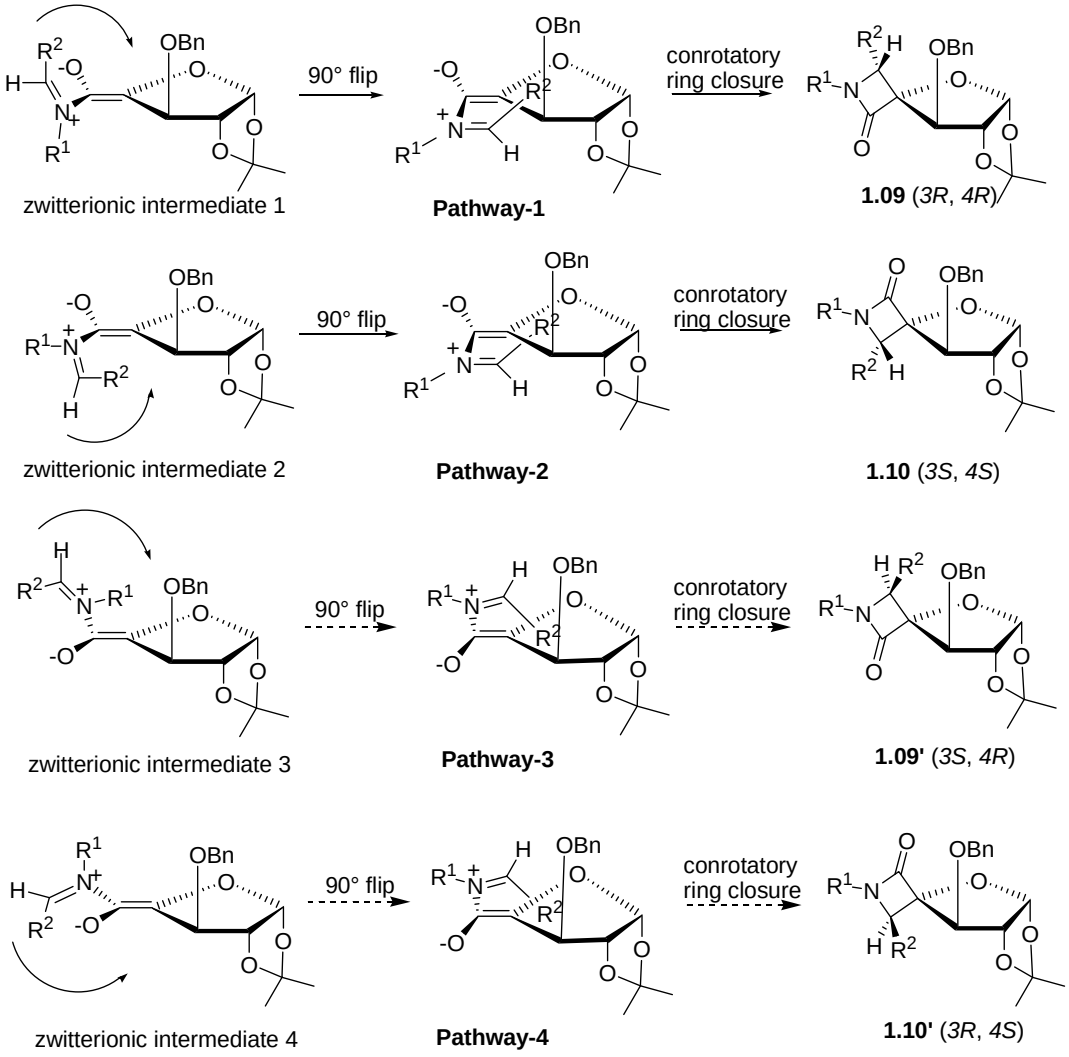


Figure 14 Plausible mechanism for explaining the observed stereochemical outcomes.

intermediate-1, the next step (90° flip) in which the imine part attains coplanarity with the ketene should proceed with some resistance from the benzyloxy substituent on the α-carbon (C-8) of the ketene. This should divert the attack of the imine to the other side (pathways 3&4) of the ketene; at least in part, if not exclusively. But defying the steric constraints reaction showed a strong inclination towards delivering products governed by the torquoelectronic effect. With the structures of the actual products found to be **1.09** and **1.10,** it is pretty clear that the torquoelectronic factor exerts a stronger effect in the reaction. Each side of the ketene is additionally differentiated into two faces: top face (pathways-1,3) and bottom face (pathways-2,4). Among the two diastereomers,

1.09 (pathway-1) was found to be major and **1.10**, minor, (pathway-2) although the diastereoselectivity was only moderate (Table-1). This can be rationalized by proposing that, the bulky 6,7-*O*-isopropylidene moiety, to some extent, prevents the attack of the imine from bottom face, so that the zwitterionic intermediate-2 (pathway-2) is formed to a lesser extent than the zwitterionic intermediate-1 (pathway-1) resulting in the observed proportion of the diastereomers.

1.5: Conclusion

In conclusion, a stereoselective synthesis of spirocyclic β-lactams from a D-(+)- glucose derived chiral acid has been achieved. The reaction showed strong propensity towards following a course governed by the torquoelectronic effect. Although four diastereomers are possible, only two diastereomers were obtained with the imine attacking from the hindered side illustrating the strong influence of the torquoelectronic effect. The facial selectivity was moderate.

1.6: Experimental

1.6.1: 1,2;5,6-di-*O*-isopropylidene-α-glucofuranose (1.02):

A suspension of anhydrous D-glucose (**1.01**) (28.0 g, 155.40 mmol), anhydrous cupric sulfate (28.2 g, 176.70 mmol) and conc. H_2SO_4 (2 mL) in dry acetone (600 mL) was stirred at room temperature for 48 h. The reaction mixture was then neutralized with K_2CO_3 (200 g) and stirred overnight. The reaction mixture was filtered through a Buchner funnel and the acetone layer was dried over sodium sulfate and evaporated *in vacuo*. The resulting solid was recrystallized from hot cyclohexane to give pure white crystalline glucose diacetonide **1.02** in 60 % yield (24 g), mp 110 °C (lit. 109-110 °C).

1.6.2: 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-glucofuranose (1.03):

A solution of diacetonide **1.02** (5.2 g, 0.02 mol) in anhydrous DMF (100 mL) was added to a suspension of NaH (2 g, 0.08 mol) under argon atmosphere, with cooling. The suspension was stirred at room temperature for 30 min. and a solution of benzyl bromide was added drop wise. The reaction mixture was stirred for 2.5 hrs. at room temperature and the excess reagent was decomposed by the careful addition of MeOH (10 mL), and the solvents were removed. The residue was extracted with DCM (3 x 50 mL). Combined organic extracts were washed with water (3 x 50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvents *in vacuo* yielded compound **1.03** as a syrup (6.7 g, 95%).

1.6.3: 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-glucofuranose (1.04):

To a solution of compound **1.03** (3 g, 8.57 mmol) in MeOH (30 mL), 0.8% H_2SO_4 (3 mL) was added and allowed to stir at room temperature till the disappearance of the starting material (TLC, 24 h). The acid was quenched with triethyl amine (3 mL). The solvent was removed under reduced pressure. The residue was dissolved in DCM, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give glycol **1.04** (2.3 g, 86%) which was pure enough to be used for next reaction without further purification.

1.6.4: 6-Benzyloxy-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxole-5-carbaldehyde (1.05):

To a vigorously stirred suspension of chromatographic grade silica gel (13 g) in DCM (80 mL) was added a 0.65 M aqueous solution of $NaIO_4$ (15 mL) drop wise with stirring. Diol **1.04** (1.77 g, 5.71 mmol) in DCM (20 mL) was then added and the reaction was monitered by TLC until disappearance of the starting material (2 h). The mixture was filtered, washed with water, dried over anhydrous Na_2SO_4 and concentrated to obtain pure aldehyde **1.05** (1.43 g, 90%).

1.6.6: 3-Benzyloxy-4,5-*O*-isopropylidene-tetrahydro-furan-2-carboxylic acid (1.06):

To the aldehyde **1.05** (0.566 g, 2.02 mmol) was added an aqueous solution of $AgNO_3$ (0.588 M, 8.91 mL). To the resulting emulsion was added aqueous KOH solution (0.91 M, 11.4 mL). A dark black precipitate was formed which was stirred for further an hour. It was then filtered through a Buchner funnel. The filtrate was cooled to 0 °C and acidified with approximately 6 M aqueous HCl to *p*H = 2. The acidified solution was then extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give acid **1.06** (0.490 g, 82%) as a white solid.

MP	**:**	140-141 °C
IR ($CHCl_3$)	**:**	1733, 2800-3300 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.26 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 4.25-4.81 (5H, m, C_2-*H*, C_3-*H*, C_4-*H*, O-C*H*$_2$-Ph), 6.02 (1H, d, *J* = 3.6 Hz, C_5-*H*), 7.16-7.29 (5H, m, Ar-*H*) 10.2 (1H, bs, -COO*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 26.2, 26.9, 72.5, 79.5, 81.8, 82.2, 105.7, 112.7, 127.7, 128.0, 128.4, 136.5, 171.8
MS (m/z)	**:**	295 (M+1)
Analysis	**:**	Calculated: C, 61.21; H, 6.16%
$C_{15}H_{18}O_6$		Observed: C, 61.38; H, 6.05%

1.6.7: 3-Benzyloxy-4,5-*O*-isopropylidene-tetrahydro-furan-2-carboxylic acid chloride (1.07):

Acid **1.06** (0.500 g, 1.70 mmol) was dissolved in 10 mL anhydrous dichloromethane and cooled to 0 °C. To the cooled solution was added oxalyl chloride (0.215 g, 1.70 mmol) drop wise. The resultant solution was refluxed for 5h. After 5h the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

1.6.8 General procedure for the synthesis of spiro azetidin-2-ones (1.09a-i & 1.10a-i):

A solution of acid chloride **1.07** (1.5 eq.) in anhydrous dichloromethane was added to a precooled solution of imine (**1.08a-i**) (1 eq.), anhydrous triethylamine (4.5 eq.) in anhydrous dichloromethane at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a diastereomeric mixture. The crude reaction mixture was purified using flash column chromatography (ethyl acetate-petroleum ether) to get diastereomers (**1.09a-i**) and (**1.10a-i**).

Procedure for the preparation of 1.09a and 1.10a:

A solution of acid chloride **1.07** (0.727 g, 2.32 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08a** (0.373 g, 1.54 mmol), anhydrous triethylamine (1 mL, 6.96 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (0.850 g, 71%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09a** and **1.10a**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-bis(4-methoxyphenyl)-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09a):

Isolated as a thick oil in 50% yield.

IR (neat) : 1759 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.35 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 3.75 (3H, s, Ar-OC*H*$_3$), 3.79 (3H, s, Ar-OC*H*$_3$), 4.47 (1H, d, *J* = 1.2 Hz, C_8-*H*), 4.62-4.68 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.83 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.39 (1H, s, C_3-*H*), 5.50 (1H, d, *J* = 4.1 Hz, C_6-*H*), 6.79 (2H, d, *J* = 9.1 Hz, Ar-*H*), 6.87 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.22-7.36 (9H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.9, 27.0, 55.2, 55.4, 61.9, 72.7, 83.2, 83.9, 95.3, 105.3, 113.9, 114.2, 114.3, 118.8, 125.3, 127.6, 128.1, 128.5, 129.0, 130.6, 136.9, 156.2, 159.6, 163.6

MS (m/z) : 518 (M+1)

Analysis : Calculated: C, 69.62; H, 6.03; N, 2.71%

$C_{30}H_{31}NO_7$ Observed: C, 69.80; H, 6.09; N, 2.60%

Optical rotation $[\alpha]^{26}_D$ = -54.5 (*c* 1.1, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-bis(4-methoxyphenyl)-5-oxa-2-aza-spiro[3.4]octan-1-one (1.10a):

Isolated as a white solid in 21% yield.

MP : 147-148 °C

IR ($CHCl_3$) : 1753 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.03 (3H, s, CH_3), 1.23 (3H, s, CH_3), 3.72 (3H, s, Ar-OCH_3), 3.75 (3H, s, Ar-OCH_3), 4.40 (1H, d, *J* = 1.2 Hz, C_8-H), 4.60-4.70 (2H, m, OCH_2-Ph, C_7-H), 4.81 (1H, d, *J* = 12.4 Hz, 1 OCH'$_2$-Ph), 4.82 (1H, s, C_3-H), 6.06 (1H, d, *J* = 4.0 Hz, C_6-H), 6.76 (2H, d, *J* = 9.1 Hz, Ar-H), 6.83 (2H, d, *J* = 8.7 Hz, Ar-H), 7.19-7.36 (9H, m, Ar-H)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.3, 26.7, 55.0, 55.3, 66.5, 72.4, 83.9, 85.4, 94.7, 106.2, 113.7, 113.8, 114.0, 114.3, 118.9, 125.2, 127.8, 128.4, 129.8, 130.3, 137.0, 156.2, 159.9, 163.3

MS (m/z) : 518 (M+1)

Analysis : Calculated: C, 69.62; H, 6.03; N, 2.71%

$C_{30}H_{31}NO_7$ Observed: C, 69.52; H, 5.87; N, 2.58%

Optical rotation $[\alpha]^{26}_D = -30.9$ (*c* 1.1, $CHCl_3$).

Procedure for the preparation of 1.09b and 1.10b:

Following the general procedure, solution of acid chloride **1.07** (0.259 g, 0.826 mmol) in anhydrous dichloromethane (10 mL) was added to a pre-cooled solution of imine **1.08b** (0.116 g, 0.550 mmol), anhydrous triethylamine (0.344 mL, 2.47 mmol) in anhydrous dichloromethane(15 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 hr. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (0.261 g, 65%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09b** and **1.10b**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-(4-methoxyphenyl)-2-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09b):

Isolated as a thick oil in 47% yield.

IR (neat) : 1757 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.27 (3H, s, C*H*$_3$), 1.65 (3H, s, C*H*$_3$), 3.71(3H, s, Ar-OC*H*$_3$), 4.40 (1H, d, *J* = 1.0 Hz, C$_8$-*H*), 4.54-4.61 (2H, m, OC*H*$_2$-Ph, C$_7$-*H*), 4.75 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.36 (1H, s, C$_3$-*H*), 5.44 (1H, d, *J* = 4.0 Hz, C$_6$-*H*), 6.77-7.03 (3H, m, Ar-*H*), 7.14-7.29 (11H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 25.8, 26.3, 55.4, 65.9, 72.0, 84.2, 85.1, 94.3, 105.4, 114.2, 117.3, 124.8, 125.4, 126.7, 127.8, 128.2, 128.7, 129.2, 129.8, 137.0, 137.1, 159.6, 163.9

MS (m/z) : 488 (M+1)

Analysis : Calculated: C, 71.44; H, 5.99; N, 2.87%

$C_{29}H_{29}NO_6$

		Observed: C, 71.38; H, 5.84; N, 2.98%
Optical rotation		$[\alpha]^{26}_{D}$ = -50 (*c* 1.0, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-(4-methoxyphenyl)-2-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one(1.10b)

Isolated as a thick oil in 18% yield.

IR (neat)	**:**	1757 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.99 (3H, s, C*H*$_3$), 1.18 (3H, s, C*H*$_3$), 3.69 (3H, s, Ar-OC*H*$_3$), 4.35 (1H, d, *J* = 1.1 Hz, C_8-*H*), 4.52-4.64 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.73 (1H, d, *J* = 12.4 Hz, OC*H'*$_2$-Ph), 4.82 (1H, s, C_3-*H*), 6.01 (1H, d, *J* = 3.9 Hz, C_6-*H*), 6.76-7.01 (3H, m, Ar-*H*), 7.12-7.30 (11H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 26.4, 26.8, 55.1, 66.4, 72.6, 84.0, 85.5, 94.7, 106.3, 113.9, 117.7, 124.2, 125.1, 126.8, 127.9, 128.0, 128.5, 129.0, 129.8, 136.9, 137.0, 160.0, 164.1
MS (m/z)	**:**	488 (M+1)
Analysis	**:**	Calculated: C, 71.44; H, 5.99; N, 2.87%
$C_{29}H_{29}NO_6$		Observed: C, 71.58; H, 5.79; N, 2.80%
Optical rotation		$[\alpha]^{26}_{D}$ = -35.8 (*c* 0.78, $CHCl_3$).

Procedure for the preparation of 1.09c and 1.10c:

Following the general procedure, solution of acid chloride **1.07** (0.637 g, 2.032 mmol) in anhydrous dichloromethane (10 mL) was added to a pre-cooled solution of imine **1.08c** (0.245 g, 1.354 mmol), anhydrous triethylamine (0.847 mL, 6.093 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (0.575 g, 62%). The crude

reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09c** and **1.10c**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-diphenyl -5-oxa-2-aza-spiro [3.4] octan-1-one (1.09c):

Isolated as a thick oil in 43% yield.

IR (neat) : 1753 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.29 (3H, s, C*H*$_3$), 1.67 (3H, s, C*H*$_3$), 4.43 (1H, d, *J* = 1.0 Hz, C_8-*H*), 4.58-4.64 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.79 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.43 (1H, s, C_3-*H*) 5.46 (1H, d, *J* = 4.1 Hz, C_6-*H*), 6.98-7.33 (15H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 26.8, 26.9, 62.2, 72.7, 83.1, 83.7, 95.5, 105.5, 114.2, 117.4, 124.2, 127.5, 127.6, 128.1, 128.3, 128.4, 128.5, 128.9, 133.4, 136.7, 137.0, 164.2

MS (m/z) : 458 (M+1)

Analysis : Calculated: C, 73.50; H, 5.94; N, 3.06%

$C_{28}H_{27}NO_5$ Observed: C, 73.31; H, 6.10; N, 3.20%

Optical rotation $[\alpha]^{26}_D$ = -75 (*c* 1.44, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-diphenyl-5-oxa-2-aza-spiro[3.4] octan-1-one(1.10c):

Isolated as a thick oil in 19% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.35 (3H, s, C*H*$_3$), 1.52 (3H, s, C*H*$_3$), 4.42 (1H, d, *J* = 1.2 Hz, C_8-*H*), 4.61-4.67 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.80 (1H, d, *J* = 12.4 Hz, OC*H'*$_2$-Ph), 4.81 (1H, s, C_3-*H*), 6.02 (1H, d, *J* = 4.0 Hz, C_6-*H*), 7.01-7.33 (15H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 26.4, 26.9, 62.0, 72.9, 83.4, 84.0, 94.8, 104.4, 115.1, 117.7, 123.8, 127.5, 127.6, 128.5, 128.7, 128.8, 129.2, 129.4, 132.9, 136.7, 137.2, 165.5

MS (m/z) : 458 (M+1)

Analysis : Calculated: C, 73.50; H, 5.94; N, 3.06%

$C_{28}H_{27}NO_5$ Observed: C, 73.59; H, 6.09; N, 3.14%

Optical rotation $[\alpha]^{26}_D = -42.1$ (*c* 1.3, $CHCl_3$).

Procedure for the preparation of 1.09d and 1.10d:

Following the general procedure, solution of acid chloride **1.07** (0.691 g, 2.20 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08d** (0.309 g, 1.468 mmol), anhydrous triethylamine (0.92 mL, 6.606 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (0.665 g, 62%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09d** and **1.10d**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09d):

Isolated as a thick oil in 42% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.26 (3H, s, C*H*$_3$), 1.63 (3H, s, C*H*$_3$), 3.66 (3H, s, Ar-OC*H*$_3$), 4.41 (1H, d, *J* = 1.1 Hz, C$_8$-*H*), 4.55-4.60 (2H, m, OC*H*$_2$-Ph, C$_7$-*H*), 4.76 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.36 (1H, s, C$_3$-*H*), 5.41 (1H, d, *J* = 4.0 Hz, C$_6$-*H*), 6.67-6.74 (2H, m, Ar-*H*), 7.14-7.30 (12H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 26.9, 27.0, 55.4, 62.3, 72.8, 83.2, 83.9, 95.5, 105.4, 114.3, 118.8, 126.4, 127.6, 127.7, 128.2, 128.3, 128.5, 128.6, 130.6, 133.6, 136.9, 156.3, 163.6

MS (m/z) : 488 (M+1)

Analysis : Calculated: C, 71.44; H, 5.99; N, 2.87%

$C_{29}H_{29}NO_6$ Observed: C, 71.61; H, 5.81; N, 2.77%

Optical rotation $[\alpha]^{26}_{D}$ = -80 (*c* 0.5, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one(1.10d):

Isolated as a thick oil in 20% yield.

IR (neat) : 1756 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.37 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 3.83 (3H, s, Ar-OC*H*$_3$), 4.37 (1H, d, *J* = 1.2 Hz, C_8-*H*), 4.61-4.72 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.82 (1H, d, *J* = 12.4 Hz, OC*H'*$_2$-Ph), 4.90 (1H, s, C_3-*H*), 6.01 (1H, d, *J* = 4.0 Hz, C_6-*H*), 6.69-6.74 (2H, m, Ar-*H*), 7.17-7.32 (12H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.1, 26.4, 54.9, 62.5, 72.7, 83.2, 83.8, 95.4, 104.9, 114.1, 119.3, 126.8, 127.6, 127.7, 128.1, 128.3, 128.4, 128.7, 130.5, 133.7, 136.7, 156.5, 165.1

MS (m/z) : 488 (M+1)

Analysis : Calculated: C, 71.44; H, 5.99; N, 2.87%

$C_{29}H_{29}NO_6$ Observed: C, 71.48; H, 6.10; N, 2.93%

Optical rotation $[\alpha]^{26}_{D}$ = -71.2 (*c* 1.1, $CHCl_3$).

Procedure for the preparation of 1.09e and 1.10e:

Following the general procedure, solution of acid chloride **1.07** (0.531 g, 1.69 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08e** (0.238 g, 1.12 mmol), anhydrous triethylamine (0.7 mL, 5.04 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark thick liquid (0.491 g, 59%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09e** and **1.10e**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-2-(4-chlorophenyl)-6,7-*O*-isopropylidene-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one(1.09e):

Isolated as a thick oil in 38% yield.

IR (neat) : 1753 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.26 (3H, s, C*H*$_3$), 1.63 (3H, s, C*H*$_3$), 4.40 (1H, d, *J* = 1.1 Hz, C_8-*H*), 4.54-4.60 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.77 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.35 (1H, s, C_3-*H*) 5.44 (1H, d, *J* = 4.0 Hz, C_6-*H*), 7.15-7.28 (14H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.8, 26.9, 62.5, 72.9, 83.2, 83.8, 95.8, 105.6, 114.4, 118.7, 127.6, 128.2, 128.5, 128.6, 128.7, 129.1, 129.4, 133.0, 135.5, 136.7, 164.2

MS (m/z) : 492 (M+1)

Optical rotation : $[\alpha]^{26}_D$ = -63.6 (*c* 1.1, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-2-(4-chlorophenyl)-6,7-*O*-isopropylidene-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.10e):

Isolated as a thick oil in 21% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.27 (3H, s, C*H*$_3$), 1.44 (3H, s, C*H*$_3$), 4.35 (1H, d, *J* = 1.1 Hz, C_8-*H*), 4.58-4.73 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.83 (1H, d, *J* = 12.3 Hz, OC*H'*$_2$-Ph), 4.84 (1H, s, C_3-*H*), 6.0 (1H, d, *J* 4.1 Hz, C_6-*H*), 7.15-7.27 (14H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.3, 26.8, 61.9, 73.1, 83.0, 83.9, 95.4, 105.7, 114.2, 118.7, 127.3, 128.1, 128.5, 128.6, 128.7, 129.0, 129.3, 133.1, 135.4, 136.7, 163.9

MS (m/z) : 492 (M+1)

Optical rotation : $[\alpha]^{26}_D$ = -80.0 (*c* 0.9, $CHCl_3$).

Procedure for the preparation of 1.09f and 1.10f:

Following the general procedure, solution of acid chloride **1.07** (0.690 g, 2.20 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08f** (0.304 g, 1.468 mmol), anhydrous triethylamine (0.9 mL, 6.606 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark thick liquid (0.733 g, 69%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09f** and **1.10f**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-styryl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09f):

Isolated as a thick oil in 49% yield.

IR (neat) : 1756 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.31 (3H, s, C*H*$_3$), 1.69 (3H, s, C*H*$_3$), 4.38 (1H, d, *J* = 1.2 Hz, C$_8$-*H*), 4.54 (1H, d, *J* = 11.6 Hz, OC*H*$_2$-Ph), 4.64 (1H, dd, *J* = 3.9, 1.2 Hz, C$_7$-*H*), 4.74 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 4.95 (1H, d, *J* = 8.8 Hz, C$_3$-*H*), 5.85 (1H, d, *J* = 3.9 Hz, C$_6$-*H*), 6.28 (1H, dd, *J* = 16.1, 8.8 Hz, Ph-CH=C*H*-CH-), 6.71 (1H, d, *J* = 16.1 Hz, Ph-C*H*=CH-) 6.98-7.41 (15H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 26.8, 26.9, 61.5, 72.7, 83.2, 83.7, 95.6, 105.9, 114.4, 117.3, 123.7, 124.3, 126.7, 127.5, 128.1, 128.3, 128.5, 128.6, 129.0, 135.8, 136.3, 136.8, 137.6, 164.0

MS (m/z) : 484 (M+1)

Analysis : Calculated: C, 74.51; H, 6.04; N, 2.89%

$C_{30}H_{29}NO_5$ Observed: C, 74.70; H, 6.21; N, 2.77%

Optical rotation $[\alpha]^{26}_D$ = -16.6 (*c* 1.2, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-styryl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.10f):

Isolated as a white solid in 20% yield.

MP	**:**	174-176 °C
IR ($CHCl_3$)	**:**	1751 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.30 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 4.40 (1H, d, *J* = 1.0 Hz, C_8-*H*), 4.53 (1H, d, *J* = 8.9 Hz, C_3-*H*), 4.55-4.64 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.69 (1H, d, *J* = 12.2 Hz, OC*H'*$_2$-Ph), 6.15 (1H, d, *J* = 3.7 Hz, C_6-*H*), 6.28 (1H, dd, *J* = 15.9, 8.9 Hz, Ph-CH=C*H*-CH-), 6.75 (1H, d, *J* = 15.9 Hz, Ph-C*H*=CH-) 7.10-7.50 (15H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 26.4, 26.7, 62.1, 71.9, 83.5, 83.7, 95.1, 105.3, 113.9, 116.9, 123.5, 124.2, 126.4, 127.4, 128.2, 128.3, 128.5, 128.6, 128.9, 135.5, 136.4, 136.8, 137.7, 166
MS (m/z)	**:**	484 (M+1)
Analysis	**:**	Calculated: C, 74.51; H, 6.04; N, 2.89%
$C_{30}H_{29}NO_5$		Observed: C, 74.63; H, 5.89; N, 3.01%
Optical rotation		$[\alpha]^{26}_D$ = -55 (*c* 2.0, $CHCl_3$).

Procedure for the preparation of 1.09g and 1.10g:

Following the general procedure, solution of acid chloride **1.07** (0.690 g, 2.20 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08g** (0.347 g, 1.468 mmol), anhydrous triethylamine (0.9 mL, 6.606 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark thick liquid (0.757 g, 67%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09g** and **1.10g**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4–methoxyphenyl)–3–styryl–5– oxa-2-aza-spiro[3.4]octan-1-one (1.09g):

Isolated as a thick oil in 45% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.38 (3H, s, CH_3), 1.75 (3H, s, CH_3), 3.76 (3H, s, Ar-OCH_3), 4.45 (1H, d, *J* = 1.0 Hz, C_8-*H*), 4.58-4.70 (2H, m, OCH_2-Ph, C_7-*H*), 4.80 (1H, d, *J* = 11.7 Hz, OC*H'*$_2$-Ph), 4.98 (1H, d, *J* = 8.8 Hz, C_3-*H*), 5.91 (1H, d, *J* = 3.7 Hz, C_6-*H*), 6.35 (1H, dd, *J* = 16.0, 8.8 Hz, Ph-CH=C*H*-CH-) 6.83 (1H, d, *J* = 16.0 Hz, Ph-C*H*=CH-) 7.20-7.42 (14H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 26.9, 27.0, 55.4, 61.6, 72.7, 83.2, 83.8, 95.6, 105.8, 114.3, 114.4, 118.7, 123.9, 126.7, 127.5, 128.1, 128.3, 128.6, 131.1, 135.8, 136.3, 136.8, 156.3, 163.3

MS (m/z) : 514 (M+1)

Analysis : Calculated: C, 72.49; H, 6.08; N, 2.72%

$C_{31}H_{31}NO_6$ Observed: C, 72.62; H, 6.24; N, 2.55%

Optical rotation $[\alpha]^{26}_D$ = -26.6 (*c* 0.5, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8–Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-styryl-5- oxa-2-aza–spiro[3.4]octan-1-one (1.10g):

Isolated as a thick oil in 22% yield.

IR (neat) : 1757 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.30 (3H, s, CH_3), 1.35 (3H, s, CH_3), 3.77 (3H, s, Ar-OCH_3), 4.36 (1H, d, *J* = 1.0 Hz, C_8-*H*), 4.57 (1H, d, *J* = 8.7 Hz, C_3-*H*), 4.64 (1H, d, *J* = 12.4 Hz, OCH_2-Ph), 4.72 (1H, dd, *J* = 3.9, 1.0 Hz, C_7-H), 4.77 (1H, d, *J* = 12.4 Hz, OC*H'*$_2$-Ph), 6.13 (1H, d, *J* = 3.9 Hz, C_6-*H*), 6.26 (1H, dd, *J* = 15.9, 8.7 Hz, Ph-CH=C*H*-CH-), 6.71 (1H, d, *J* = 15.9 Hz, Ph-C*H*=CH-) 6.84 (2H, d, *J* = 9.1 Hz, Ar-*H*), 7.23-7.43 (12H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) : δ_C 26.1, 26.4, 55.4, 65.9, 72.5, 83.7, 85.6, 95.0, 106.6, 113.5, 114.3, 119.0, 123.8, 126.8, 127.9, 128.0, 128.3, 128.5, 128.6, 130.9, 135.8,

(50 MHz) 137.0, 138.0, 156.4, 162.5

MS (m/z) : 514 (M+1)

Analysis : Calculated: C, 72.49; H, 6.08; N, 2.72%

$C_{31}H_{31}NO_6$ Observed: C, 72.55; H, 5.94; N; 2.84%

Optical rotation $[\alpha]^{26}_D$ = -45.0 (*c* 0.4, $CHCl_3$).

Procedure for the preparation of 1.09h and 1.10h:

Following the general procedure, solution of acid chloride **1.07** (0.835 g, 2.66 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08h** (0.345 g, 1.77 mmol), anhydrous triethylamine (1.1 mL, 7.96 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (0.903 g, 72%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09h** and **1.10h**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-phenyl-2-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09h):

Isolated as a thick oil in 46% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.33 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.28 (3H, s, Ar-C*H*$_3$), 4.47 (1H, d, *J* = 1.1 Hz, C_8-*H*), 4.65 (1H, d, *J* = 11.6 Hz, OC*H*$_2$-Ph), 4.66 (1H, dd, *J* = 4.1, 1.1 Hz, C_7-*H*), 4.83 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.44 (1H, s, C_3-*H*), 5.48 (1H, d, *J* = 4.1 Hz, C_6-*H*), 7.04 (2H, d, *J* = 8.4 Hz, Ar-*H*) 7.18-7.35 (12H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 20.7, 26.7, 26.8, 62.0, 72.6, 83.0, 83.6, 95.4, 105.4, 114.1, 117.3, 127.5, 127.6, 128.0, 128.1, 128.3, 128.4, 129.4, 133.3, 133.8, 134.5, 136.7, 163.9

MS (m/z) : 472 (M+1)

Analysis	**:**	Calculated: C, 73.86; H, 6.19; N, 2.97%
$C_{29}H_{29}NO_5$		Observed: C, 74.02; H, 6.02; N, 3.06%
Optical rotation		$[\alpha]^{26}_D$ = -56.6 (*c* 1.2, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-phenyl-2-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.10h):

Isolated as a thick oil in 26% yield.

IR (neat)	**:**	1758 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.34 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 2.33 (3H, s, Ar-C*H*$_3$), 4.42 (1H, d, *J* = 1.1 Hz, C_8-*H*), 4.57-4.66 (2H, m, OC*H*$_2$-Ph, C_7-*H*), 4.79 (1H, d, *J* = 12.3 Hz, OC*H'*$_2$-Ph), 4.87 (1H, s, C_3-*H*), 6.06 (1H, d, *J* = 3.9 Hz, C_6-*H*), 7.03 (2H, d, *J* = 8.1 Hz, Ar-*H*) 7.11-7.47 (12H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 20.8, 26.3, 26.4, 66.6, 72.5, 82.5, 82.6, 94.6, 105.6, 113.9, 117.5, 127.5, 127.6, 127.9, 128.2, 128.3, 128.5, 129.4, 133.5, 133.9, 134.4, 136.7, 163.7
MS (m/z)	**:**	472 (M+1)
Analysis	**:**	Calculated: C, 73.86; H, 6.19; N, 2.97%
$C_{29}H_{29}NO_5$		Observed: C, 73.98; H, 6.33; N, 2.81%
Optical rotation		$[\alpha]^{26}_D$ = -28.8 (*c* 0.9, $CHCl_3$).

Procedure for the preparation of 1.09i and 1.10i:

Following the general procedure, solution of acid chloride **1.07** (0.655 g, 2.09 mmol) in anhydrous dichloromethane (15 mL) was added to a pre-cooled solution of imine **1.08i** (0.271 g, 1.39 mmol), anhydrous triethylamine (0.9 mL, 6.255 mmol) in anhydrous dichloromethane (20 mL) at -40 °C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced

pressure to get the crude product as a dark viscous liquid (0.688 g, 70%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **1.09i** and **1.10i**.

(-)-(*3R,4R,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.09i):

Isolated as a thick oil in 45% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.33 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.34 (3H, s, Ar-C*H*$_3$), 4.46 (1H, d, *J* = 1.0 Hz, C$_8$-*H*), 4.61-4.71 (2H, m, OC*H*$_2$-Ph, C$_7$-*H*), 4.83 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 5.42 (1H, s, C$_3$-*H*), 5.49 (1H, d, *J* = 4.0 Hz, C$_6$-*H*), 7.01-7.39 (14H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 21.1, 26.8, 26.9, 62.0, 72.7, 83.2, 83.8, 95.3, 105.4, 114.2, 117.5, 124.1, 127.5, 127.6, 128.0, 128.5, 128.9, 129.2, 130.3, 136.8, 137.1, 138.1, 164.3

MS (m/z) : 472 (M+1)

Analysis : Calculated: C, 73.86; H, 6.19; N, 2.97 %

$C_{29}H_{29}NO_5$ Observed: C, 73.71; H, 6.38; N, 2.92%

Optical rotation $[\alpha]^{26}_D$ = -40.0 (*c* 0.3, $CHCl_3$).

(-)-(*3S,4S,6R,7R,8R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (1.10i):

Isolated as a thick oil in 25% yield.

IR (neat) : 1755 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.31 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 2.32 (3H, s, Ar-C*H*$_3$), 4.41 (1H, d, *J* = 1.0 Hz, C$_8$-*H*), 4.59-4.67 (2H, m, OC*H*$_2$-Ph, C$_7$-*H*), 4.78 (1H, d, *J* = 11.6 Hz, OC*H'*$_2$-Ph), 4.87 (1H, s, C$_3$-*H*), 6.06 (1H, d, *J* = 4.0 Hz, C$_6$-*H*), 7.01-7.39 (14H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 21.0, 26.3, 26.7, 61.9, 72.1, 83.5, 84.0, 95.5, 104.9, 114.7, 117.3, 124.1, 127.3, 127.6, 128.2, 128.6, 128.9, 129.3, 130.2, 136.7, 137.9, 138.1, 163.8

MS (m/z) : 472 (M+1)

Analysis	:	Calculated: C, 73.86; H, 6.19; N, 2.97 %
$C_{29}H_{29}NO_5$		Observed: C, 74.04; H, 6.12; N, 3.12%
Optical rotation		$[\alpha]^{26}_D$ = -28.3 (*c* 1.2, $CHCl_3$).

1.6.9: Procedure for the preparation of *O*-debenzylated spiro-β-lactam 1.11c:

One of the major diastereomers of spiro-β-lactams, **1.09c** (0.216 g, 0.472 mmol) was dissolved in dry methanol (10 mL). 10% Pd/C (0.050 g) and ammonium formate (0.90 g, 1.416 mmol) were added to it and the resulting solution was refluxed for 3 hrs. After completion (TLC) the solution was filtered through a sintered funnel and the residue was washed with methanol. The filtrate was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to furnish the crude product. The crude product was recrystallized from ethyl acetate-pet. ether to obtain pale yellow crystals of debenzylated product **1.11c** (0.152 g, 88%).

(-)-(*3R,4R,6R,7R,8R*)-8-hydroxy-6,7-*O*-isopropylidene-2,3-diphenyl-5-oxa-2-aza spiro [3.4] octan-1-one (1.11c):

MP	:	186-188 °C
IR ($CHCl_3$)	:	1755, 3352 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	:	δ_H 1.30 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 4.42 (1H,d, *J* = 1.1 Hz, C_8-*H*), 4.64 (1H, dd, *J* = 4.0, 1.1 Hz, C_7-*H*), 5.53 (1H, s, C_3-*H*), 5.60 (1H, bs, -O*H*), 5.80 (1H, d, *J* = 4.0 Hz, C_6-*H*), 7.01-7.40 (10H, m, Ar-H)
^{13}C NMR ($CDCl_3$) (50 MHz)	:	δ_C 26.5, 26.6, 61.9, 76.0, 86.3, 96.4, 105.6, 114.0, 117.5, 124.3, 127.7, 128.5, 128.7, 129.0, 133.4, 136.9, 164.8
MS (m/z)	:	368 (M+1)
Analysis	:	Calculated: C, 68.65; H, 5.76; N, 3.81%
$C_{21}H_{21}NO_5$		Observed: C, 68.61; H, 5.89; N, 3.72%

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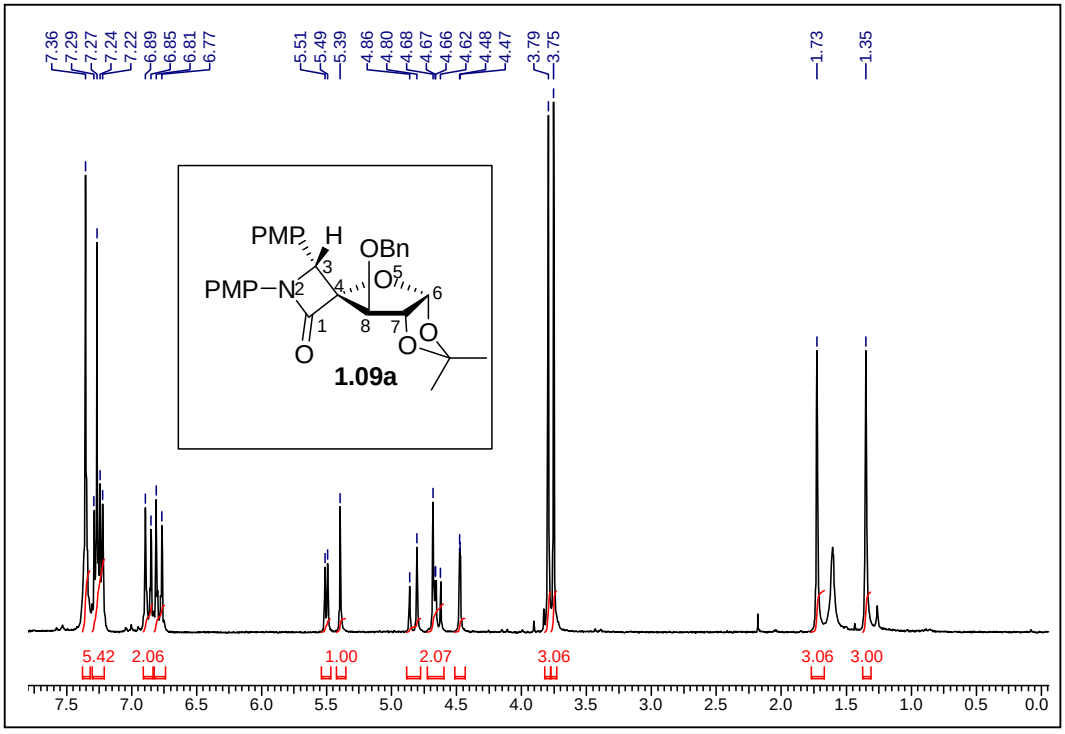
Chapter 1

Spectra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4.47
3.79
3.75
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OBn
PMP−N
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O
O
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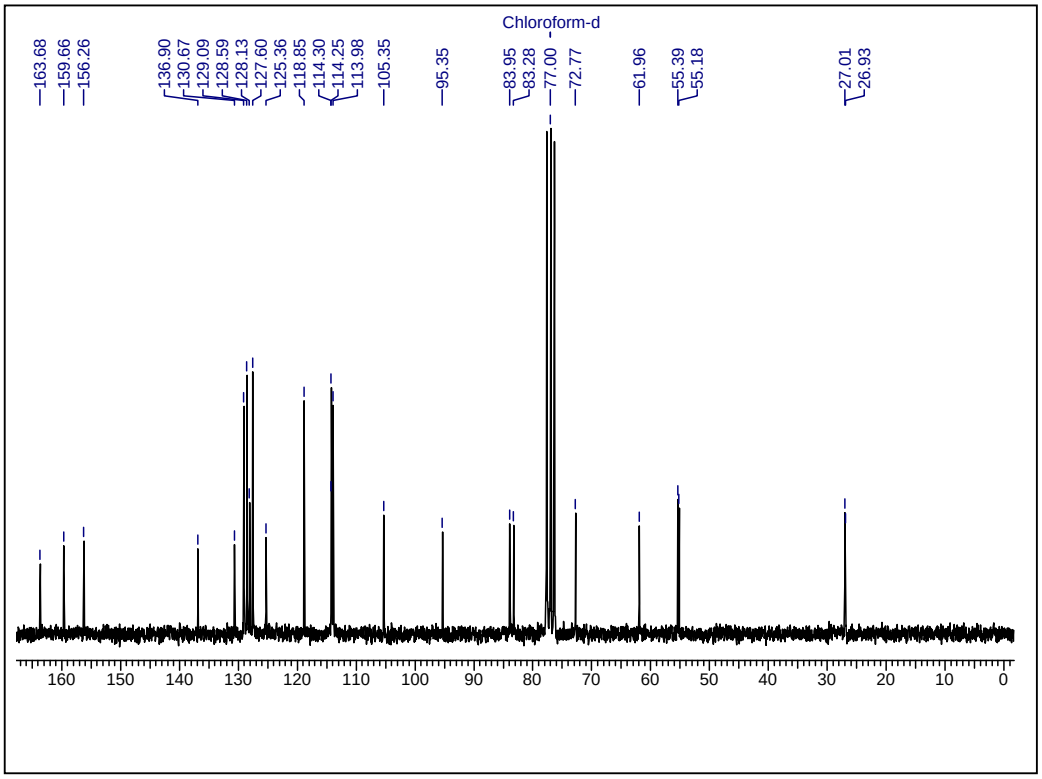
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114.30
114.25
113.98
105.35
95.35
83.95
83.28
77.00
72.77
61.96
55.39
55.18
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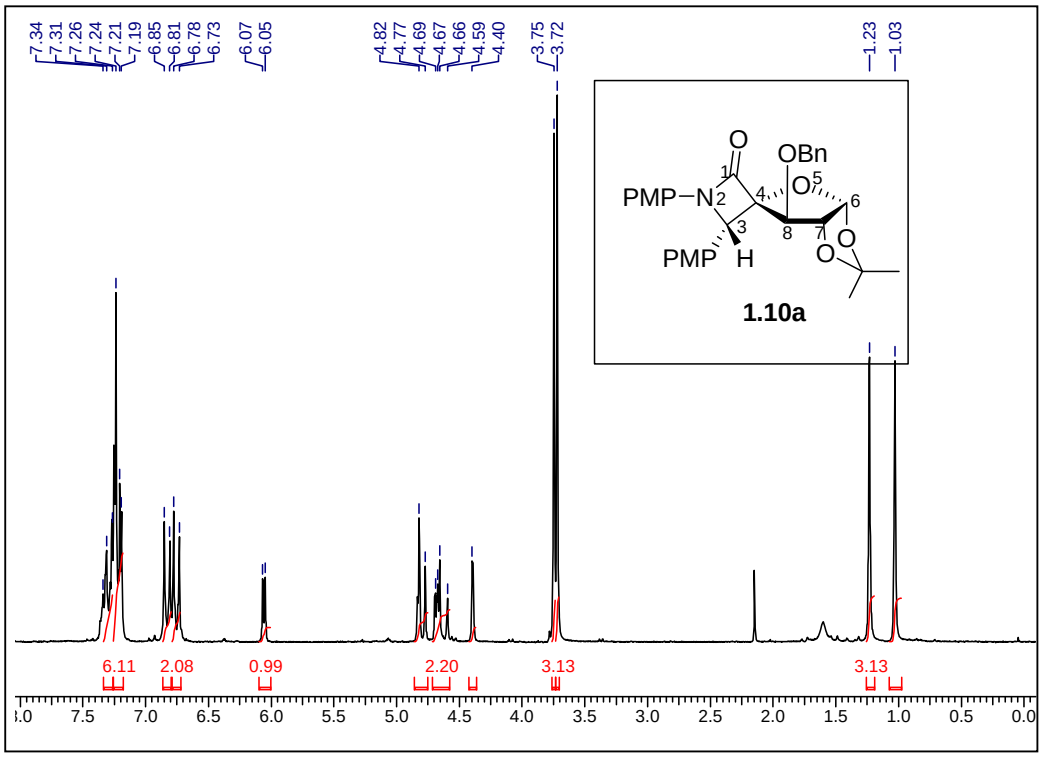
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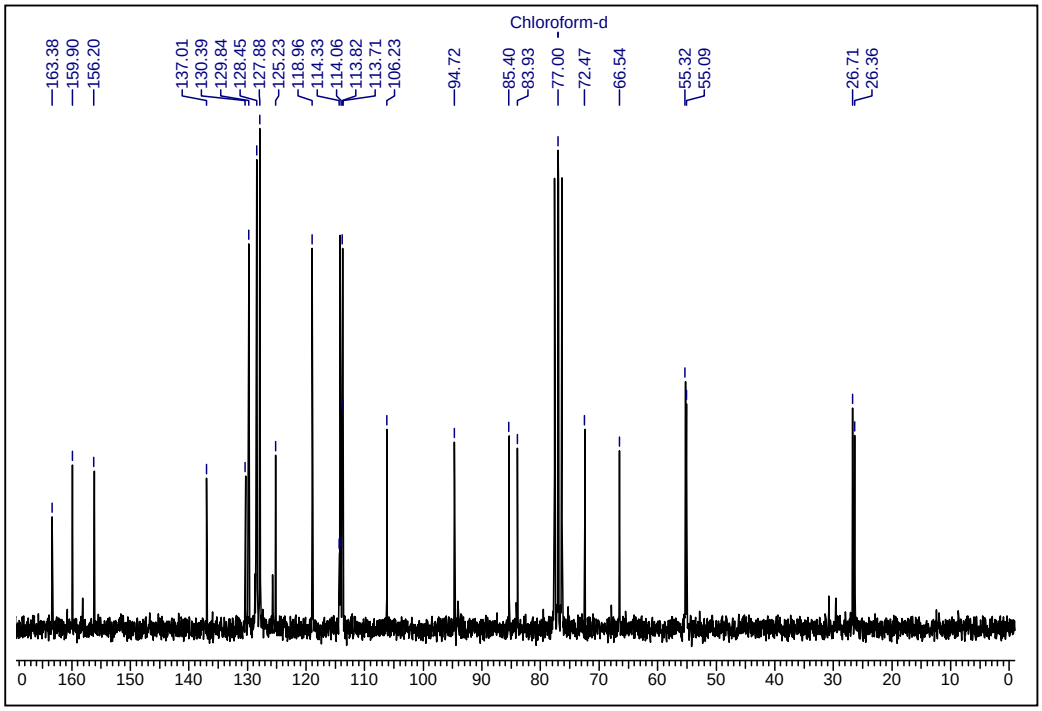
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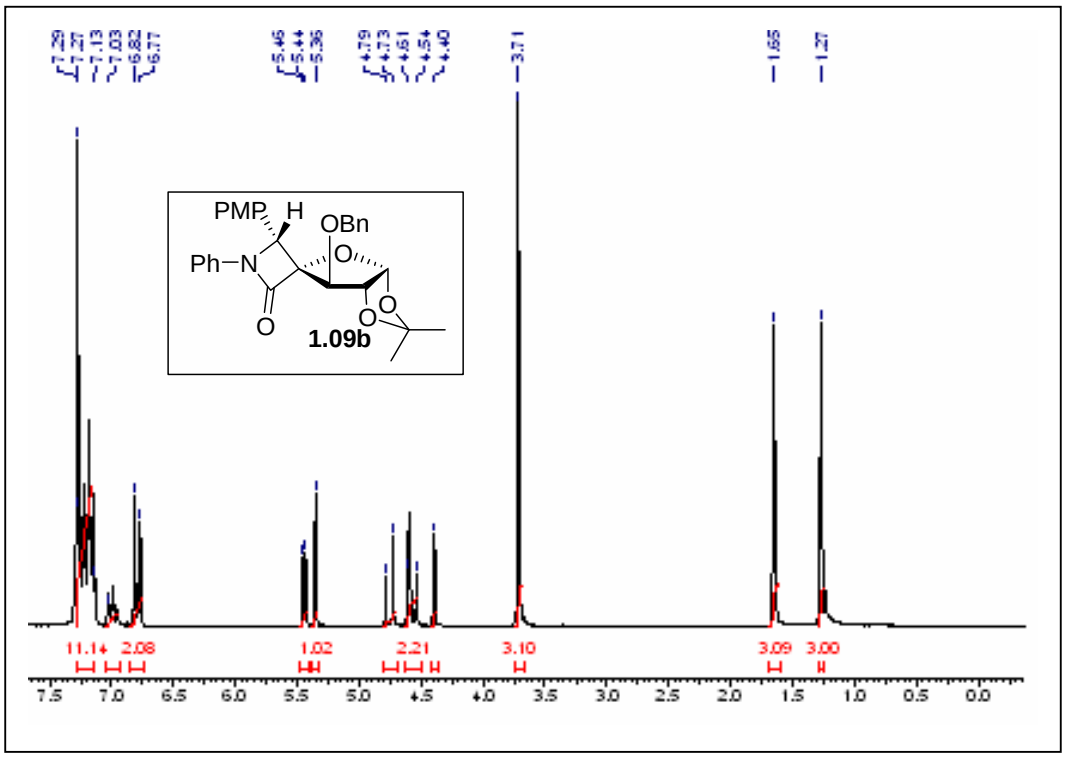
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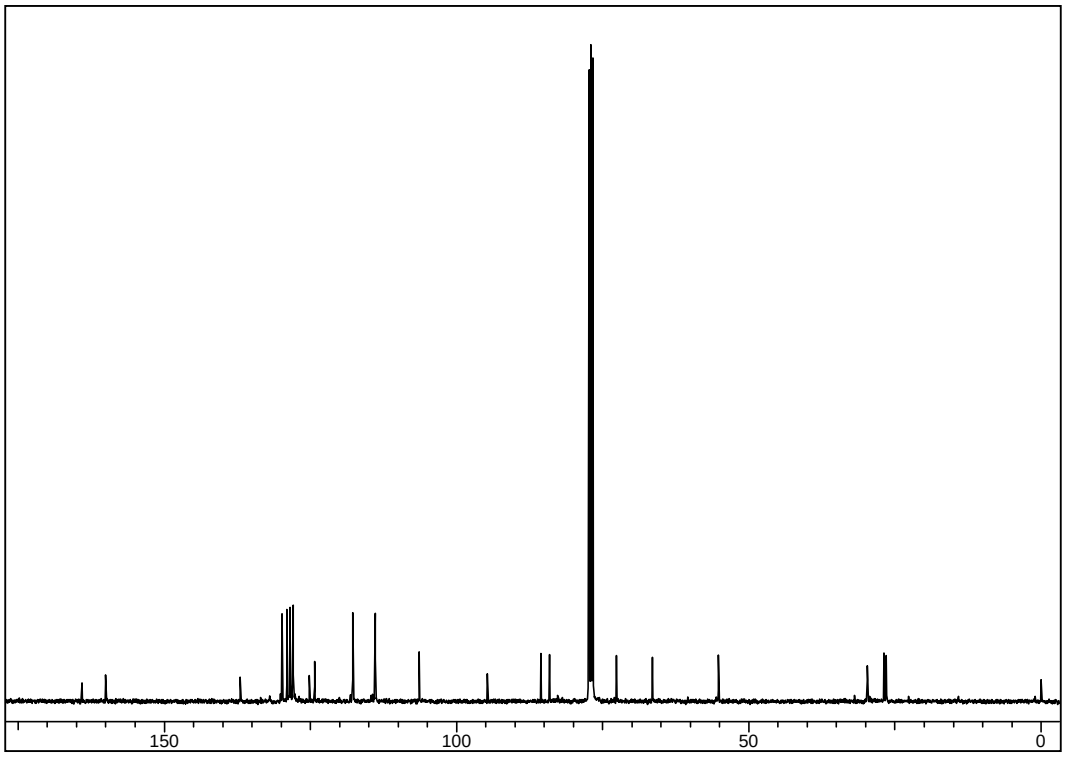
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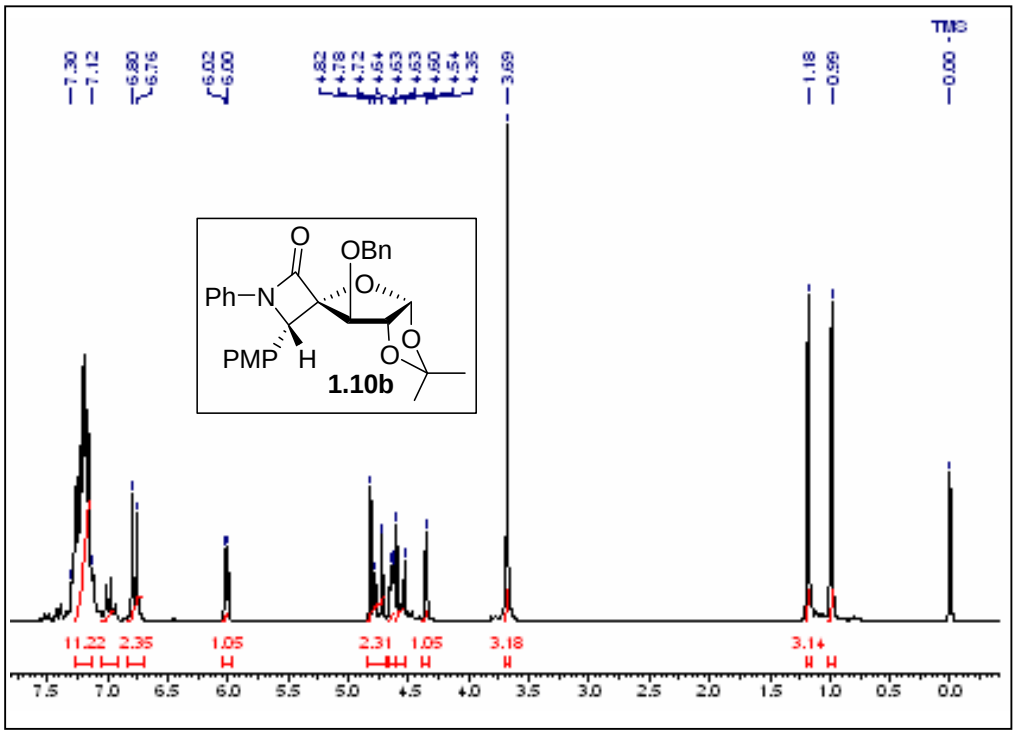
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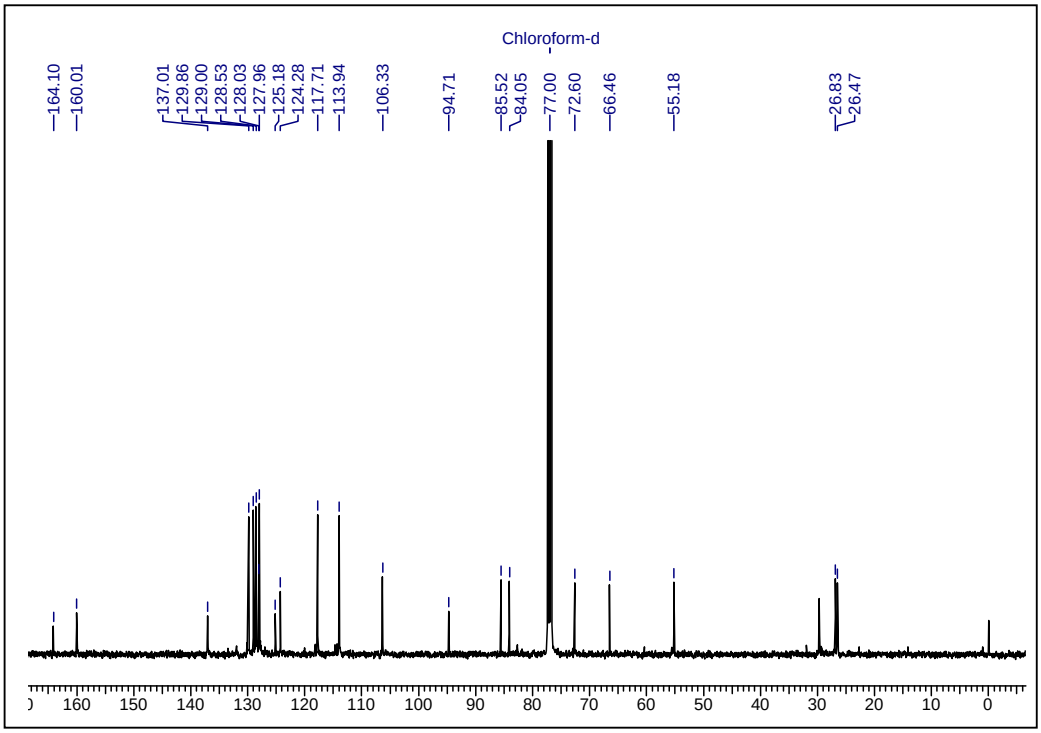
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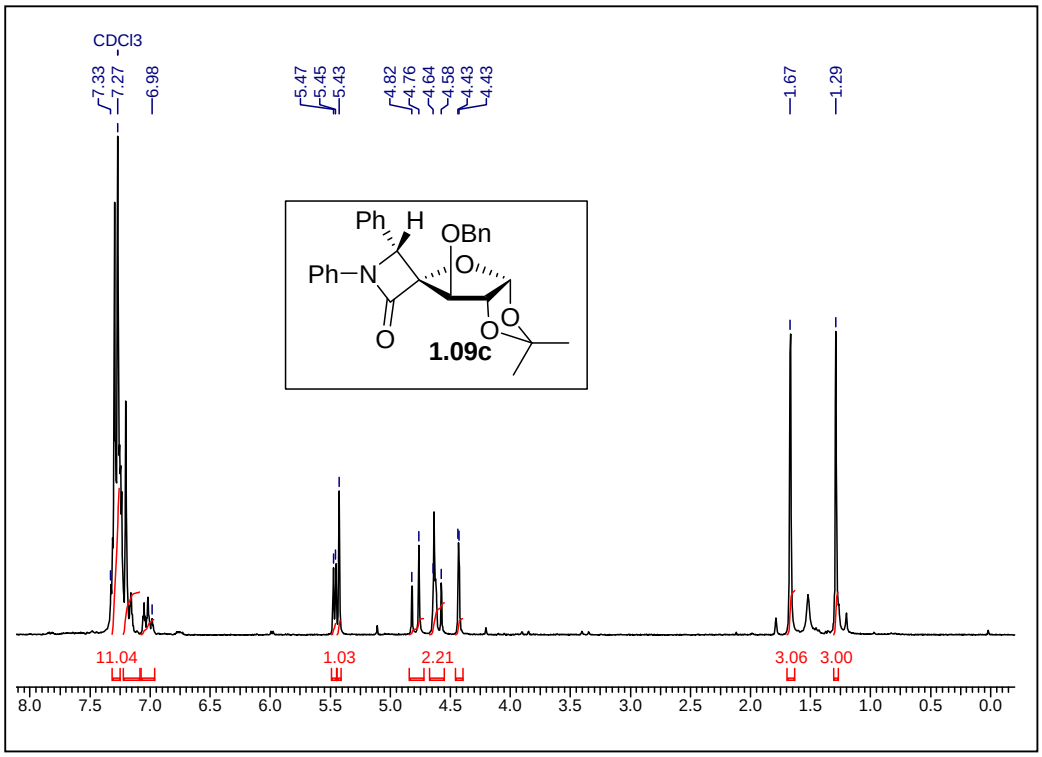
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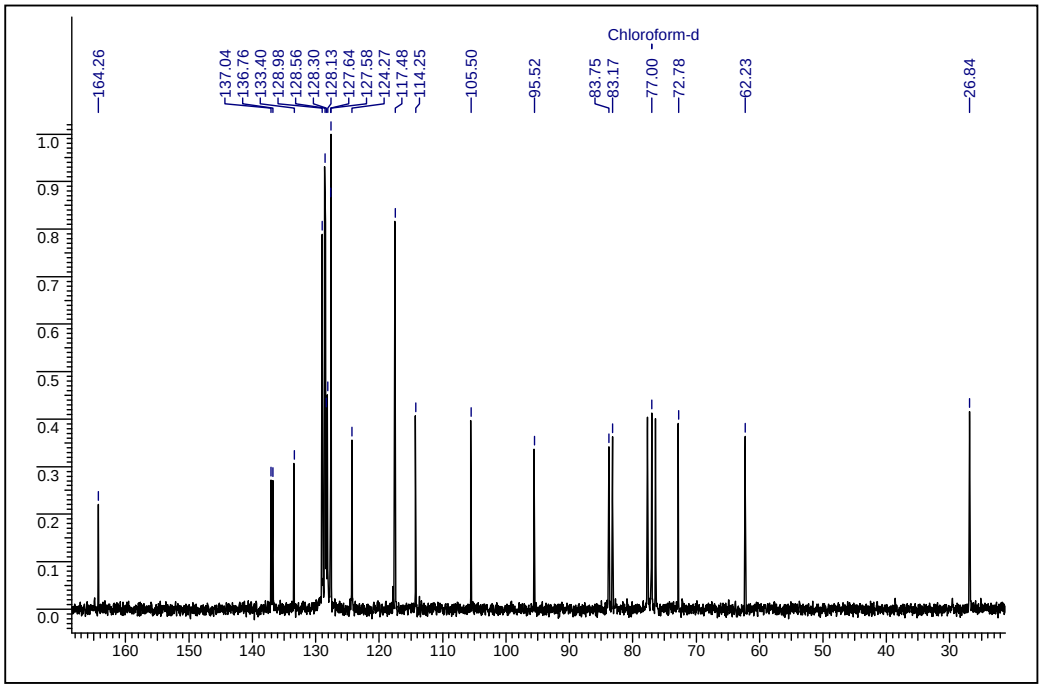
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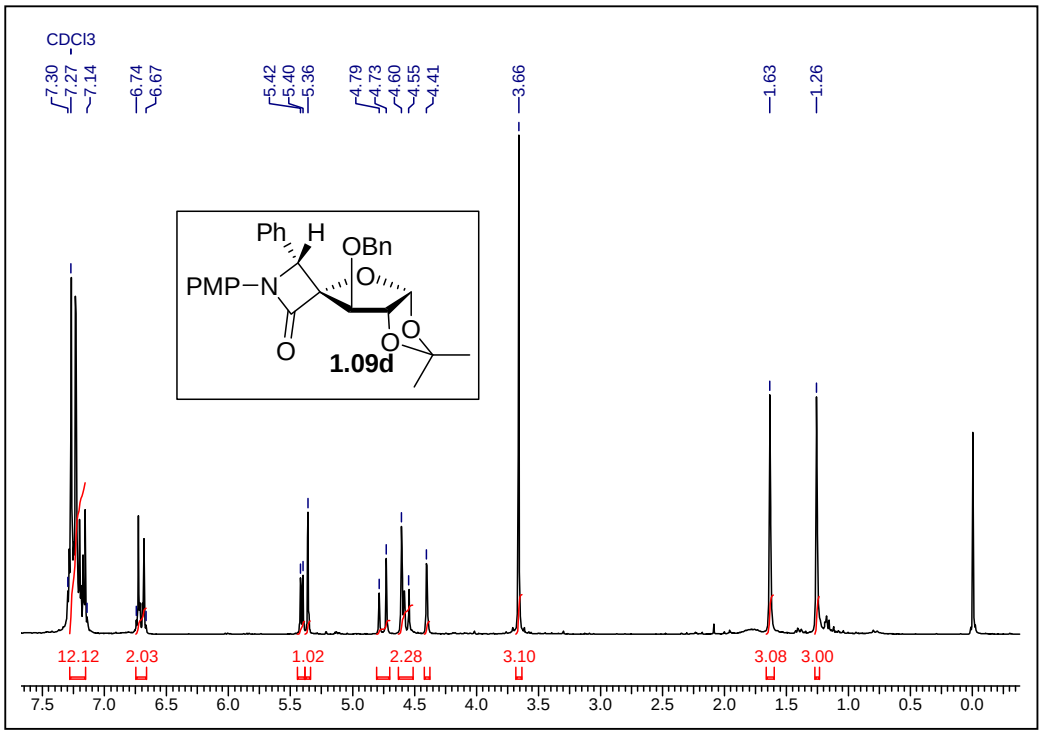
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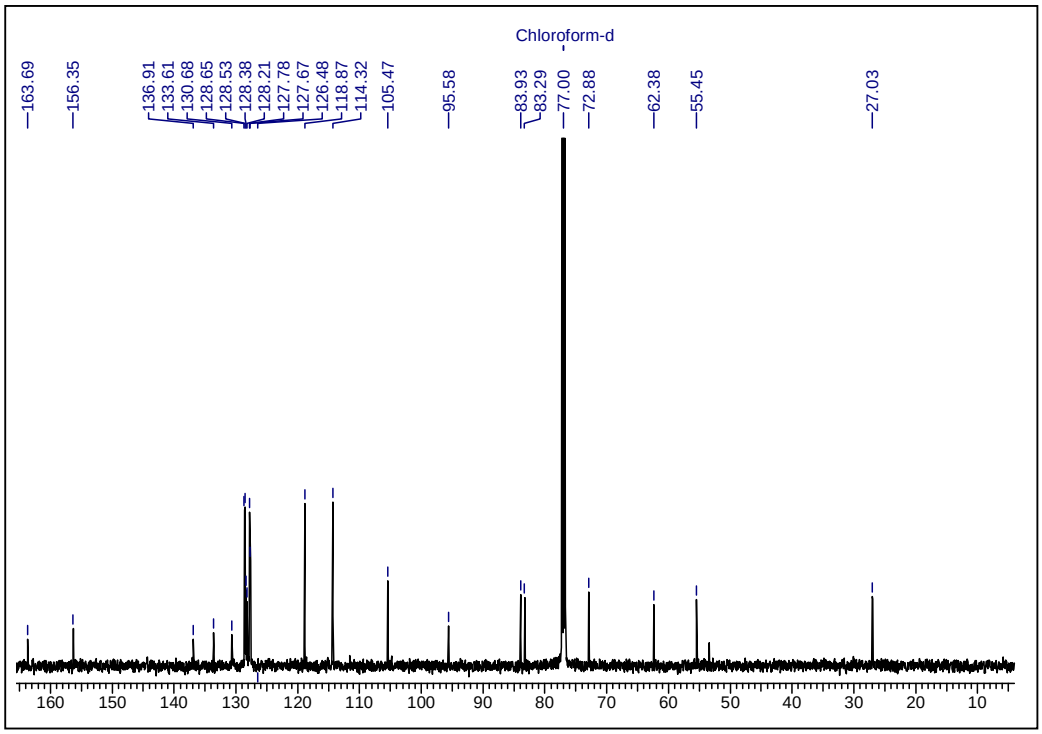
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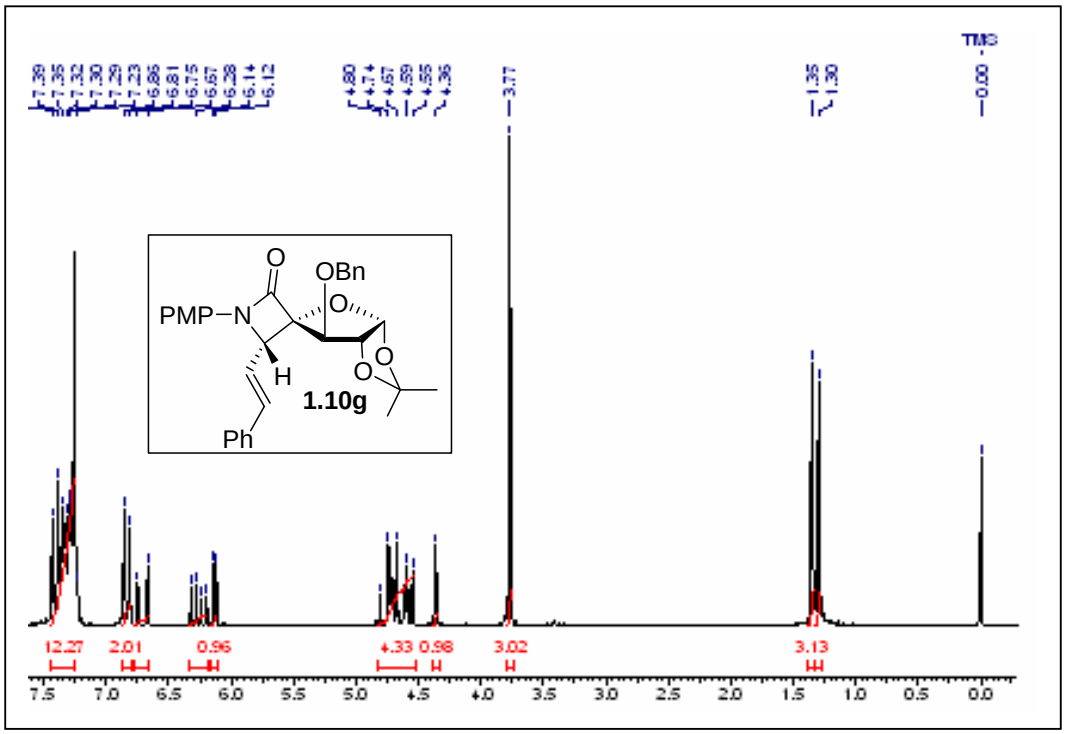
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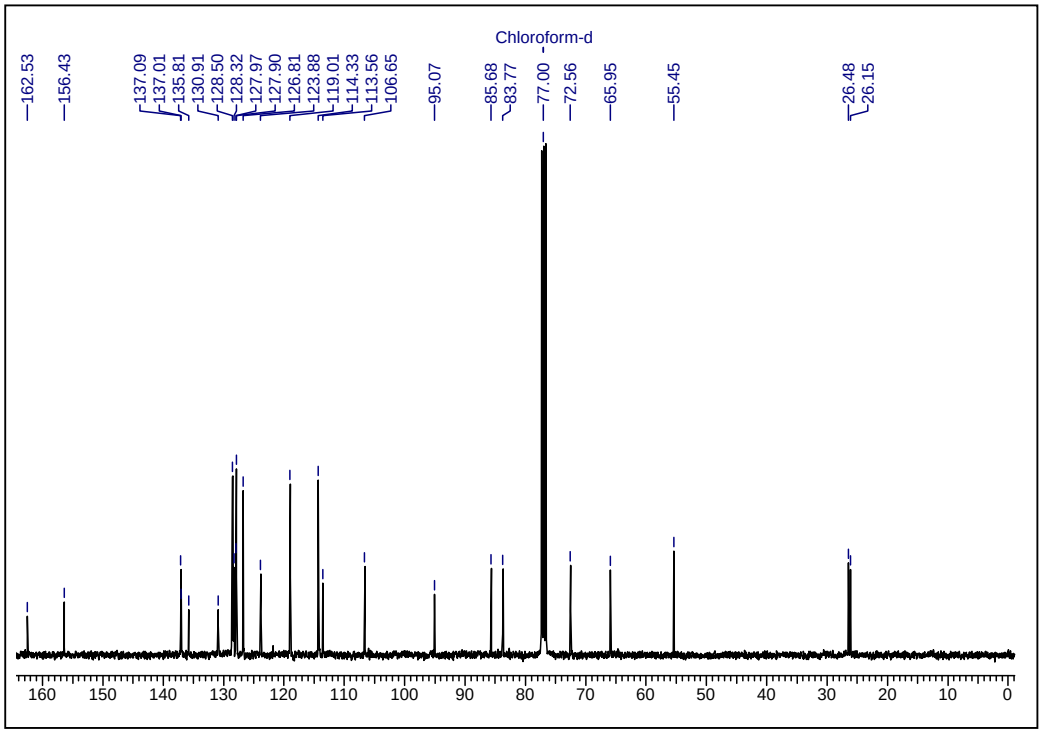
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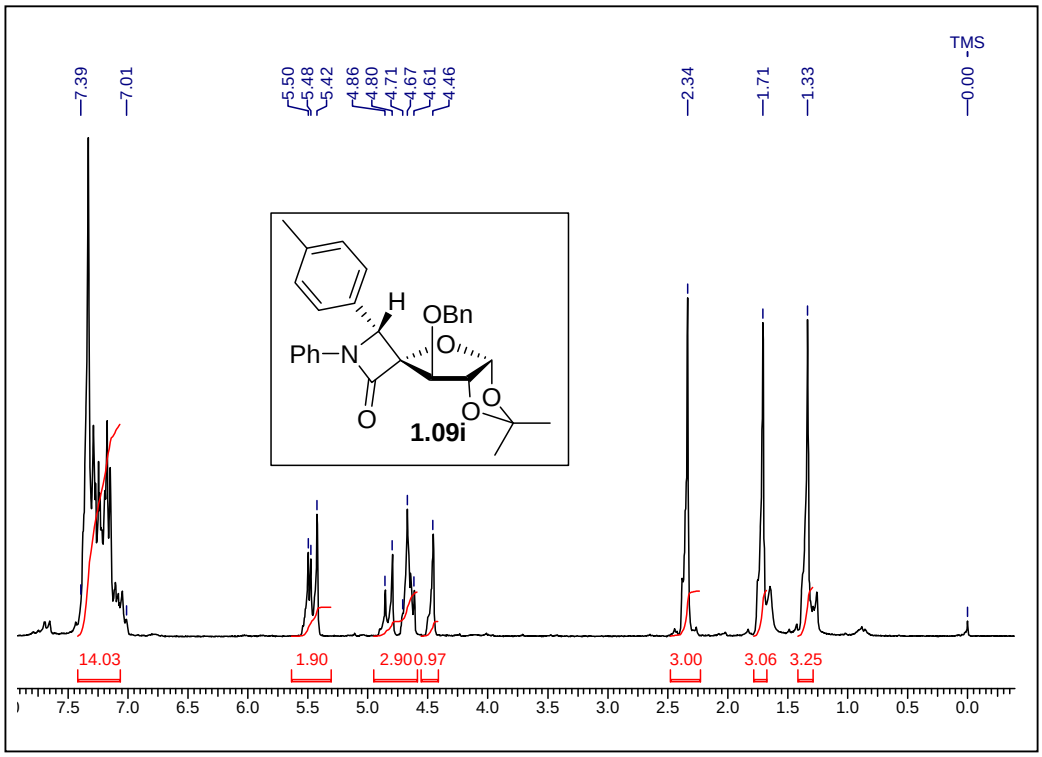
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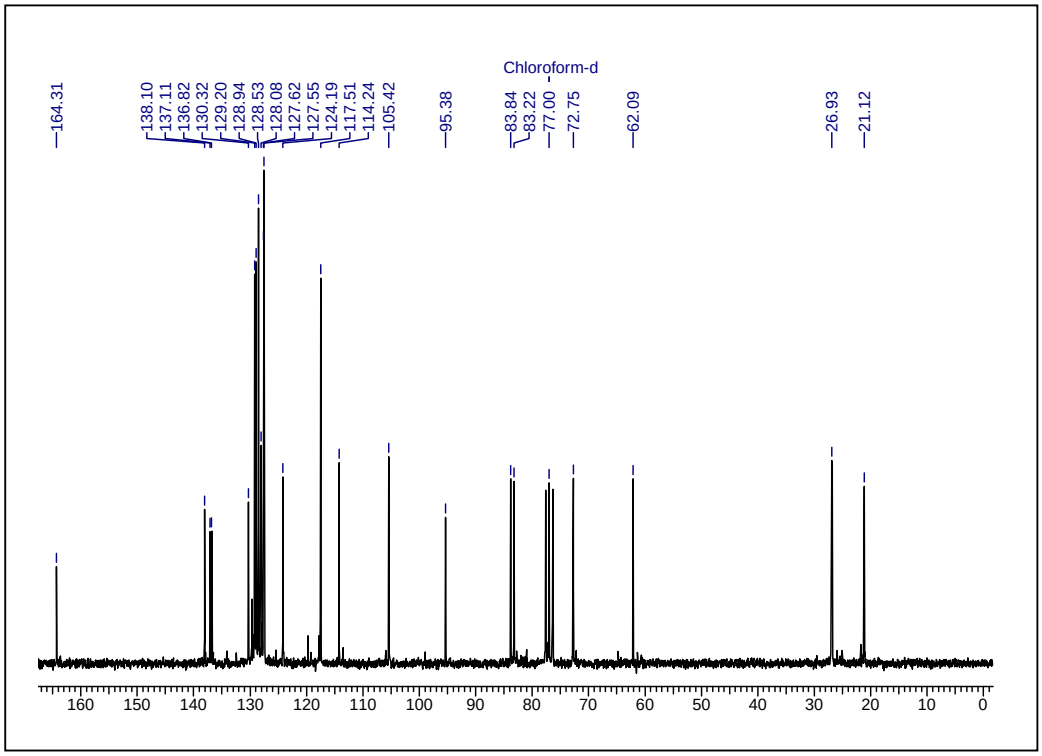
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140
130
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CHAPTER 2

STEREOSELECTIVE SYNTHESIS OF SPIRO AZETIDIN-2-ONES FROM L-(+)-DIETHYL TARTRATE DERIVED CHIRAL POOL AND THEIR TRANSFORMATION INTO ENANTIOPURE AZETIDIN-2,3-DIONES AND 3-HYDROXY AZETIDIN-2-ONES.

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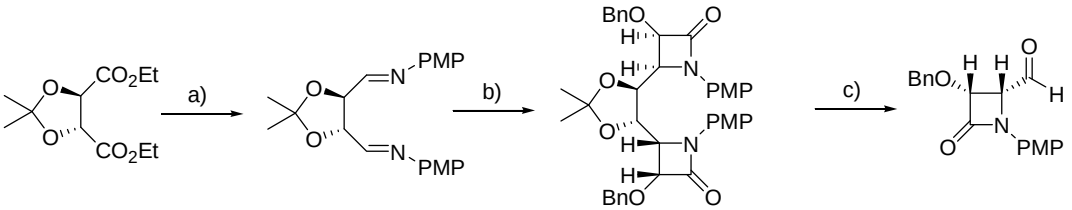
2.1: Introduction

This chapter describes the synthesis of spiro azetidin-2-ones from an L-(+)-diethyl tartrate derived chiral pool and their transformation into enantiopure azetidin-2,3-diones and 3-hydroxy azetidin-2-ones.

***Application of L-(+)-diethyl tartrate as a chiral starting material in azetidin-2-one synthesis*:** Different derivatives of L-(+)-tartaric acid have found vast applications in synthetic organic chemistry.[1] L-(+)-Diethyl tartrate is one such derivative of tartaric acid, widely used in organic synthesis. In fact, the legendary Sharpless asymmetric epoxidation which employs L-(+)-diethyl tartrate, remains a big milestone in organic synthesis.[2] Apart from this, it has also been a particularly liked chiral pool for various organic molecules. Thus owing to its widespread use, it has also found applications in β-lactam chemistry. It has been used for synthesis of different β-lactams as well in synthesis of different natural products which involve intermediates which are β-lactam structures derived from L-(+)-diethyl tartrate or tartaric acid.

It has been used as a starting material for the synthesis of 4-formyl β-lactams. Bhawal *et al*. in their report on the synthesis of 4-formyl β-lactams (Scheme 2.01) describe the use of L-(+)-diethyl tartrate as a chiral starting material.[3] The synthesis is especially efficient as one mole of L-(+)-diethyl tartrate gives rise to two moles of 4-formyl β-lactam.

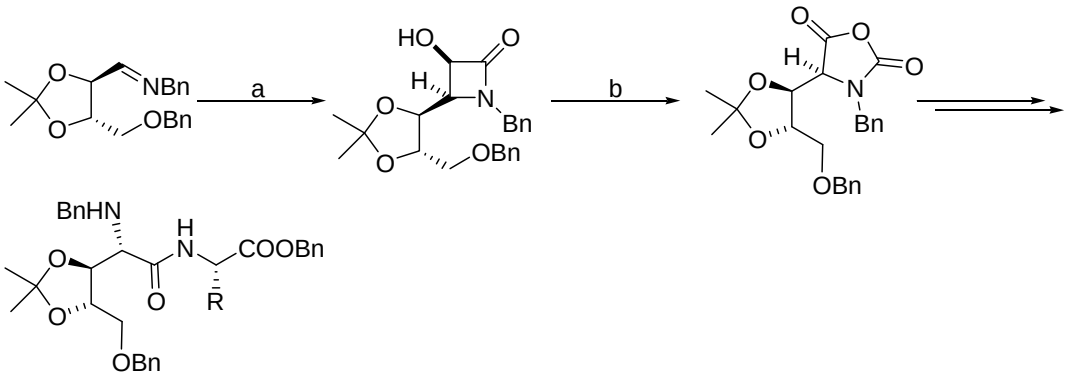
Scheme 2.01



Reagents and conditions: a) DIBAL-H, PMP-NH_2, toluene, -78 °C to r. t., 15 h; b) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, -23 °C to r. t., 14 h; c) i) 2.5 M $HClO_4$, THF, r. t., 4-8 h; ii) $NaIO_4$, acetone/H_2O, r. t., 4-12 h.

Palomo *et al.* have synthesized a β-lactam intermediate from tartaric acid which was further elaborated to polyoxamic acid derivative.[4] The reaction of the imine derived from tartaric acid with acetoxyketene proved to be highly diastereoselective giving only one diastereomers of β-lactam (Scheme 2.02). However, to the best of our knowledge, use of L-(+)-diethyl tartrate in the synthesis of spiro-β-lactams is not known.

Scheme 2.02



Reagents and conditions: a) $AcOCH_2COCl$, Et_3N, DCM, 0 °C-rt, 16h, then LiOH, H_2O_2, THF-H_2O, 0 °C, 3h, 90%; b) NaOCl, DCM, TEMPO (cat.), *p*H 7.0, 0 °C, 1min.

***Importance of azetidin-2,3-diones*:** Azetidin-2,3-diones is a class of β-lactams which has risen to prominence in its own right. It is a class of strained molecules, wherein the strain is attributed to the presence of two sp^2 carbon atoms as a part of a four membered ring. Azetidin-2,3-diones have been shown to be very useful synthons (Figure 1). They have been shown to be promising building blocks[5] and precursors for highly functionalized β-lactams.[6] Apart from the synthesis of functionalized β-lactams, other applications of azetidin-2,3-diones involve synthesis of α-amino acid *N*-carboxy anhydrides which have applications in peptide chemistry.[7] More recently, another elegant application of azetidin-2,3-diones in peptide synthesis has been reported using their reactions with primary amines.[8]

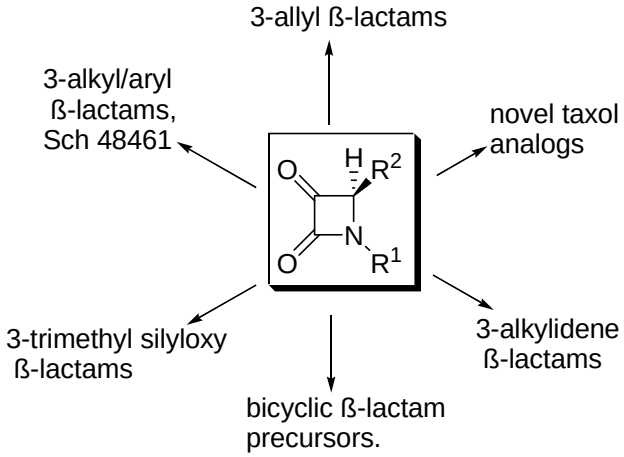


Figure 1: Applications of azetidin-2,3-diones

***Importance of 3-hydroxy-azetidin-2-ones*:** 3-hydroxy azetidin-2-ones or 3-hydroxy-β-lactams constitute another class of β-lactams which has found many applications as a useful synthon. They are a source of enantiomerically pure α-hydroxy-β-amino acids, which are present in many biologically important compounds. Enantiomerically pure α-hydroxy-β-amino acids constitute an important class of compounds due to their utility as substrates for the synthesis of a wide variety of peptide isosteres[9] and as being constituents of several natural products that exhibit potent biological activity such as bestatin[10] (an inhibitor of amino peptidases), KRI 1314[11] (a renin inhibitor), microginin[12] (an ACE inhibitor) and dideoxykanamycin A[13] (an antibacterial agent). Perhaps, the one of the most significant application of 3-hydroxy-azetidin-2-ones has been the synthesis of phenyl isoserine side chain of taxol. In recent years, taxol, a unique complex diterpene, isolated from the bark of *Taxus brevifolia*[14] (pacific yew) is considered to be the most exciting drug in the anticancer chemotherapy, in particular, for the treatment of lung, breast and ovarian cancer.[15] Unfortunately, this wonder drug is a plant derived product that too available in very small quantities. Large scale sacrifice of yew tree in order to produce this drug is not acceptable solution to the problem of making the drug available in sufficient quantities.[16] This has led to the search for semi-synthetic routes to taxol using other plant-derived products isolated in useful quantities. For instance, 10-deacetylbaccatin III is available in the needles and leaves of *Taxus baccata*[17] (regenerable sources) in sufficient quantities and can be linked with (2*R*, 3*S*)-*N*-benzoyl-3-phenylisoserine[18] to produce taxol.

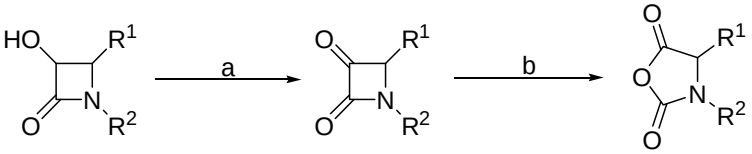
2.2: Background for the present work

***Synthesis of azetidin-2,3-diones*:**

A few methods are available in the literature for the synthesis of azetidin-2,3-diones.[19]

The most popular method is oxidation of 3-hydroxy-β-lactams. [7,19a] Palomo *et al*. have used phosphorus pentoxide-dimethyl sulfoxide system for the oxidation of 3-hydroxy-azetidin-2-one (Scheme 2.03).[7] They have further used the so obtained azetidin-2,3-dione for synthesis of *N*-carboxy anhydrides which are of high importance in amino acid chemistry.

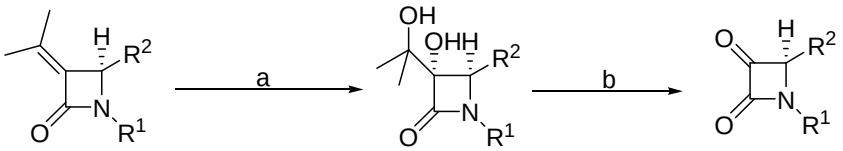
Scheme 2.03



R^1=CH_2OSiPh_2tBu, CH_3, Ph
R^2= PMP, Bn
Reagents and conditions: a) P_2O_5-DMSO; b) *m*-CPBA, DCM, -40 °C, 1h.

Chmielewski *et al*. have reported a method for the synthesis of azetidin-2,3-diones which involves dihydroxylation of *exo*-alkylidene β-lactam followed by glycolic cleavage of the resultant diol (Scheme 2.04).[19b,c]

Scheme 2.04



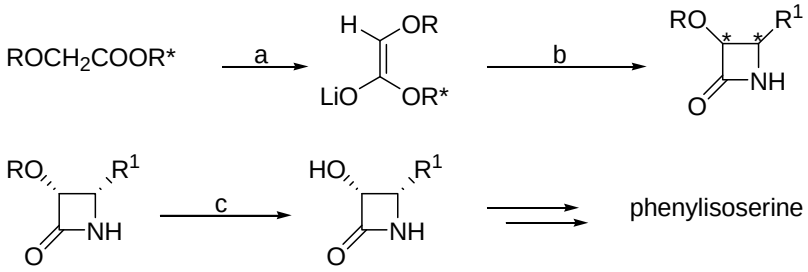
Reagents and conditions: a) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, CCl_4; b) H_6IO_5, EtOAc

***Synthesis of 3-hydroxy azetidin-2-diones*:**

There are various strategies employed for the synthesis of 3-hydroxy azetidin-2-ones. The most commonly used methods are 1) ester enolate-imine cycloaddition and 2) ketene-imine cycloaddition. One of each is described below.

The ester enolate-imine cyclocondensation method[20] provides a very efficient and practical route to 3-hydroxy-β-lactams (Scheme 2.05) with very high enantiomeric purity (> 96%).

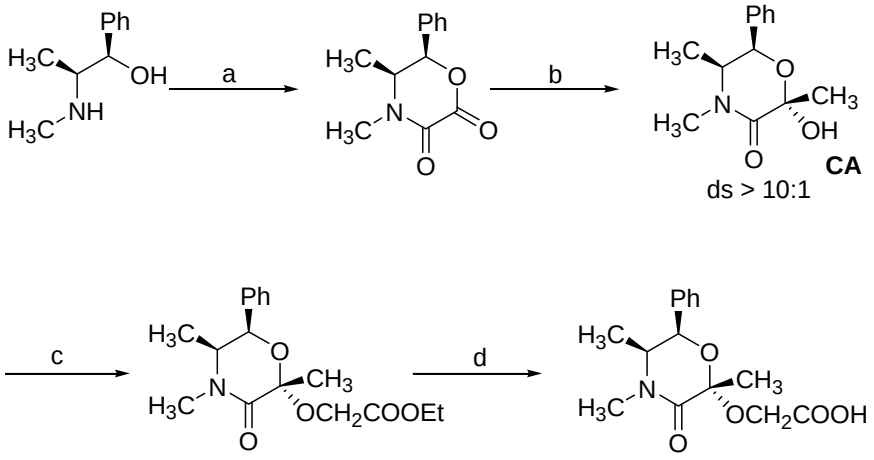
Scheme 2.05



R= Si^ipr_3
R^1=Ph
R*=(-)menthyl
Reagents and conditions: a) LDA, THF; b) R^1-CH=N-TMS c) *n*-Bu_4NF, THF

In an example of use of ketene-imine cycloaddition i.e. the Staudinger cycloaddition reaction, our group has reported an ephedrine derived reusable chiral auxiliary for the synthesis of 3-hydroxy azetidin-2-ones (Scheme 2.06 & 2.07).[21]

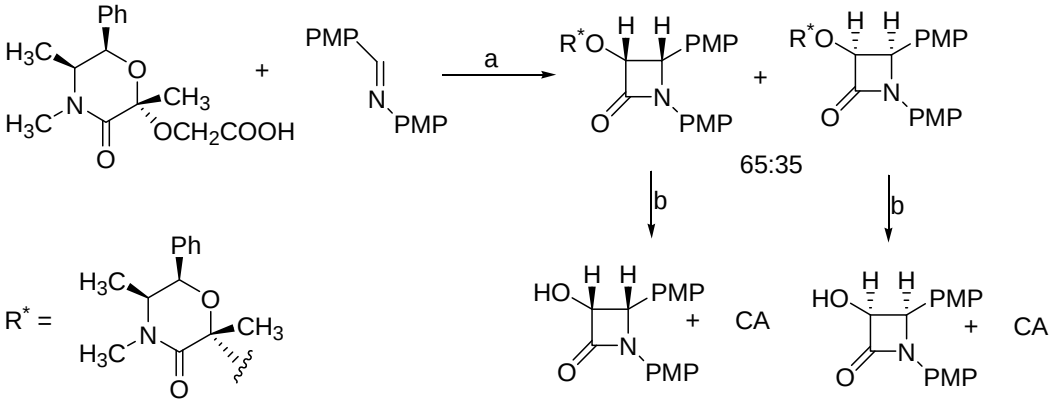
Scheme 2.06



CA = chiral auxiliary

Reagents and conditions: a) $(COCl)_2$, Et_3N, DMAP, CH_2Cl_2; b) CH_3MgI, ether, 1 h; c) NaH, $BrCH_2CO_2Et$, THF+DMF (1:1), 70 °C, 16 h; d) aq. NaOH, THF, 0 °C to rt, 6 h.

Scheme 2.07



CA= chiral auxiliary

Reagents and conditions: a) triphosgene, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h; b) PTSA, THF-H_2O, reflux, 10-12 h.

Apart from these there are few more examples available in the literature for the synthesis of 3-hydroxy azetidin-2-ones.[22-31]

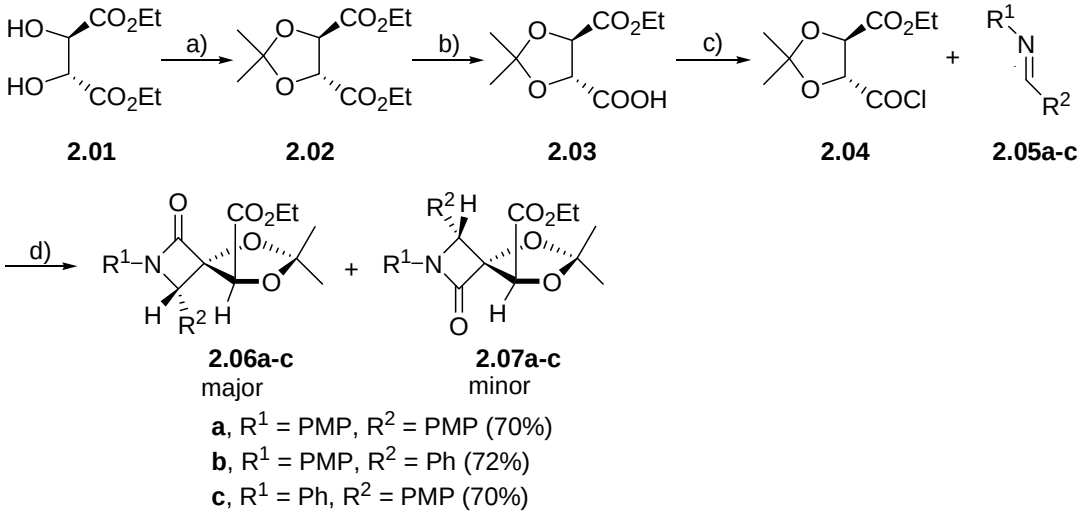
2.3: Present work

This chapter deals with the synthesis of spiro azetidin-2-ones from L-(+)-diethyl tartrate and their subsequent conversion into azetidin-2,3-diones and 3-hydroxy azetidin-2-ones. The results which we had obtained from our work in Chapter 1 gave us important information about the mechanistic aspects of the ketene-imine cycloaddition reaction leading to spiro-β-lactams. These results inspired us to extend the work further. We were thus interested in a starting material which would give us a ketene having structural similarity with the one derived from D-(+)-glucose, allowing stereochemical predictability, and at the same time deliver spiro-β-lactams, having the potential to be transformed into more useful products. L-(+)-diethyl tartrate emerged as the most suitable contender, suiting our requirements. We envisaged that the spiro-β-lactams we aimed at, with L-(+)-diethyl tartrate as a starting material, had the acetonide moiety in the right position to be transformed into azetidin-2,3-diones.

2.4: Results and Discussion

We started our synthesis of spiro-β-lactams with acetonide protection of L-(+)-diethyl tartrate using a reported procedure (Scheme 2.08).[32] The reaction of L-(+)-diethyl tartrate (**2.01**) with 2,2-dimethoxy propane in the presence of catalytic *p*-toluene sulfonic acid in refluxing benzene gave the required acetonide **2.02** in excellent yield. Compound **2.02** was then subjected to selective hydrolysis of one of the ester groups using NaOH in THF-water combination.[33] The reaction proceeded with good yield to deliver mono acid **2.03**. Carboxylic acid **2.03** on refluxing with oxalyl chloride in anhydrous DCM afforded the required acid chloride **2.04**. The acid chloride **2.04** was then used as a ketene precursor in a Staudinger cycloaddition reaction with different imines (**2.05a-c**) to get diastereomeric mixtures of spiro-β-lactams **2.06a-c** and **2.07a-c**. The yields of reactions were 70-72% and diastereoselectivity was around 60:40. For all entries the diastereomeric mixture could be separated by careful flash column chromatography into pure diastereomers.

Scheme 2.08



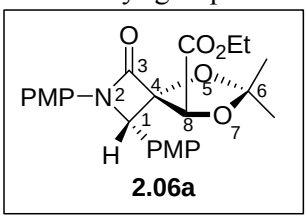
2.01 **2.02** **2.03** **2.04** **2.05a-c**

2.06a-c major **2.07a-c** minor

a, R^1 = PMP, R^2 = PMP (70%)
b, R^1 = PMP, R^2 = Ph (72%)
c, R^1 = Ph, R^2 = PMP (70%)

Reagents and conditions: a) 2,2-dimethoxy propane, benzene, PTSA, reflux, 5h. b) NaOH,THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) Et_3N, DCM, -40 °C-rt, 15h.

Among the series of major diastereomers, compound **2.06a** is chosen as a representative for characterization and spectral discussion. The IR spectrum of **2.06a** showed an intense band at 1759 cm^{-1}, corresponding to the two carbonyl groups. In ^1H NMR, one of the acetonide methyls appeared as a singlet at 1.04 ppm. The three methyl protons from the ester moiety displayed a triplet at 1.12 ppm (J = 7.2 Hz). The other acetonide methyl appeared as a singlet at 1.60 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.74 and 3.81 ppm. The two protons from the methylene group from the ester moiety together displayed a multiplet between 4.16-4.29 ppm. The proton on C-8 appeared as a singlet at 5.02 ppm. The sole proton on the lactam ring i.e. the proton on (C1-H) displayed a singlet at 5.19 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.79 and 6.91 ppm (J = 8.9 Hz). The remaining four aromatic protons displayed a multiplet between 7.25-7.31 ppm.



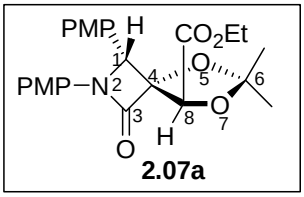
2.06a

In the ^{13}C NMR spectrum, the methyl carbon from the ester moiety appeared at 13.7 ppm. The two acetonide methyl carbons appeared closely at 25.6 and 26.5 ppm, whereas the two methyl carbons from the two PMP groups resonated at 55.1 and 55.2 ppm. The methylene carbon from the ester moiety appeared at 61.8 ppm which was also supported by additional evidence in form of a DEPT spectrum. The carbon C-1 of the lactam ring appeared at 68.0 ppm and carbon C-8 appeared at 78.1 ppm. The spiranic carbon appeared at 92.5 ppm. The quaternary carbon of the acetonide moiety resonated

at 113.6 ppm. A total of six peaks for aromatic carbons were seen in the region 113.9-130.3 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.2 and 159.8 ppm. The ester carbonyl carbon resonated at 163.3 ppm whereas the carbon atom from the lactam carbonyl appeared at 167.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 442 corresponding to M+1.

From the series of minor isomers, **2.07a-c**, **2.07a** is chosen as a representative for characterization and spectral discussion. The IR spectrum of **2.07a** showed an intense band at 1755 cm^{-1}, corresponding to the two carbonyl moieties. In ^{1}H NMR, one of the acetonide methyls appeared as a singlet at 1.06 ppm. The three methyl protons from the ester moiety displayed a triplet at 1.11 ppm (J = 7.2 Hz). The other acetonide methyl appeared as a singlet at 1.47 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.75 and 3.80 ppm. The two protons from the methylene group from the ester moiety together displayed a multiplet between 4.18-4.30 ppm. The only proton on the lactam ring i.e. the proton on (C1-H) displayed a singlet at 4.87 ppm. The proton on C-8 appeared as a singlet at 5.03 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.79 and 6.87 ppm (J = 9.0 Hz). The remaining four aromatic protons appeared as a multiplet between 7.25-7.30 ppm.



2.07a

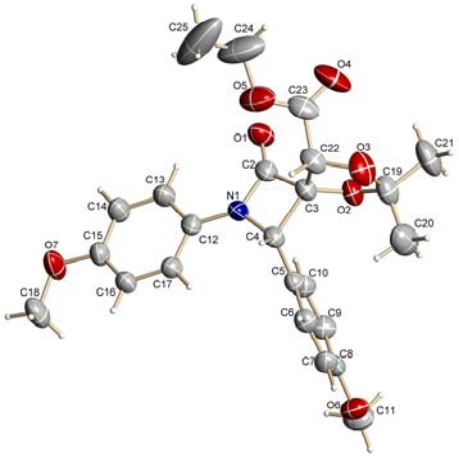
In the ^{13}C NMR spectrum, the methyl carbon from the ester moiety appeared at 13.8 ppm. The two acetonide methyl carbons appeared closely at 25.6 and 26.1 ppm, whereas the two methyl carbons from the two PMP groups resonated at 55.0 and 55.2 ppm. The methylene carbon from the ester moiety appeared at 61.7 ppm which was also supported by additional evidence in form of a DEPT spectrum. The carbon C-1 of the lactam ring appeared at 65.7 ppm and carbon C-8 appeared at 77.0 ppm. The spiranic carbon appeared at 90.9 ppm. The quaternary carbon of the acetonide moiety resonated at 113.1 ppm. A total of six peaks for aromatic carbons were seen in the region 113.7-130.3 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.3 and 159.7 ppm. The ester carbonyl carbon resonated at 163.4 ppm whereas the carbon atom from the lactam carbonyl appeared at 167.6 ppm.

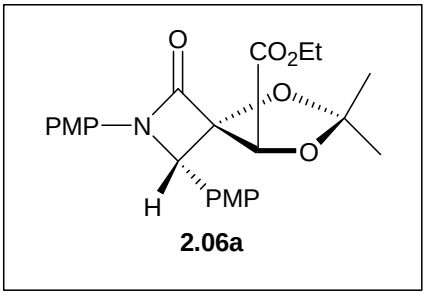
The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 442 corresponding to M+1.

To find out the absolute configurations of newly formed chiral centers we invoked X-ray diffraction studies. To our delight, one of the major diastereomers **2.06a** readily afforded diffractable crystals of very good quality, thereby allowing X-ray diffraction studies. The X-ray diffraction studies revealed that both the newly generated stereocenters *viz* C-1 and C-4 in **2.06a** had absolute configuration *S*.

X-ray diffractable crystals of **2.06a** were grown by slow evaporation of the solution mixture in ethyl acetate and pet-ether. The X-ray data of **2.06a** was collected on a SMART APEX CCD single crystal X-ray diffractometer with omega and phi scan mode and different number of scans and exposure times for different crystals using λ MoK_α = 0.71073 Å radiation, at T = 293(2) K with Oscillation / frame -0.3º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997).

Crystal Data for 2.06a ($C_{24}H_{27}NO_7$): *M* = 441.47, Crystal dimensions 0.52 x 0.47 x 0.33 mm, multirun data acquisition. Total scans = 3, total frames = 1818, exposure / frame = 10.0 sec / frame, range = 1.98 to 27.00º, completeness to of 27.0 º is 100.0 %. Crystals belong to Monoclinic, space group $P2_1/c$, *a* = 10.8952(5), *b* = 23.954(1), *c* = 9.4343(5) Å, β = 109.280(3) º ,*V* = 2324.1(2) $Å^3$, *Z* = 4, D_c = 1.262mg m^{-3}, μ (MoK_α) = 0.093 mm^{-1}, *T* = 293(2) K, 16695 reflections measured, 4083 unique [I>2σ(I)], R value 0.0482, wR2 = 0.1268. X-ray analysis revealed the stereochemistry at C(3) and C(4) positions. The supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request /cif. Please quote reference number CCDC 647625.





2.06a

Figure 2: ORTEP diagram of 2.06a

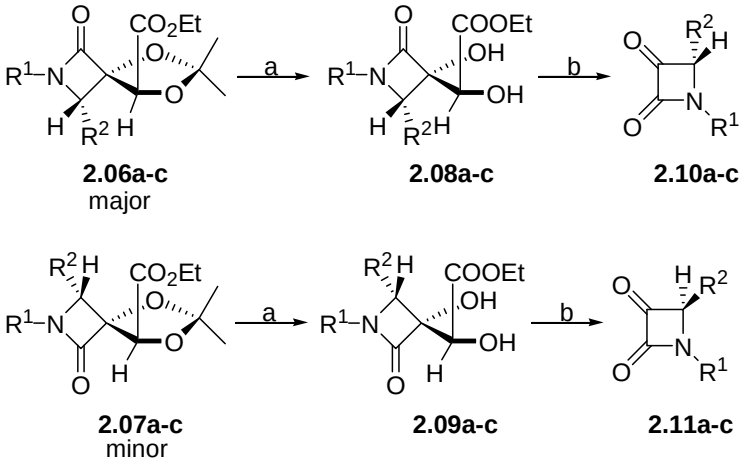
However none of the minor diastereomers could be obtained as crystalline solids. We therefore, deferred the confirmation of the absolute configurations of the newly formed stereocenters of the minor diastereomer to the next step.

***Transformation of spiro azetidin-2-ones into azetidin-2,3-diones*:**

As mentioned earlier, we had started the work with L-(+)-diethyl tartrate as a starting material, aiming at the synthesis of azetidin-2,3-diones.

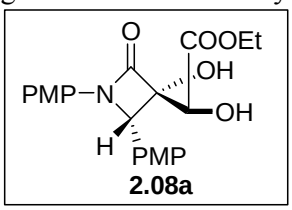
We started by subjecting the both the diastereomers of each of the spiro azetidin-2-ones (**2.06a-c, 2.07a-c**) to acetonide deprotection using $FeCl_3$ in DCM (Scheme 2.09). The reaction proceeded smoothly to yield the corresponding diols (**2.08a-c, 2.09a-c**) in very good yields.

Scheme 2.09



Reagents and conditions: a) $FeCl_3$, DCM, rt, 2h.
b) $NaIO_4$, acetone-water, rt, 6-8h.

From the series of major diastereomers, for characterization and spectral discussion, diol **2.08a** has been chosen as a representative. The IR spectrum of **2.08a** showed a broad and intense band 1736 cm^{-1} corresponding to the two carbonyl functionalities. It also displayed a broad band at around 3398 cm^{-1} for the diol moiety. In the ^{1}H NMR, the three methyl protons from the ester moiety displayed a triplet at 1.29 ppm (J = 7.1 Hz). A singlet was seen at 2.05 ppm for two protons of the hydroxy groups. The methyl groups from the two PMP moieties appeared as two singlets at 3.75 and 3.80 ppm. The two protons from the methylene group from the ester moiety displayed a quartet at 4.32 ppm. The proton attached to the carbon atom bearing the COOEt moiety appeared as a singlet at 5.27 ppm. The proton on the lactam ring appeared at 5.30 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.79 and 6.91 ppm (J = 9.0, 8.9 Hz). The remaining four aromatic protons appeared as a multiplet between 7.21-7.30 ppm.

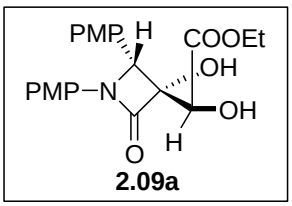


2.08a

In the ^{13}C NMR spectrum, the methyl carbon from the ester moiety appeared at 13.9 ppm. The two methyl carbons from the two PMP groups resonated at 55.1 and 55.2 ppm. The methylene carbon from the ester moiety appeared at 62.3 ppm which was also supported by additional evidence in form of a DEPT spectrum. The carbon atom from the lactam ring bearing the PMP group appeared at 63.3 ppm and carbon bearing the COOEt moiety appeared at 71.0 ppm. The quaternary carbon adjacent to the carbonyl carbon of the β-lactam appeared at 86.3 ppm. A total of five peaks corresponding to the aromatic carbons appeared from 114.1-130.0. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.3 and 159.8 ppm. The ester carbonyl carbon resonated at 164.2 ppm whereas the carbon atom from the lactam carbonyl appeared at 171.5 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 402 corresponding to M+1.

From the series of minor diastereomers, diol **2.09a** is chosen as a representative for characterization and spectral discussion. The IR spectrum of **2.09a** showed a broad band at 1736 cm^{-1} corresponding to the two carbonyl functionalities. It also displayed a broad band at around 3391 cm^{-1} for the diol moiety. In the ^{1}H NMR, the three methyl protons from the ester moiety displayed a triplet at 1.26 ppm (J = 7.2 Hz). A singlet was seen at 2.04 ppm for two protons of the hydroxy groups. The



2.09a

methyl groups from the two PMP moieties appeared as two singlets at 3.74 and 3.79 ppm. The two protons from the methylene group from the ester moiety displayed a quartet at 4.30 ppm. The proton on the lactam ring appeared at 4.63 ppm whereas the proton attached to the carbon atom bearing the COOEt moiety appeared as a singlet at 5.30 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.78 and 6.91 ppm (J = 9.1, 8.9 Hz). The remaining four aromatic protons came as a multiplet between 7.23-7.30 ppm.

In the ^{13}C NMR spectrum, the methyl carbon from the ester moiety appeared at 13.5 ppm. The two methyl carbons from the two PMP groups resonated at 55.2 and 55.3 ppm. The methylene carbon from the ester moiety appeared at 61.9 ppm which was also supported by additional evidence in form of a DEPT spectrum. The carbon atom from the lactam ring bearing the PMP group appeared at 63.2 ppm and the carbon bearing the COOEt moiety appeared at 71.1 ppm. The quaternary carbon adjacent to the carbonyl carbon of the β-lactam appeared at 86.8 ppm. A total of five peaks corresponding to aromatic carbons appeared from 114.1-130.0. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.9 and 159.7 ppm. The ester carbonyl carbon resonated at 164.3 ppm whereas the carbon atom from the lactam carbonyl appeared at 171.5 ppm.

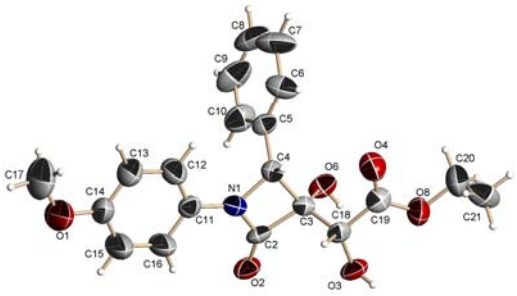
The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 402 corresponding to M+1.

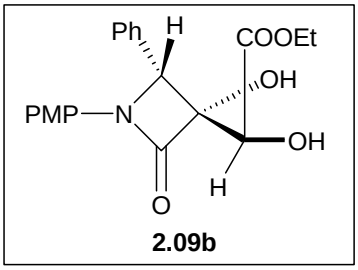
To our delight, after several attempts, one of the compounds in the series of diols obtained from the minor diastereomers of the spiro-β-lactams could be crystallized. As the deprotection of acetonide in the parent spiro-β-lactam had no effect on the stereochemistry, X-ray analysis of a diol obtained from the spiro-β-lactam would give us the absolute configuration of the original spiro-β-lactam. Accordingly, crystals of compound **2.09b** were used for X-ray diffraction analysis. X-ray analysis revealed that both the chiral carbons of the β-lactam ring had '*R*' as absolute configuration. From this finding, it was clear that the precursor spiro-β-lactam had absolute configuration (1*R*,4*R*).

Crystal Data 2.09b ($C_{20}H_{21}NO_6$): Single crystals of the compound were grown by slow evaporation of the solution in pet-ether and ethyl acetate. Colourless crystal of approximate size 0.51 x 0.11 x 0.03 mm, was used for data collection on *Bruker SMART*

APEX CCD diffractometer using Mo K_α radiation. □ range = 2.07 to 24.99 º, completeness to □ of 24.99 º is 99.4 %. $C_{20}H_{21}NO_6$, M = 371.38. Crystals belong to Monoclinic, space group $P2_1$, a = 11.324 (1) b = 5.3940(7)), c = 15.822(2) Å, □= 98.893(3) °, V = 954.8(2) $Å^3$, Z = 2, D_c = 1.292g /cc, T = 293(2) K, 4764 reflections measured, 2759 unique [I>2σ(I)], R value 0.0695, wR2 = 0.1553. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997) 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.

X-ray analysis revealed the stereochemistry at C(3) and C(4) positions. The end atom C(21) has positional disorder.





2.09b

Figure 3: ORTEP diagram of 2.09b

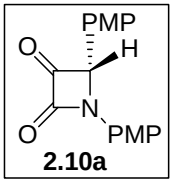
Having obtained the diols, we proceeded further with their conversion into azetidin-2,3-diones. The diols (**2.08a-c, 2.09a-c**) smoothly underwent glycolic cleavage with sodium periodate in acetone-water mixture to yield enantiopure azetidin-2,3-diones, **2.10a-c** and **2.11a-c** in excellent yields (Scheme 2.09, Table 1). Major diastereomers of spiro azetidin-2-ones (**2.06a-c**) yielded azetidin-2,3-diones (**2.10a-c**) with absolute configuration 4*S*, while the minor diastereomers of spiro azetidin-2-ones yielded azetidin-2,3-diones (**2.11a-c**) with 4*R* absolute configuration.

Table 1. Synthesis of azetidin-2,3-diones, **2.10a-c** & **2.11a-c**

S. no.	Starting (spiro-β-lactam)	Product (Dione)	R^1	R^2	Yield (%)[a]	Configu-ration	Specific rotation $[\alpha]^{26}_D$ ($CHCl_3$)
1.	**2.06a**	**2.10a**	PMP	PMP	74	4*S*	+53.3 (*c* 0.9)
2.	**2.06b**	**2.10b**	PMP	Ph	78	4*S*	+123.0 (*c* 2.0)
3.	**2.06c**	**2.10c**	Ph	PMP	81	4*S*	+80.0 (*c* 0.8)
4.	**2.07a**	**2.11a**	PMP	PMP	77	4*R*	-54.6 (*c* 1.5)
5.	**2.07b**	**2.11b**	PMP	Ph	74	4*R*	-123.6 (*c* 1.1)
6.	**2.07c**	**2.11c**	Ph	PMP	75	4*R*	-79.2 (*c* 5.3)

[a] Isolated overall yields from spiro-β-lactams.

Among the series of azetidin-2,3-diones derived from the major diastereomers of spiro-β-lactams, compound **2.10a** is chosen as a representative for characterization and spectral discussion. The IR spectrum of **2.10a** showed bands at 1755 and 1809 cm^{-1}. In the ^1H NMR, the methyl groups from the two PMP moieties appeared as two singlets at 3.79 and 3.80 ppm. The proton on the lactam ring (C4-H) appeared at 5.51 ppm. A total of four aromatic protons displayed a multiplet between 6.85-6.94 ppm. Two doublets for two protons each were observed at 7.24 ppm (J = 9.3 Hz) and 7.46 (J = 9.1 Hz) corresponding to the aromatic protons.

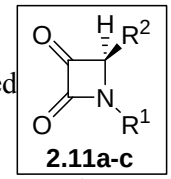


2.10a

In the ^{13}C NMR spectrum, the two methyl carbons from the two PMP groups resonated at 55.2 and 55.4 ppm. The carbon C-4 of the lactam ring appeared at 74.4 ppm. A total of six peaks were seen between 114.6-129.8 ppm which were attributed to the aromatic ring carbons. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 157.8 and 160.1 ppm. The lactam carbonyl carbon appeared at 160.8 whereas the carbon atom of the keto carbonyl appeared at 191.1 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 298 corresponding to M+1.

Azetidin-2,3-diones (**2.11a-c**) obtained in a similar way from the minor diastereomers of spiro-β-lactams (**2.07a-c**) exhibited spectral data identical to the corresponding enantiomeric azetidin-2,3-diones obtained from the series of major diastereomers of spiro-β-lactams. They also showed satisfactory elemental analysis. The specific rotations, as expected, were opposite in sign and numerically in very good agreement with those of enantiomeric azetidin-2,3-diones obtained from the series of major diastereomers of spiro-β-lactams.



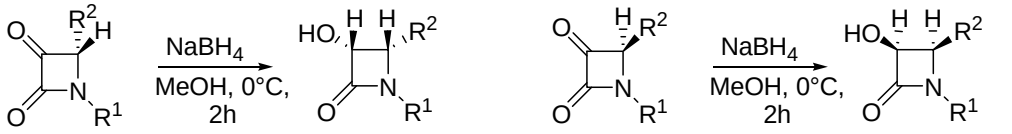
2.11a-c

***Reduction of azetidin-2,3-diones to 3-hydroxy azetidin-2-ones*:**

Nucleophilic attack on the keto group of azetidin-2,3-diones is believed to be directed by the substituent on the adjacent carbon i.e. the C-4 carbon of the β-lactam. In fact, the reduction of azetidin-2,3-ones to 3-hydroxy azetidin-2-ones has been reported in a publication dealing with the synthesis of taxol and bestatin side chains.[34] However, the azetidin-2,3-diones subjected to reduction in the above mentioned work are racemic. This underlines the fact that, it is difficult to synthesize enantiopure azetidin-2,3-diones with aromatic substituents on N-1 and C-4 of the β-lactam. Our work thus provides the same 3-hydroxy azetidin-2-ones, which are useful synthons, in enantiopure form by the reduction of corresponding enantiopure azetidin-2,3-diones. Another intention behind carrying out these reductions was that of confirming the enantiopurity of the azetidin-2,3-diones. The azetidin-2,3-diones we have synthesized are all unknown, new compounds, but the reduced products i.e. the 3-hydroxy azetidin-2-ones we were expecting out of these reduction reactions, are all reported compounds, allowing comparison of specific rotations.

We carried out the reductions using sodium borohydride in methanol at 0 °C (Scheme 2.10). The reaction proceeded cleanly to yield the corresponding 3-hydroxy azetidin-2-ones in excellent yields and complete diastereoselectivity. As expected, the attack of hydride on the keto group took place from the opposite side of the aromatic substituent on the adjacent carbon C-4. Thus, azetidin-2,3-diones **2.10a-c** yielded 3-hydroxy-β-lactams **2.12a-c** (3*R*,4*S*), while azetidin-2,3-diones **2.11a-c** afforded 3-hydroxy-β-lactams **2.13a-c** (3*S*,4*R*). The absolute configurations were determined by comparison of specific rotations with reported values. For example, one of the 3-hydroxy-β-lactams **2.13a**, had specific rotation $\{[\alpha]^{26}_{D}$ = -180.0 (*c* 0.8, $CHCl_3)\}$ for which the reported value is $\{[\alpha]^{26}_{D}$ = -179.1 (*c* 2.2, $CHCl_3)^{21}\}$.

Scheme 2.10



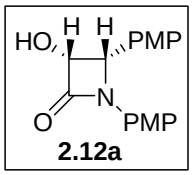
2.10a-c **2.12a-c**

2.12a, R^1 = PMP, R^2 = PMP (92%)
2.12b, R^1 = PMP, R^2 = Ph (90%)
2.12c, R^1 = Ph, R^2 = PMP (90%)

2.11a-c **2.13a-c**

2.13a, R^1 = PMP, R^2 = PMP (92%)
2.13b, R^1 = PMP, R^2 = Ph (87%)
2.13c, R^1 = Ph, R^2 = PMP (89%)

Compound **2.12a** is chosen for spectral description and characterization, from the series **2.12a-c**. The IR spectrum of **2.12a** showed bands at 1728 and 3310 cm^{-1} corresponding to the lactam carbonyl and the hydroxy group respectively. In the ^1H NMR, the proton of hydroxy group appeared as a broad singlet at 3.04 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.75 and 3.79 ppm. The proton on the carbon atom of the lactam ring bearing the PMP moiety (C4-H) appeared as a doublet at 5.15 ppm (J = 5.3 Hz). The proton attached to the carbon bearing the hydroxy group (C3-H) appeared as a doublet at 5.21 ppm (J = 5.3 Hz). The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.79 and 6.92 ppm (J = 8.8, 8.7 Hz). The remaining four aromatic protons showed a multiplet between 7.19-7.37 ppm.

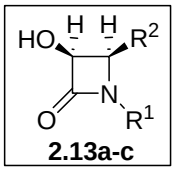


2.12a

In the ^{13}C NMR spectrum, the two methyl carbons from the two PMP groups resonated at 55.0 and 55.1 ppm. The C-4 carbon, bearing the PMP group resonated at 61.7 ppm, whereas, the C-3 carbon bearing the hydroxy group appeared at 76.7 ppm. A set of six peaks corresponding to the aromatic carbons appeared between 113.6-130.7 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 155.5 and 159.0 ppm. The carbonyl carbon of the lactam moiety appeared at 166.4 ppm.

The structure was further supported by the mass spectrum which displayed a peak at m/z 300 corresponding to M+1.

3-hydroxy azetidin-2-ones (**2.13a-c**) obtained in a similar way from the other series of azetidin-2,3-diones (**2.11a-c**), exhibited spectral data identical to the corresponding enantiomeric 3-hydroxy azetidin-2-ones (**2.12a-c**) obtained from the azetidin-2,3-diones (**2.10a-c**). They (**2.13a-c**) also showed satisfactory elemental analysis and the specific rotations, as expected, were opposite in sign and numerically in very good agreement with those of enantiomeric 3-hydroxy azetidin-2-ones (**2.12a-c**).



2.13a-c

***Explanation of stereochemistry of the spiro azetidin-2-ones*:**

We had started this work on the stereoselective synthesis of spiro azetidin-2-ones from an L-(+)-diethyl tartrate derived ketene, banking upon the results we had obtained in our work related to the stereoselective synthesis of spiro azetidin-2-ones from a glucose derived chiral ketene (Chapter 1). We, thus, had expected the same products that we actually got from the Staudinger cycloaddition reaction of L-(+)-diethyl tartrate derived ketene with various imines.

Figure 4 depicts all the theoretically possible products of the Staudinger cycloaddition between a diethyl tartrate derived ketene and imines. With the attack of imine possible from four directions, theoretically four diastereomers are possible. We envisaged, based on our experience of the D-(+)-glucose derived ketene, that the torquoelectronic effect of the oxygen substituent on the ketene would prohibit attack from its side completely eliminating the possibility of formation of products **2.06'** and **2.07'**. The reaction indeed followed the expected course and the only products obtained were **2.06a-c** and **2.07a-c**, which arise from the attack of imine taking place from opposite side of the oxygen substituent.

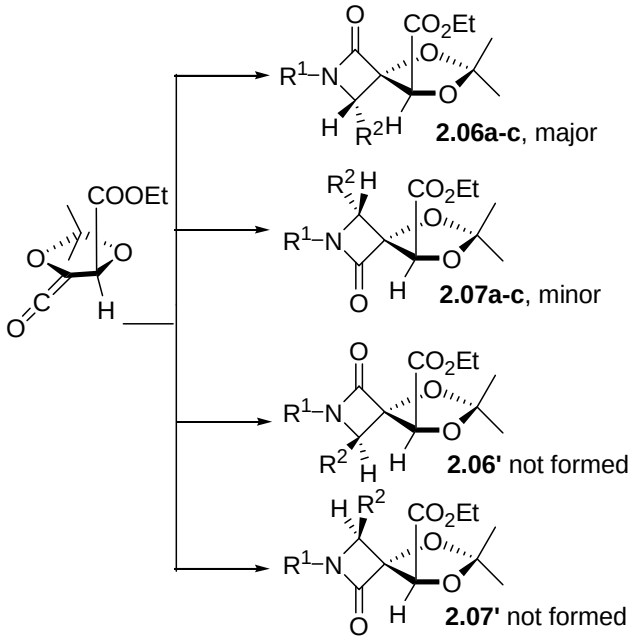


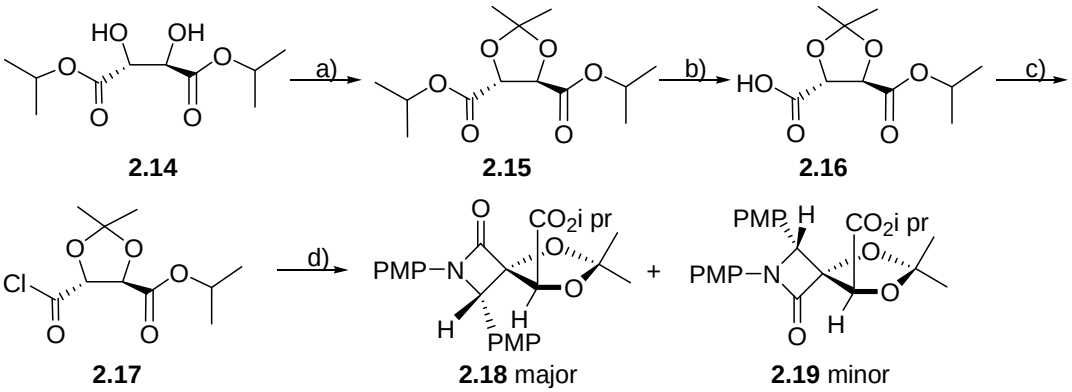
Figure 4: Theoretically possible products from L-(+)-diethyl tartrate derived ketene.

***Effect of change in the ester moiety on diastereoselectivity*:**

When a ketene derived from diethyl tartrate was used in the Staudinger cycloaddition, two products were formed (**2.06 & 2.07a-c**) with a diastereoselectivity of 60:40. We wanted to explore, whether varying the structure of ketene i.e. introducing bulkier esters has any influence on the diastereoselectivity. We thus started with different tartaric acid esters and generated spiro azetidin-2-ones following the same route as we used with diethyl tartrate.

To begin with, we started with diisopropyl tartrate (**2.14**), by protecting it as its acetonide (**2.15**) (Scheme 2.11). Compound **2.15** on partial hydrolysis afforded the required mono acid **2.16** in good yield. This acid was then refluxed with oxalyl chloride in dichloromethane to obtain the acid chloride **2.17**. This acid chloride **2.17** was then used as a ketene precursor in a Staudinger cycloaddition reaction with an imine derived from *p*-anisaldehyde and *p*-anisidine in presence of triethyl amine as a base, at -40 °C to get a diastereomeric mixture of spiro azetidin-2-ones **2.18** and **2.19**. The diastereomeric ratio was **2.18:2.19** = 65:35 (Table 2).

Scheme 2.11



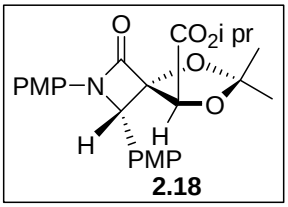
2.14 **2.15** **2.16** **2.17** **2.18** major **2.19** minor

Reagents and conditions: a) 2,2-dimethoxy propane,benzene, PTSA, reflux, 5h.b) NaOH, THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) PMP-N=CH-PMP (**2.05a**), Et_3N, DCM, -40 °C-rt, 15h.

Table 2. Synthesis of substituted spiro-β-lactams from different L-(+)-tartaric acid esters

Entry No.	Starting Acid chloride	Products	Temperature °C	Diastereo-selectivity
1	**2.04**	**2.06a, 2.07a**	-40	60:40
2	**2.04**	**2.06a, 2.07a**	-78	62:38
3	**2.17**	**2.18, 2.19**	-40	65:35
4	**2.17**	**2.18, 2.19**	-78	67:33
5	**2.23**	**2.24, 2.25**	-40	64:36
6	**2.23**	**2.24, 2.25**	-78	65:35
7	**2.28**	**2.29, 2.30**	-40	65:35
8	**2.28**	**2.29, 2.30**	-78	67:33

The major diastereomer **2.18** showed a strong band at 1759 cm^{-1} corresponding to the two carbonyl moieties in the IR spectrum. In the ^1H NMR, one of the acetonide methyls appeared as a singlet at 0.98 ppm. The two methyl groups from the isopropyl moiety of the ester group showed a doublet integrating for six protons at 1.16 ppm (J = 6.3 Hz). The other methyl group of the acetonide moiety appeared as a singlet at 1.52 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.66 and 3.73 ppm. The proton on C-8 bearing the COO-*i*pr group appeared as a singlet at 4.91 ppm. The methine proton from the isopropyl group showed a septet at 5.03 ppm (J = 6.3 Hz). The proton on the lactam i.e. C1-H, displayed a singlet at 5.12



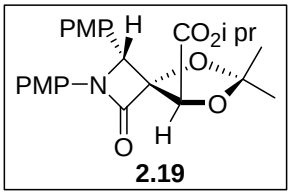
2.18

ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.80 and 6.91 ppm (J = 9.0 Hz). The remaining four aromatic protons displayed a multiplet between 7.16-7.24 ppm.

In the ^{13}C NMR spectrum, the two methyl carbons from the isopropyl group appeared at 21.3 and 21.6 ppm. The two methyl carbons of the acetonide moiety appeared at 25.5 and 26.5 ppm whereas the two methyl groups of the two PMP moieties resonated at 55.1 and 55.2 ppm. The methine carbon from the isopropyl group appeared at 67.7 ppm. The carbon C-1 of the lactam ring appeared at 69.8 ppm and carbon C-8 appeared at 78.0 ppm. The spiranic carbon appeared at 92.5 ppm. The quaternary carbon of the acetonide moiety resonated at 113.4 ppm. A total of six peaks for aromatic carbons were seen in the region 113.9-130.3 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.2 and 159.8 ppm. The ester carbonyl carbon resonated at 163.3 ppm whereas the carbon atom from the lactam carbonyl appeared at 167.2 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 456 corresponding to M+1.

The minor diastereomer **2.19** showed a strong band at 1754 cm^{-1} corresponding to the carbonyl groups, in the IR spectrum. In the ^{1}H NMR, one of the acetonide methyls appeared as a singlet at 0.97 ppm. The two methyl groups from the isopropyl moiety of the ester group showed a doublet integrating for six protons at 1.15 ppm (J = 6.3 Hz). The other methyl group of the acetonide moiety appeared as a singlet at 1.38 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.68 and 3.73 ppm. The proton on the lactam, i.e. C1-H, displayed a singlet at 4.81 ppm. The proton on C-8 bearing the COO-*i*pr group appeared as a singlet at 4.93 ppm. The methine proton from the isopropyl group showed a septet at 5.10 ppm (J = 6.3 Hz). The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.74 and 6.85 ppm (J = 9.0 Hz). The remaining four aromatic protons exhibited a multiplet between 7.11-7.24 ppm.



2.19

In the ^{13}C NMR spectrum, the two methyl carbons from the isopropyl group appeared at 21.3 and 21.6 ppm. The two methyl carbons of the acetonide moiety appeared at 25.7 and 26.2 ppm whereas the two methyl groups of the two PMP moieties resonated at 55.1 and 55.3 ppm. The methine carbon from the isopropyl group appeared at 65.8 ppm. The carbon C-1 of the lactam ring appeared at 69.7 ppm and carbon C-8

appeared at 77.1 ppm. The spiranic carbon appeared at 90.9 ppm. The quaternary carbon of the acetonide moiety resonated at 113.1 ppm. A total of six peaks for aromatic carbons were seen in the region 113.8-130.4 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.4 and 159.8 ppm. The ester carbonyl carbon resonated at 163.5 ppm whereas the carbon atom from the lactam carbonyl appeared at 167.1 ppm.

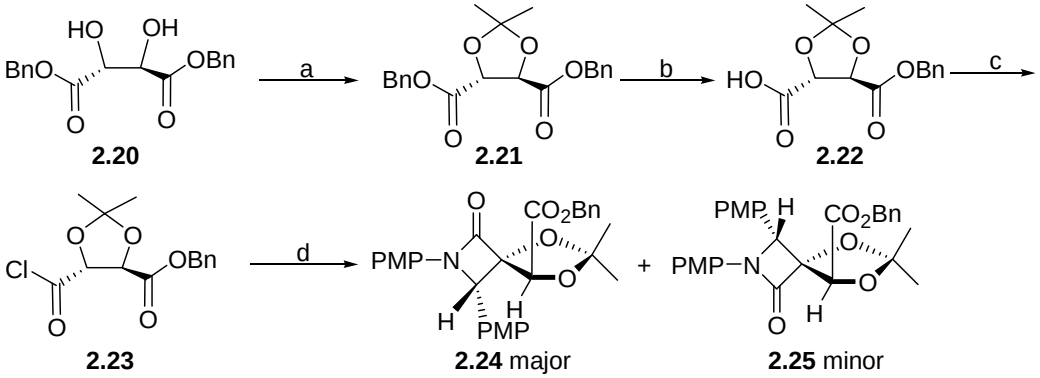
The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 456 corresponding to M+1.

We also carried out the reaction at -78 °C, when spiro-β-lactams **2.18** and **2.19** were obtained in a diastereomeric ratio of 67:33.

Next, we started with dibenzyl tartrate as our starting material. Dibenzyl tartrate **2.20** was protected as its acetonide derivative **2.21** (Scheme 2.12). Compound **2.21** on hydrolysis with one equivalent of base afforded mono acid **2.22** in good yield. Acid **2.22** was refluxed with oxalyl chloride in dichloromethane to get acid chloride **2.23**. Acid chloride **2.23** was used as a ketene precursor in a Staudinger cycloaddition reaction with an imine (**2.05a**) derived from *p*-anisaldehyde and *p*-anisidine, in presence of triethyl amine at -40 °C to get a diastereomeric mixture of spiro-β-lactams, **2.24** and **2.25** in a ratio of 64:36 (Table 2).

However, despite all attempts, the two diastereomers couldn't be isolated in pure form. Different combinations of solvents were tried as eluents in chromatography but the diastereomers were always obtained as inseparable mixtures.

Scheme 2.12



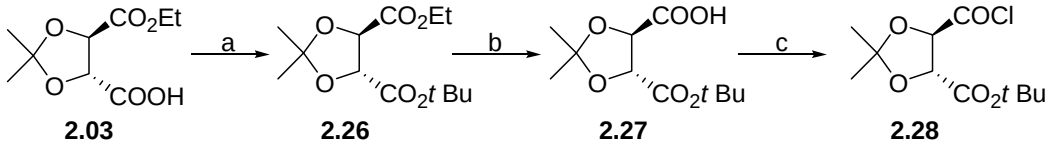
Reagents and conditions: a) 2,2-dimethoxy propane,benzene, PTSA, reflux, 5h.b) NaOH, THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h d) PMP-N=CH-PMP (**2.05a**), Et_3N, DCM, -40 °C-rt, 15h.

When the reaction was tried at -78 °C, products **2.24** and **2.25** were obtained in a ratio of 65:35.

We next wanted to try the synthesis of spiro-β-lactams with the *t*-butyl ester in place. As tertiary butyl esters are stubborn towards basic hydrolysis, we devised an indirect route to the required acid and in turn the acid chloride.

We started with the acid (**2.03**) derived from diethyl tartrate and esterified[35] it using $(BOC)_2O$ in *t*-butanol with DMAP as a catalyst to get mixed ester **2.26** (Scheme 2.13). This ester **2.26** was then subjected to basic hydrolysis using NaOH. The reaction as expected proceeded to hydrolyze the ethyl ester, leaving the *t*-butyl ester untouched to yield acid **2.27**. Acid **2.27** was then refluxed with oxalyl chloride in dichloromethane to obtain acid chloride **2.28**.

Scheme 2.13

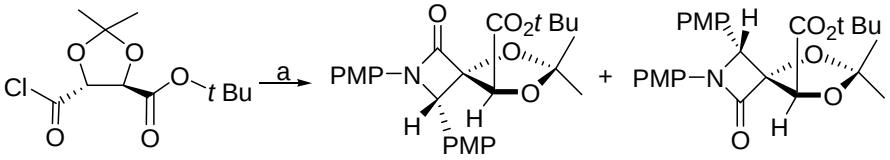


2.03 **2.26** **2.27** **2.28**

Reagents and conditions: a) $(BOC)_2O$, *t*-BuOH, DMAP, 8h. b) NaOH,THF-H_2O, rt, 4-6h. c) $(COCl)_2$, DCM, reflux, 5h.

Acid chloride **2.28** on being subjected to a Staudinger cycloaddition reaction with imine **2.05** at -40 °C, yielded a diastereomeric mixture of spiro-β-lactams **2.29** and **2.30** in a ratio of 65:35 (Scheme 2.14, Table 2).

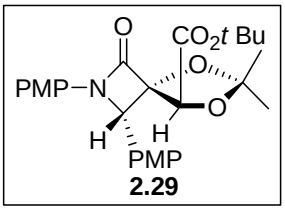
Scheme 2.14



2.28 **2.29** major **2.30** minor

Reagents and conditions: a) PMP-N=CH-PMP (**2.05a**), Et_3N, DCM, 15h.

In the IR spectrum, the major diastereomer **2.29** showed an intense band at 1757 cm^{-1} corresponding to the two carbonyl moieties. In the ^1H NMR, one of the acetonide methyls appeared as a singlet at 0.99 ppm. The nine protons of the *t*-butyl group appeared as a singlet at 1.27 ppm. The other methyl group of the acetonide moiety appeared as a singlet at 1.50 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.66 and 3.73 ppm. A singlet at 4.83 ppm was assigned to the proton on the carbon carrying the ester moiety (C8-H), whereas, the



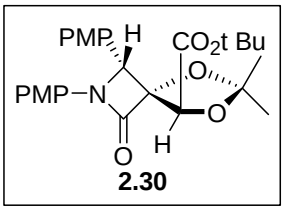
2.29

proton on the lactam ring (C1-H) appeared as a singlet at 5.07 ppm. The eight aromatic protons showed two multiplets of four protons each at 6.70-6.85 and 7.18-7.29 ppm.

In the ^{13}C NMR spectrum, the two methyl carbons of the acetonide moiety appeared at 25.5 and 26.5 ppm. The three carbon atoms from the *t*-butyl group resonated together at 27.7 ppm. The two methyl groups of the two PMP moieties resonated at 55.1 and 55.3 ppm. The carbon C-1 of the lactam ring appeared at 67.5 ppm and carbon C-8 appeared at 78.0 ppm. The tertiary carbon from the *t*-butyl group appeared at 83.3 ppm. The spiranic carbon appeared at 92.4 ppm. The quaternary carbon of the acetonide moiety resonated at 113.1 ppm. A total of six peaks for aromatic carbons were seen in the region 113.9-130.5 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.2 and 159.8 ppm. The ester carbonyl carbon resonated at 163.4 ppm whereas the carbon atom from the lactam carbonyl appeared at 166.3 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 470 corresponding to M+1.

In the minor diastereomer **2.30**, the IR spectrum showed an intense band at 1755 cm^{-1} corresponding to the carbonyl moieties. In the ^{1}H NMR, one of the acetonide methyls appeared as a singlet at 0.93 ppm. The nine protons of the *t*- butyl group appeared as a singlet at 1.27 ppm. The other methyl group of the acetonide moiety appeared as a singlet at 1.44 ppm. The methyl groups from the two PMP moieties appeared as two singlets at 3.66 and 3.70 ppm. The proton on the lactam i.e. C1-H, displayed a singlet at 4.73 ppm. The proton on carbon C-8 bearing, the COO-*t*Bu group appeared as a singlet at 4.84 ppm. The eight aromatic protons showed two multiplets of four protons each at 6.69-6.81 and 7.11-7.29 ppm.



2.30

In the ^{13}C NMR spectrum, the two methyl carbons of the acetonide moiety appeared at 25.5 and 26.1 ppm. The three carbon atoms from the *t*-butyl group resonated together at 27.8 ppm. The two methyl groups of the two PMP moieties resonated at 55.2 and 55.3 ppm. The carbon C-1 of the lactam ring appeared at 67.7 ppm and carbon C-8 appeared at 78.1 ppm. The tertiary carbon from the *t*-butyl group appeared at 83.3 ppm. The spiranic carbon appeared at 92.5 ppm. The quaternary carbon of the acetonide moiety resonated at 113.4 ppm. A total of six peaks for aromatic carbons were seen in the region 113.9-130.4 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings appeared at 156.2 and 159.8 ppm. The ester carbonyl

carbon resonated at 163.3 ppm whereas the carbon atom from the lactam carbonyl appeared at 166.7 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 470 corresponding to M+1.

We also carried out the reaction at -78 °C, when spiro-β-lactams **2.29** and **2.30** were obtained in a diastereomeric ratio of 67:33.

***Summary*:** We undertook this study with an intention of altering the diastereoselectivity for better by modifying the ketene. One side of the ketene had an oxygen atom exerting its torquoelectronic effect, thereby prohibiting the attack of the imine. The remaining side had two faces resulting into two products. We had envisaged that changing the ester moiety would make the imine attack preferentially from the other face, improving the selectivity. However we couldn't get much enhancement in diastereoselectivity, presumably because of the distance between the ester moiety and the reaction centre.

2.5: Conclusion

In conclusion, stereoselective synthesis of spiro-β-lactams was achieved, starting with L-(+)-diethyl tartrate. These spiro-β-lactams were successfully transformed into enantiopure azetidin-2,3-diones and 3-hydroxy azetidin-2-ones, both of which are useful classes of synthons. Different tartaric acid esters were also used as starting materials to study the effect of the change in the ester moiety on the diastereoselectivity of the Staudinger cycloaddition reaction leading to spiro-β-lactams. Changing the ester moiety, however, had little effect on the diastereoselectivity of the process.

2.6: Experimental

2.6.1: (4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid diethyl ester (2.02):

A mixture of L-(+)-diethyl tartrate (**2.01**) (0.700 g, 3.39 mmol), 2,2-dimethoxy propane (0.500 mL, 4.068 mmol) *p*-toluene sulfonic acid (catalytic) in anhydrous benzene was refluxed with a Dean-Stark apparatus in place for removal of benzene-methanol azeotrope for 5h. The solution was then cooled and neutralized with anhydrous K_2CO_3, filtered and washed with water. The aqueous layer was washed with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and it was then concentrated on rotary evaporator to get crude compound as a colorless syrup. The crude product was purified by column chromatography (20% ethyl acetate-petroleum ether) to get compound **2.02** (0.62g, 75%) as a colorless, thick liquid.

2.6.2 (4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid monoethyl ester (2.03):

Compound **2.02** (0.500 g, 2.03 mmol) was dissolved in 5 mL THF. To this solution was added in a drop wise manner a solution of NaOH (0.081 g, 2.03 mmol) in 10 mL water. The resultant solution was allowed to stir at room temperature for 4-6 h. The solution was then concentrated *in vacuo* to remove THF. The aqueous residue was then washed with ethyl acetate (10 mL) to remove any unreacted starting material. The aqueous layer was then acidified with 6N HCl to *p*H=2 at 0 °C. The acidified aqueous solution was then extracted with ethyl acetate (3 x 10 mL). The organic layer was then washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain mono acid **2.03** (0.30g, 68%) as a thick colorless liquid which was pure enough to be used as such in the next step.

IR ($CHCl_3$) : 1733, 2800-3300 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.32 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.50 (3H, s, CH_3), 1.52 (3H, s, CH_3), 4.30 (2H, q, *J* = 7.2 Hz, OCH_2), 4.80 (1H, d, *J* = 5.3 Hz, OC*H*), 4.88 (1H, d, *J* = 5.3 Hz, OC*H*), 10.2 (1H, bs, -COO*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.9, 26.2, 62.1, 76.5, 114.2, 169.5, 174.1

MS (m/z) : 219 (M+1)

Analysis : Calculated: C, 49.54; H, 6.47%

$C_9H_{14}O_6$ Observed: C, 49.37; H, 6.59%

2.6.3 (4*R*,5*R*)-5-Chlorocarbonyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester (2.04):

Acid **2.03** (0.342 g, 1.56 mmol) was dissolved in anhydrous DCM (8 mL) and this solution was cooled to 0 °C. To this cooled solution was added, oxalyl chloride (0.164 mL, 1.88 mmol) slowly in a drop wise manner. The solution was then refluxed for 5h. After 5h the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

2.6.4 General procedure for the synthesis of spiro azetidin-2-ones (2.06a-c & 2.07a-c):

A solution of acid chloride **2.04** (1.5 eq.) in anhydrous dichloromethane was added to a precooled solution of imine (**2.05a-c**) (1 eq.), anhydrous triethylamine (4.5 eq.) in anhydrous dichloromethane at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a diastereomeric mixture. The crude reaction mixture was purified using flash column chromatography (ethyl acetate-petroleum ether) to get diastereomers (**2.06a-c**) and (**2.07a-c**).

Procedure for the preparation of 2.06a and 2.07a:

A solution of acid chloride **2.04** (0.371 g, 1.84 mmol) in anhydrous dichloromethane in 10 mL, was added to a pre-cooled solution of imine **2.05a** (0.296 g, 1.23 mmol), anhydrous triethylamine (0.77 mL, 5.53 mmol) in anhydrous dichloromethane (15 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 10 mL), and brine (10 mL). The organic layer was dried

over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (0.480 g, 70%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **2.06a** and **2.07a**.

(1*S*,4*S*,8*R*)-1,2–Bis-(4-methoxyphenyl)-6,6-dimethyl-3-oxo-5,7–dioxa-2-azaspiro [3.4]octane-8-carboxylic acid ethyl ester (2.06a):

Isolated as a colorless solid in 42% yield.

MP : 163-164 °C

IR ($CHCl_3$) : 1759 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.04 (3H, s, C*H*$_3$), 1.12 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.60 (3H, s, C*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.16-4.29 (2H, m, OCH_2), 5.02 (1H, s, C_8-*H*), 5.19 (1H, s, C_1-*H*), 6.79 (2H, d, *J* = 8.9 Hz, Ar-*H*), 6.91 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.25-7.31 (4H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.7, 25.6, 26.5, 55.1, 55.2, 61.8, 68.0, 78.1, 92.5, 113.6, 113.9, 114.1, 118.7, 124.9, 129.2, 130.3, 156.2, 159.8, 163.3, 167.9

MS (m/z) : 442 (M+1)

Analysis $C_{30}H_{31}NO_7$: Calculated: C, 65.29; H, 6.16; N, 3.17%.
Observed: C, 65.18; H, 6.29; N, 3.03%.

Optical rotation : $[\alpha]^{26}_D$ = +1.4 (*c* 2.7, $CHCl_3$).

(1*R*,4*R*,8*R*)-1,2–Bis-(4-methoxyphenyl)-6,6-dimethyl-3-oxo-5,7–dioxa-2-azaspiro [3.4]octane-8-carboxylic acid ethyl ester (2.07a):

Isolated as a viscous, brown liquid in 28% yield.

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.06 (3H, s, C*H*$_3$), 1.11 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.47 (3H, s, C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.18-4.30 (2H, m, OCH_2CH_3), 4.87 (1H, s, C_1-*H*), 5.03 (1H, s, C_8-*H*), 6.79 (2H, d, *J* = 9.0 Hz, Ar-*H*), 6.87 (2H, d, *J* = 9.0 Hz, Ar-*H*), 7.25-7.30 (4H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 13.8, 25.6, 26.1, 55.0, 55.2, 61.7, 65.7, 77.0, 90.9, 113.1, 113.7, 114.2, 118.7, 124.5, 129.1, 130.3, 156.3, 159.7, 163.4, 167.6

MS (m/z) : 442 (M+1)

Analysis $C_{30}H_{31}NO_7$: Calculated: C, 65.29; H, 6.16; N, 3.17%.
Observed: C, 65.42; H, 6.10; N, 3.25%

Optical rotation : $[\alpha]^{26}_D = -7.0$ (*c* 2.8, $CHCl_3$).

Procedure for the preparation of 2.06b and 2.07b:

Following the general procedure, solution of acid chloride **2.04** (1.04 g, 4.39 mmol) in anhydrous dichloromethane (20 mL) was added to a pre-cooled solution of imine **2.05b** (0.618 g, 2.93 mmol), anhydrous triethylamine (1.83 mL, 13.18 mmol) in anhydrous dichloromethane (30 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 15 mL), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (1.30 g, 72%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **2.06b** and **2.07b**.

(1*S*,4*S*,8*R*)-2-(4-Methoxy-phenyl)-1-phenyl-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (2.06b):

Isolated as a viscous liquid in 43% yield.

IR ($CHCl_3$) : 1759 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.04 (3H, s, C*H*$_3$), 1.12 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 4.16-4.29 (2H, m, OC*H*$_2$), 5.03 (1H, s, C$_8$-*H*), 5.19 (1H, s, C$_1$-*H*), 6.79 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.23-7.39 (7H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 13.7, 25.6, 26.5, 55.1, 61.8, 67.5, 78.1, 92.3, 113.6, 114.1, 118.7, 127.9, 128.2, 128.6, 130.3, 133.4, 156.2, 163.3, 167.9

MS (m/z) : 412 (M+1)

Analysis : Calculated: C, 67.14; H, 6.12; N, 3.40%.

$C_{23}H_{25}NO_6$ Observed: C, 67.21; H, 6.20; N, 3.22%.

Optical rotation : $[\alpha]^{26}_D = -1.1$ (*c* 1.8, $CHCl_3$).

(1*R*,4*R*,8*R*)-2-(4-Methoxy-phenyl)-1-phenyl-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (2.07b):

Isolated as a viscous liquid in 29% yield.

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.04 (3H, s, C*H*$_3$), 1.12 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 4.19-4.38 (2H, m, OC*H*$_2$), 4.92 (1H, s, C$_1$-*H*), 5.05 (1H, s, C$_8$-*H*), 6.81 (2H, d, *J* = 9.0 Hz, Ar-*H*), 7.23-7.40 (7H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.9, 25.6, 26.0, 55.3, 61.3, 65.7, 77.1, 91.5, 113.4, 114.3, 118.9, 127.5, 128.4, 128.6, 130.3, 133.2, 156.6, 163.4, 167.4

MS (m/z) : 412 (M+1)

Analysis : Calculated: C, 67.14; H, 6.12; N, 3.40%.

$C_{23}H_{25}NO_6$ Observed: C, 67.22; H, 6.01; N, 3.57%.

Optical rotation : $[\alpha]^{26}_D = -22.6$ (*c* 2.3, $CHCl_3$).

Procedure for the preparation of 2.06c and 2.07c:

Following the general procedure, solution of acid chloride **2.04** (2.37 g, 10.02 mmol) in anhydrous dichloromethane (20 mL) was added to a pre-cooled solution of imine **2.05c** (1.41 g, 6.68 mmol), anhydrous triethylamine (4.18 mL, 30.06 mmol) in anhydrous dichloromethane (30 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 25 mL), and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark viscous liquid (2.88 g, 70%). The crude

reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **2.06c** and **2.07c**.

(1*S*,4*S*,8*R*)-1-(4-Methoxy-phenyl)-2-phenyl-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (2.06c):

Isolated as a viscous liquid in 42% yield.

IR ($CHCl_3$) : 1760 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.05 (3H, s, C*H*$_3$), 1.10 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.60 (3H, s, C*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.13-4.30 (2H, m, OC*H*$_2$), 5.03 (1H, s, C_8-*H*), 5.24 (1H, s, C_1-*H*), 6.91 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.21-7.36 (7H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.7, 25.6, 26.6, 55.1, 61.9, 68.0, 78.2, 92.5, 113.8, 113.9, 117.5, 124.4, 124.8, 129.0, 129.2, 136.8, 159.9, 164.1, 167.8

MS (m/z) : 412 (M+1)

Analysis $C_{23}H_{25}NO_6$: Calculated: C, 67.14; H, 6.12; N, 3.40%.

Observed: C, 67.29; H, 6.15; N, 3.18%.

Optical rotation : $[\alpha]^{26}_D$ = +1.3 (*c* 4.5, $CHCl_3$).

(1*R*,4*R*,8*R*)-1-(4-Methoxy-phenyl)-2-phenyl-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid ethyl ester (2.07c):

Isolated as a viscous liquid in 28% yield.

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.07 (3H, s, C*H*$_3$), 1.09 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.47 (3H, s, C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.18-4.36 (2H, m, OC*H*$_2$), 4.92 (1H, s, C_1-*H*), 5.04 (1H, s, C_8-*H*), 6.89 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.16-7.36 (7H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.9, 25.7, 26.2, 55.2, 61.8, 65.7, 77.2, 91.0, 113.3, 113.9, 117.5, 124.6, 125.1, 129.0, 129.2, 136.8, 159.8, 164.2, 167.7

MS (m/z) : 412 (M+1)

Analysis : Calculated: C, 67.14; H, 6.12; N, 3.40%.

$C_{23}H_{25}NO_6$

Observed: C, 67.28; H, 6.29; N, 3.29%.

Optical rotation : $[\alpha]^{26}_{D} = -40$ (*c* 3.0, $CHCl_3$).

2.6.5 General procedure for the synthesis of diols (2.08a-c & 2.09a-c):

Spiro azetidin-2-one (**2.06 & 2.07a-c**) (1 mmol, 1 eq.) was dissolved in dichloromethane (15 mL). To this solution was added anhydrous $FeCl_3$ (2 mmol, 2 eq.) at room temperature in a portion wise manner. The solution was kept stirring for approximately 2h. After completion of reaction (TLC), the reaction mixture was passed through a bed of celite, and the residue washed with DCM (5 mL). The filtrate along with washings was concentrated *in vacuo* to furnish crude diols (**2.08 & 2.09a-c**). The crude product was purified by column chromatography (ethyl acetate-petroleum ether) to get pure diols in good yields.

(*3S*,*4S*)-Hydroxy-[3-hydroxy-1,4-bis-(4-methoxy phenyl)-2-oxo-azetidin-3-yl]-acetic acid ethyl ester (2.08a):

Following a general procedure, spiro azetidin-2-one **2.06a** (0.200g, 0.453 mmol) on reaction with anhydrous $FeCl_3$ (0.147g, 0.907 mmol) in DCM (7 mL) yielded, after work-up crude diol **2.08a**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.08a** (0.162g, 89%) as a thick oil.

IR ($CHCl_3$) : 1736, 3398 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 2.05 (2H, s, O*H*), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.32 (2H, quart, *J* = 7.1 Hz, OCH_2CH_3), 5.27 (1H, s, C*H*COOEt), 5.30 (1H, s, NC*H*), 6.79 (2H, d, *J* = 9.0 Hz, Ar-*H*), 6.91 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.21-7.30 (4H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.9, 55.1, 55.3, 62.3, 63.3, 71.0, 86.3, 114.1, 119.0, 124.5, 129.0, 130.0, 156.3, 159.8, 164.2, 171.5

MS (m/z) : 402 (M+1)

Analysis $C_{21}H_{23}NO_7$: Calculated: C, 62.83; H, 5.78; N, 3.49%

Observed: C, 62.72; H, 5.94; N, 3.60%

Optical rotation : $[\alpha]^{26}_{D} = +20$ (*c* 1.1, $CHCl_3$).

(*3R*,*4R*)-Hydroxy-[3-hydroxy-1,4-bis-(4-methoxyphenyl)-2-oxo-azetidin-3-yl]-acetic acid ethyl ester (2.09a):

Following a general procedure, spiro azetidin-2-one **2.07a** (0.200g, 0.453 mmol) on reaction with anhydrous $FeCl_3$ (0.147g, 0.907 mmol) in DCM (7 mL) yielded, after work-up crude diol **2.09a**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.09a** (0.160g, 88%) as a thick oil.

IR ($CHCl_3$) : 1736, 3391 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.26 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.04 (2H, s, O*H*), 3.74 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.30 (2H, quart, *J* = 7.2 Hz, OCH_2CH_3), 4.63 (1H, s, NC*H*), 5.30 (1H, s, C*H*COOEt), 6.78 (2H, d, *J* = 9.1 Hz, Ar-*H*), 6.91 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.23-7.30 (4H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.5, 55.2, 55.3, 61.9, 63.2, 71.1, 86.8, 114.1, 119.2, 124.5, 129.1, 130.0, 156.9, 159.7, 164.3, 171.5

MS (m/z) : 402 (M+1)

Analysis $C_{21}H_{23}NO_7$: Calculated: C, 62.83; H, 5.78; N, 3.49%

Observed: C, 62.75; H, 5.69; N, 3.32%

Optical rotation : $[\alpha]^{26}_{D} = -25.6$ (*c* 2.5, $CHCl_3$).

(*3S*,*4S*)-Hydroxy-[3-hydroxy-1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-acetic acid ethyl ester (2.08b):

Following a general procedure, spiro azetidin-2-one **2.06b** (0.180g, 0.437 mmol) on reaction with anhydrous $FeCl_3$ (0.142g, 0.875 mmol) in DCM (7 mL) yielded, after work-up crude diol **2.08b**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.08b** (0.137g, 85%) as a thick oil.

IR ($CHCl_3$) : 1738, 3395 cm^{-1}

^{1}H NMR : δ_H 1.23 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 2.05 (2H, s, O*H*), 3.74 (3H,

($CDCl_3$) (200 MHz)		s, OC*H*$_3$), 4.27 (2H, quart, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 5.27 (1H, s, C*H*COOEt), 5.31 (1H, s, NC*H*), 6.79 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.23-7.39 (7H, m, Ar-*H*)
MS (m/z)	**:**	372 (M+1)
Analysis $C_{20}H_{21}NO_6$	**:**	Calculated: C, 64.68; H, 5.70; N, 3.77% Observed: C, 64.81; H, 5.55; N, 3.89%
Optical rotation	**:**	$[\alpha]^{26}_D$ = +157 (*c* 0.7, $CHCl_3$).

(3*R*,4*R*)-Hydroxy-[3-hydroxy-1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-acetic acid ethyl ester (2.09b):

Following a general procedure, spiro azetidin-2-one **2.07b** (0.155g, 0.377 mmol) on reaction with anhydrous $FeCl_3$ (0.122g, 0.754 mmol) in DCM (7 mL) yielded, after work-up crude diol **2.09b**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.09b** (0.120g, 86%) as a colorless solid.

IR ($CHCl_3$)	**:**	1735, 3398 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.26 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 2.1 (2H, s, O*H*), 3.76 (3H, s, OC*H*$_3$), 4.35 (2H, quart, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 4.64 (1H, s, NC*H*), 5.32 (1H, s, C*H*COOEt), 6.79 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.23-7.39 (7H, m, Ar-*H*)
MS (m/z)	**:**	372 (M+1)
Analysis $C_{20}H_{21}NO_6$	**:**	Calculated: C, 64.68; H, 5.70; N, 3.77% Observed: C, 64.77; H, 5.52; N, 3.91%
Optical rotation	**:**	$[\alpha]^{26}_D$ = -30 (*c* 1.2, $CHCl_3$).

(*3S*,*4S*)-Hydroxy-[3-hydroxy-4-(4-methoxy-phenyl)-2-oxo-1-phenyl-azetidin-3-yl]-acetic acid ethyl ester (2.08c):

Following a general procedure, spiro azetidin-2-one **2.06c** (0.175g, 0.425 mmol) on reaction with anhydrous $FeCl_3$ (0.138g, 0.851 mmol) in DCM (7 mL) yielded, after work-up crude diol **2.08c**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.08c** (0.142g, 90%) as a thick oil.

IR ($CHCl_3$) : 1735, 3398 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.30 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 2.05 (2H, s, O*H*), 3.81 (3H, s, OCH_3), 4.33 (2H, quart, *J* = 7.1 Hz, OCH_2CH_3), 5.26 (1H, s, C*H*COOEt), 5.31 (1H, s, NC*H*), 6.92 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.23-7.39 (7H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 13.9, 55.2, 62.5, 63.3, 71.0, 86.2, 114.2, 117.7, 124.2, 124.5, 129.0, 136.6, 159.9, 164.6, 171.5

MS (m/z) : 372 (M+1)

Analysis $C_{20}H_{21}NO_6$: Calculated: C, 64.68; H, 5.70; N, 3.77%

Observed: C, 64.49; H, 5.83; N, 3.61%

Optical rotation : $[\alpha]^{26}_D = +15.1$ (*c* 1.1, $CHCl_3$).

(3*R*,4*R*)-Hydroxy-[3-hydroxy-4-(4-methoxy-phenyl)-2-oxo-1-phenyl-azetidin-3-yl]-acetic acid ethyl ester (2.09c):

Following a general procedure, spiro azetidin-2-one **2.07c** (0.275g, 0.669 mmol) on reaction with anhydrous $FeCl_3$ (0.217g, 1.338 mmol) in DCM (10 mL) yielded, after work-up crude diol **2.09c**. This crude diol was purified by column chromatography (40% ethyl acetate-pet. ether) to obtain pure diol **2.09c** (0.210g, 85%) as a thick oil.

IR ($CHCl_3$) : 1735, 3392 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.25 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.1 (2H, s, O*H*), 3.79 (3H, s, OCH_3), 4.29 (2H, quart, *J* = 7.2 Hz, OCH_2CH_3), 4.63 (1H, s, NC*H*), 5.34 (1H, s, C*H*COOEt), 6.90 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.20-7.35 (7H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 14.0, 55.0, 62.4, 63.9, 72.9, 85.8, 113.9, 117.6, 124.3, 124.5, 129.1, 136.5, 159.7, 165.3, 170.8

MS (m/z) : 372 (M+1)

Analysis $C_{20}H_{21}NO_6$: Calculated: C, 64.68; H, 5.70; N, 3.77%

Observed: C, 64.81; H, 5.49; N, 3.93%

Optical rotation : $[\alpha]^{26}_{D}$ = -12.3 (*c* 0.6, $CHCl_3$).

2.6.6 General procedure for the synthesis of diones (2.10a-c & 2.11a-c):

To a solution of diol (**2.08 & 2.09a-c**) (1 mmol, 1 eq.) in acetone-water (2:1, 15 mL) was added powdered $NaIO_4$ (4 mmol, 4 eq.) and the solution was stirred for 6-8 h. After completion of the reaction (TLC), the reaction mixture was filtered through a Buchner funnel and the residue was washed with acetone (10 mL). The combined filtrates were evaporated *in vacuo* to remove acetone. The residue was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get the crude dione (**2.10 & 2.11a-c**). The crude product was purified by column chromatography (ethyl acetate-petroleum ether) to get pure dione in excellent yield.

(*4S*)-1,4-bis (4-methoxy phenyl)-azetidine-2,3-dione (2.10a)

Following a general procedure, diol **2.08a** (0.105g, 0.261 mmol) in acetone-water (2:1, 6 mL) on reaction with $NaIO_4$ (0.223g, 1.044 mmol) yielded after work-up, crude dione **2.10a**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.10a** (0.065g, 84%) as a yellow solid.

MP : 144 °C

IR ($CHCl_3$) : 1755, 1809 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.79 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 5.51 (1H, s, C_4H), 6.85-6.94 (4H, m, Ar*H*), 7.24 (2H, d, *J* = 9.3 Hz, Ar*H*), 7.46 (2H, d, *J* = 9.1 Hz, Ar*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 55.2, 55.4, 74.4, 114.6, 114.8, 119.6, 123.5, 127.7, 129.8, 157.8, 160.1, 160.8, 191.1

MS (m/z) : 298 (M+1)

Analysis $C_{17}H_{15}NO_4$: Calculated: C, 68.68; H, 5.09; N, 4.71%

Observed: C, 64.85; H, 5.19; N, 4.62%

Optical rotation : $[\alpha]^{26}_{D}$ = +53.3 (*c* 0.9, $CHCl_3$).

(*4R*)-1,4-bis (4-methoxy phenyl)-azetidine-2,3-dione (2.11a):

Following a general procedure, diol **2.09a** (0.248g, 0.618 mmol) in acetone-water (2:1, 6 mL) on reaction with $NaIO_4$ (0.529g, 2.47 mmol) yielded after work-up, crude dione **2.11a**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.11a** (0.156g, 85%) as a yellow solid.

The spectral data of **2.11a** was identical with that of **2.10a**.

Analysis : Calculated: C, 68.68; H, 5.09; N, 4.71%

$C_{17}H_{15}NO_4$ Observed: C, 64.50; H, 5.22; N, 4.67%

Optical rotation : $[\alpha]^{26}_D$ = -54.6 (*c* 1.5, $CHCl_3$).

(*4S*)- 1-(4-Methoxy-phenyl)-4-phenyl-azetidine-2,3-dione (2.10b):

Following a general procedure, diol **2.08b** (0.068g, 0.183 mmol) in acetone-water (2:1, 6 mL) on reaction with $NaIO_4$ (0.156g, 0.732 mmol) yielded after work-up, crude dione **2.10b**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.10b** (0.043g, 91%) as a yellow solid.

MP : 127 °C

IR ($CHCl_3$) : 1755, 1812 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.75 (3H, s, OC*H*$_3$), 5.52 (1H, s, C$_4$*H*), 6.90 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.24-7.38 (7H, m, Ar*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 55.3, 74.4, 114.6, 114.8, 119.7, 123.5, 127.8, 129.9, 157.8, 160.4, 191.2

MS (m/z) : 268 (M+1)

Analysis : Calculated: C, 71.90; H, 4.90; N, 5.24%

$C_{17}H_{15}NO_4$ Observed: C, 71.81; H, 5.13; N, 5.39%

Optical rotation : $[\alpha]^{26}_D$ = +123.0 (*c* 2.0, $CHCl_3$).

(4*R*)- 1-(4-Methoxy-phenyl)-4-phenyl-azetidine-2,3-dione (2.11b):

Following a general procedure, diol **2.09b** (0.122g, 0.328 mmol) in acetone-water (2:1, 6 mL) on reaction with $NaIO_4$ (0.140g, 0.656 mmol) yielded after work-up, crude dione **2.11b**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.11b** (0.074g, 86%) as a yellow solid.

The spectral data of **2.11b** was identical with that of **2.10b**.

Analysis : Calculated: C, 71.90; H, 4.90; N, 5.24%

$C_{17}H_{15}NO_4$ Observed: C, 71.76; H, 4.69; N, 5.45%

Optical rotation : $[\alpha]^{26}_D$ = -123.6 (*c* 1.1, $CHCl_3$).

(*4S*)-4-(4-Methoxy-phenyl)-1-phenyl-azetidine-2,3-dione (2.10c):

Following a general procedure, diol **2.08c** (0.105g, 0.283 mmol) in acetone-water (2:1, 6 mL) on reaction with $NaIO_4$ (0.242g, 1.132 mmol) yielded after work-up, crude dione **2.10c**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.10c** (0.067g, 90%) as a yellow semi-solid.

IR ($CHCl_3$) : 1755, 1809 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.72 (3H, s, OC*H*$_3$), 5.47 (1H, s, C$_4$*H*), 6.84 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.15-7.45 (7H, m, Ar*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 55.3, 74.5, 114.2, 114.8, 118.2, 123.4, 127.7, 129.5, 160.5, 160.7, 191.7

MS (m/z) : 268 (M+1)

Analysis : Calculated: C, 71.90; H, 4.90; N, 5.24%

$C_{17}H_{15}NO_4$ Observed: C, 71.98; H, 5.07; N, 5.12%

Optical rotation : $[\alpha]^{26}_D$ = +80.0 (*c* 0.8, $CHCl_3$).

(4*R*)-4-(4-Methoxy-phenyl)-1-phenyl-azetidine-2,3-dione (2.11c):

Following a general procedure, diol **2.09c** (0.250g, 0.673 mmol) in acetone-water (2:1, 9 mL) on reaction with $NaIO_4$ (0.575g, 2.69 mmol) yielded after work-up,

crude dione **2.11c**. This crude dione was purified by column chromatography (20% ethyl acetate-pet. ether) to obtain pure dione **2.11c** (0.157g, 88%) as a yellow semi-solid.

The spectral data of **2.11c** was identical with that of **2.10c**.

Analysis : Calculated: C, 71.90; H, 4.90; N, 5.24%

$C_{17}H_{15}NO_4$ Observed: C, 72.05; H, 4.67; N, 5.41%

Optical rotation : $[\alpha]^{26}_D$ = -79.2 (*c* 5.3, $CHCl_3$).

2.6.7 General procedure for the synthesis of 3-hydroxy azetidin-2-ones (2.12a-c & 2.13a-c):

Dione (**2.10 & 2.11a-c**) (1 mmol, 1 eq.) was dissolved in methanol (5 mL) and cooled to 0 °C using an ice bath. To this solution was added at 0 °C, sodium borohydride (1.5 mmol, 1.5 eq.) in a portion-wise manner. It was then left stirring for 2h at 0 °C. After completion (TLC), the reaction was quenched with a little ice and allowed to stir for 15 min. Methanol was then removed *in vacuo* and the residue extracted with DCM (3 x 15 mL). Organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated on the rotary evaporator to get crude 3-hydroxy azetidin-2-one (**2.12 & 2.13a-c**). The crude compound was purified by column chromatography (ethyl acetate-petroleum ether) to obtain the pure 3-hydroxy azetidin-2-one in good yield

(3*R*,4*S*)-3-Hydroxy-1,4-bis-(4-methoxy-phenyl)-azetidin-2-one (2.12a):

Following the general procedure, dione **2.10a** (0.048g, 0.161 mmol), on reaction with $NaBH_4$ (0.01g, 0.24 mmol) at 0 °C in methanol (3 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.12a** (0.044g, 92%) as a white solid.

MP : 146-148 °C

IR ($CHCl_3$) : 1728, 3310 cm^{-1}

^{1}H NMR : δ_H 3.04 (1H, bs, O*H*), 3.75 (3H, s, OCH_3), 3.79 (3H, s, OCH_3),

($CDCl_3$) 5.15 (1H, d, *J* = 5.3 Hz, C*H*N), 5.21 (1H, d, *J* = 5.3 Hz, C_3H), 6.79

(200 MHz) (2H, d, *J* = 8.8 Hz, Ar*H*), 6.92 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.19-7.37 (4H, m, Ar*H*)

^{13}C NMR (CDCl$_3$) (50 MHz) : δ_C 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 $C_{17}H_{17}NO_4$: Calculated: C, 68.21; H, 5.72; N, 4.68%

Observed: C, 68.35; H, 5.64; N, 4.53%

Optical rotation : Observed: $[\alpha]^{26}_D = +180.0$ (*c* 0.4, $CHCl_3$).

Reported (enantiomer): $[\alpha]^{26}_D = -179.1$ (*c* 2.2, $CHCl_3$).[21]

(3*S*,4*R*)-3-Hydroxy-1,4-bis-(4-methoxy-phenyl)-azetidin-2-one (2.13a):

Following the general procedure, dione **2.11a** (0.073g, 0.245 mmol), on reaction with $NaBH_4$ (0.014g, 0.368 mmol) at 0 °C in methanol (3 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.13a** (0.067g, 92%) as a white solid.

The spectral data of **2.13a** was identical with that of **2.12a**.

Analysis $C_{17}H_{17}NO_4$: Calculated: C, 68.21; H, 5.72; N, 4.68%

Observed: C, 68.09; H, 5.61; N, 4.80%

Optical rotation : Observed: $[\alpha]^{26}_D = -180.0$ (*c* 0.8, $CHCl_3$).

Reported: $[\alpha]^{26}_D = -179.1$ (*c* 2.2, $CHCl_3$).[21]

(3*R*,4*S*)-3-Hydroxy-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2.12b):

Following the general procedure, dione **2.10b** (0.074g, 0.275 mmol), on reaction with $NaBH_4$ (0.016g, 0.412 mmol) at 0 °C in methanol (3 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.12b** (0.067g, 90%) as a white solid.

MP : 196-197 °C

IR (CHCl$_3$) : 1713, 3310 cm^{-1}

^{1}H NMR : δ_H 2.88 (1H, bs, O*H*), 3.76 (3H, s, OCH_3), 5.20 (1H, d, *J* = 5.4

($CDCl_3$) (200 MHz)		Hz, C*H*N), 5.27 (1H, d, *J* = 5.4 Hz, C_3H), 6.80 (2H, d, *J* = 8.8 Hz, Ar*H*), 7.23-7.55 (7H, m, Ar*H*)
^{13}C NMR ($DMSO\ d_6$) (50 MHz)	**:**	δ_C 55.4, 62.1, 77.8, 114.6, 118.2, 127.9, 128.2, 128.4, 131.0, 135.1, 155.8, 166.4
MS (m/z)	**:**	270 (M+1)
Analysis $C_{16}H_{15}NO_3$	**:**	Calculated: C, 71.36; H, 5.61; N, 5.20% Observed: C, 71.49; H, 5.64; N, 5.04%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D = +177.7$ (*c* 0.18, $CHCl_3$). Reported: $[\alpha]^{26}_D = +180.0$ (*c* 0.4, $CHCl_3$).[21]

(3*S*,4*R*)-3-Hydroxy-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2.13b):

Following the general procedure, dione **2.11b** (0.037g, 0.137 mmol), on reaction with $NaBH_4$ (0.010g, 0.206 mmol) at 0 °C in methanol (3 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.13b** (0.032g, 87%) as a white solid.

The spectral data of **2.13b** was identical with that of **2.12b**.

Analysis $C_{16}H_{15}NO_3$	**:**	Calculated: C, 71.36; H, 5.61; N, 5.20% Observed: C, 71.21; H, 5.77; N, 5.31%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D = -180.0$ (*c* 0.2, $CHCl_3$).

(3*R*,4*S*)-3-Hydroxy-4-(4-methoxy-phenyl)-1-phenyl-azetidin-2-one (2.12c):

Following the general procedure, dione **2.10c** (0.094g, 0.348 mmol), on reaction with $NaBH_4$ (0.019g, 0.522 mmol) at 0 °C in methanol (5 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.12c** (0.085g, 90%) as a white solid.

MP	**:**	212-213 °C
IR ($CHCl_3$)	**:**	1717, 3318 cm^{-1}
^{1}H NMR	**:**	δ_H 2.65 (1H, bs, O*H*), 3.82 (3H, s, OCH_3), 5.18 (1H, d, *J* = 5.4

($CDCl_3$) (200 MHz)		Hz, C*H*N), 5.29 (1H, d, *J* = 5.4 Hz, C_3H), 6.95 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.07-7.45 (7H, m, Ar*H*)
^{13}C NMR (DMSO d_6) (50 MHz)	**:**	δ_C 55.3, 61.8, 77.1, 114.6, 117.6, 124.4, 124.6, 128.7, 129.1, 137.0, 160.1, 166.2
MS (m/z)	**:**	270 (M+1)
Analysis $C_{16}H_{15}NO_3$	**:**	Calculated: C, 71.36; H, 5.61; N, 5.20% Observed: C, 71.51; H, 5.43; N, 5.37%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D$ = +174.0 (*c* 1.8, $CHCl_3$).

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxy-phenyl)-1-phenyl-azetidin-2-one (2.13c):

Following the general procedure, dione **2.11c** (0.100g, 0.370 mmol), on reaction with $NaBH_4$ (0.021g, 0.555 mmol) at 0 °C in methanol (5 mL) after work-up gave crude 3-hydroxy azetidin-2-one. This crude compound was purified by column chromatography (50% ethyl acetate-pet. ether) to obtain pure 3-hydroxy azetidin-2-one **2.13c** (0.089g, 89%) as a white solid.

The spectral data of **2.13c** was identical with that of **2.12c**.

Analysis $C_{16}H_{15}NO_3$	**:**	Calculated: C, 71.36; H, 5.61; N, 5.20% Observed: C, 71.41; H, 5.49; N, 5.29%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D$ = -173.3 (*c* 1.2, $CHCl_3$).

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid diisopropyl ester (2.15):

A mixture of diisopropyl tartrate (**2.14**) (2.0 g, 8.54 mmol), 2,2-dimethoxy propane (1.26 mL, 10.25 mmol) *p*-toluene sulfonic acid (catalytic) in anhydrous benzene was refluxed with a Dean-Stark apparatus in place for removal of benzene-methanol azeotrope for 5h. The solution was then cooled and neutralized with anhydrous K_2CO_3, filtered and washed with water. The aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and it was then concentrated on rotary evaporator to get crude compound as a colorless syrup. The crude product was purified

by column chromatography (20% ethyl acetate-petroleum ether) to get compound **2.15** (1.82g, 78%) as a colorless, thick liquid.

^{1}H NMR ($CDCl_3$) (200 MHz) **:** δ_H 1.29 (12H, d, *J* = 6.3 Hz, 2 x CH(C*H*$_3$)$_2$), 1.50 (6H, s, 2 x C*H*$_3$), 4.70 (2H, s, 2 x OC*H*CO), 5.13 (2H, sept, *J* = 6.3 Hz, OC*H*(CH$_3$)$_2$),

MS (m/z) : 275 (M+1)

Analysis : Calculated: C, 56.92; H, 8.08%

$C_{13}H_{22}O_6$ Observed: C, 56.80; H, 8.15%

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid monoisopropyl ester (2.16):

Compound **2.15** (2.10 g, 7.67 mmol) was dissolved in 20 mL THF. To this solution was added in a drop wise manner a solution of NaOH (0.307 g, 7.67 mmol) in 40 mL water. The resultant solution was allowed to stir at room temperature for 4-6 h. The solution was then concentrated *in vacuo* to remove THF. The aqueous residue was then washed with ethyl acetate (3 x 10 mL) to remove any unreacted starting material. The aqueous layer was then acidified with 6N HCl to *p*H=2 at 0 °C. The acidified aqueous solution was then extracted with ethyl acetate (3 x 25 mL). The organic layer was then washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain mono acid **2.16** (1.24g, 70%) as a thick colorless liquid which was pure enough to be used as such in the next step.

IR ($CHCl_3$) : 1733, 2800-3300 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) **:** δ_H 1.32 (6H, d, *J* = 6.3 Hz, OCH(C*H*$_3$)$_2$), 1.50 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 4.76 (1H, d, *J* = 5.4 Hz, OC*H*CO), 4.87 (1H, d, *J* = 5.4 Hz, OC*H*CO), 5.15 (1H, sept, *J* = 6.3 Hz, OC*H*(CH$_3$)$_2$), 10.1 (1H, bs, -COO*H*)

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

Analysis : Calculated: C, 51.72; H, 6.94%

$C_{10}H_{16}O_6$ Observed: C, 51.88; H, 6.85%

(4*R*,5*R*)-5-Chlorocarbonyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid isopropyl ester (2.17):

Acid **2.16** (1.0 g, 4.3 mmol) was dissolved in anhydrous DCM (15 mL) and this solution was cooled to 0 °C. To this cooled solution was added, oxalyl chloride (0.452 mL, 5.17 mmol) slowly in a drop wise manner. The solution was then refluxed for 5h. After 5h the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

Procedure for the preparation of 2.18 and 2.19:

A solution of acid chloride **2.17** (0.950 g, 3.79 mmol) in anhydrous dichloromethane in 15 mL, was added to a pre-cooled solution of imine **2.05a** (0.609 g, 2.52 mmol), anhydrous triethylamine (1.57 mL, 11.34 mmol) in anhydrous dichloromethane (20 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 15 mL), and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (1.20g, 70%). From the ^{1}H NMR of this crude product, it was inferred that the diastereomeric ratio was 65:35. The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **2.18** and **2.19**.

(1*S*,4*S*,8*R*)-1,2-Bis-(4-methoxy-phenyl)-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid isopropyl ester (2.18):

Isolated as dark brown viscous liquid in 46%.

IR ($CHCl_3$) : 1759 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 0.98 (3H, s, C*H*$_3$), 1.16 (6H, d, *J* = 6.3 Hz, OCH(C*H*$_3$)$_2$), 1.52 (3H, s, C*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.73 (3H, s, OC*H*$_3$), 4.91 (1H, s, C_8-*H*), 5.03 (1H, sept, *J* = 6.3 Hz, OC*H*(CH$_3$)$_2$), 5.12 (1H, s, C_1*H*), 6.80 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.91 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.16-7.24 (4H, m, Ar*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 21.3, 21.6, 25.5, 26.5, 55.1, 55.2, 67.7, 69.8, 78.0, 92.5, 113.4, 113.9, 114.2, 118.7, 124.9, 129.1, 130.3, 156.2, 159.8, 163.3, 167.2

MS (m/z) : 456 (M+1)

Analysis : Calculated: C, 65.92; H, 6.42; N, 3.08%

$C_{25}H_{29}NO_7$ Observed: C, 65.79; H, 6.36; N, 3.21%

Optical rotation : Observed: $[\alpha]^{26}_D$ = -8.0 (*c* 0.5, $CHCl_3$).

(1*R*,4*R*,8*R*)-1,2-Bis-(4-methoxy-phenyl)-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid isopropyl ester (2.19):

Isolated as dark brown viscous liquid in 24%.

IR ($CHCl_3$) : 1754 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 0.97 (3H, s, C*H*$_3$), 1.15 (6H, d, *J* = 6.3 Hz, OCH(C*H*$_3$)$_2$), 1.38 (3H, s, C*H*$_3$), 3.68 (3H, s, OC*H*$_3$), 3.73 (3H, s, OC*H*$_3$), 4.81 (1H, s, C$_1$*H*), 4.93 (1H, s, C$_8$-*H*), 5.10 (1H, sept, *J* = 6.3 Hz, OC*H*(CH$_3$)$_2$), 6.74 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.85 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.11-7.24 (4H, m, Ar*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 21.4, 21.6, 25.7, 26.2, 55.1, 55.3, 65.8, 69.7, 77.1, 90.9, 113.1, 113.8, 114.2, 118.8, 125.4, 129.1, 130.4, 156.4, 159.8, 163.5, 167.1

MS (m/z) : 456 (M+1)

Analysis : Calculated: C, 65.92; H, 6.42; N, 3.08%

$C_{25}H_{29}NO_7$ Observed: C, 65.98; H, 6.28; N, 3.15%

Optical rotation : Observed: $[\alpha]^{26}_D$ = -24.0 (*c* 5.0, $CHCl_3$).

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid dibenzyl ester (2.21):

A mixture of dibenzyl tartrate (**2.20**) (2.19 g, 6.66 mmol), 2,2-dimethoxy propane (0.982 mL, 7.99 mmol) *p*-toluene sulfonic acid (catalytic) in anhydrous benzene was refluxed with a Dean-Stark apparatus in place for removal of benzene-methanol azeotrope for 5h. The solution was then cooled and neutralized with anhydrous K_2CO_3, filtered and washed with water. The aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and it was then concentrated on rotary evaporator to get crude compound as a colorless syrup. The crude product was purified

by column chromatography (15% ethyl acetate-petroleum ether) to get compound **2.21** (1.87g, 76%) as a colorless, thick liquid.

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.48 (6H, s, 2 x C*H*$_3$), 4.83 (2H, s, 2 x OC*H*CO), 5.22 (4H, s, OC*H*$_2$Ph), 7.34 (10H, s, Ar*H*)

MS (m/z) : 371 (M+1)

Analysis : Calculated: C, 68.10; H, 5.99%

$C_{21}H_{22}O_6$ Observed: C, 68.22; H, 5.79%

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid monobenzyl ester (2.22):

Compound **2.21** (1.5g, 4.054 mmol) was dissolved in 15 mL THF. To this solution was added in a drop wise manner a solution of NaOH (0.162g, 4.054 mmol) in 30 mL water. The resultant solution was allowed to stir at room temperature for 4-6 h. The solution was then concentrated *in vacuo* to remove THF. The aqueous residue was then washed with ethyl acetate (3 x 10 mL) to remove any unreacted starting material. The aqueous layer was then acidified with 6N HCl to *p*H=2 at 0 °C. The acidified aqueous solution was then extracted with ethyl acetate (3 x 25 mL). The organic layer was then washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain mono acid **2.22** (0.79g, 70%) as a thick colorless liquid which was pure enough to be used as such in the next step.

IR (CHCl$_3$) : 1735, 2800-3300 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : δ_H 1.48 (6H, s, 2 x C*H*$_3$), 4.69 (1H, d, *J* = 5.4 Hz, OC*H*CO), 4.86 (2H, s, OC*H*$_2$), 5.23 (1H, d, *J* = 5.4 Hz, OC*H*CO), 7.27-7.34 (5H, m, Ar*H*), 10.1 (1H, bs, -COO*H*)

MS (m/z) : 281 (M+1)

Analysis : Calculated: C, 59.99; H, 5.75%

$C_{14}H_{16}O_6$ Observed: C, 59.83; H, 5.79%

(4*R*,5*R*)-5-Chlorocarbonyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid benzyl ester (2.23):

Acid **2.22** (0.950 g, 3.39 mmol) was dissolved in anhydrous DCM (15 mL) and this solution was cooled to 0 °C. To this cooled solution was added, oxalyl chloride (0.326 mL, 3.73 mmol) slowly in a drop wise manner. The solution was then refluxed for 5h. After 5h the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

Procedure for the preparation of 2.24 and 2.25:

A solution of acid chloride **2.23** (1.01 g, 3.39 mmol) in anhydrous dichloromethane in 15 mL, was added to a pre-cooled solution of imine **2.05a** (0.544 g, 2.26 mmol), anhydrous triethylamine (1.41 mL, 10.17 mmol) in anhydrous dichloromethane (20 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 15 mL), and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (1.15g, 68%). From the ^{1}H NMR of this crude product, it was inferred that the diastereomeric ratio of compounds **2.24:2.25** was 64:36. However, despite all attempts using chromatography, the two diastereomers couldn't be separated in pure form.

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid 4-tert-butyl ester 5-ethyl ester (2.26):

To a solution of $(BOC)_2O$ (0.626 mL, 2.729 mmol) and acid **2.03** (0.425g, 1.94 mmol) in *t*-butanol (15 mL) was added DMAP (0.024g, 0.194 mmol) at room temperature and the resultant solution was left stirring for 8h. After completion (TLC), the solvents were removed *in vacuo* to get crude product **2.26**. This crude product was purified by column chromatography (15% ethyl acetate-pet. ether) to obtain pure compound **2.26** (0.480g, 90%) as a thick liquid.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.31 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.49 (15H, s, $OC(CH_3)_3$, 2 x CH_3), 4.27 (2H, q, J = 7.2 Hz, OCH_2), 4.62 (1H, d, J = 5.9 Hz, OC*H*), 4.68 (1H, d, J = 5.9 Hz, OC*H*)

^{13}C NMR : δ_C 14.0, 26.3, 26.4, 27.7, 61.6, 77.1, 77.7, 82.4, 113.4, 168.7, 169.6

($CDCl_3$)

(50 MHz)

MS (m/z) : 275 (M+1)

Analysis : Calculated: C, 56.92; H, 8.08%

$C_{13}H_{22}O_6$ Observed: C, 56.77; H, 8.19%

(4*R*,5*R*)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid mono-tertiary-butyl ester (2.27):

Compound **2.26** (0.356g, 1.29 mmol) was dissolved in 5 mL THF. To this solution was added in a drop wise manner a solution of NaOH (0.052 g, 1.29 mmol) in 10 mL water. The resultant solution was allowed to stir at room temperature for 4-6 h. The solution was then concentrated *in vacuo* to remove THF. The aqueous residue was then washed with ethyl acetate (3 x 5 mL) to remove any unreacted starting material. The aqueous layer was then acidified with 6N HCl to *p*H=2 at 0 °C. The acidified aqueous solution was then extracted with ethyl acetate (3 x 15 mL). The organic layer was then washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain mono acid **2.27** (0.217g, 68%) as a thick colorless liquid which was pure enough to be used as such in the next step.

IR ($CHCl_3$) : 1737, 2800-3300 cm^{-1}

^{1}H NMR : δ_H 1.51 (15H, s, OC(CH_3)$_3$, 2 x CH_3), 4.67 (1H, d, J = 5.7 Hz, OC*H*), 4.80 (1H, d, J = 5.7 Hz, OC*H*), 10.2 (1H, bs, -COO*H*)

($CDCl_3$)

(200 MHz)

^{13}C NMR : δ_C 26.5, 26.6, 27.6, 76.8, 77.3, 81.9, 112.6, 168.8, 171.1

($CDCl_3$)

(50 MHz)

MS (m/z) : 247 (M+1)

Analysis : Calculated: C, 53.65; H, 7.37%

$C_{11}H_{18}O_6$ Observed: C, 53.79; H, 7.22%

(4*R*,5*R*)- 5-Chlorocarbonyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid tert-butyl ester (2.28):

Acid **2.27** (1.2 g, 4.87 mmol) was dissolved in anhydrous DCM (15 mL) and this solution was cooled to 0 °C. To this cooled solution was added, oxalyl chloride

(0.468 mL, 5.36 mmol) slowly in a drop wise manner. The solution was then refluxed for 5h. After 5h the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

Procedure for the preparation of 2.29 and 2.30:

A solution of acid chloride **2.28** (1.3g, 4.91 mmol) in anhydrous dichloromethane (15 mL), was added to a pre-cooled solution of imine **2.05a** (0.868g, 3.60 mmol), anhydrous triethylamine (2.25 mL, 16.2 mmol) in anhydrous dichloromethane (20 mL) at -40° C over a period of 15-20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC) the reaction mixture was diluted with dichloromethane and washed successively with water (3 x 15 mL), and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (1.63g, 71%). From the ^{1}H NMR of this crude product, it was inferred that the diastereomeric ratio of compounds **2.29:2.30** was 65:35. The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate-petroleum ether) to get two diastereomers **2.29** and **2.30**.

(1*S*,4*S*,8*R*)-1,2-Bis-(4-methoxy-phenyl)-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid tert-butyl ester (2.29):

Isolated as dark brown viscous liquid in 46%.

IR ($CHCl_3$)	**:**	1757 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.99 (3H, s, C*H*$_3$), 1.27 (9H, s, OC(C*H*$_3$)$_3$), 1.50 (3H, s, C*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.73 (3H, s, OC*H*$_3$), 4.83 (1H, s, C$_8$-*H*), 5.07 (1H, s, C$_1$*H*), 6.70-6.85 (4H, m, Ar*H*), 7.18-7.29 (4H, m, Ar*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 25.5, 26.5, 27.7, 55.1, 55.3, 67.5, 78.0, 83.3, 92.4, 113.1, 113.9, 114.2, 118.6, 125.0, 129.1, 130.5, 156.2, 159.8, 163.4, 166.3
MS (m/z)	**:**	470 (M+1)
Analysis $C_{26}H_{31}NO_7$	**:**	Calculated: C, 66.51; H, 6.65; N, 2.98% Observed: C, 66.43; H, 6.71; N, 2.81%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D = +34.3$ (*c* 0.6, $CHCl_3$).

(1*R*,4*R*,8*R*)-1,2-Bis-(4-methoxy-phenyl)-6,6-dimethyl-3-oxo-5,7-dioxa-2-aza-spiro[3.4]octane-8-carboxylic acid tert-butyl ester (2.30):

Isolated as dark brown viscous liquid in 25%.

IR ($CHCl_3$)	**:**	1755 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.93 (3H, s, C*H*$_3$), 1.27 (9H, s, OC(C*H*$_3$)$_3$), 1.44 (3H, s, C*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 4.73 (1H, s, C_1*H*), 4.84 (1H, s, C_8-*H*), 6.69-6.81 (4H, m, Ar*H*), 7.11-7.29 (4H, m, Ar*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 25.5, 26.1, 27.8, 55.2, 55.3, 67.7, 78.1, 83.3, 92.5, 113.4, 113.9, 114.5, 118.9, 124.6, 129.4, 130.4, 156.2, 159.8, 163.3, 166.7
MS (m/z)	**:**	470 (M+1)
Analysis $C_{26}H_{31}NO_7$	**:**	Calculated: C, 66.51; H, 6.65; N, 2.98% Observed: C, 66.68; H, 6.60; N, 3.07%
Optical rotation	**:**	Observed: $[\alpha]^{26}_D$ = -16.6 (*c* 0.6, $CHCl_3$).

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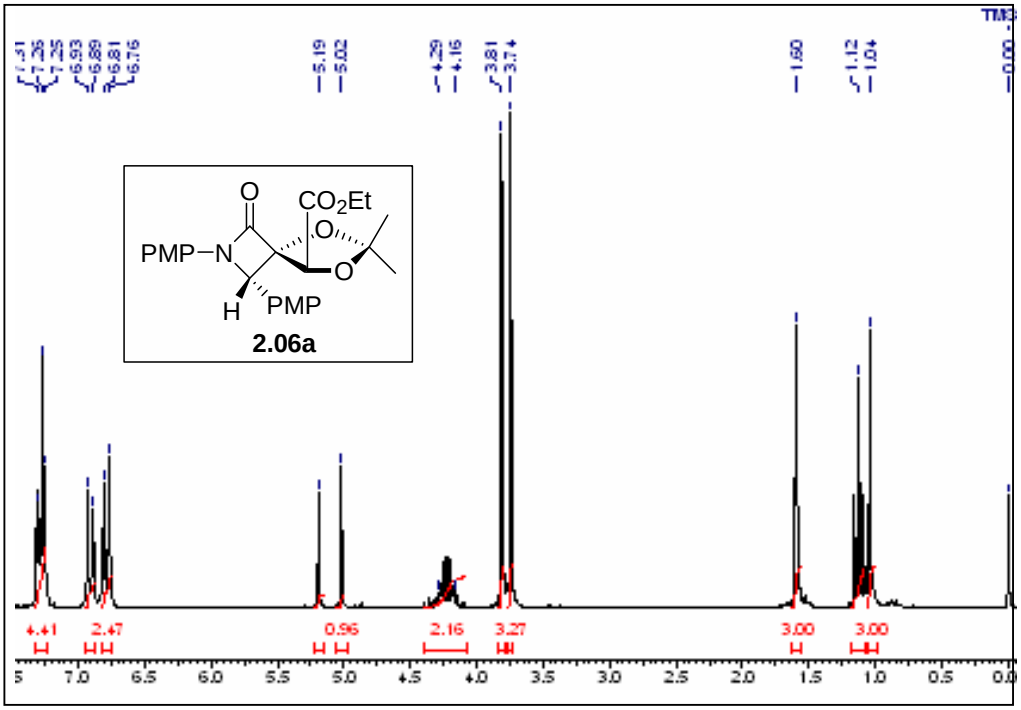
Chapter 2

Spectra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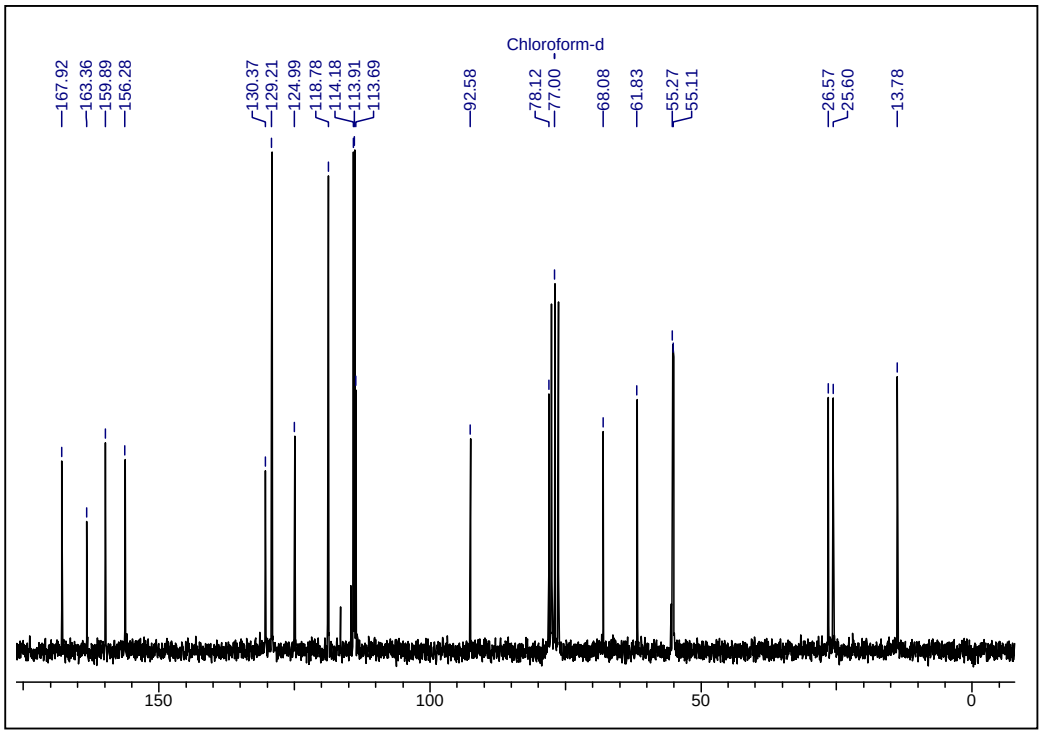
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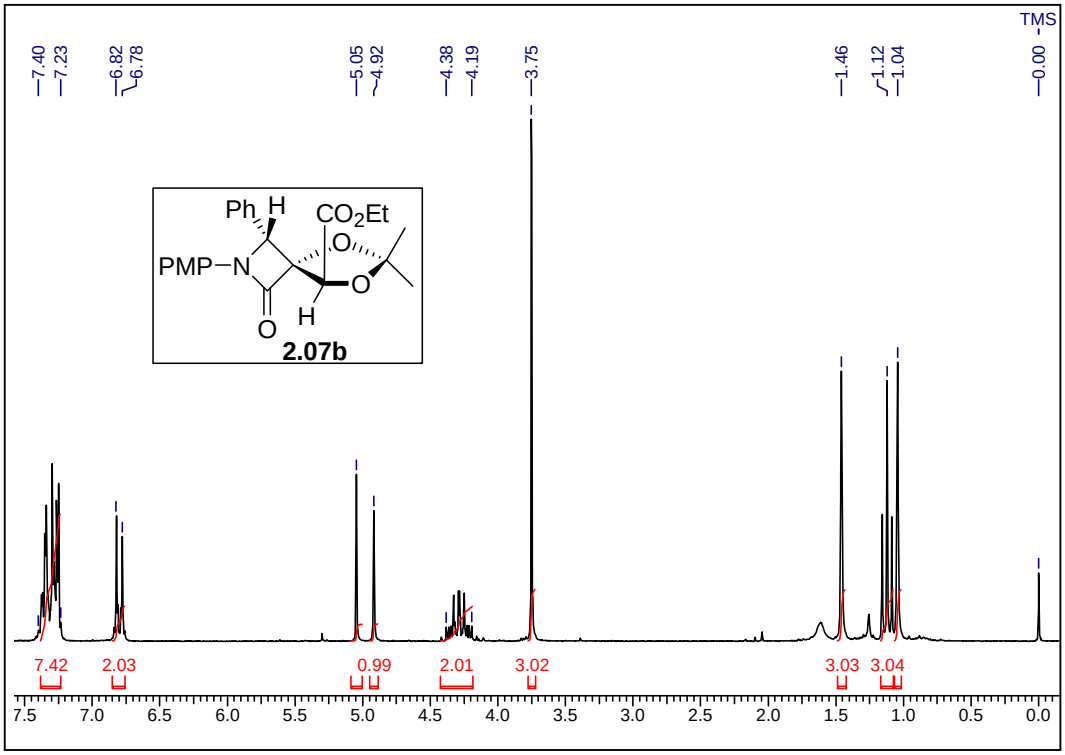
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O
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2.03
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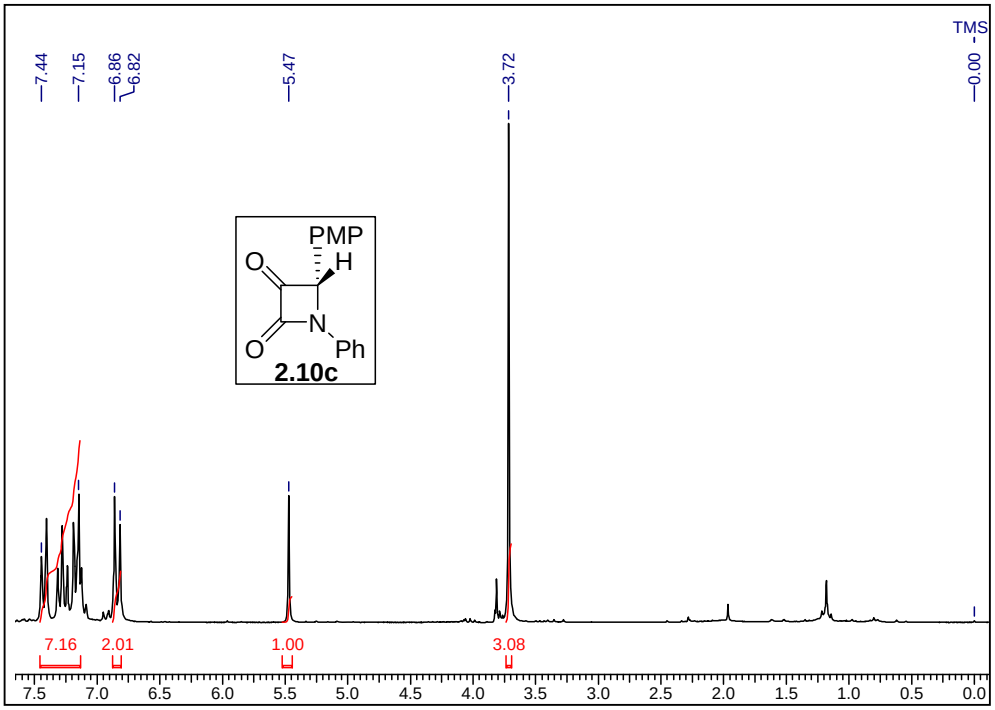
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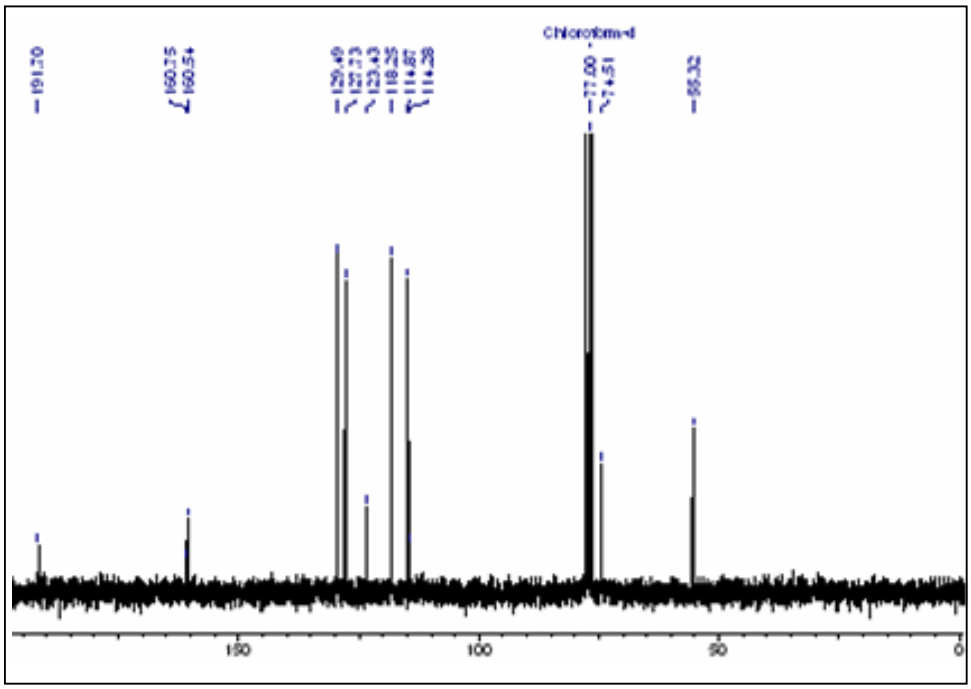
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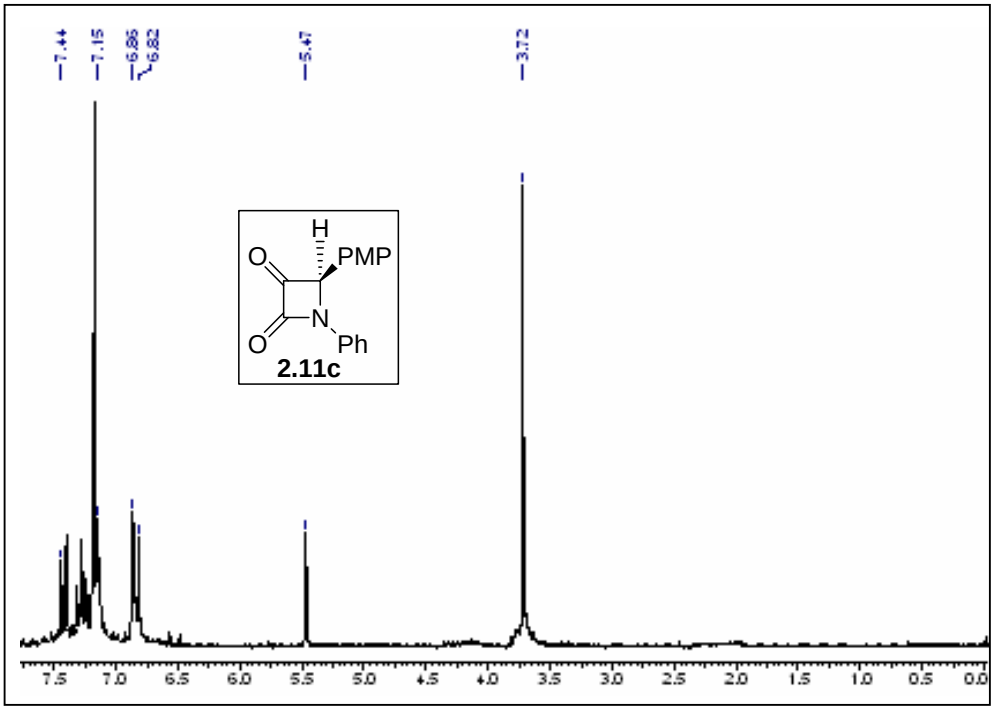
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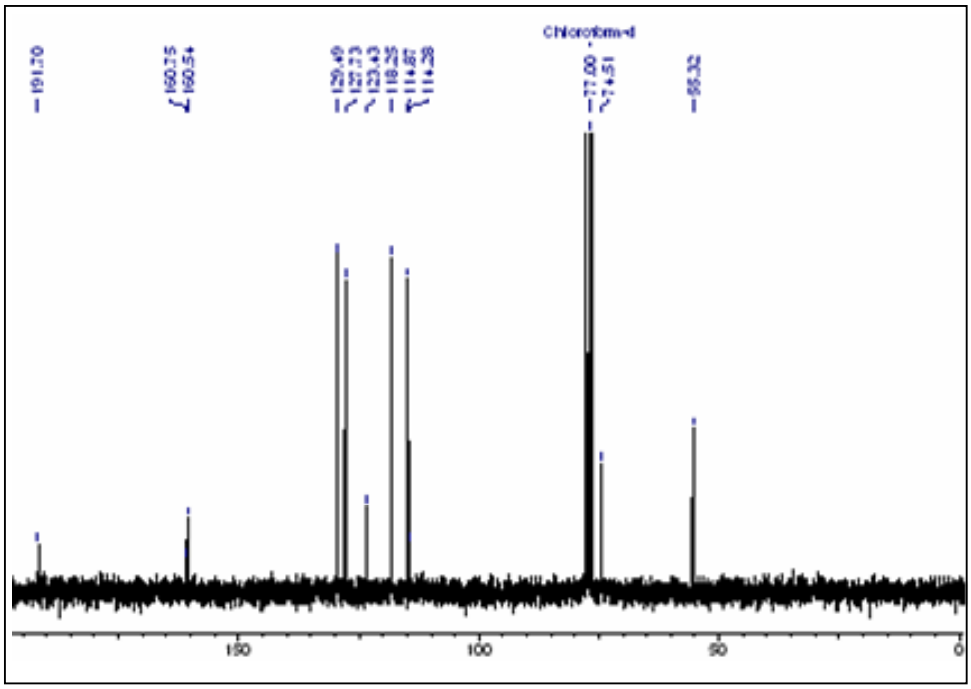
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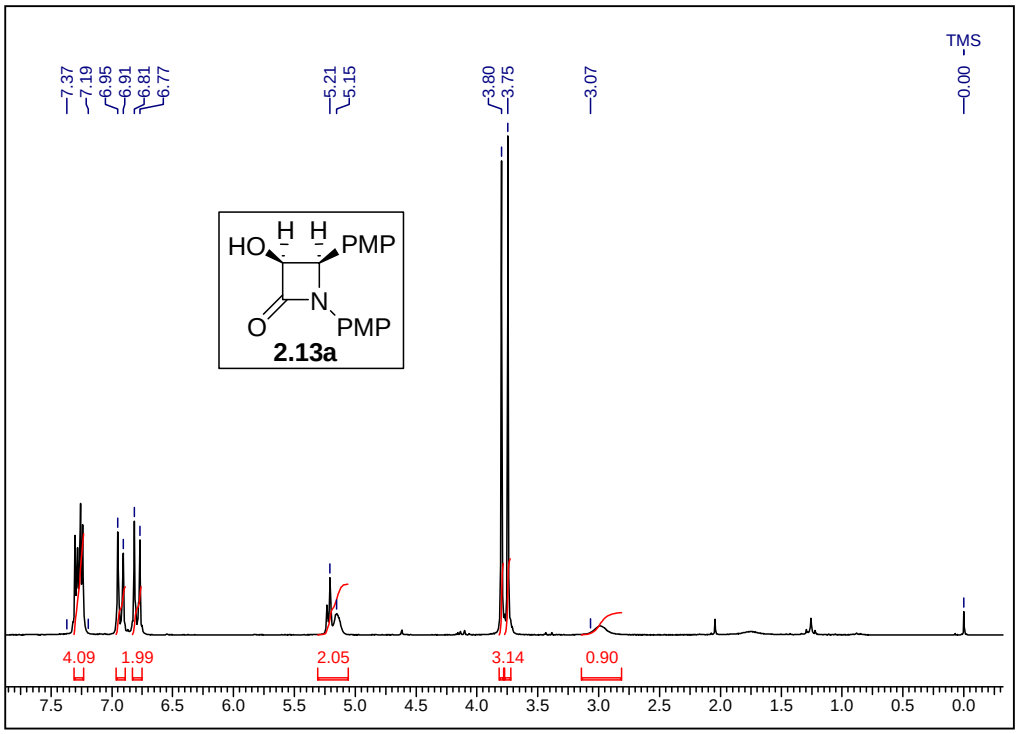
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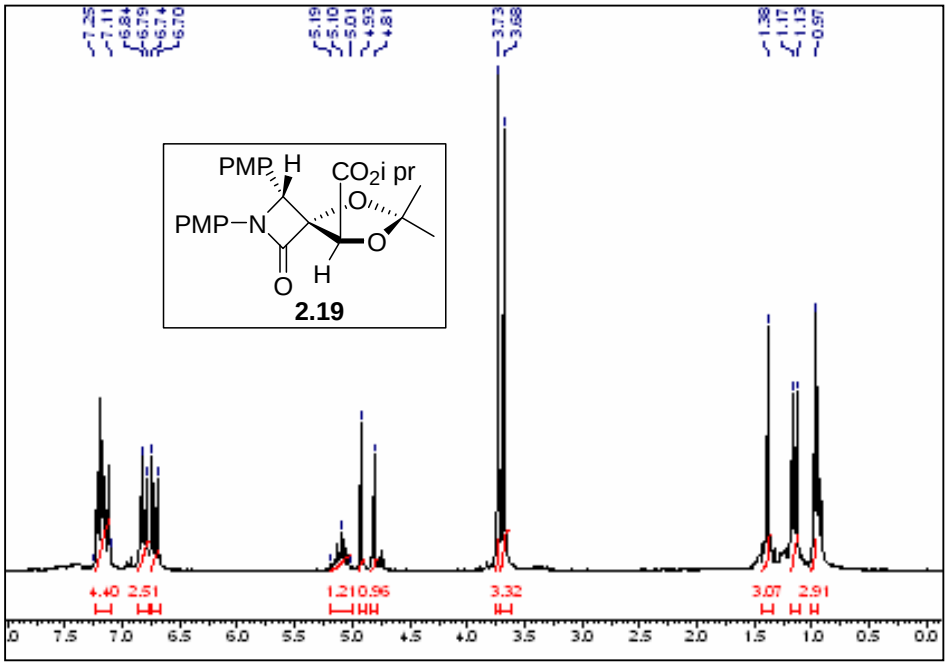
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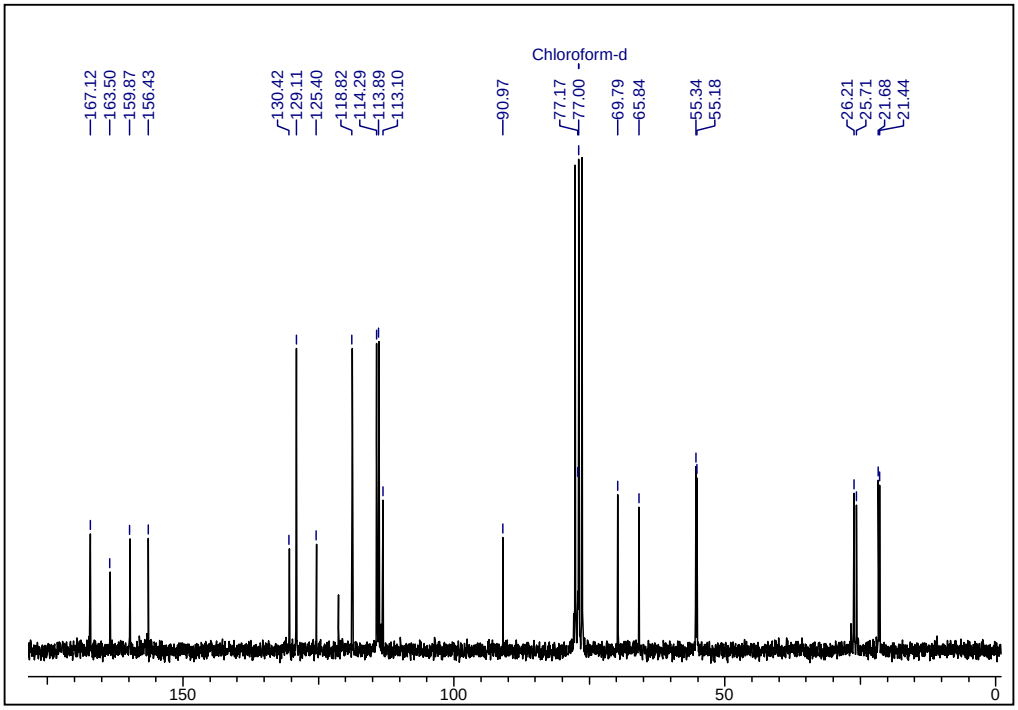
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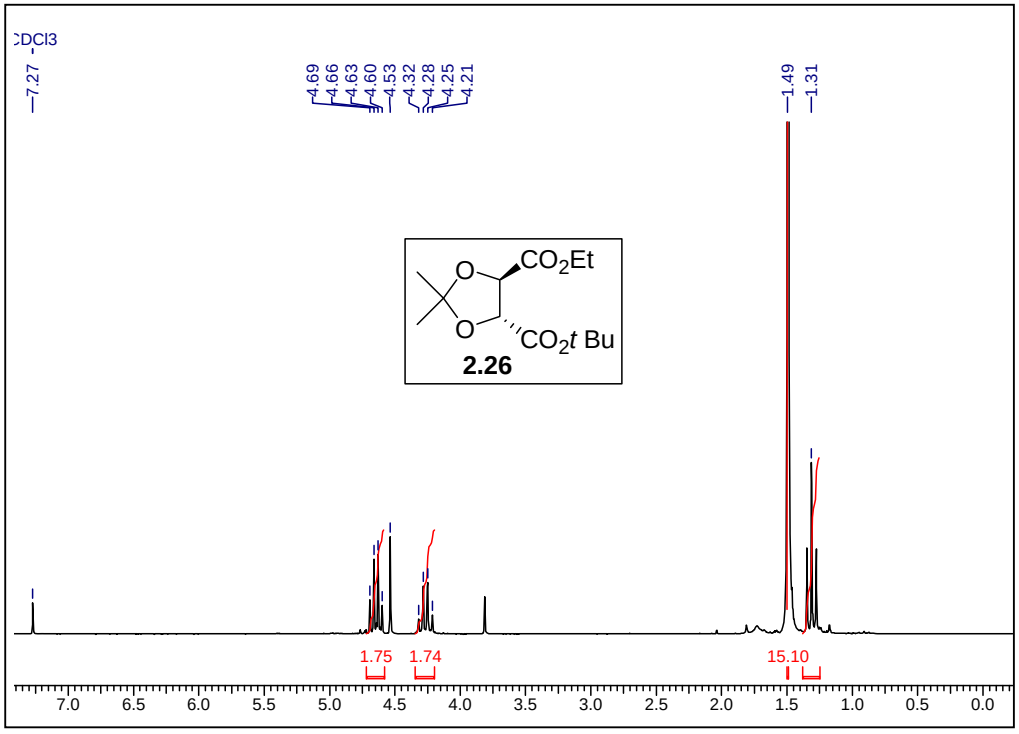
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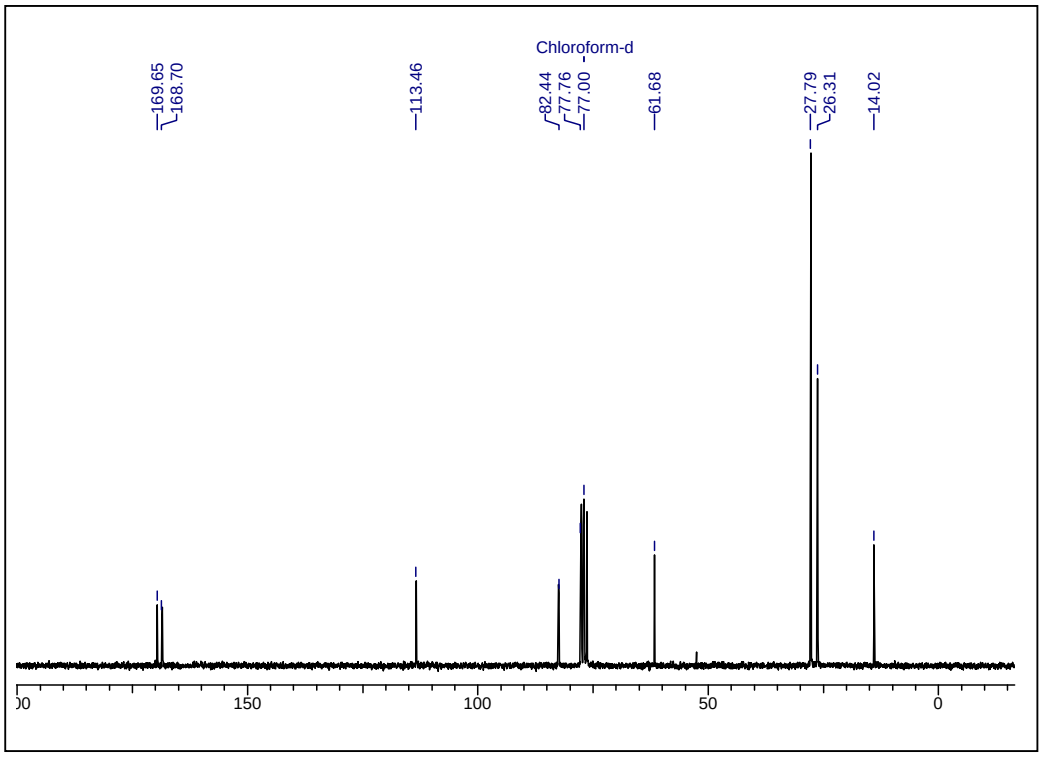
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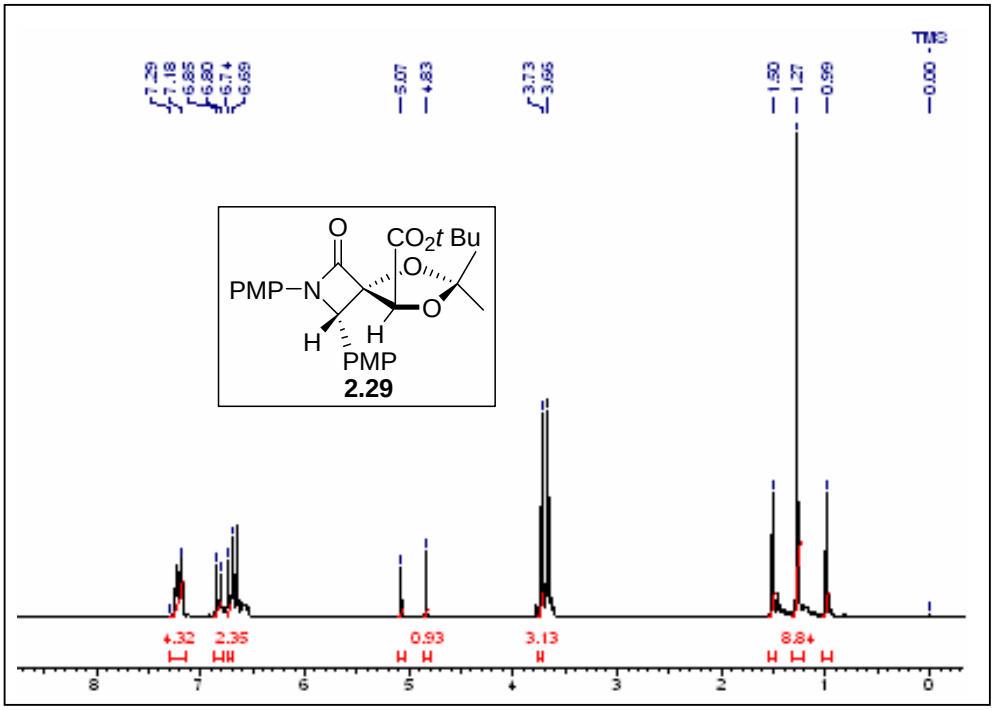
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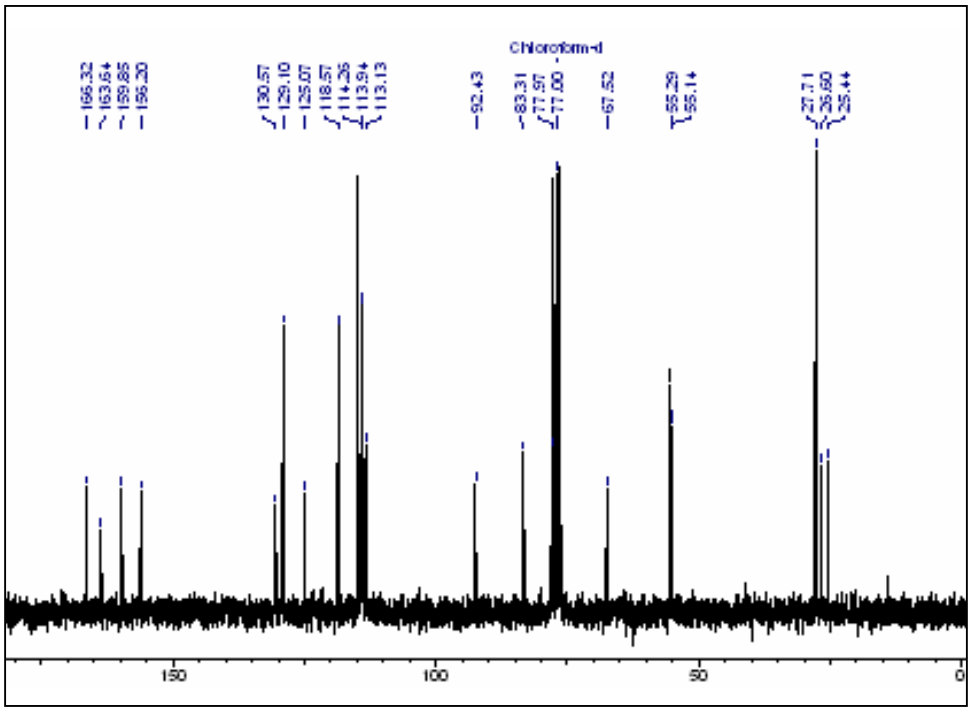
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CHAPTER 3

AN EFFICIENT FORMAL SYNTHESIS OF (*S*)-DAPOXETINE FROM ENANTIOPURE 3-HYDROXY AZETIDIN-2-ONE.

This work has been published in *Tetrahedron* (in press).

3.1: Introduction

This chapter deals with an efficient, formal synthesis of (*S*)-dapoxetine from an enantiopure, substituted 3-hydroxy azetidin-2-one.

***Significance of (S)-dapoxetine*:** Stress related ailments have seen a precipitous rise world over, with life becoming faster paced than ever. Depression is one such psychiatric disorder affecting people of all ages and genders around the globe. It has adverse effects on economic productivity, individual well being and social functioning. It is thus a huge burden for individuals, families and societies.[1]

Approximately 121 million people suffer from depression world over and the number is rising at an alarming rate. Depressive disorders are the 4th leading cause, worldwide, of life years caused due to disability (next to infectious diseases, heart disease and respiratory infection). Depressive disorders are expected to rank 2nd in global diseases by 2020 (next only to heart disease). Depression is also the mental disorder most commonly leading to suicide.[2]

There are two main types of depressions:

[A] Clinical depression (or major depression) and

[B] Bipolar disorder (also called manic depression).

Both the illnesses have mild, medium and severe forms depending upon the number and the intensity of the symptoms. A major depression can bring about a drastic change in a person's general perspective towards life. Bipolar disorder is less common form of depression. This illness involves cycles of depression alternating with a "high" known as mania.

Antidepressant medications are widely used effective treatments for depression. Existing antidepressant drugs are known to influence the functioning of certain neurotransmitters (chemicals used by brain cells to communicate), primarily serotonin, norepinephrine, and dopamine, known as monoamines. Older medications – tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) - affect the activity of both of these neurotransmitters simultaneously. Their disadvantage is that they can be difficult to tolerate due to side effects or, in the case of MAOIs, dietary and medication restrictions play an important part. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), have fewer side effects than the older drugs, making it easier for patients to adhere to treatment. Both generations of medications are effective

in relieving depression, although some people will respond to one type of drug, but not another. Medications that take entirely different approaches to treating depression are now in development.

More than 80% of people with depression improve when they receive appropriate treatment with medication, psychotherapy, or the combination. Depression is the leading cause of psychiatric disability claims, generating up to $20 billion a year in direct costs. In view of all the above mentioned facts, treatment for depression is much sought after. (*S*)-(+)-N,N-dimethyl-N-[2-(1-naphthalenyloxy) ethyl] benzenemethanamine or (*S*)-dapoxetine (**3.01**) (Figure 1) is a potent serotonin reuptake inhibitor for treating depression and other disorders as bulimia or anxiety.

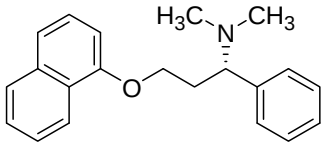


Figure 1. (*S*)-Dapoxetine **(3.01)**

(*S*)-dapoxetine has also been found to be useful against premature ejaculation in men. Premature ejaculation is thought to be the most common male sexual dysfunction, with a prevalence of 21–33%.[3] It can be a source of distress for many men, although some are less affected or cope more effectively with the condition.[4-5] In men who are affected by this problem, premature ejaculation can adversely affect self-image, hamper sexual satisfaction and the sexual relationship and negatively affect the overall quality of life of men and their partners.[6-7]

***Dapoxetine and Pharmacology*:** Delay in ejaculation is one of the side effects of SSRIs and TCAs that make them useful in the treatment of premature ejaculation (PE).[8] It has been found in the literature that premature ejaculation is more common among men with higher levels of education because of their interest in the sexual satisfaction of their partner.[9] SSRI antidepressants have been shown to delay ejaculation in men treated for different psychiatry disorders. SSRIs are considered the most effective treatment currently available for PE. These include paroxetine, fluoxetine, sertraline and more. The use of these drugs that require chronic therapy is limited by the neuropsychiatric side effects. New SSRI drugs specifically targeted to treat premature ejaculation (e.g.

dapoxetine) can be taken on, an as needed basis and have recently shown positive results in phase III clinical trials. Nevertheless dapoxetine is not yet approved by any regulatory authority around the world. There is speculation that some of the associated effects that are caused by its use are, lowered libido and nausea. However, as recent phase III clinical trials have shown very encouraging results, dapoxetine is being looked upon as a potentially important drug against premature ejaculation. Other pharmaceutical products known to delay male orgasm are; opioids, cocaine, and diphenhydramine.[10]

3.2: Background for the present work

***Literature survey*:**

Discovery of (*S*)-dapoxetine is credited to David T. Wong of Eli Lilly[11] and company. (*S*)-dapoxetine is found to be a potent selective serotonin re-uptake inhibitor (SSRIs) but is slightly different from the SSRIs (such as (S)-Fluoxetine, (-) Paroxetine and Sertraline (Figure 2)) widely prescribed for depression and other psychiatric disorders as bulimia or anxiety. Dapoxetine is very much structurally related to Fluoxetine (Prozac) with antidepressant activity.

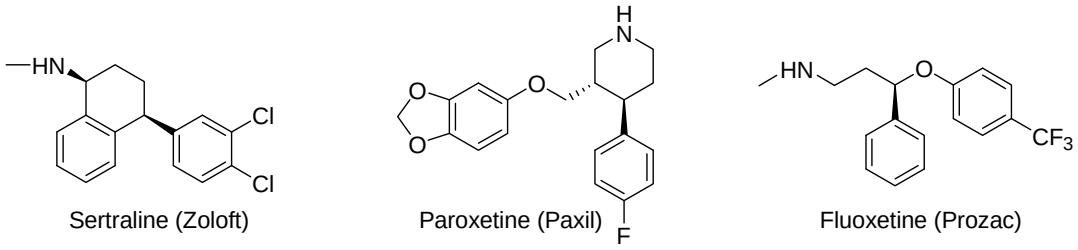


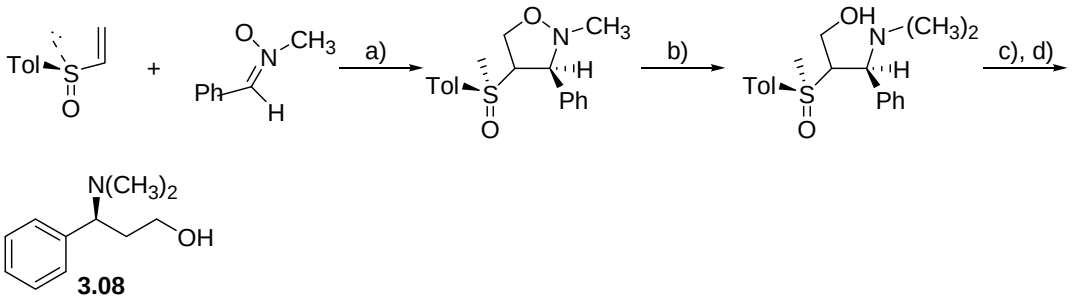
Figure 2. Sertraline, Paroxetine, Fluoxetine

Dapoxetine is the D-enantiomer of LY 243917 and found to be 3.5 times more potent as a serotonin reuptake inhibitor than the L-enantiomer of LY 243917. Dapoxetine would make it join the ranks of sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levittra®), the erectile dysfunction drugs and cabergoline (Dostinex ®) as a drug invented to improve male sexual health.[12]

***Koizumi's approach*:**

Koizumi *et. al* have reported a synthesis of most advanced intermediate, **3.08**, which constitutes a formal synthesis of (*S*)-dapoxetine[13] (Scheme 3.01). 1,3-dipolar cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulfoxide with acyclic nitrones is the asymmetry inducing step of the protocol. The product of this cycloaddition reaction on further elaboration led to synthesis of intermediate **3.08**.

Scheme 3.01

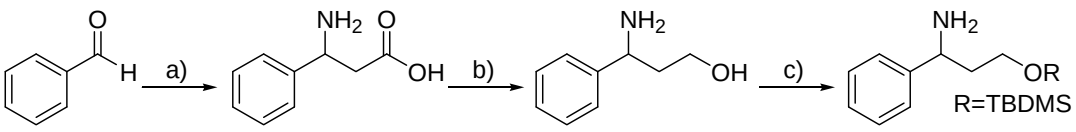


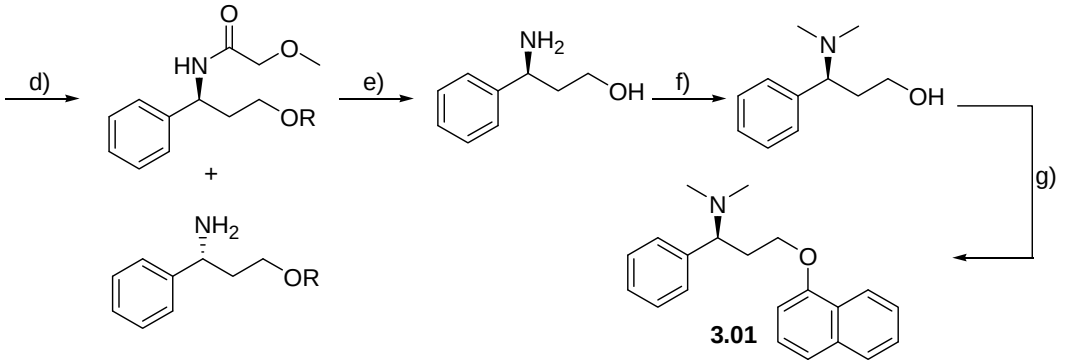
Reagents and conditionsI: a) benzene, reflux, 20h, 40%; b) i) MeI; ii) Zn-AcOH, rt; c) $TiCl_4$-AcOH-AcONa, rt; d) Raney Ni-EtOH, rt.

***Gotor approach*:**

Very recently Gotor and co-workers reported lipase catalyzed resolution of chiral 1,3-amino alcohols, and its application in the asymmetric synthesis of (*S*)-dapoxetine.[14] Starting with benzaldehyde, they first achieved the synthesis of requisite, *O*-protected amino alcohol in racemic form (Scheme 3.02). This protected amino alcohol was then resolved using the enzyme, *Candida antarctica* lipase A (CAL-A). The required enantiomer was obtained in 93% ee. The resolved enantiomer was further transformed into (*S*)-dapoxetine using simple synthetic manipulations.

Scheme 3.02



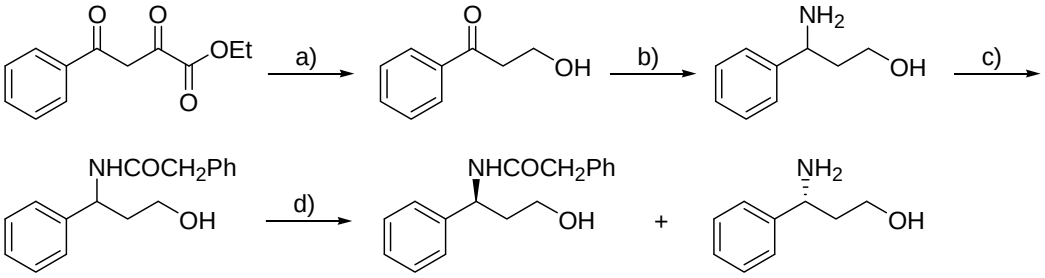


Reagents and conditions: a) $CH_2(COOH)_2$, NH_4OAc, EtOH, 80 °C, 12h; b) LAH, THF, 65 °C, 3h; c) TBDMSCl, imidazole, DCM, rt; d) Acyl donor, enzyme, solvent, 30 °C, 250 rpm; e) HCl, 6M, 50 °C; f) $(CH_2O)n$, HCOOH, rt; g) PPh_3, DEAD, 1-naphthol, THF, rt.

***Fadnavis approach*:**

Fadnavis *et al.* also reported preparation of enantiomerically pure (*R*) and (*S*)-3-amino-3-phenyl-1-propanol, a prominent intermediate of the (*S*)-dapoxetine, *via* resolution with immobilized *penicillin G acylase*.[15] Starting with Ethyl 2, 4-dioxo-4-phenylbutyrate, 3-amino-3-phenyl-1-propanol was synthesized in racemic form which was subsequently converted into its *N*-phenyl acetyl derivative (Scheme 3.03). This derivative was resolved with *penicillin G acylase*, immobilized on an epoxy resin, in around 99% ee. Authors claim in this publication that conversion of the crucial intermediate, amino alcohol, to dapoxetine is currently in progress.

Scheme 3.03

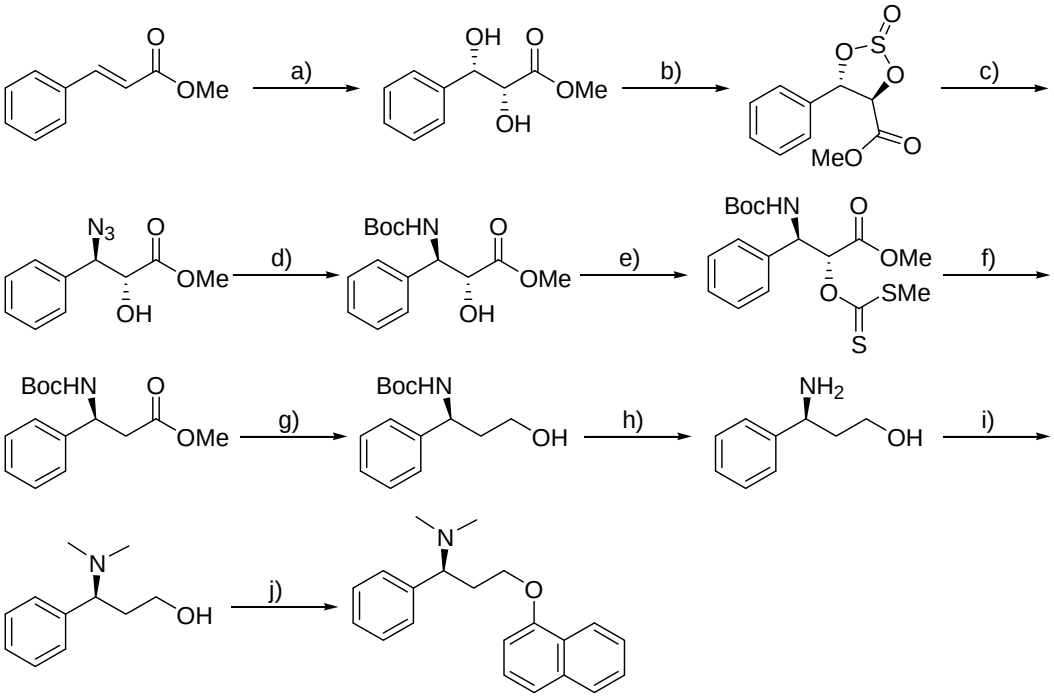


Reagents and conditions: a)Bakers yeast, diisopropyl ether, 48h; b) NH_4OAc, $NaBH_3CN$, EtOH, rt, 36h, 65%; c) $PhCH_2COCl$, NaOH, rt, 4h; d) *penicillin G acylase*, 4h, water.

***Srinivasan approach*:**

A recent report by Srinivasan *et. al.* makes use of Sharpless asymmetric dihydroxylation as an asymmetry inducing step for the synthesis of (*S*)-dapoxetine.[16] Starting with a *trans*-cinnamyl ester, they achieved an enantioselective synthesis of (*S*)-dapoxetine in ten steps in an overall yield of 17% (Scheme 3.04).

Scheme 3.04



Reagents and conditions: a) $(DHQ)_2PHAL$ (5 mol%), OsO_4, NMO, *t*-BuOH, rt, 16h; b) $SOCl_2$, Et_3N, DCM, 0 °C-rt, 1h; c) NaN_3 (5 eq.), DMF, rt, 48h; d) H_2/Pd-C, EtOAc, rt, 24h, $(Boc)_2O$, Et_3N; e) MeI, CS_2, MsCl, Et_3N, DCM, 0 °C-rt, 12h; f) *n*-Bu_3SnH, AIBN, toluene, reflux; g) LAH, THF, rt, 12h; h) TFA, DCM, rt; i) HCHO, HCOOH; j) Ph_3P, DEAD, 1-naphthol, THF, rt.

Use of radiochemical reaction has also been employed for the synthesis of (*S*)-dapoxetine from (*S*)-(+)-N-methyl-α-[2-(1-naphthalenyloxy)ethyl]benzene methanamine hydrochloride using methyl iodide.[17]

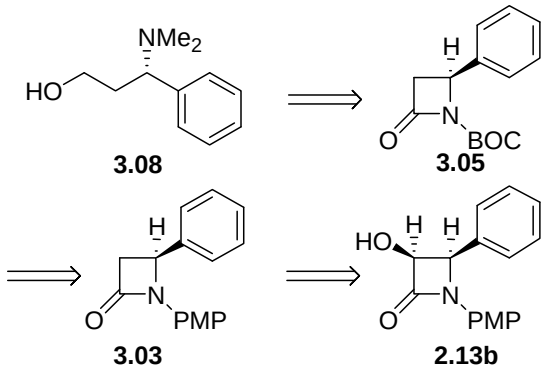
3.3: Present work

Considering the medicinal importance of the molecule, we were interested in the synthesis of (*S*)-dapoxetine. We have been working on the synthesis of biologically important products using β-lactam synthon method.[18] Our experience of the β-lactam synthon method inspired us to achieve the synthesis of (*S*)-dapoxetine using a substituted β-lactam as a starting material. We herein report an enantioselective, formal synthesis of (*S*)-dapoxetine from a substituted 3-hydroxy-β-lactam. To the best of our knowledge there is no other synthesis of (*S*)-dapoxetine reported using β-lactam as a starting material.

The retro synthetic strategy is shown in Scheme 3.05. We envisaged that, intermediate **3.08** can be obtained from carbamate substituted β-lactam **3.05** which in

turn can be accessed from the 3-hydroxy β-lactam **2.13b**. The starting 3-hydroxy β-lactam **2.13b** can be obtained from easily available chiral starting material (+)-diethyl L-tartrate in good yield following our own methodology described in Chapter 2.

Scheme 3.05

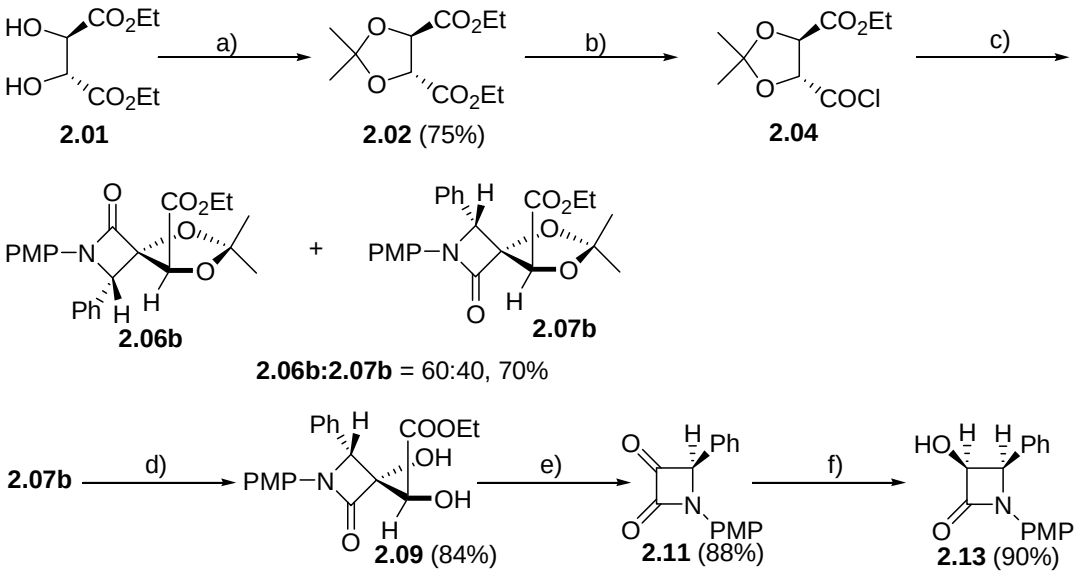


PMP = *p*-methoxy phenyl

3.4: Results and Discussion

We started our work by first synthesizing the required 3-hydroxy-β-lactam as shown in Scheme 3.06.

Scheme 3.06



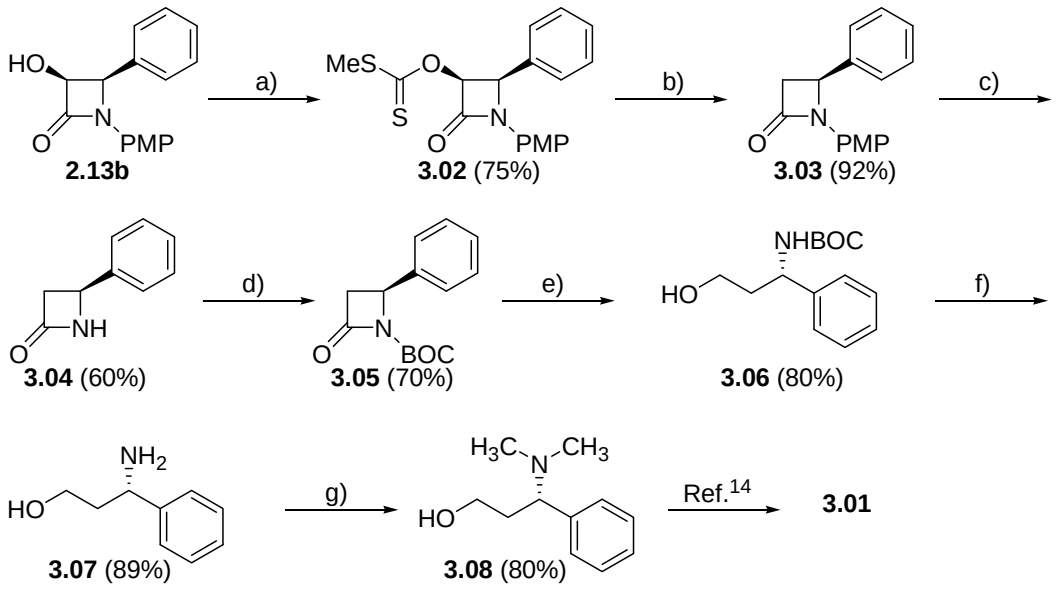
Reagents and conditions: a) 2,2-dimethoxy propane, benzene, PTSA, reflux, 5 h; b) i) NaOH,THF-H_2O, rt, 4-6 h. ii) $(COCl)_2$, DCM, reflux, 5 h; c) PMP-N=CH-Ph (**2.05b**), Et_3N, DCM, -40 °C-rt, 15 h; d) $FeCl_3$, DCM, rt, 2 h; e) $NaIO_4$, acetone-water, rt, 6-8 h; f) $NaBH_4$, MeOH, 0 °C, 2 h.

Diethyl L-tartrate **2.01** was protected as its acetonide **2.02**. Compound **2.02** was subjected to partial hydrolysis to afford a mono acid, which was further converted to its acid chloride **2.04**, by refluxing with oxalyl chloride in anhydrous dichloromethane in very good yield. This acid chloride **2.04** was used as such for Staudinger cycloaddition reaction with the imine (**2.05b**) derived from benzaldehyde and *p*-anisidine, to furnish a diastereomeric mixture (60:40) of β-lactams **2.06b** & **2.07b**. The required diastereomer **2.07b** was obtained in enantiopure form by column chromatography.

Spiro β-lactam **2.07b** was then subjected to the deprotection of acetonide using ferric chloride to obtain diol **2.09b**, which on periodate cleavage yielded azetidin-2,3-dione **2.11b** in excellent yield. Stereoselective reduction of the keto group of azetidin-2,3-dione **2.11b** was achieved using sodium borohydride to get 3-hydroxy β-lactam (**2.13b**) in very good yield.

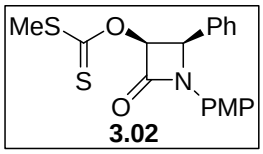
Having synthesized the required 3-hydroxy β-lactam, we moved ahead with the synthesis of intermediate **3.08**. We first converted the hydroxy group of 3-hydroxy β-lactam **2.13b** into its xanthate derivative to get compound **3.02** (Scheme 3.07). The conversion was carried out using sodium hydride, carbon disulphide and methyl iodide in THF as a solvent.

Scheme 3.07



Reagents and conditions: a) NaH, CS_2, CH_3I, THF, 0 °C-rt, 6 h; b) Bu_3SnH, AIBN, toluene, reflux, 3-4 h; c) CAN, CH_3CN-H_2O, 0 °C, 1 h; d) $(Boc)_2O$, DMAP, DCM, 0 °C-rt, 6 h; e) LAH, THF, 0 °C-rt, 4 h; f) TFA, DCM, 0 °C-rt, 2 h; g) HCHO, $NaBH_3CN$, CH_3COOH, CH_3CN, rt, 2h.

Compound **3.02** exhibited a band at 1755 cm^{-1} in its IR spectrum, characteristic of a β-lactam carbonyl. In the ^1H NMR, the methyl group from the xanthate moiety appeared at 2.29 ppm as a singlet. The methyl group from the PMP moiety appeared as another singlet at 3.76 ppm. The proton on C-4 of the lactam ring appeared as a doublet (J = 4.8 Hz) at 5.42 ppm. The other proton of the lactam ring (C3-H) appeared as a doublet (J = 4.8 Hz) at 6.68 ppm. The two protons *ortho* to the methoxy group of the PMP ring appeared as a doublet (J = 8.9 Hz) at 6.81 ppm. The remaining seven aromatic protons displayed a multiplet between 7.27-7.37ppm.



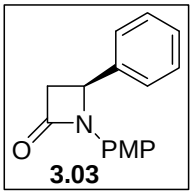
3.02

In the ^{13}C NMR spectrum, the carbon atom of the methyl group from the xanthate appeared at 18.8 ppm. The methyl carbon from the PMP moiety appeared at 55.3 ppm. The C-4 of the lactam ring appeared at 61.6 ppm whereas the carbon C-3 of the lactam ring appeared at 81.6 ppm. A total of seven peaks for aromatic carbons were seen in the region 114.3-131.8 ppm. The quaternary aromatic carbon bearing the methoxy substituent in the PMP ring appeared at 156.5 ppm. The lactam carbonyl carbon appeared at 160.5 whereas the thiocarbonyl carbon atom appeared very downfield at 213.6 ppm.

The structure was further supported by the mass spectrum which displayed a peak at m/z 360 corresponding to M+1.

We next proceeded with reductive removal of xanthate ester. On refluxing xanthate **3.02** with *n*-Bu_3SnH and catalytic AIBN in toluene, compound **3.03** was obtained in excellent yield.

Compound **3.03** displayed a band at 1755 cm^{-1} in its IR spectrum, characteristic of a β-lactam carbonyl. In the ^1H NMR, one of the protons from the methylene group of the lactam ring exhibited a doublet of a doublet (J = 2.5, 15 Hz) at 2.83 ppm. The larger coupling constant is for the geminal coupling with other proton of the methylene group, while the lower coupling constant is characteristic *trans* coupling constant between two β-lactam ring protons. The other proton from the methylene group also displayed a similar doublet of a doublet (J = 5.5, 15 Hz) at 3.45 ppm. Here the larger coupling constant is again for the geminal coupling with other methylene proton whereas the coupling constant of 5.5 Hz is characteristic of *cis* coupling between two β-lactam ring protons. The methyl group from the PMP moiety appeared as a singlet at 3.64 ppm. The proton on C-4 of the lactam ring appeared as a doublet of a doublet (J = 2.5, 5.5 Hz) at 4.88



3.03

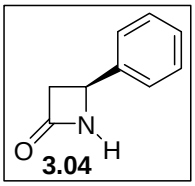
ppm. The two coupling constants are for *trans* and *cis* couplings respectively with the two methylene protons. The two protons *ortho* to the methoxy group of the PMP ring appeared as a doublet (J = 8.9 Hz) at 6.69 ppm. The remaining seven aromatic protons displayed a multiplet between 7.13-7.28 ppm.

In the ^{13}C NMR spectrum, the methylene carbon appeared at 46.8 ppm. The C-4 of the lactam appeared at 53.9 ppm while the methoxy carbon from the PMP moiety appeared at 55.3. A total of seven peaks for aromatic carbons were seen in the region 114.1-138.2 ppm. The quaternary aromatic carbon bearing the methoxy substituent in the PMP ring appeared at 155.8 ppm. The lactam carbonyl carbon appeared at 163.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 254 corresponding to M+1.

We then subjected compound **3.03** to oxidative removal of the PMP group. Compound **3.03** was reacted with CAN in acetonitrile-water mixture at 0 °C to furnish compound **3.04** in good yield.

In the IR spectrum, compound **3.04** displayed bands at 1765 and 3411 cm^{-1} corresponding to lactam carbonyl and the N-H bond respectively. In the ^{1}H NMR, one of the protons of the methylene group displayed a doublet of a doublet (J = 2.09, 14.09 Hz) at 2.81 ppm. The other methylene proton appeared as a multiplet between 3.32-3.44 ppm. The proton on C-4 of the lactam ring appeared as a multiplet at 4.66 ppm. The N-H proton appeared as a broad signal at 6.23 ppm. The five aromatic protons appeared as a multiplet between 7.19-7.30 ppm.



3.04

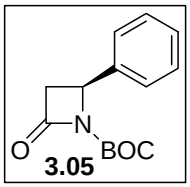
In the ^{13}C NMR spectrum, the methylene carbon appeared at 47.4 ppm whereas the C-4 carbon appeared at 49.7 ppm. Four peaks were observed at 125.3, 127.6, 128.4 and 140.2 which were attributed to the aromatic carbons. The lactam carbonyl carbon appeared at 167.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 148 corresponding to M+1.

The next step was to protect the lactam nitrogen as its Boc derivative. Accordingly, compound **3.04** was stirred with $(Boc)_2O$ and DMAP in DCM to obtain the Boc protected compound **3.05** in very good yield.

Compound **3.05** displayed a band at 1805 cm^{-1} in its IR spectrum. In the ^{1}H NMR, the nine protons from the Boc group displayed a singlet at 1.31 ppm. One of the

protons from the methylene group displayed a doublet of a doublet (J = 3.15, 16 Hz) at 2.85 ppm whereas the other methylene proton displayed another doublet of a doublet (J = 6.1, 16 Hz) at 3.36 ppm. The proton on C-4 of the lactam ring exhibited a multiplet at 4.85 ppm. The five aromatic protons appeared as a multiplet between 7.25-7.36 ppm.



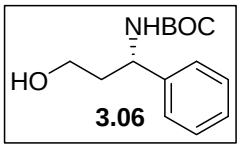
3.05

In the ^{13}C NMR spectrum, the three methyl carbon atoms of the Boc group displayed a peak together at 27.7 ppm. The methylene carbon appeared at 45.9 ppm which was also supported by the DEPT spectrum. The C-4 of lactam ring appeared at 53.6 ppm. The quaternary carbon from the Boc group appeared at 83.1 ppm. Four peaks were seen at 125.8, 128.4, 128.7 and 138.1 ppm which were assigned to the aromatic carbons. The Boc carbonyl carbon appeared at 147.3 ppm whereas the lactam carbonyl appeared downfield at 164.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at m/z 248 corresponding to M+1.

We moved further by reductive opening of the lactam ring with lithium aluminium hydride. Compound **3.05** was stirred with lithium aluminium hydride in THF which furnished compound **3.06** in very good yield. Compound **3.06** had the core structure of the target molecule.

Compound **3.06** displayed a band at 3337 cm^{-1} corresponding to the hydroxy group. In the ^{1}H NMR, the nine protons of the Boc group appeared as a singlet at 1.44 ppm. Two protons from one of the methylene groups (C-CH_2-C) appeared as a multiplet between 1.79-2.17 ppm. The O-*H* and N-*H* protons came together as a broad signal at 2.7 ppm. The two protons from the other methylene group (OCH_2) appeared as a multiplet between 3.65-3.72 ppm. The proton, on the carbon atom bearing the NHBoc group, appeared as a multiplet at 4.99 ppm. The five aromatic protons appeared as a multiplet between 7.27-7.38 ppm.



3.06

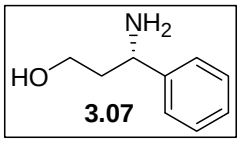
In the ^{13}C NMR spectrum, the three methyl carbon atoms of the Boc group displayed a peak together at 28.2 ppm. One of the methylene groups (C-CH_2-C) appeared at 39.3 ppm. The methine carbon bearing the NHBoc group appeared at 51.5 ppm. The other methylene carbon displayed a peak at 58.9 ppm. Both the methylene peaks were also confirmed by a DEPT experiment. The quaternary carbon of the Boc group appeared at 79.9 ppm. Four peaks were seen at 126.3, 127.4, 128.7 and 141.9 ppm

which were assigned to the aromatic carbons. The Boc carbonyl carbon appeared at 156.3 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 252 corresponding to M+1.

We proceeded further with the deprotection of the NHBoc moiety. Compound **3.06** was stirred with trifluoroacetic acid in DCM to obtain compound **3.07**. The structure of compound **3.07** was established with the help of spectral and analytical data.

The IR spectrum of compound **3.07** showed a broad band at 3200-3380 cm^{-1} corresponding to the amino as well as the hydroxy group. In the ^{1}H NMR, two protons of one of the methylene group (C-*CH*$_2$-C) appeared as a multiplet around 1.77-2.32 ppm. The protons of the other methylene group (O*CH*$_2$) and the proton on the carbon atom bearing the amine functionality showed a merged signal, appearing as a multiplet at 3.63-3.69 ppm. The protons of the amino group and hydroxy group appeared as a broad signal together at 3.86 ppm. The five aromatic protons appeared as a multiplet at 7.15-7.38 ppm.



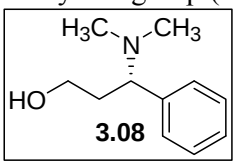
3.07

In the ^{13}C NMR spectrum, one of the methylene groups (C-*CH*$_2$-C) appeared at 35.9 ppm. The methine carbon bearing the amino group appeared at 55.1 ppm whereas the other methylene group (O*CH*$_2$) appeared at 58.9 ppm. Aromatic carbons were seen clustered together at 126.2, 126.9, 128.6 and 128.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 152 corresponding to M+1.

We then performed the last step of our synthetic scheme. The bis-methylation of the amino group was carried out by stirring compound **3.07** with aqueous formaldehyde, acetic acid and sodium cyanoborohydride in acetonitrile at room temperature for 2 hours. The reductive amination proceeded cleanly yielding the dimethyl amino compound **3.08** in good yield. The structure of compound **3.08** was established using spectral and analytical data.

The IR spectrum of compound **3.08** showed a band at 3335 cm^{-1} corresponding to the hydroxy group. In the ^{1}H NMR, one of the protons from the methylene group (C-*CH*$_2$-C) appeared as a multiplet between 1.66-1.76 ppm. The six protons of the dimethyl amino group displayed a singlet at 2.18 ppm. The other proton from the methylene group (C-*CH*$_2$-C) displayed a multiplet between 2.32-2.48 ppm. The proton on the carbon atom bearing the dimethyl amino group (NC-*H*) appeared as a multiplet between 3.69-3.80 ppm. The



3.08

two protons of the other methylene group (OCH_2) displayed a multiplet between 3.80-3.90 ppm. The proton of the hydroxy functionality displayed a broad signal at 5.16 ppm. The five aromatic protons clustered together as a multiplet between 7.15-7.32 ppm.

In the ^{13}C NMR spectrum, one of the methylene carbons (C-CH_2-C) appeared at 32.1. The two methyl carbons from the dimethyl amino moiety appeared together at 41.0 ppm. The other methylene group (OCH_2) displayed a peak at 63.1 ppm. The methine carbon bearing the dimethyl amino moiety appeared at 70.0 ppm. The aromatic carbons appeared together as a cluster of peaks between 127.1-136.1 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 180 corresponding to M+1 and it also showed satisfactory elemental analysis. The specific rotation of intermediate **3.08** was in good agreement with reported values; $[\alpha]_D^{25} = +39.0$ (*c* 6.0, $CHCl_3$); Lit. [16] $[\alpha]_D^{25} = +39.2$ (*c* 0.6, $CHCl_3$).

Transformation of compound **3.08** into (*S*)-dapoxetine (**3.01**) is a well established synthetic protocol.[14,16] Thus, enantioselective synthesis of intermediate **3.08** in 17% overall yield, in seven steps from a substituted 3-hydroxy azetidin-2-one, constitutes a formal synthesis of (*S*)-dapoxetine.

3.5: Conclusion

In conclusion, an enantioselective formal synthesis of (*S*)-dapoxetine; an SSRI type of drug against depression and a potential cure of premature ejaculation in men, was achieved from an enantiopure, substituted 3-hydroxy β-lactam in seven steps, in 17% overall yield. The synthesis illustrates the use of β-lactam synthon method for molecules of medicinal interest.

3.6: Experimental

3.6.1: (3*S*,4*R*) Dithiocarbonic acid *O*-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl] ester *S*-methyl ester (3.02):

To a cooled suspension of NaH (60%; 0.47 g, 11.8 mmol) in anhyd. THF (5 mL) was added 3-hydroxy- β-lactam **2.13b** (0.80 g, 2.97 mmol) as a solution in THF (5 mL) slowly. After the addition was complete, the reaction mixture was stirred at r.t. for 30 min. The solution was cooled to 0 °C and a solution of CS_2 (0.53 mL, 8.91 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 1.5 h at 0 °C, MeI (1.10 mL, 17.8 mmol) was then added at the same temperature, and the reaction mixture was stirred at r.t. for 3 h. After the reaction was complete (TLC), a sat. aq. soln. of NH_4Cl (10 mL) was added, and THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic layer was washed with H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product, which was then purified by flash column chromatography (10% EtOAc/petroleum ether) to furnish compound **3.02** (0.79 g, 75%) as a white solid.

MP	**:**	135 °C
IR ($CHCl_3$)	**:**	1755 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	2.29 (3H, s, SC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 5.42 (1H, d, *J* = 4.8 Hz, C*H*-N), 6.68 (1H, d, *J* = 4.8 Hz, C*H*-OC=S), 6.81 (2H, d, *J* = 8.9 Hz, Ar-*H*), 7.27-7.37 (7H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	18.8, 55.3, 61.6, 81.6, 114.3, 118.8, 128.1, 128.3, 128.7, 130.0, 131.8, 156.5, 160.5, 213.6
MS (m/z)	**:**	360 (M+1)
Analysis $C_{18}H_{17}NO_3S_2$	**:**	Calculated: C, 60.14; H, 4.77; N, 3.90; S, 17.84%. Observed: C, 60.12; H, 4.72; N, 3.96; S, 17.86%.
Optical rotation	**:**	$[\alpha]^{30}_D$ = +33.3 (*c* 0.9, $CHCl_3$).

3.6.2: (*S*)-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (3.03):

A solution of Bu_3SnH (0.58 mL, 2.15 mmol) and AIBN (15 mg) in anhydrous toluene (5 mL) was added drop wise to a refluxing solution of xanthate **3.02** (0.26 g, 0.72 mmol) in anhydrous toluene (10 mL) under argon atmosphere. The reaction

mixture was then refluxed for 3h (TLC). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc–petroleum ether) to afford **3.03** (0.168g, 92%) as a white fluffy solid.

MP : 98 °C

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.83 (1H, dd, *J* = 2.5, 15 Hz, OCC*H*$_2$), 3.45 (1H, dd, *J* = 5.5, 15 Hz, OCC*H*$_2$'), 3.64 (3H, s, OC*H*$_3$), 4.88 (1H, dd, J = 2.5, 5.5 Hz, C*H*-N), 6.69 (2H, d, *J* = 8.9 Hz, Ar), 7.13-7.28 (7H, m, Ar-*H*),

^{13}C NMR ($CDCl_3$) (50 MHz) : 46.8, 53.9, 55.3, 114.1, 118.0, 125.8, 128.4, 129.0, 131.3, 138.2, 155.8, 163.9

MS (m/z) : 254 (M+1)

Analysis $C_{16}H_{15}NO_2$: Calculated: C, 75.87; H, 5.97; N, 5.53%.
Observed: C, 75.95; H, 6.09; N, 5.60%.

Optical rotation : $[\alpha]^{30}_D$ = -40 (*c* 0.2, $CHCl_3$).

3.6.3: (*S*)-4-Phenyl-azetidin-2-one (3.04):

A solution of $(NH_4)_2Ce(NO_3)_6$ (0.97 g, 1.77 mmol) in water (7 mL) was added drop wise to a solution of (*S*)-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one **(3.03)** (0.15 g, 0.59 mmol) in acetonitrile (7 mL) at 0 °C. The mixture was stirred at this temperature for 1h. Water (10 mL) was added, it was extracted with ethyl acetate (3 x 15 mL) and washed with a saturated solution of $NaHCO_3$ (2 x 10 mL). The aqueous layer of $NaHCO_3$ was extracted again with ethyl acetate (1 x 10 mL), and the combined organic extracts were washed with 40% $NaHSO_3$ (3 x 10 mL) and brine (10 mL). It was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to get the crude product, which was purified by flash column chromatography (70% EtOAc/pet. ether) to furnish **3.04** (0.052 g, 60 %) as a very viscous liquid.

IR ($CHCl_3$) : 1765, 3411 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.81 (1H, dd, *J* = 2.09, 14.09 Hz, OCC*H*$_2$), 3.32-3.44 (1H, m, OCC*H*$_2$'), 4.66 (1H, m, C*H*-N), 6.23 (1H, bs, N*H*), 7.19-7.30 (5H, m, Ar-*H*),

^{13}C NMR : 47.4, 49.7, 125.3, 127.6, 128.4, 140.2, 167.9

($CDCl_3$)
(50 MHz)

MS (m/z) : 148 (M+1)

Analysis : Calculated: C, 73.45; H, 6.16; N, 9.52%.
C_9H_9NO Observed: C, 73.39; H, 6.09; N, 9.61%.

Optical rotation : $[\alpha]^{30}_D$ = -40 (*c* 0.1, $CHCl_3$).

3.6.4: (*S*)-2-Oxo-4-phenyl-azetidine-1-carboxylic acid tert-butyl ester (3.05):

$(Boc)_2O$ (0.94 mL, 4.08 mmol) and DMAP (0.398 g, 3.26 mmol) were added to a solution of azetidin-2-one **3.04** (0.400 g, 2.72 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the reaction mixture was stirred for 6 h. Then, CH_2Cl_2 (10 mL) was added and it was washed with a saturated solution of $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography (20% EtOAc/pet. ether) to furnish title β-lactam **3.05** (0.470 g, 70 %) as a viscous liquid.

IR ($CHCl_3$) : 1805 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.31 (9H, s, OC(CH_3)$_3$), 2.85 (1H, dd, *J* = 3.15, 16 Hz, OCCH_2), 3.36 (1H, dd, *J* = 6.1, 16 Hz, OCCH_2'), 4.85 (1H, m, C*H*-N), 7.25-7.36 (5H, m, Ar-*H*),

^{13}C NMR ($CDCl_3$) (50 MHz) : 27.7, 45.9, 53.6, 83.1, 125.8, 128.4, 128.7, 138.1, 147.3, 164.9

MS (m/z) : 248 (M+1)

Analysis : Calculated: C, 68.00; H, 6.93; N, 5.66%.
$C_{14}H_{17}NO_3$ Observed: C, 68.05; H, 6.91; N, 5.60%.

Optical rotation : $[\alpha]^{30}_D$ = -33.3 (*c* 0.3, $CHCl_3$)

3.6.5: *S*-(3-Hydroxy-1-phenyl-propyl)-carbamic acid tert-butyl ester (3.06):

To a suspension of LAH (0.204 g, 5.37 mmol) in THF (5 mL) was added β-lactam **3.05** (0.332 g, 1.33 mmol) in THF (5 mL) drop-wise at 0 °C under inert

atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 4 h. After completion of the reaction (TLC), a saturated solution of Na_2SO_4 was added to the reaction mixture at 0 °C and it was stirred for an hour. THF was then evaporated on rotary evaporator and to the residue was added ethyl acetate (15 mL). It was washed with water (10 mL). The aqueous layer was washed with ethyl acetate (2 x 5 mL). Combined organic extracts were washed with brine (5 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to get the crude product which was purified by column chromatography using (40% EtOAc/pet. ether) to furnish **3.06** (0.269g, 80%) as a white solid.

MP : 104 °C

IR ($CHCl_3$) : 3337 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.44 (9H, s, OC(CH_3)$_3$), 1.79-2.17 (2H, m, CCH_2C), 2.7 (2H, bs, O*H*, N*H*), 3.65-3.72 (2H, m, OCH_2), 4.99 (1H, m, C*H*-N), 7.27-7.38 (5H, m, Ar-*H*),

^{13}C NMR ($CDCl_3$) (50 MHz) : 28.2, 39.3, 51.5, 58.9, 79.9, 126.3, 127.4, 128.7, 141.9, 156.3

MS (m/z) : 252 (M+1)

Analysis $C_{14}H_{21}NO_3$: Calculated: C, 66.91; H, 8.42; N, 5.57%.
Observed: C, 66.81; H, 8.57; N, 5.65%.

Optical rotation : $[\alpha]^{30}_D$ = -53.1 (*c* 7.0, acetone)

3.6.6: (*S*)-3-Amino-3-phenyl-propan-1-ol (3.07):

To a solution of **3.06** (0.030 g, 0.12 mmol) in DCM (2 mL) was added TFA (0.3 mL) dropwise at 0 °C. It was kept at 0 °C for half an hour and then allowed to come to room temperature and stirred for further 1.5 h. After completion (TLC), the reaction mixture was concentrated in *vacuo* to remove DCM and TFA. The residue was then dissolved in methanol (3 mL) and Et_3N (0.016 mL, 0.12 mmol) was added and the resultant solution was passed through a short column of silica gel with methanol as an eluent. The methanol fractions were concentrated in *vacuo* to furnish **3.07** as a white hygroscopic solid (0.016 g, 89%).

IR ($CHCl_3$) : 3200-3380 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : 1.77-2.32 (2H, m, CC*H*$_2$C), 3.63-3.69 (3H, m, OC*H*$_2$, C*H*-N), 3.86 (3H, bs, N*H*$_2$, O*H*), 7.15-7.38 (5H, m, Ar-*H*),

^{13}C NMR (CDCl$_3$) (50 MHz) : 35.9, 55.1, 58.9, 126.2, 126.9, 128.6, 128.9

MS (m/z) : 152 (M+1)

Analysis $C_9H_{13}NO$: Calculated: C, 71.49; H, 8.67; N, 9.26%.
Observed: C, 71.32; H, 8.80; N, 9.35%.

Optical rotation : $[\alpha]^{30}_D$ = -11.4 (*c* 2.0, $CHCl_3$)

3.6.7: (*S*)-3-Dimethylamino-3-phenyl-propan-1-ol (3.08):

To a solution of **3.07** (0.12 g, 0.807 mmol) in acetonitrile was added, 30% aqueous formaldehyde solution (0.325 mL) followed by sodium cyanoborohydride (0.081 g, 1.29 mmol) and it was allowed to stir at room temperature. A few drops of glacial acetic acid were added to maintain the *p*H near neutrality. The solution was stirred at room temperature for 2h. After completion of the reaction (TLC) the reaction mixture was concentrated in *vacuo*. To the residue was added 2N aq. KOH (10 mL). It was then extracted with ethyl acetate (3 x 10 mL). The ethyl acetate layer was then washed with 1N HCl (3 x 5 mL). The combined HCl extracts were basified with solid KOH and then extracted with ethyl acetate (3 x 10 mL). Combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to afford the crude product which was purified by column chromatography (40% EtOAc/MeOH) to furnish **3.08** (0.115 g, 80%) as a hygroscopic solid.

IR (CHCl$_3$) : 3335 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz) : 1.66-1.76 (1H, m, CC*H*$_2$C), 2.18 (6H, s, N(CH$_3$)$_2$), 2.32-2.48 (1H, m, CC*H*$_2$'C), 3.69-3.80 (1H, m, C*H*-N), 3.80-3.90 (2H, m, OC*H*$_2$), 5.16 (1H, bs, O*H*), 7.15-7.32 (5H, m, Ar-*H*),

^{13}C NMR (CDCl$_3$) (50 MHz) : 32.1, 41.0, 63.1, 70.0, 127.1, 127.9, 128.3, 128.8, 129.0, 136.1

MS (m/z) : 180 (M+1).

Analysis : Calculated: C, 73.70; H, 9.56; N, 7.81%.

$C_{11}H_{17}NO$ Observed: C, 73.78; H, 9.48; N, 7.88%.

Optical rotation : $[\alpha]^{30}_{D} = +39.0$ (*c* 6.0, $CHCl_3$)

References:

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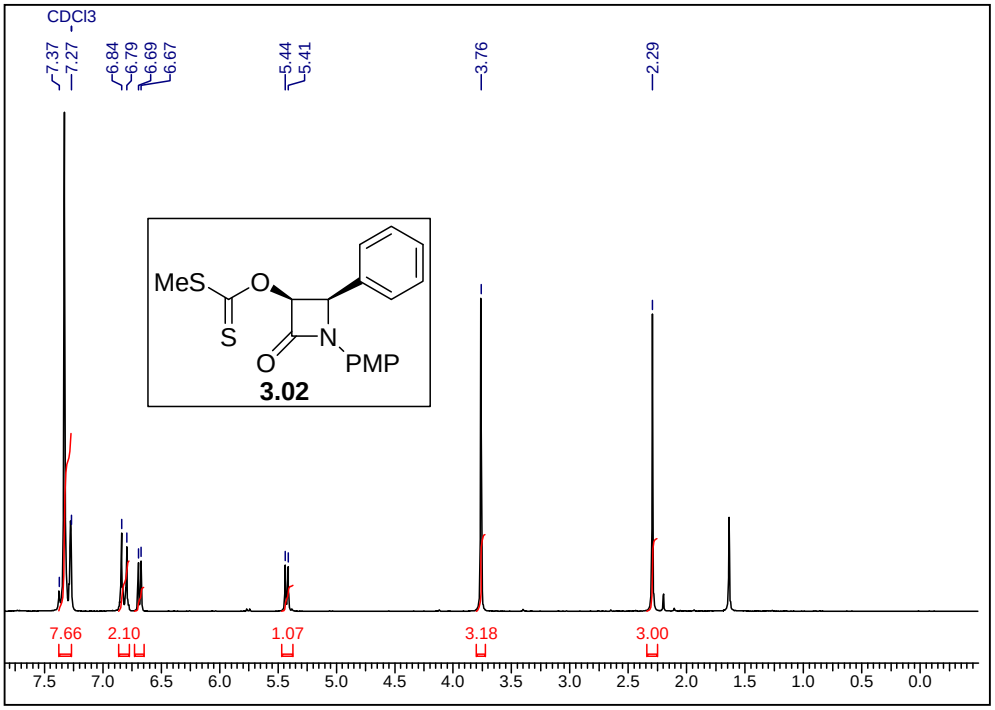
Chapter 3

Spectra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N
O
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2.10
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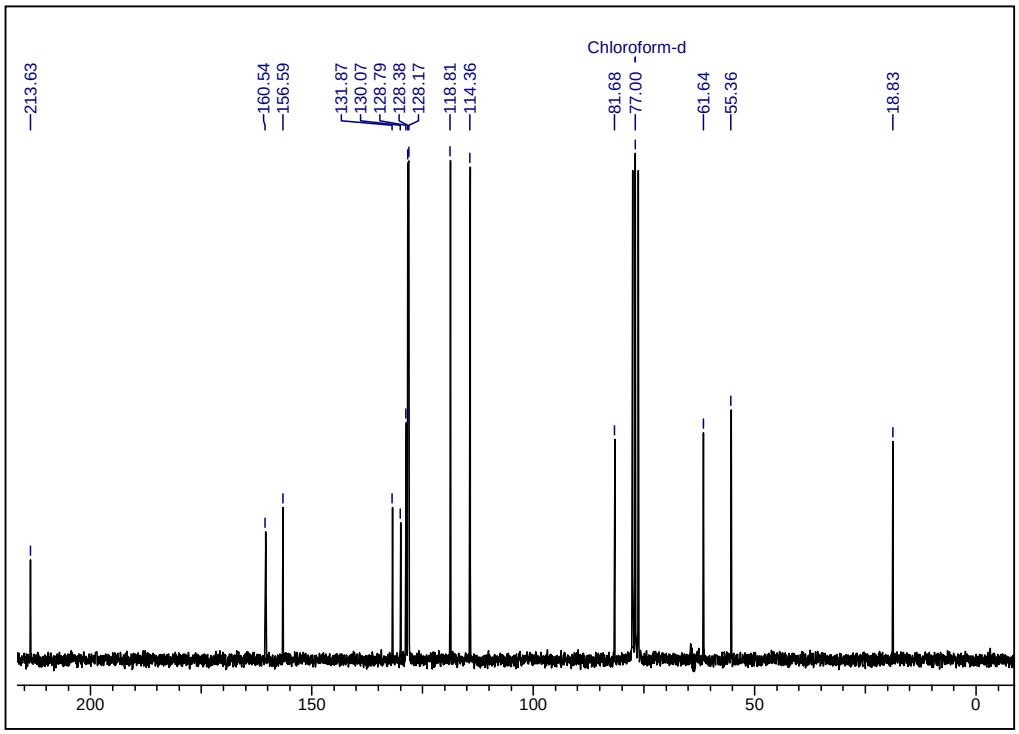
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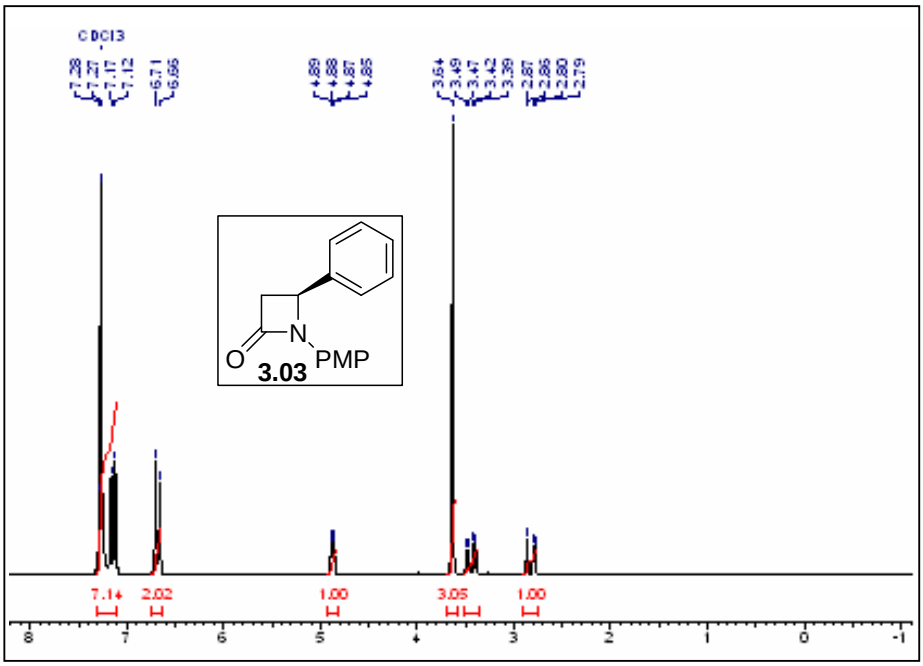
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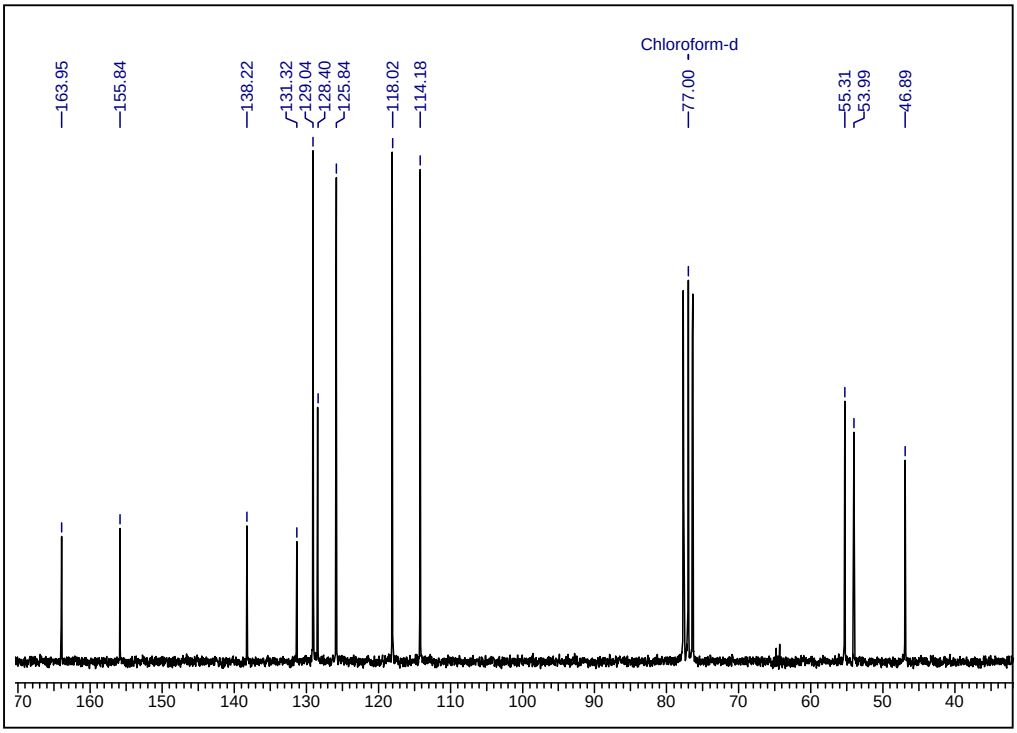
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60
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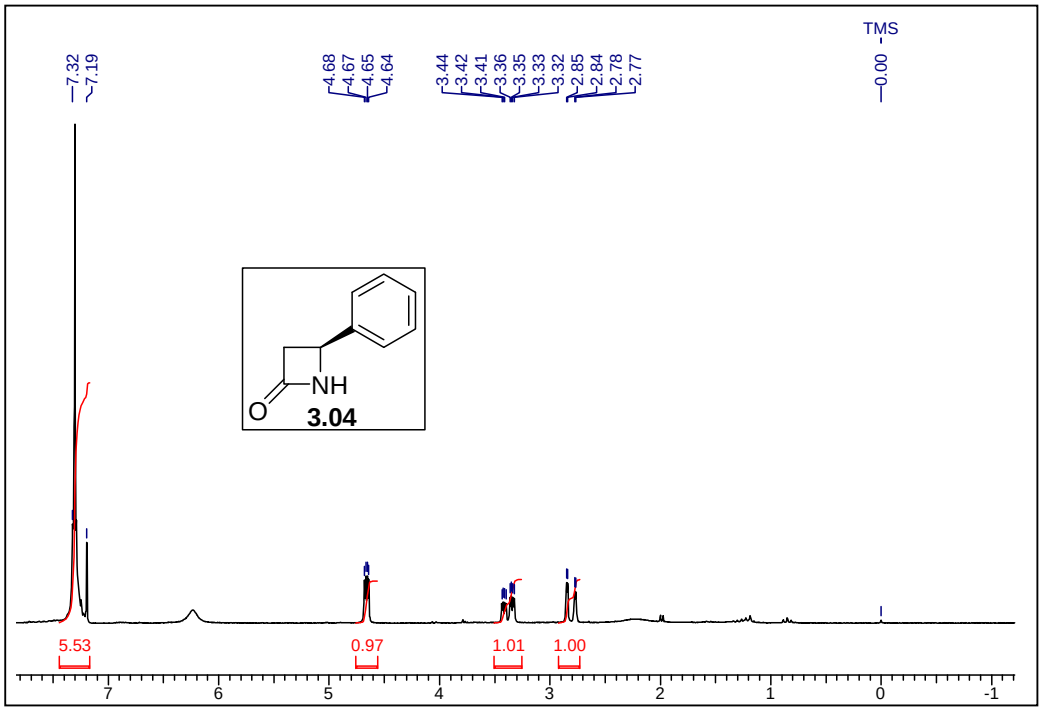
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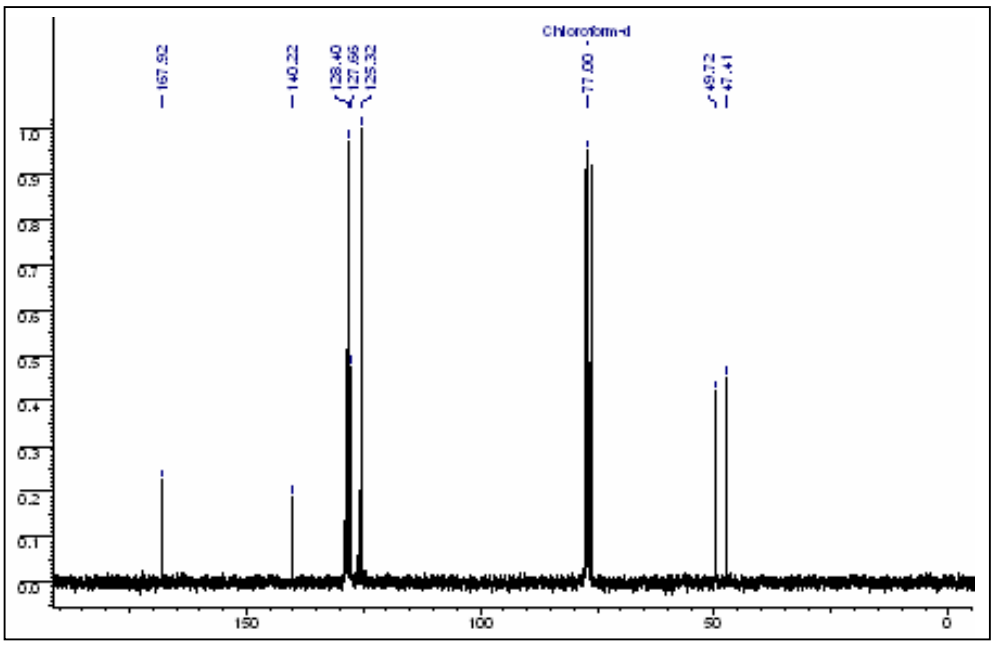
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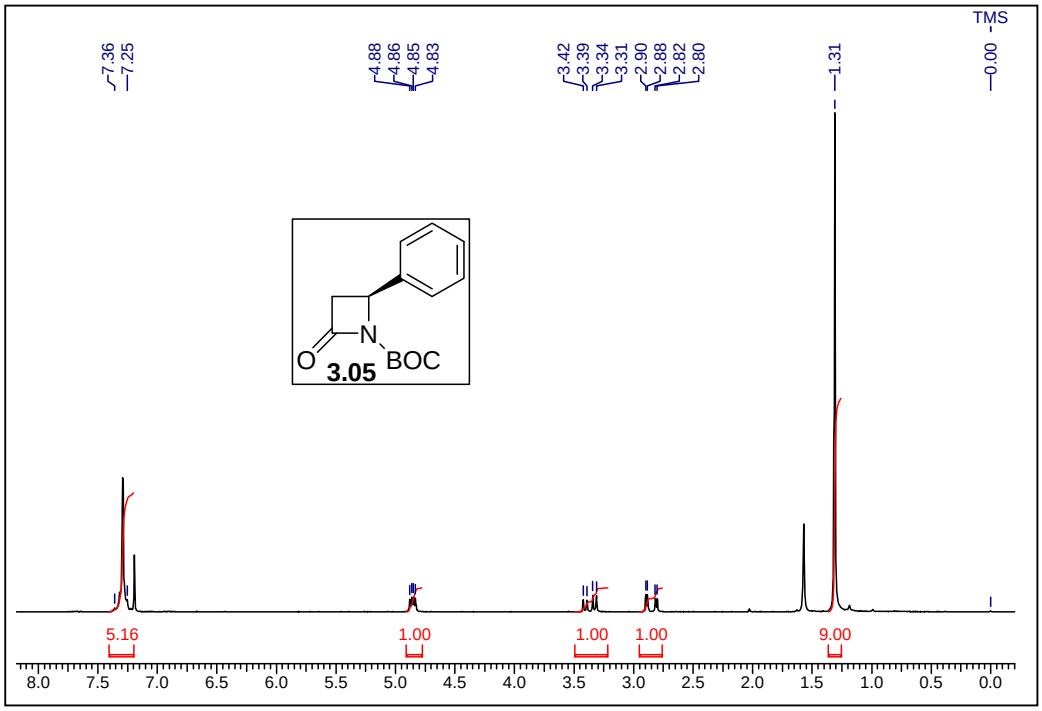
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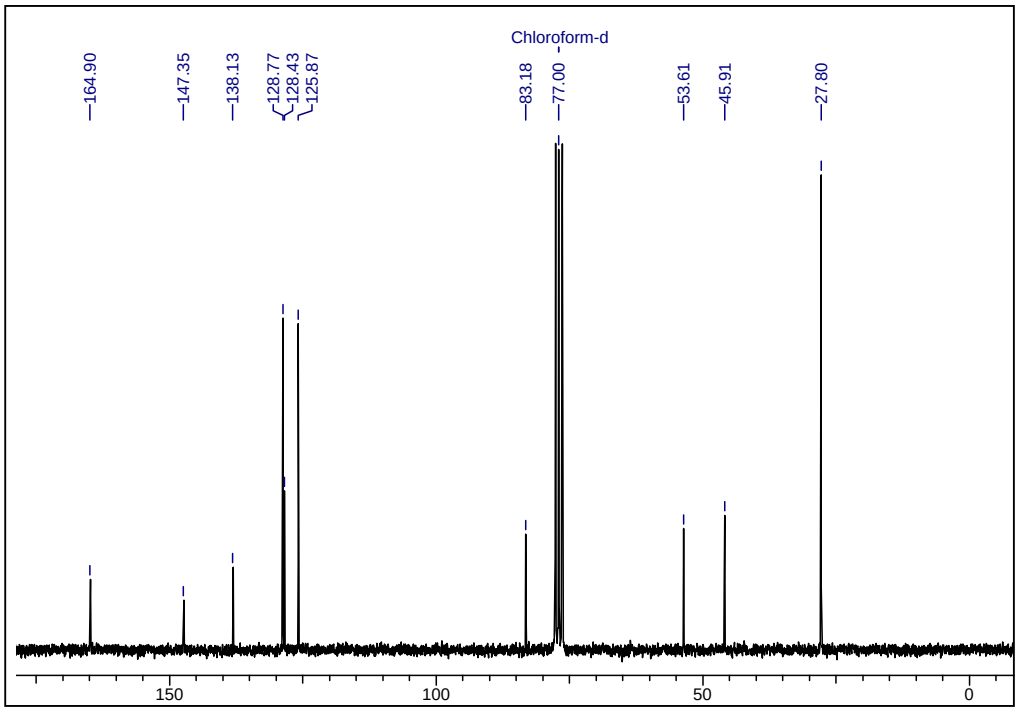
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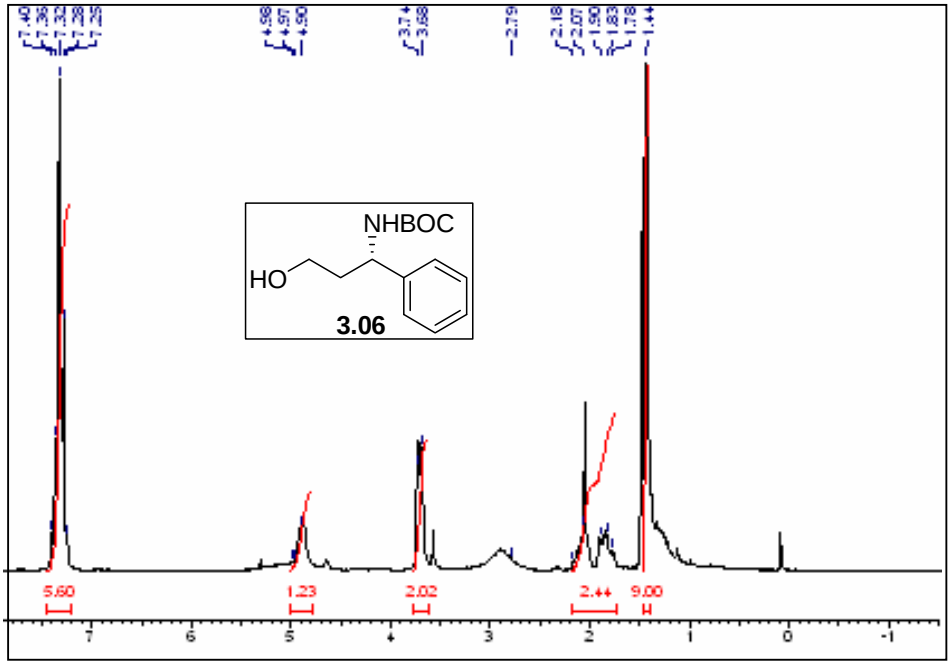
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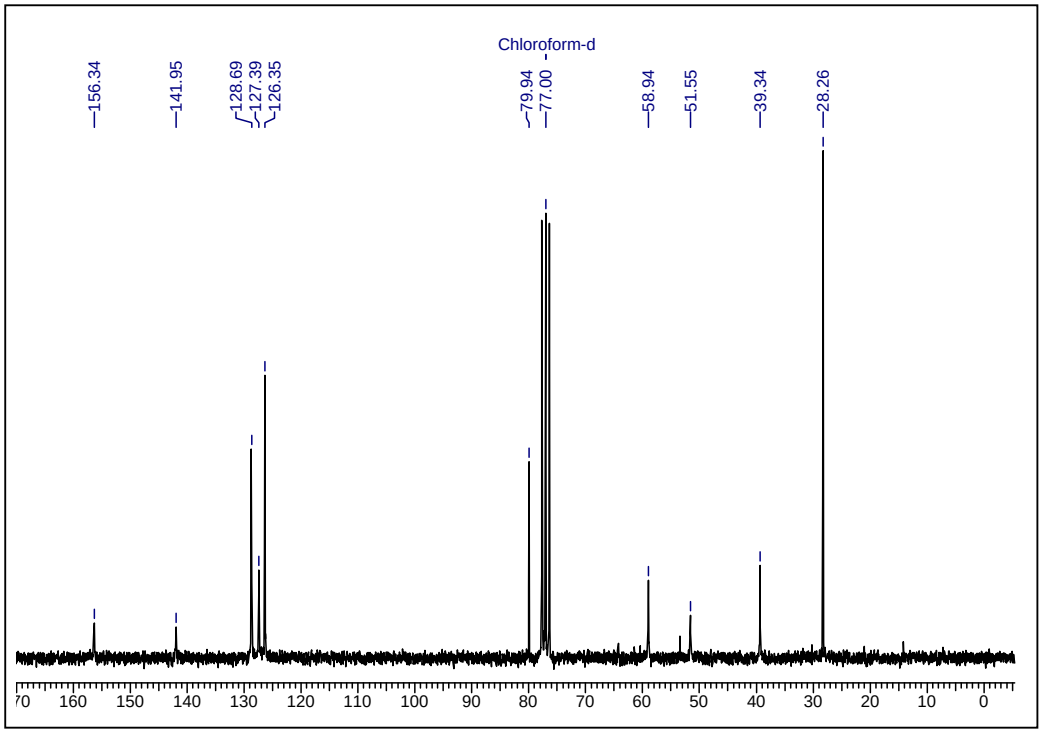
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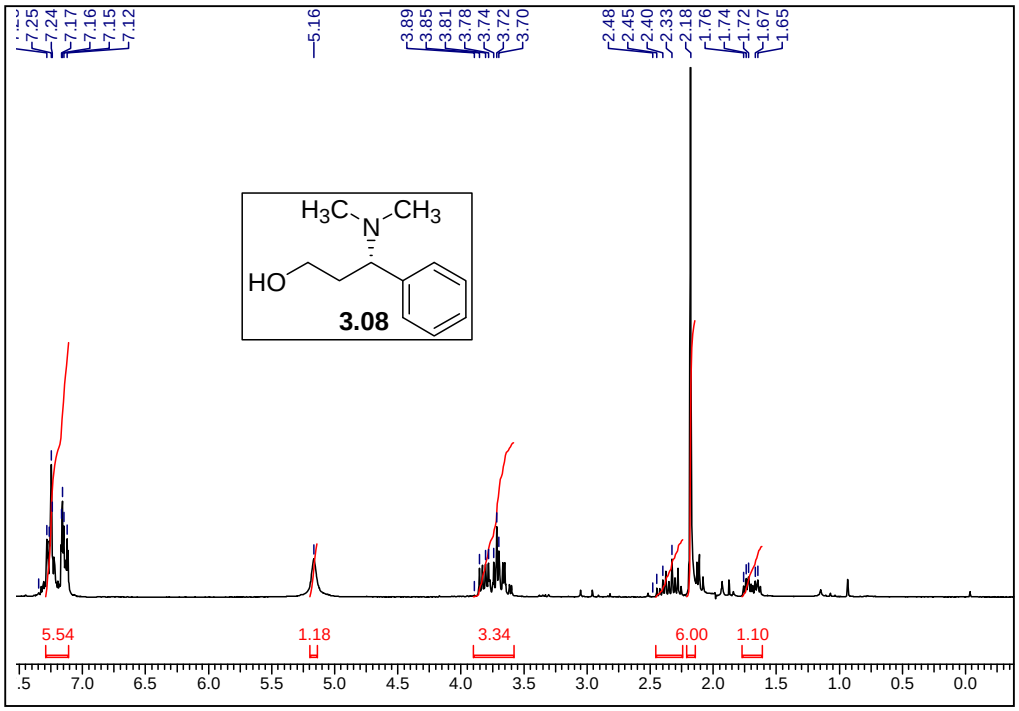
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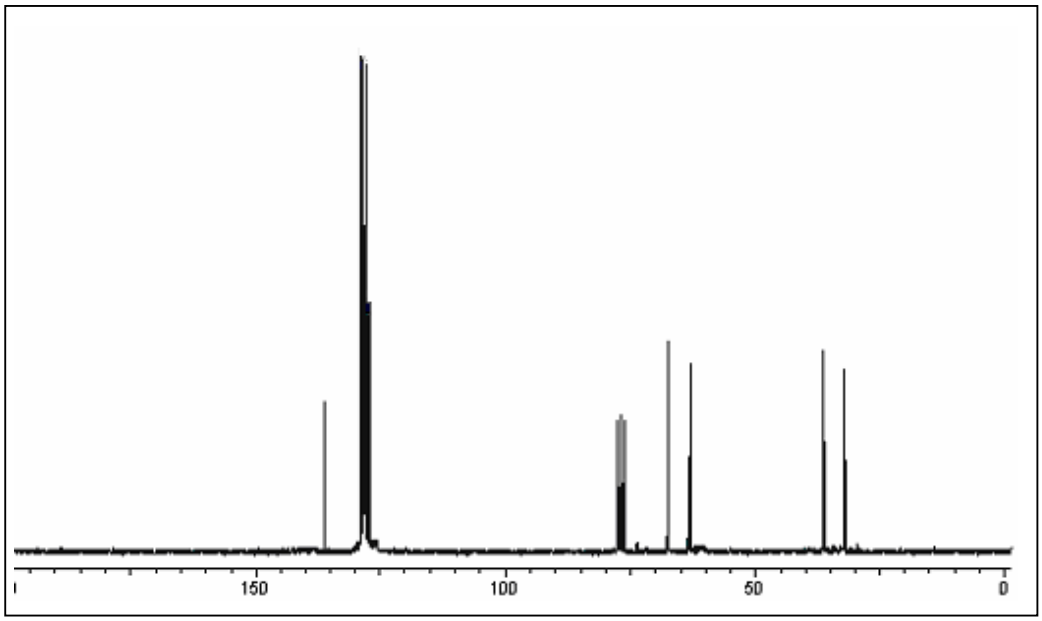
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CHAPTER 4
SECTION A
STEREOSELECTIVE SYNTHESIS OF CHOLESTEROL ABSORPTION INHIBITOR SCH 48461 FROM ENANTIOPURE AZETIDIN-2,3-DIONE.

4.1: Introduction

This section of the chapter deals with an enantioselective synthesis of SCH 48461, a cholesterol absorption inhibitor, from enantiopure azetidin-2,3-diones.

***Significance of SCH 48461*:** Coronary heart diseases (CHD) have become one of the biggest causes of mortality in recent times, across the globe and especially in the industrialized parts of the planet.[1] Atherosclerosis, a prevalent CHD is mainly caused due to clogging of arteries carrying oxygen rich blood to the heart. This clogging takes place because of deposition of cholesterol on the inner walls of the arteries. As the deposition increases and hardening takes place, the arteries are narrowed, causing resistance to flow of blood towards heart causing pain in chest (a condition called angina) and heart attacks.

Cholesterol is essential for healthy cells, but if there is too much in the blood it can lead to coronary heart disease. Cholesterol is carried in the blood stream by molecules called lipoproteins. There are several different types of lipoproteins, but two of the main ones are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). LDL also known as 'bad cholesterol' carries cholesterol from liver to the cell. HDL, often termed as 'good cholesterol' carries the cholesterol from cells, back to the liver where it broken down and thrown out of the body. Normally there is about 70% of LDL in the blood with the amount varying from person to person, but if the amount increases to higher levels, HDL is not able to remove it.

In people who have already attained high blood cholesterol levels, medical treatment becomes necessary and lifestyle rectifications like changing diet and exercising, can serve only as a supplementary tool.

There are various kinds of treatments available for CHD. Medicines are widely prescribed, Aspirin, a landmark drug, by far, being the longest known. In addition, there are also drugs of the class, anti-coagulants which prevent blood clotting and clot busters; but these have some serious side effects in case the patient has bleeding disorders. Cholesterol lowering medicines called statins are also used against CHDs. They act by blocking formation of cholesterol and increasing number of LDL receptors in liver which help to remove LDL cholesterol from blood. Beta blockers are also recommended against CHD. They work by blocking the effects of stress hormones which make the

heart beat harder and faster. However, beta blockers are not suitable if one has diabetes or respiratory disorder, like asthama.

ACE (angiotensin converting enzyme) inhibitors are also used to cure the symptoms of CHD. They block the activity of a hormone called angiotensin II which narrows blood vessels. Angiotensin II receptor antagonists are also prescribed for CHD. Their mode of action is similar to that of ACE inhibitors but is associated with fewer side effects.

Anti-arrythmic medicines are sometimes used to control the rhythm of heart, but they are effective only when taken in right dose so that exactly right amount is present in the bloodstream. Nitrates are often recommended against CHD, which are also popularly known as vaso-dilators. Sorbitate nitrate is a widely recommended vaso-dilator. They are advantageous as they are available in different forms, *viz*, tablets, sprays, skin patches and ointments. They can have some side effects namely, dizziness, headache and flushed skin.

Cardiac glycosides such as, digoxin are also recommended against heart diseases. They function by making heart muscles contract or squeeze together more strongly. This enables the heart to push blood around the body with greater force.

Sometimes, however, the problem intensifies to such an extent that medicines are not enough and one has to resort to surgical procedures. Different types of operations can be performed upon a patient suffering from CHD. Coronary angioplasty or a coronary bypass can be performed to address CHD. In cases where the problem has become even more severe, heart transplant needs to be invoked. Laser surgery is also a new type of operation by which channels are created in heart, allowing the blood to flow more easily.

Although all the treatments mentioned above have brought relief to CHD patients, newer methods to treat CHD are still being pursued. One such method is use of cholesterol absorption inhibitors. This class of compounds is relatively new and it functions by preventing the uptake of cholesterol from the small intestine into the circulatory system. Among compounds that have exhibited cholesterol absorption inhibitory activity, most prominent is a class of substituted azetidin-2-ones. Important among this class of compounds showing cholesterol absorption inhibitory activity are (-)-SCH 48461[2], ezetimibe (SCH 58235)[3] and (+)-SCH 54016[4] (Figure 1).

These compounds were first discovered at the Schering-Plough institute. In fact, a part of name of these compounds 'SCH' derives itself from the word 'Schering' from the name of the institute. They have displayed excellent cholesterol absorption inhibitory activity.

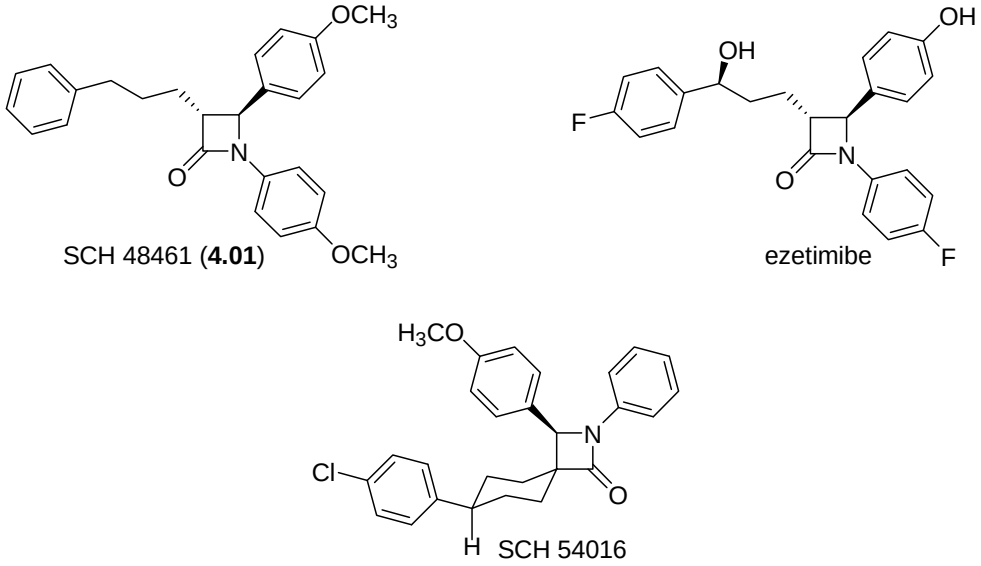


Figure 1. SCH 48461 (**4.01**), ezetimibe and SCH 54016

Their mode of action in brief is as follows:

There are two sources of cholesterol in the upper intestine: dietary (from food) and biliary (from bile). Dietary cholesterol, in the form of lipid emulsions, combines with bile salts, to form bile salt micelles from which cholesterol can then be absorbed by the intestinal enterocyte. Once absorbed by the enterocyte, cholesterol is reassembled into large intestinal lipoproteins called chylomicrons. These chylomicrons are then secreted into the lymphatics and circulated to the liver. These cholesterol particles are then secreted by the liver into the blood as VLDL (very low density lipoproteins) particles, precursors to LDL.

As a class, cholesterol absorption inhibitors block the uptake of micellar cholesterol, thereby reducing the incorporation of cholesteryl esters into chylomicron particles. By reducing the cholesterol content in chylomicrons and chylomicron remnants, cholesterol absorption inhibitors effectively reduce the amount of cholesterol that is delivered back to the liver.

The reduced delivery of cholesterol to the liver increases hepatic LDL receptor activity and thereby increases clearance of circulating LDL. The net result is a reduction in circulating LDL particles. Managing cholesterol at the site of absorption is an increasingly popular strategy, being used against CHD and hence cholesterol absorption inhibitors like SCH 48461 (**4.01**) are becoming valuable drug candidates.

(-)-SCH 48461 (**4.01**) (Figure 1) is a substituted azetidin-2-one with *trans* stereochemistry. Its chemical name is (3*R*,4*S*)-1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-one. Detailed studies of effect of SCH 48461 on cholesterol levels have been done wherein the compound was evaluated for its effect on lipid parameters in patients with primary hypercholesterolemia.[4b] The study has demonstrated a very clear, clinically and statistically significant cholesterol-lowering effect of SCH 48461 in patients with primary hypercholesterolemia.

4.2: Background for the present work

***Literature survey*:**

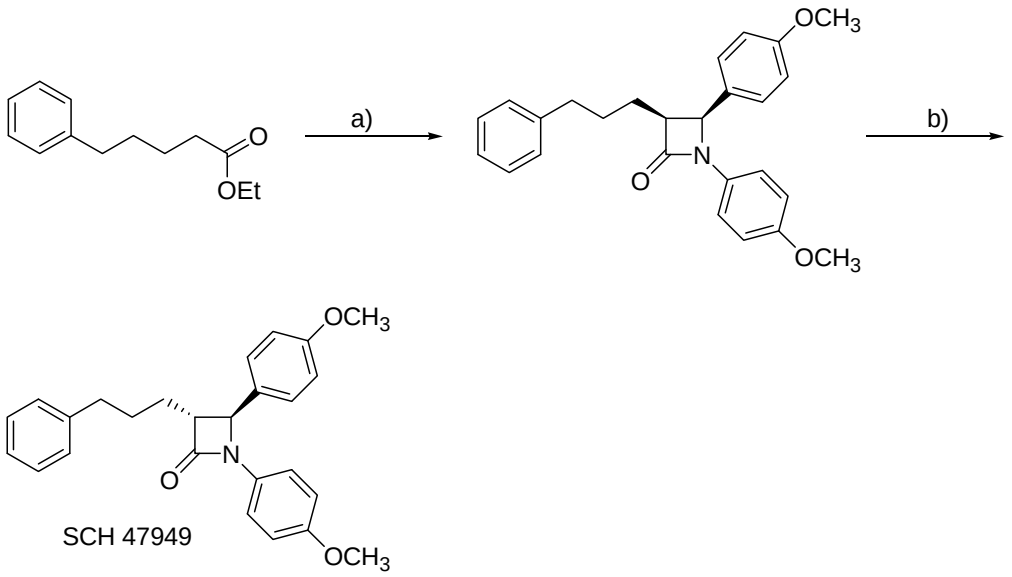
There are a few methods available in the literature for the synthesis of (-)-SCH 48461 in racemic as well as enantiopure form.

***Burnett et. al.*:**

Burnett *et. al.* who discovered the series of these compounds have used the ester-enolate imine cyclocondensation to synthesize compound SCH 47949 which is another name of racemic SCH 48461 (Scheme 4.01).[2] Compound SCH 47949 was then resolved by chiral chromatography to get enantiomers (-)-SCH 48461 and (+)-SCH 48462. Compound (-)-SCH 48461 was found to be having cholesterol absorption inhibitory activity. At this stage however, absolute configurations of (-)-SCH 48461 were not known.

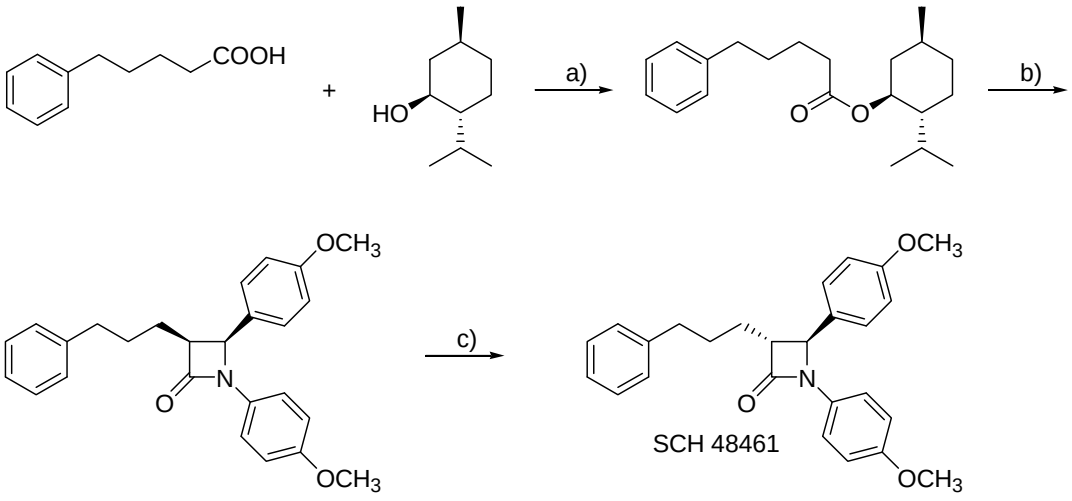
Another report by Burnett D. A. describes an enantioselective synthesis (-)-SCH 48461 in which absolute configuration of the molecule was elucidated.[5] Starting with menthyl ester of 5-phenyl valeric acid as a chiral starting material synthesis of SCH 48461 was achieved (Scheme 4.02).

Scheme 4.01



Reagents and conditions: a) i) LDA, THF, -78 °C, ii) PMP-N=CH-PMP; b) *t*-BuOK, THF, 0 °C.

Scheme 4.02



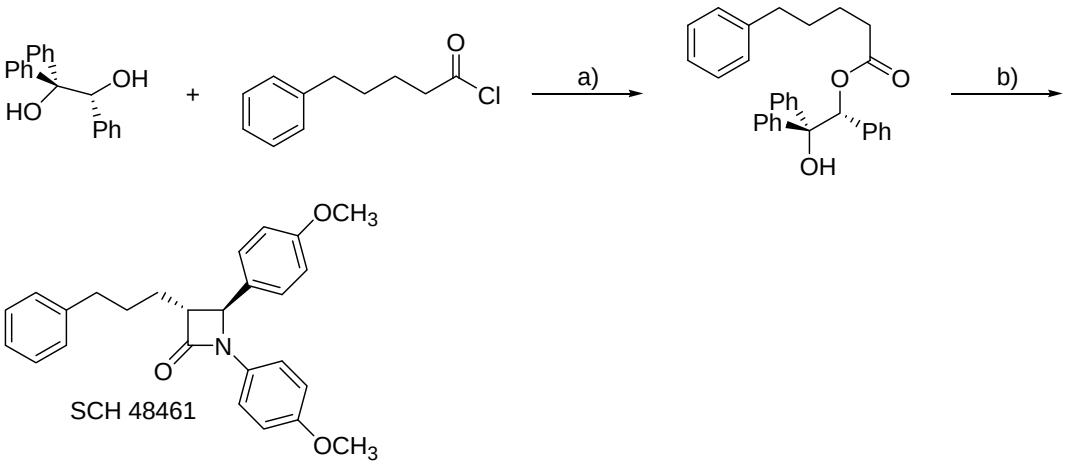
Reagents and conditions: a) $(COCl)_2$, DCM; b)i) LDA, THF, -78 °C, ii) PMP-N=CH-PMP; c)*t*-BuOK

***Braun et. al.*:**

Braun *et. al.* have reported an (*R*)-triphenyl glycol derived chiral ester as a starting material for an enantioselective synthesis of SCH 48461 (Scheme 4.03).[6] It is

another example of use of ester enolate-imine cyclocondensation for synthesis of SCH 48461.

Scheme 4.03

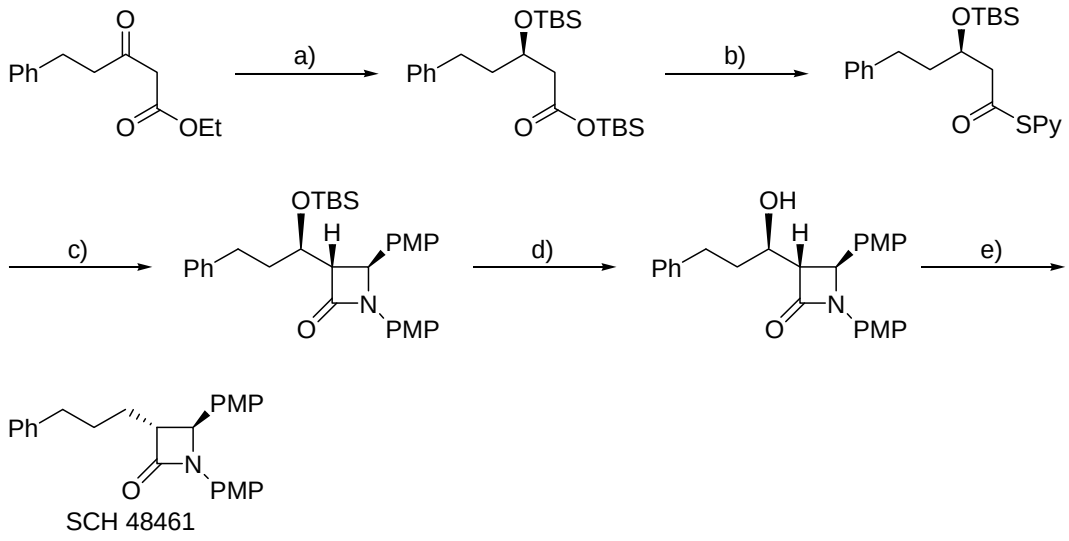


Reagents and conditions: a) pyridine, DCM, 0 °C-rt, 2h; b)i) LDA, THF, -78 °C, ii) PMP-N=CH-PMP

***Benaglia et. al.*:**

Benaglia *et. al.* have used a chiral pyridyl-thioester as a starting material for the synthesis of SCH 48461 (Scheme 4.04).[7] This chiral starting material was in turn obtained by asymmetric reduction of ethyl 5-phenyl-3-oxovalerate using Baker's yeast.

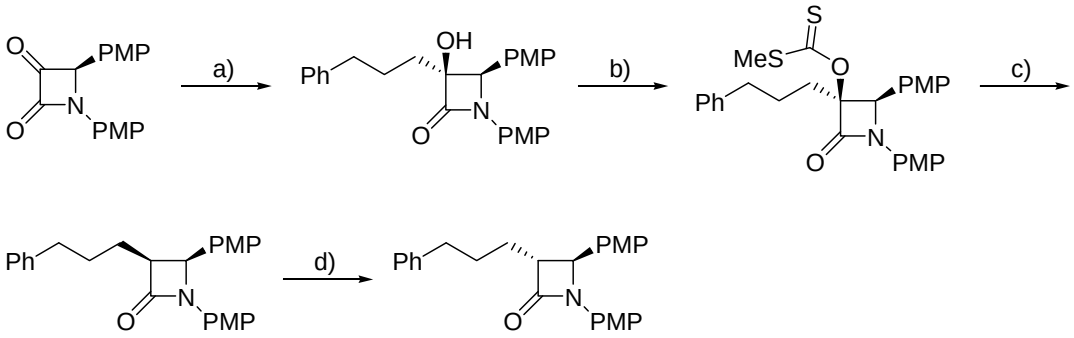
Scheme 4.04



Reagents and conditions: a) KOH, Baker's yeast, TBSCl; b) K_2CO_3, $(PyS)_2$; c) $TiCl_4$, Et_3N, PMP-N=CH-PMP; d) $Bu_4N^+F^-$; e) Thiocarbonyldiimidazole, Bu_3SnH

In our group we have devised a route to 3-alkyl/aryl azetidin-2-ones from azetidin-2-ones.[8] As a part of the same work, SCH 48461 was synthesized in racemic form (Scheme 4.05).

Scheme 4.05



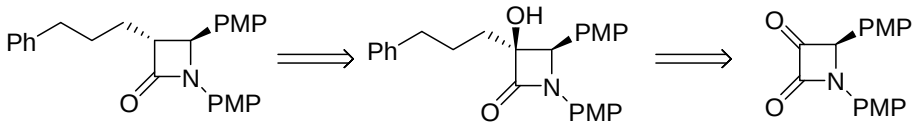
Reagents and conditions: a) $Ph(CH_2)_3MgBr$, THF, 0 °C-rt, 2h; b) NaH, CS_2, MeI, THF, 0 °-rt, 3h; c) Bu_3SnH, AIBN, toluene, reflux, 3h; d) *t*-BuOK, THF, 0 °C-rt, 2h

4.3: Present work

The medicinal importance of the molecule SCH 48461 prompted us to synthesize it in enantiopure form. We envisaged that an enantiopure azetidin-2,3-dione would be a suitable starting material for an enantioselective synthesis of SCH 48461.

The retro synthetic strategy is shown in Scheme 4.06. The target molecule **4.01** can be accessed from appropriately substituted 3-hydroxy azetidin-2-one **4.02**, which in turn can be obtained from suitable enantiopure azetidin-2,3-dione **2.11a**.

Scheme 4.06

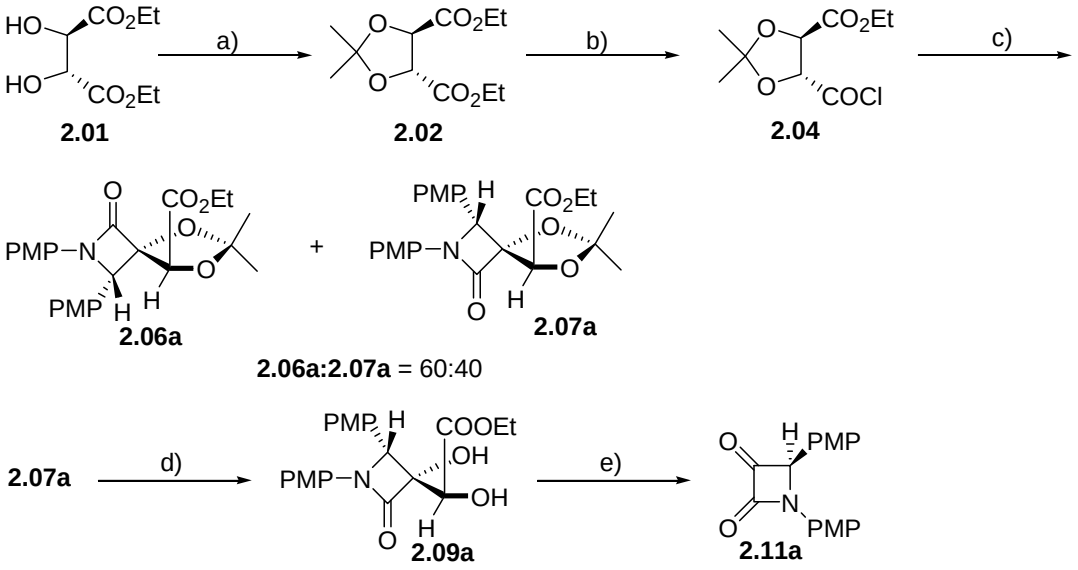


4.01 **4.02** **2.11a**

4.4: Results and Discussion

We started our work by first synthesizing the required azetidin-2,3-dione as shown in Scheme 4.07.

Scheme 4.07



Reagents and conditions:a) 2,2-dimethoxy propane benzene, PTSA, reflux, 5h.b) i) NaOH,THF-H_2O, rt, 4-6h. ii) $(COCl)_2$, DCM, reflux, 5h c) PMP-N=CH-PMP (**2.05a**), Et_3N, DCM, -40°C-rt, 15h. d) $FeCl_3$, DCM, rt, 2h. e) $NaIO_4$, acetone-water, rt, 6-8h.

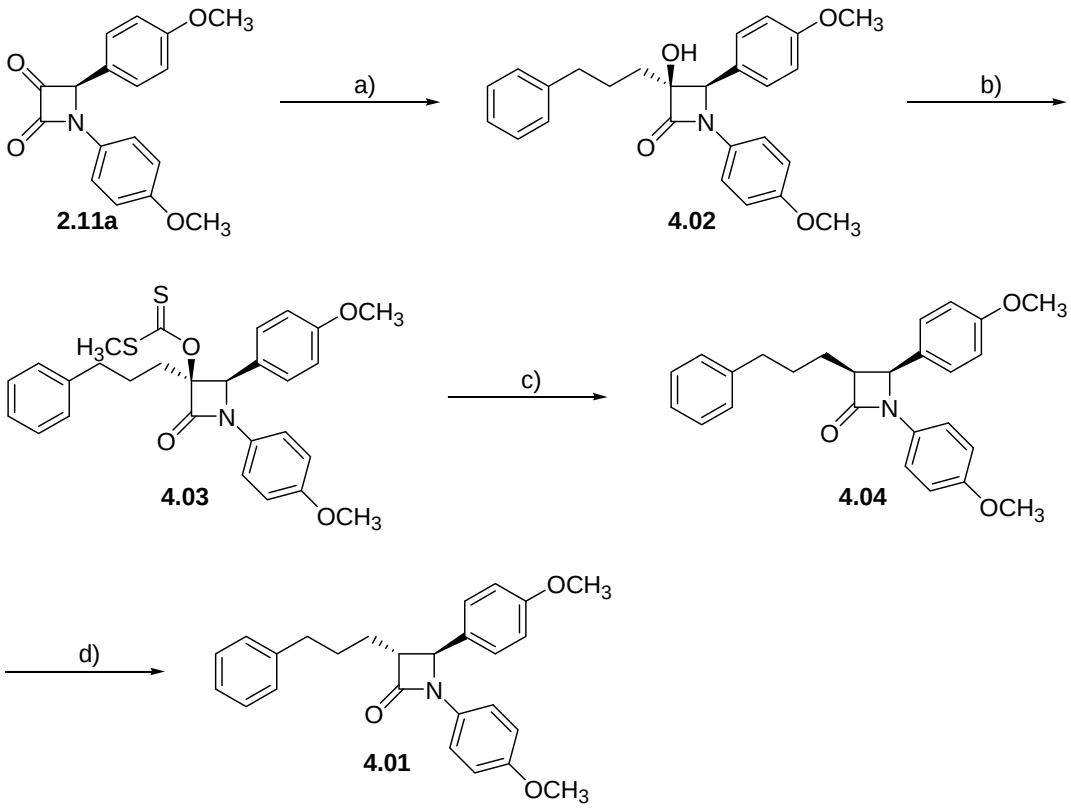
Diethyl L-tartrate **2.01** was protected as its acetonide **2.02**. Compound **2.02** was subjected to partial hydrolysis to afford mono acid, which was further converted to its acid chloride **2.04** by refluxing with oxalyl chloride in anhydrous dichloromethane in very good yield. This acid chloride **2.04** was used as such for Staudinger cycloaddition reaction with the imine (**2.05a**) derived from *p*-anisaldehyde and *p*-anisidine, to furnish diastereomeric mixture (60:40) of β-lactams **2.06a** & **2.07a**. The required diastereomer **2.07a** was obtained in enantiopure form by column chromatography.

Spiro β-lactam **2.07a** was then subjected to the deprotection of acetonide using ferric chloride to obtain diol **2.09a**, which on periodate cleavage yielded azetidin-2,3-dione **2.11a** in excellent yield.

Having synthesized the requisite azetidin-2,3-dione in enantiopure form, we proceeded further with synthesis of SCH 48461. We first performed a Grignard reaction on the azetidin-2,3-dione. Grignard reagent generated from 3-phenyl propyl bromide was reacted with azetidin-2,3-dione **2.11a** at 0 °C (Scheme 4.08). The reaction proceeded to yield compound **4.02** in good yield. It is known that the nucleophilic attack on the keto group of the azetidin-2,3-diones takes place from the opposite side of substituent on C-4.[9] In our work in Chapter 2, we had the same experience with the

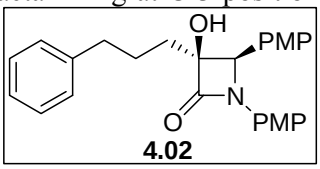
sodium borohydride reduction of azetidin-2,3-diones. Based on this evidence we assigned absolute configuration (3*S*,4*R*) to compound **4.02**.

Scheme 4.08



Reagents and conditions: a) $Ph(CH_2)_3MgBr$, THF, 0 °C-rt, 2h; b) NaH, CS_2, MeI, THF, 0 °C-rt, 3h; c) Bu_3SnH, AIBN, toluene, reflux, 3h; d) *t*-BuOK, THF, 0 °C-rt, 2h

Compound **4.02** displayed bands at 3384 and 1731 cm^{-1} in its IR spectrum, corresponding to the hydroxy and β-lactam carbonyl moieties respectively. In the ^1H NMR, two protons of the methylene group attached to the lactam ring at C-3 position and two those of the immediately next methylene group (HO-C-CH_2-CH_2-C) together exhibited a multiplet ranging between 2.01-2.10 ppm. The benzylic methylene displayed a triplet (J = 6.5 Hz) at 2.77 ppm. The methyl groups of the two PMP moieties appeared as two singlets at 3.80 and 3.85 ppm. The proton on carbon C-4 of the lactam appeared as a singlet at 4.98 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.81 (J = 9.1 Hz) and 6.94 ppm (J = 8.6 Hz). The remaining nine aromatic protons displayed a multiplet around 7.17-7.37 ppm.

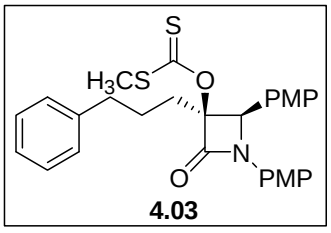


In the ^{13}C NMR spectrum, the internal methylene carbon flanked by two other methylene groups appeared at 25.2 ppm. The other methylene groups displayed peaks at 34.9 and 35.8 ppm. The two methyl carbons from the two PMP groups resonated at 55.1 and 55.3 ppm. The C-4 carbon atom of the lactam ring appeared at 66.9, whereas, the C-3 carbon atom of the lactam ring appeared at 85.7 ppm. A set of ten peaks corresponding to the aromatic carbons, appeared between 114.3-141.8 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings displayed peaks at 156.3 and 159.8 ppm. The lactam carbonyl carbon atom appeared at 167.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m/z* 418 corresponding to M+1.

We then proceeded further with the conversion of compound **4.02** into its xanthate derivative **4.03**. The hydroxy group of compound **4.02** was converted into its xanthate using sodium hydride, carbon disulphide and methyl iodide in THF as a solvent.

The IR spectrum of compound **4.03** showed a band at 1755 cm^{-1} corresponding to the carbonyl moiety of the lactam. In the ^{1}H NMR, a multiplet for two methylene protons from the propyl chain, appeared at 1.80-2.10 ppm. The methyl group of the xanthate moiety displayed a singlet at 2.2 ppm. One of the methylene protons from the propyl chain displayed a multiplet at 2.40-2.62 ppm. The two benzylic methylene protons displayed a triplet (J = 7.8 Hz) at 2.70 ppm. Another methylene proton from the propyl chain appeared as a multiplet at 2.86-3.02 ppm. The methyl groups of the two PMP moieties appeared as two singlets at 3.80 and 3.85 ppm. The proton on carbon C-4 of the lactam appeared as a singlet at 5.12 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.75 (J = 9.0 Hz) and 6.85 ppm (J = 8.8 Hz). The remaining nine aromatic protons displayed a multiplet around 7.14-7.38 ppm.



4.03

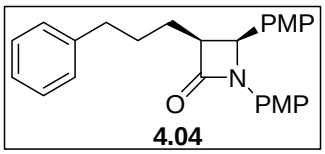
In the ^{13}C NMR spectrum, the methyl group from the xanthate ester appeared at 19.2 ppm. The carbon atom of the internal methylene group, flanked by two other methylene groups displayed a peak at 24.9 ppm. The remaining two methylene carbons appeared at 31.9 and 35.5 ppm. The two methyl carbon atoms from the two PMP groups appeared at 55.1 and 55.3 ppm. The C-4 carbon atom of the lactam ring appeared at 66.8, whereas, the C-3 carbon atom of the lactam ring appeared at 95.0 ppm. A set of

nine peaks corresponding to the aromatic carbon atoms appeared in the region 113.6-141.3. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings displayed peaks at 156.3 and 159.6 ppm. The lactam carbonyl carbon atom appeared at 162.4 ppm, whereas the thiocarbonyl carbon atom appeared at 210.8 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m/z* 508 corresponding to M+1.

We then moved ahead with reductive removal of the xanthate to obtain the deoxygenated β-lactam. Compound **4.03** when refluxed with tributyl tin hydride in presence of catalytic AIBN in toluene as a solvent gave compound **4.04** in high yield. β-lactam **4.04** had relative stereochemistry, *cis* which was inferred from the coupling constants in ^{1}H NMR spectrum of the compound.

The IR spectrum of compound **4.04** displayed a peak at 1741 cm^{-1} characteristic of a β-lactam carbonyl. In the ^{1}H NMR, a multiplet was observed at 1.18-1.66 ppm corresponding to four protons of two methylene groups. Another multiplet for the two protons of the remaining methylene group was observed between 2.35-2.49 ppm. The proton on C-3 of the β-lactam displayed a multiplet between 3.46-3.57 ppm. The methyl groups of the two PMP moieties appeared as two singlets at 3.75 and 3.83 ppm. The proton on C-4 of the β-lactam ring displayed a doublet (J = 5.7 Hz) at 5.11 ppm. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.78 (J = 8.9 Hz) and 6.90 ppm (J = 8.9 Hz). The remaining nine aromatic protons displayed a multiplet around 7.00-7.27 ppm.



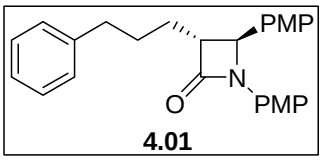
4.04

In the ^{13}C NMR spectrum, the internal methylene group flanked by two methylene groups displayed a peak at 24.9 ppm. The remaining two methylene groups exhibited peaks at 28.8 and 35.6 ppm. The two methyl carbon atoms from the two PMP groups appeared at 54.5 and 55.2 ppm. The C-3 carbon atom of the lactam ring appeared at 55.3 ppm, whereas the C-4 carbon atom of the lactam ring displayed a peak at 57.9 ppm. A set of ten peaks corresponding to the aromatic carbons appeared in the region 114.0-141.7 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings displayed peaks at 155.7 and 159.4 ppm. The lactam carbonyl carbon atom appeared at 167.4 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m/z* 402 corresponding to M+1.

To complete the synthesis of SCH 48461, as the last step we needed to epimerize the C-3 center of the β-lactam ring. Compound **4.04** was reacted with *t*-BuOK in THF as a solvent to obtain compound **4.01**. The epimerization as expected delivered the thermodynamically favored *trans* product, thereby completing the synthesis of SCH 48461 (**4.01**).

The IR spectrum of compound **4.01** showed a band at 1741 cm^{-1} corresponding to the β-lactam carbonyl. In the ^{1}H NMR, four protons for two methylene groups displayed a multiplet from 1.76-1.97. The benzylic methylene displayed a triplet (J = 7.0 Hz) at 2.65 ppm. The proton on C-3 of the lactam ring displayed a multiplet around 3.07-3.10 ppm. The methyl groups of the two PMP moieties appeared as two singlets at 3.74 and 3.80 ppm. The proton on C-4 of the lactam ring exhibited a doublet (J = 2.3 Hz) at 4.56 ppm. The low coupling constant of 2.3 Hz is typical of *trans* disposed β-lactam protons. The two protons *ortho* to the methoxy group from each of the PMP rings appeared as two doublets at 6.77 (J = 9.0 Hz) and 6.89 ppm (J = 9.0 Hz). The remaining nine aromatic protons displayed a multiplet around 7.17-7.32 ppm.



4.01

In the ^{13}C NMR spectrum, the internal methylene flanked by two other methylene groups displayed a peak at 28.3 ppm. The carbon atom of the methylene group attached to the lactam ring at C-3 exhibited a peak at 28.9, whereas, the benzylic methylene appeared at 35.6 ppm. The two methyl carbon atoms from the two PMP groups appeared at 55.2 and 55.3 ppm. The C-3 carbon atom appeared at 60.4 ppm while, the C-4 carbon atom appeared at 60.8 ppm. Ten peaks for aromatic carbon atoms clustered together in the region 114.2-141.6 ppm. The quaternary aromatic carbons bearing the methoxy substituent in both the PMP rings displayed peaks at 155.8 and 159.5 ppm. The lactam carbonyl carbon atom appeared at 167.2 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m/z* 402 corresponding to M+1 and the compound also showed satisfactory elemental analysis. The specific rotation of compound **4.01** was in good agreement with the reported value {$[\alpha]^{30}_{D}$ = -20.0 (*c* 0.5, MeOH); Lit.[2] {$[\alpha]_{D}$ = -19.0 (*c* 0.48, MeOH)}.

4.5: Conclusion

In conclusion, an enantioselective synthesis of SCH 48461, which is a cholesterol absorption inhibitor, was achieved from azetidin-2,3-dione in 30% overall yield. The synthesis demonstrates use of β-lactam synthon method for molecules of medical significance.

4.6: Experimental

4.6.1 (3*S*,4*R*) 3-Hydroxy-1,4-bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-one (4.02):

To a solution of dione **2.11a** (0.594g, 2.00 mmol) in anhydrous THF (10 mL) was added 3-phenylpropyl magnesium bromide (3.00 mmol) in anhydrous THF (5 mL) at 0 °C. The reaction mixture was stirred for 6 h at room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added and the majority of THF was removed under reduced pressure. The aqueous layer was then extracted with EtOAc (3 x 15 mL), combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product purified by flash column chromatography (pet. ether-ethyl acetate, 85%) to obtain **4.02** (0.458g, 55%) as a thick oil.

IR ($CHCl_3$) : 1731, 3384 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.01-2.10 (4H, m, HO-C-C*H*$_2$-C*H*$_2$-C), 2.77 (2H, t, *J* = 6.5 Hz, Ph-C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 4.98 (1H, s, *N*-CH), 6.81 (2H, d, *J* = 9.1 Hz, Ar), 6.94 (2H, d, *J* = 8.6 Hz, Ar), 7.17-7.37 (9H, m, Ar)

^{13}C NMR ($CDCl_3$) (50 MHz) : 25.2, 34.9, 35.8, 55.1, 55.3, 66.9, 85.7, 114.3, 114.4, 118.8, 125.6, 125.7, 125.8, 128.3, 128.4, 130.6, 141.8, 156.3, 159.8, 167.9

MS (m/z) : 418 (M+1)

Analysis $C_{26}H_{27}NO_4$: Calculated: C, 74.80; H, 6.52; N, 3.35%.
Observed: C, 74.91; H, 6.48; N, 3.28%.

Optical rotation : $[\alpha]^{30}_D$ = -17.0 (*c* 2.0, $CHCl_3$).

4.6.2 (3*S*,4*R*) Dithiocarbonic acid O-[1,2-bis-(4-methoxy-phenyl)-4-oxo-3-(3-phenyl-propyl)-azetidin-3-yl] ester S-methyl ester (4.03):

To a cooled suspension of NaH (60%; 0.028g, 0.71 mmol) in anhydrous THF (2 mL) was added compound **4.02** (0.074g, 0.177 mmol) as a solution in THF (2 mL) slowly. After the addition was complete the reaction mixture was stirred at room temperature for 30 min. The solution was cooled to 0 °C and a solution of CS_2 (0.032 mL, 0.531 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 1.5 h at 0 °C, MeI (0.066 mL, 1.062 mmol) was then added at the same temperature, and the

reaction mixture was stirred at room temperature for 3 h. After the reaction was complete (TLC), a sat. aq. solution of NH_4Cl (3 mL) was added and THF was removed under reduced pressure. The residue was dissolved in DCM (15 mL) and the organic layer was washed with water (10 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford crude product which was then purified by flash column chromatography (pet. ether-ethyl acetate, 90%) to get the pure product **4.03** (0.080g, 89%) as a thick oil.

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.80-2.10 (2H, m, -C*H*$_2$-), 2.2 (3H, s, SC*H*$_3$), 2.40-2.62 (1H, m, -C*H*$_2$-), 2.70 (2H, t, *J* = 7.8 Hz, Ph-C*H*$_2$-), 2.86-3.02 (1H, m, -C*H*$_2$-), 3.80 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 5.12 (1H, s, *N*-CH), 6.75 (2H, d, *J* = 9.0 Hz, Ar), 6.85 (2H, d, *J* = 8.8 Hz, Ar), 7.14-7.38 (9H, m, Ar)

^{13}C NMR ($CDCl_3$) (50 MHz) : 19.2, 24.9, 31.9, 35.5, 55.1, 55.3, 66.8, 95.0, 113.6, 114.2, 118.9, 125.4, 125.8, 128.2, 128.4, 130.5, 141.3, 156.3, 159.6, 162.4, 210.8

MS (m/z) : 508 (M+1)

Analysis $C_{28}H_{29}NO_4S_2$: Calculated: C, 66.24; H, 5.76; N, 2.76; S, 12.63%.
Observed: C, 66.38; H, 6.83; N, 2.63; S, 12.55%.

Optical rotation : $[\alpha]^{30}_D$ = +24.0 (*c* 0.5, $CHCl_3$).

4.6.3 (3*S*,4*S*) 1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-one (4.04):

A solution of tri-butyl tin hydride (0.091 mL, 0.345 mmol) and AIBN (3 mg) in anhydrous toluene (5 mL) was added drop wise to a refluxing solution of xanthate (0.070g, 0.138 mmol) in anhydrous toluene (15 mL) under argon atmosphere. The reaction mixture was then refluxed for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (pet. ether-ethyl acetate, 90%) to afford compound **4.04** (0.050g, 90%) as a white solid.

MP : 90-92 °C

IR ($CHCl_3$) : 1741 cm^{-1}

^{1}H NMR : 1.18-1.66 (4H, m, -C*H*$_2$-C*H*$_2$-), 2.35-2.49 (2H, m, -C*H*$_2$-), 3.46-3.57

($CDCl_3$) (200 MHz)		(1H, m, O=C-CH), 3.75 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.11 (1H, d, J = 5.7 Hz, N-CH), 6.78 (2H, d, J = 8.9 Hz, Ar), 6.90 (2H, d, J = 8.9 Hz, Ar), 7.00-7.27 (9H, m, Ar)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	24.9, 28.8, 35.6, 54.5, 55.2, 55.3, 57.9, 114.0, 114.1, 118.3, 125.6, 126.6, 127.1, 128.2, 128.3, 131.2, 141.7, 155.7, 159.4, 167.4
MS (m/z)	**:**	402 (M+1)
Analysis $C_{26}H_{27}NO_3$	**:**	Calculated: C, 77.78; H, 6.78; N, 3.49%. Observed: C, 77.65; H, 6.89; N, 3.70%.
Optical rotation	**:**	$[\alpha]^{30}_D$ = +5.0 (c 0.4, $CHCl_3$)

4.6.4 (3*R*,4*S*) 1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propyl)-azetidin-2-one (4.01):

Compound **4.04** (0.05g, 0.124 mmol) was dissolved in anhydrous THF (3 mL). *t*-BuOK (3 mg, 0.026 mmol) was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was partitioned between HCl (1N, 2 mL) and ether (7 mL). The aqueous layer was extracted with ether (2 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude product as a *cis/trans* mixture (16:84). Crystallization from DCM - pet. ether mixture gave pure *trans* azetidin-2-one **4.01** (0.064g, 68%) as white crystals.

MP	**:**	46-48 °C
IR ($CHCl_3$)	**:**	1741 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.76-1.97 (4H, m, -CH_2-CH_2-), 2.65 (2H, t, J = 7.0 Hz, Ph-CH_2), 3.07-3.10 (1H, m, O=C-CH), 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.56 (1H, d, J = 2.3 Hz, N-CH), 6.77 (2H, d, J = 9.0 Hz, Ar), 6.89 (2H, d, J = 9.0 Hz, Ar), 7.17-7.32 (9H, m, Ar)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	28.3, 28.9, 35.6, 55.2, 55.3, 60.4, 60.8, 114.2, 114.4, 118.8, 125.8, 127.1, 128.2, 128.3, 129.9, 131.2, 141.6, 155.8, 159.5, 167.2
MS (m/z)	**:**	402 (M+1)
Analysis $C_{26}H_{27}NO_3$	**:**	Calculated: C, 77.78; H, 6.78; N, 3.49%. Observed: C, 77.89; H, 6.91; N, 3.34%.

Optical rotation : $[\alpha]^{30}_{D} = -20$ (*c* 0.5, MeOH)

CHAPTER 4
SECTION B
STUDIES TOWARD L-(+)-PROLINE DERIVED CHIRAL AUXILIARY FOR DIASTEREOSELECTIVE SYNTHESIS OF AZETIDIN-2-ONES.

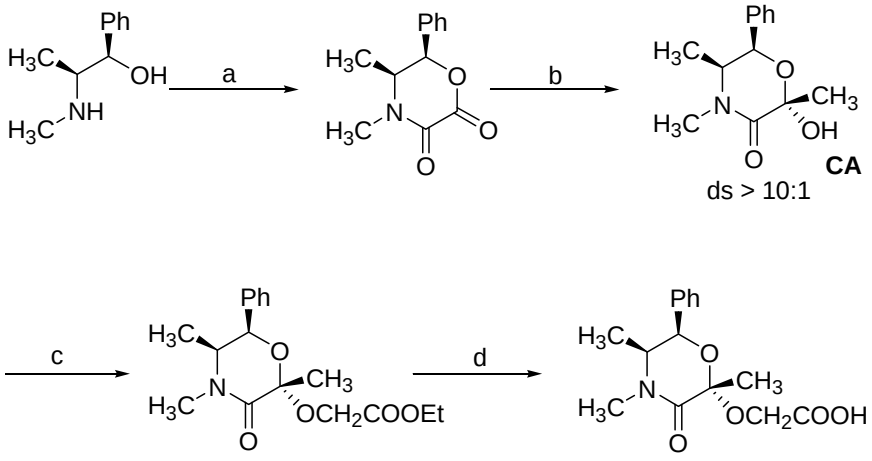
4.7: Introduction

This sub-topic of the chapter deals with attempts made towards diastereoselective synthesis of β-lactams from an L-proline derived chiral auxiliary. These β-lactams, we had planned to later transform into 3-hydroxy β-lactams. A detailed account of various methods available for diastereoselective synthesis of β-lactams has been given in the introduction part of Chapter 1, whereas the applications and various methods available for the synthesis of 3-hydroxy β-lactams have been described in Chapter 2.

4.8: Background for the present work

As a part of our research program aimed at diastereoselective synthesis of β-lactams, we have reported a method for diastereoselective synthesis of β-lactams from an ephedrine derived chiral auxiliary[10] (Scheme 4.09, 4.10). These β-lactams were further transformed into 3-hydroxy β-lactams in one step, with recovery of the chiral auxiliary without erosion of its enantiopurity.

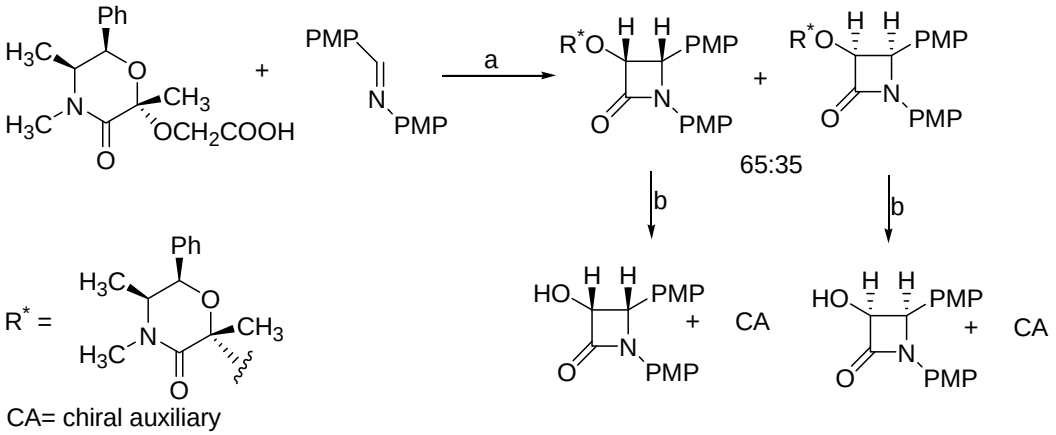
Scheme 4.09



CA = chiral auxiliary

Reagents and conditions: a) $(COCl)_2$, Et_3N, DMAP, CH_2Cl_2; b) CH_3MgI, ether, 1 h; c) NaH, $BrCH_2CO_2Et$, THF+DMF (1:1), 70 °C, 16 h; d) aq. NaOH, THF, 0 °C to rt, 6 h.

Scheme 4.10



CA= chiral auxiliary

Reagents and conditions: a) triphosgene, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h; b) PTSA, THF-H_2O, reflux, 10-12 h.

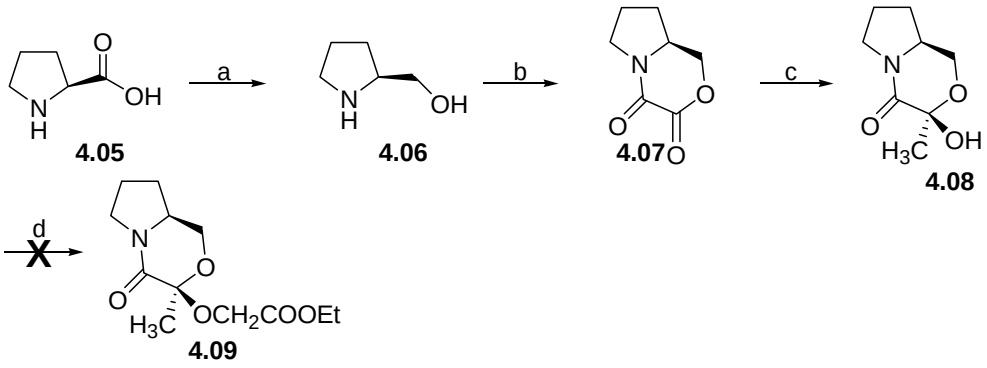
4.9: Present work

L-proline on reduction with LAH yields prolinol which is a highly polar 1,2 amino alcohol. Its structure is quite similar to that of ephedrine. This fact prompted us to apply similar strategy to prolinol and achieve diastereoselective synthesis of β-lactams, which could be further transformed into synthetically important 3-hydroxy β-lactams. We expected that, applying same strategy to prolinol would give us a similar chiral auxiliary, but with a bicyclic skeleton.

4.10: Results and Discussion

We started our work with synthesis of (*S*)-prolinol. Commercially available L-proline (**4.05**) on reduction with LAH afforded (*S*)-prolinol (**4.06**) in very good yield (Scheme 4.11).

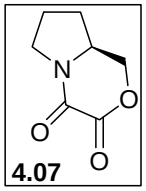
Scheme 4.11



Reagents and conditions: a) LAH, THF, reflux, 3h. b) $(COCl)_2$, DCM, Et_3N, DMAP, 0 °C, 4h. c) CH_3MgI, ether, -20 °C, 2h, d) NaH, $BrCH_2COOEt$, THF-DMF, 70 °C and various other conditions

Prolinol was then cyclized with oxalyl chloride using Et_3N as a base in presence of DMAP to afford compound **4.07**. The reaction was carried out under high dilution conditions.

Compound **4.07** displayed bands at 1691 and 1766 cm^{-1} corresponding to the amide and ester carbonyl respectively. In the ^1H NMR, four protons of two methylene groups (N-CH_2-CH_2-CH_2-CH) of the pyrrolidine ring displayed two multiplets between 1.54-1.68 and 1.97-2.22 ppm. Another multiplet for two protons appeared at 3.60-3.68 ppm, which was assigned to the methylene group bonded to the nitrogen of the ring (N-CH_2). The methylene group attached to the oxygen atom (OCH_2) exhibited a multiplet around 4.13-4.33 ppm, whereas the methine proton (N-C*H*) displayed a multiplet at 4.50-4.57 ppm.



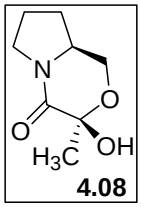
4.07

In the ^{13}C NMR, the two methylene groups (N-CH_2-*C*H_2-*C*H_2-CH) of the pyrrolidine ring displayed peaks at 23.4 and 28.2 ppm. The methylene group attached to the nitrogen atom appeared at 45.4 ppm. The methine carbon was seen at 55.6 ppm. The methylene group attached to the oxygen atom appeared at 70.5 ppm. The two carbonyl carbons displayed peaks at 151.1 and 156.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 156 corresponding to M+1.

Having synthesized the dione, we proceeded with a Grignard reaction on the same. Methyl magnesium iodide was reacted with compound **4.07** in ether as a solvent to obtain compound **4.08**. The ^1H NMR spectrum of compound **4.08** indicated formation of only one diastereomer.

Compound **4.08** exhibited one band at 1635 cm^{-1} corresponding to the amide carbonyl and another broad band centering at 3394 cm^{-1} corresponding to the hydroxy group. In the ^1H NMR, a multiplet for one proton was seen between 1.39-1.54 ppm which was attributed to one of the methylene protons (N-CH_2-CH_2-CH_2-CH) of the rings. The methyl group resonated as a singlet at 1.61 ppm. Three protons from the methylene groups (N-CH_2-CH_2-CH_2-CH) displayed another multiplet between 1.87-2.03 ppm. A set of multiplets clustered together between 3.40-3.95, integrating for six protons. The signals corresponded to two methylene groups (N-CH_2, OCH_2) and the methine proton (NC*H*) with the hydroxy proton buried within.



4.08

In the ^{13}C NMR, the four methylene carbons displayed peaks at 22.7, 28.7, 45.0 and 64.0 ppm, which was confirmed by a DEPT experiment. The methyl group

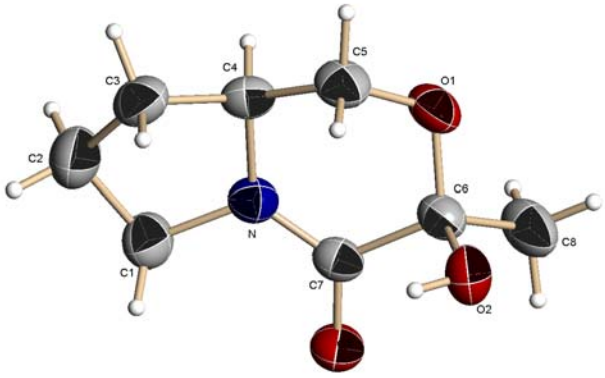
exhibited a peak at 26.0 ppm, whereas the methine carbon appeared at 58.1 ppm. The only quaternary carbon displayed a peak at 94.7 ppm, while the carbonyl carbon resonated at 168.5 ppm.

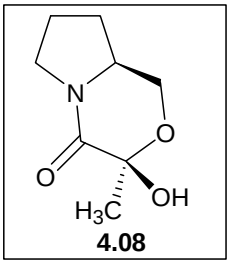
The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 172 corresponding to M+1.

The stereochemistry of the newly generated stereocenter was deduced with the help of single crystal X-ray analysis. The single crystal X-ray analysis revealed that the newly formed stereocenter had absolute configuration '*R*'.

Crystal Data for 4.08 ($C_8H_{13}NO_3$): Single crystals of the compound were grown by slow evaporation of the solution in pet-ether and ethyl acetate. Colourless crystal of approximate size 0.31 x 0.16 x 0.02 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation range = 2.58 to 25.00 º, completeness to of 25.00 º is 100.0 %. $C_8H_{13}NO_3$, M = 171.19. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 9.8250(8) b = 6.6050(5) Å, c = 13.295(1)Å, V = 862.77(12) $Å^3$, Z = 4, D_c = 1.318 g /cc, T = 293(2) K, 4360 reflections measured, 1509 [unique [I>2σ(I)], R value 0.0352, wR2 = 0.0828. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) 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.

X-ray analysis revealed the conformation of the molecule and shows that C-6 has *R* configuration.





4.08

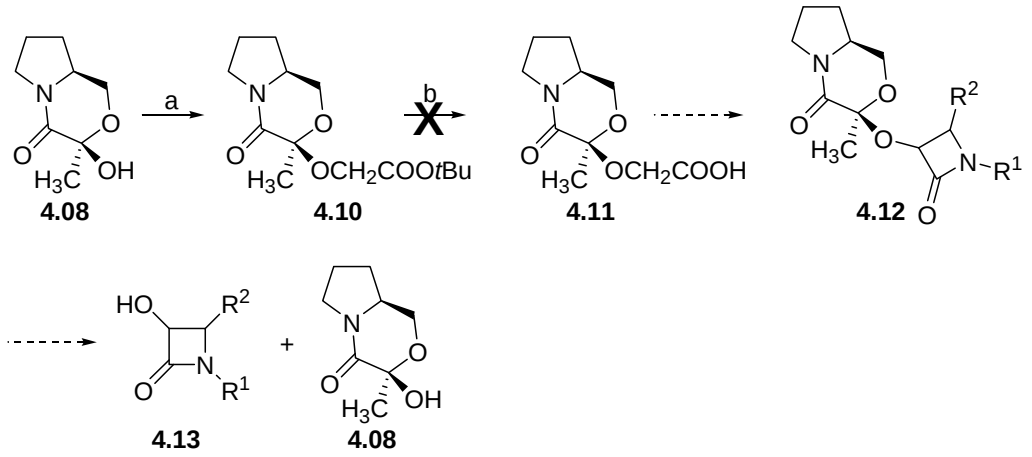
Our next step was to *O*-alkylate compound **4.08** using ethyl bromoacetate to obtain compound **4.09**. We tried alkylation using NaH as a base and ethyl bromoacetate as an alkylating agent in THF as a solvent (Table 1). When reaction was carried out at reflux temperature a very complex reaction mixture was obtained. Changing solvent from THF to a THF-DMF (1:1) mixture and heating at 80°C had no effect, and a similar intractable reaction mixture was obtained. We then tried the reaction in neat DMF at 80 °C, but the reaction met with same fate. Replacing NaH with KH as a base also did not make any difference and we got a very complex mixture.

Table 1. Attempted alkylations of compound **4.08** using ethyl bromoacetate

S.No	**Reagents and Conditions**	**Result**
1.	NaH, THF, $BrCH_2COOEt$, reflux	Complex reaction mixture
2.	NaH, THF-DMF (1:1), $BrCH_2COOEt$, 80 °C	Complex reaction mixture
3.	NaH, DMF, $BrCH_2COOEt$, 80 °C	Complex reaction mixture
4.	KH, THF, $BrCH_2COOEt$, reflux	Complex reaction mixture
5.	KH, DMF, $BrCH_2COOEt$, 80 °C	Complex reaction mixture

We then decided to change the method and tried the alkylation with *t*-butyl bromoacetate as an alkylating agent (Scheme 4.12). We had envisaged that the resultant *t*-butyl ester could be hydrolyzed in acidic medium to obtain the necessary chiral acid as a precursor for β-lactam formation. Accordingly, compound **4.08** was reacted with *t*-butyl bromoacetate in benzene as a solvent and 50% aqueous NaOH as a base in presence of *n*-tetrabutyl ammonium hydrogen sulphate as a phase transfer catalyst. The reaction proceeded cleanly yielding compound **4.10**.

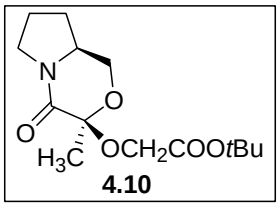
Scheme 4.12



4.08 **4.10** **4.11** **4.12** **4.13** **4.08**

Reagents and conditions: a) $BrCH_2COOtBu$, aq. NaOH, C_6H_6, *n*-Bu_4NHSO_4. b) *p*TSA, C_6H_6 and various other conditions.

Compound **4.10**, in its IR spectrum displayed bands at 1654 and 1751 cm^{-1} corresponding to the amide and ester carbonyl respectively. In the ^1H NMR, nine protons of the *t*-butyl group appeared as a singlet at 1.46 ppm. The methyl group attached to the quaternary stereocenter appeared as a singlet at 1.53 ppm. Four protons of two methylene groups (N-CH_2-CH_2-CH_2-CH) displayed a multiplet between 1.85-2.08 ppm. Another multiplet integrating for five protons appeared at 3.45-3.96 ppm which was attributed to two methylene groups and the methine proton ((N-CH_2, OCH_2, NC*H*). The two protons of the methylene group from the ester moiety exhibited a singlet at 4.08 ppm.



4.10

In the ^{13}C NMR, the carbon atom of the methyl group attached to the quaternary chiral carbon appeared at 21.0 ppm. The two methylene groups (N-CH_2-CH_2-CH_2-CH) of the pyrrolidine ring displayed a peak at 22.6 and 28.8 ppm. The *t*-butyl group displayed a peak at 28.0 ppm. The methylene group attached to the nitrogen atom (NCH_2) appeared at 44.8 ppm. The methine carbon (N-*CH*) appeared at 57.7, whereas the ester methylene group displayed a peak at 60.3 ppm. The methylene group of the six membered ring (OCH_2) appeared at 63.6 ppm. The quaternary carbon of the *t*-butyl group appeared at 81.7 ppm, while the quaternary chiral carbon displayed a peak at 97.8 ppm. The two carbonyl carbons appeared at 165.3 and 168.9 ppm.

The structure was further supported by the mass spectrum which displayed a peak at *m*/*z* 286 corresponding to M+1.

The next step of our plan was hydrolysis of the *t*-butyl ester **4.10** to get acid **4.11**. We tried the reaction with PTSA as an acidic catalyst in benzene under reflux conditions,[11] but, unfortunately, the reaction afforded a very complex reaction mixture. To our dismay, other acidic catalysts like formic acid, trifluoroacetic acid also failed to deliver the desired acid **4.11**.

We had planned to use this acid as a precursor for β-lactam **4.12**. Acid **4.11**, on reaction in dichloromethane, with an imine, in presence of a suitable acid activator like triphosgene[12] and triethyl amine as a base would have yielded β-lactam **4.12**. We had envisioned that β-lactam **4.12** on acid treatment in presence of water would have undergone hydrolysis to yield 3-hydroxy β-lactam **4.13**, along with the recovered chiral auxiliary **4.08**.

4.11: Conclusion

In conclusion, attempts were made towards synthesis of a proline derived reusable chiral auxiliary for the synthesis of 3-hydroxy β-lactams.

4.12: Experimental

4.12.1 (*S*)-Pyrrolydin-2-yl methanol (Prolinol) (4.06):

In a round bottomed flask, LAH (1.026g, 27.13 mmol) was taken and anhydrous THF (30 mL) was added to it to form an emulsion. It was then heated to reflux. To this refluxing emulsion was added L-Proline (2.0g, 17.39 mmol) in a portion wise manner. After the addition was complete, the reaction mixture was kept refluxing for 3h. The reaction was then quenched with aqueous NaOH solution. After NaOH addition was complete, the solution was again refluxed for 15 min. to avoid formation of solid mass of reaction mixture. The quenched reaction mixture was then filtered in hot condition and the residue was washed with THF. The combined filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford compound **4.06** as a colorless liquid (1.71g, 97%). The compound was used as such for next step.

4.12.2 (*S*)-Tetrahydro-pyrrolo[2,1-c][1,4]oxazine-3,4-dione (4.07):

Prolinol (**4.06**) (0.200g, 1.980 mmol) was dissolved in anhydrous DCM (30 mL). To this solution, after cooling to 0 °C, was added triethyl amine (1.10 mL, 7.92 mmol), DMAP (0.0121g, 0.099 mmol). Through an addition funnel was then added, a solution of oxalyl chloride (0.259 mL, 2.97 mmol) in anhydrous DCM (10 mL), slowly over a period of 3 h. It was stirred for an additional hour. After that, the solution was washed with water and the organic layer was concentrated *in vacuo* to get crude **4.07** as a viscous, dark liquid. The crude compound was purified with flash column chromatography (80% ethyl acetate-pet. ether) to obtain pure compound **4.07** (0.153g, 50%) as a viscous semisolid.

IR ($CHCl_3$) : 1691, 1766 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.54-1.68 (1H, m, N-CH_2-C*H*$_2$-C*H*$_2$-CH), 1.97-2.22 (3H, m, N-CH_2-C*H*$_2$-C*H*$_2$-CH), 3.60-3.68 (2H, m, N-C*H*$_2$), 4.13-4.33 (2H, m, OC*H*$_2$), 4.50-4.57 (1H, m, NC*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : 23.4, 28.2, 45.4, 55.6, 70.5, 151.1, 156.9.

MS (m/z) : 156 (M+1)

Analysis $C_7H_9NO_3$: Calculated: C, 54.19; H, 5.85; N, 9.03%.

Observed: C, 54.33; H, 5.71; N, 9.10%.

4.12.3 3-Hydroxy-3-methyl-tetrahydro-pyrrolo[2,1-c][1,4]oxazin-4-one (4.08):

To a solution of dione **4.07** (0.200g, 1.29 mmol) in anhydrous ether was added at -20 °C, solution of methyl magnesium iodide (1.07g, 6.45 mmol) in anhydrous ether. The reaction was kept stirring at -20 °C for 2h (TLC). After 2h, the reaction was quenched with aq. NH_4Cl at the same temperature. The reaction mixture was diluted with ethyl acetate (15 mL) and washed successively with water (3 x 5 mL) and brine (10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound **4.08**. The crude compound was purified by flash column chromatography (60% ethyl acetate pet. ether) to furnish pure **4.08** (0.143g, 65%) as a white solid.

IR ($CHCl_3$) : 1635, 3394 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.39-1.54 (1H, m, N-CH_2-C*H*$_2$-C*H*$_2$-CH), 1.61 (3H, s, CH_3), 1.87-2.03 (3H, m, N-CH_2-C*H*$_2$-C*H*$_2$-CH), 3.40-3.95 (6H, m, NC*H*$_2$, OC*H*$_2$, NC*H*, O*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : 22.7, 26.0, 28.7, 45.0, 58.1, 64.0, 94.7, 168.5

MS (m/z) : 172 (M+1)

Analysis $C_8H_{13}NO_3$: Calculated: C, 56.13; H, 7.65; N, 8.18%.
Observed: C, 56.02; H, 7.53; N, 8.37%.

Optical rotation : $[\alpha]^{30}_D = 20$ (*c* 0.1, $CHCl_3$)

4.12.4 (3-Methyl-4-oxo-hexahydro-pyrrolo[2,1-c][1,4]oxazin-3-yloxy)-acetic acid tert-butyl ester (4.10):

Compound **4.08** (0.072g, 0.42 mmol), was dissolved in benzene and aq. NaOH (2 mL, 50%) and tetra-*n*-butyl ammonium hydrogen sulphate (0.071g, 0.21 mmol) was added to it. The resultant emulsion was stirred for 15 min. After that, tertiary butyl bromoacetate (0.186 mL, 1.26 mmol) was added quickly in drop wise manner and the reaction was left stirring for a period of 4 h (TLC). Ethyl acetate (10 mL) was then added to the reaction mixture and it was washed with water (3 x 5 mL), followed by

brine (10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish crude **4.10**. The crude product was purified by flash column chromatography (40% ethyl acetate-pet. ether) to afford pure **4.10** (0.102g, 85%) as a colorless liquid.

IR ($CHCl_3$)	**:**	1654, 1751 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.46 (9H, s, $C(CH_3)_3$), 1.53 (3H, s, CH_3), 1.85-2.08 (4H, m, $N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH$), 3.45-3.96 (5H, m, NCH_2, OCH_2, NCH), 4.08 (2H, s, OCH_2)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	21.0, 22.6, 28.0, 28.8, 44.8, 57.7, 60.3, 63.6, 81.7, 97.8, 165.3, 168.9
MS (m/z)	**:**	286 (M+1)
Analysis $C_{14}H_{23}NO_5$	**:**	Calculated: C, 58.93; H, 8.12; N, 4.91%. Observed: C, 58.80; H, 8.15; N, 5.02%.
Optical rotation	**:**	$[\alpha]^{30}_D$ = -2.8 (*c* 4.2, $CHCl_3$)

CHAPTER 4
SECTION C
STUDIES TOWARDS SYNTHESIS OF SOME NOVEL PHOSPHORUS CONTAINING AZETIDIN-2-ONES FROM DIPHENYL PHOSPHINIC ACID DERIVED IMINES.

4.13: Introduction

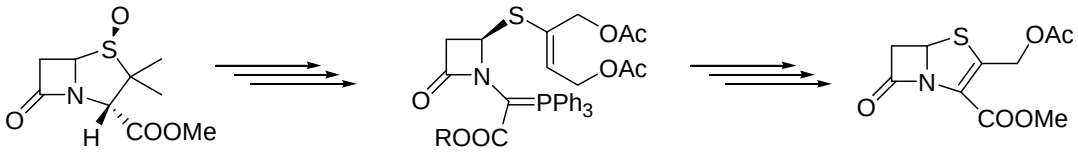
This section of the Chapter 4 deals with our attempts towards synthesis of some novel phosphorus containing azetidin-2-ones, from diphenyl phosphinic acid derived imine.

4.14: Background for the present work

Phosphorus containing β-lactams are comparatively less explored class of β-lactams. There are a few reports in which such phosphorus containing β-lactams have been used as synthetic intermediates.

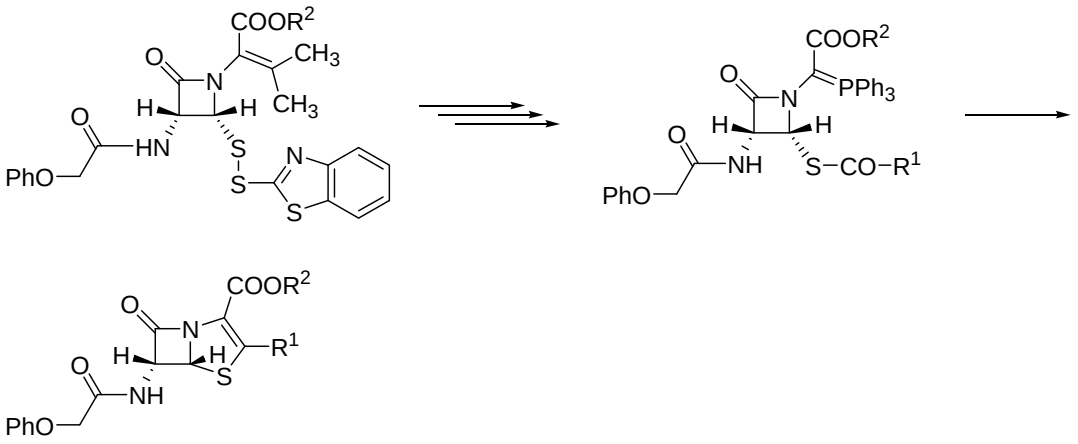
Franceschi *et al*. have reported a synthesis of optically active (5*R*)-2-acetoxymethyl-2-penem-3-carboxylates; a class of penems, from (5*R*)-methylpenicillanate *S*-oxide *via* a phosphorus substituted β-lactam (Scheme 4.13)[13].

Scheme 4.13



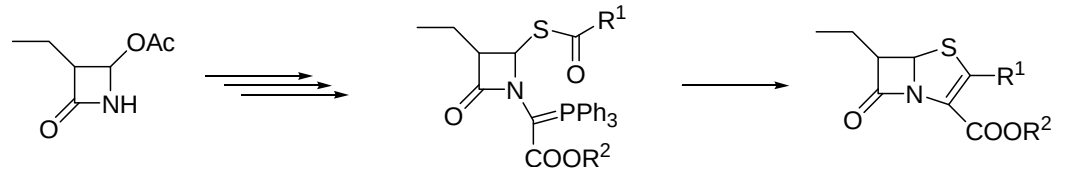
Prof. R. B. Woodward and group have also reported a synthesis of penem class of compounds using substituted β-lactams having a phosphorane moiety, as an intermediate (Scheme 4.14).[14]

Scheme 4.14



Another similar report by Lombardi *et al*. describes synthesis of 2-penems using a substituted β-lactams having a phosphorane moiety as an intermediate (Scheme 4.15).[15]

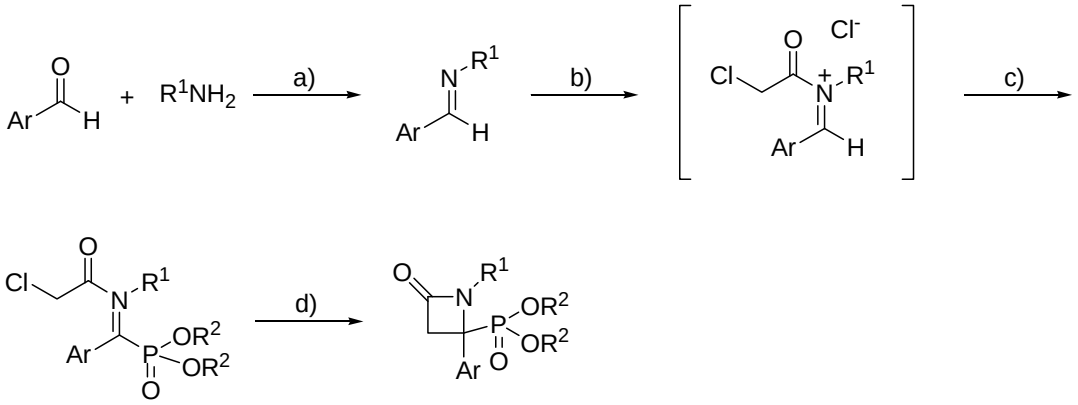
Scheme 4.15



Apart from use of phosphorus containing β-lactams as intermediates, there are a few reports which deal with the synthesis of β-lactams having a different phosphorus containing groups as substituents on the lactam ring.

Stevens *et al*. have reported a synthesis of 4-aryl-4-phosphono-β-lactams by acylation of iminium salts with chloroacetyl chloride followed by phosphite addition and ring closure using sodium hydride as a base (Scheme 4.16).[16]

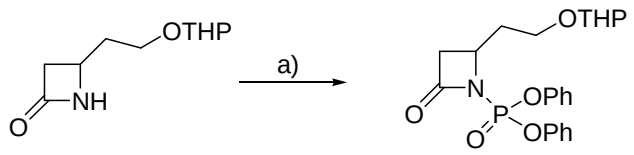
Scheme 4.16



Reagents and conditions: a) $MgSO_4$, DCM; b) $ClCH_2COCl$; c) $P(OR^2)_3$; d) NaH, THF

In yet another report, Just *et al*. describe synthesis of *N*-phosphorylated β-lactams in their report on the synthesis of bicyclic β-lactams (Scheme 4.17).[17]

Scheme 4.17



Reagents and conditions: a) n-BuLi, THF, diphenylchlorophosphate, -78 °C

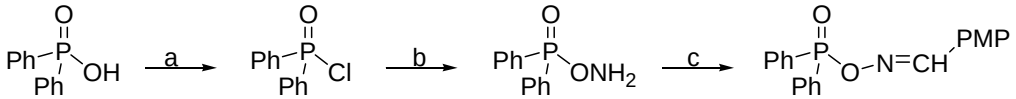
4.15: Present work

We were interested in synthesizing phosphorus containing β-lactams as a part of our research program of synthesis of novel β-lactams. We envisioned that starting with a phosphorus containing imine would give us the desired β-lactam, having a phosphorus containing substituent on the nitrogen atom of the β-lactam. We had also planned to attempt transformation of so obtained β-lactam into an *N*-unsubstituted β-lactam. With this in mind we planned the synthesis of an imine starting with diphenyl phosphinic acid. To best of our knowledge, there is no literature report which describes a synthesis of β-lactams starting with a phosphorus containing imine.

4.16: Results and Discussion

We started the scheme with diphenyl phosphinic acid. Commercially available diphenyl phosphinic acid (**4.14**) was transformed into corresponding acid chloride (**4.15**) by refluxing it with thionyl chloride, which is a reported procedure (Scheme 4.18).[18] Diphenyl phosphinic chloride (**4.15**) was then converted into *O*-(diphenylphosphinyl) hydroxylamine (**4.16**) using a reported method wherein compound **4.16** was treated with hydroxyl amine hydrochloride.[19] Having prepared compound **4.16**, we then planned to synthesize an imine from it. Thus, compound **4.16** on reaction with *p*-anisaldehyde in presence of anhydrous magnesium sulphate as a dehydrating agent yielded imine **4.17** in good yield.

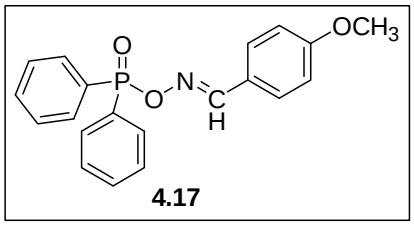
Scheme 4.18



4.14 **4.15** **4.16** **4.17**

Reagents and conditions: a) $SOCl_2$, C_6H_6, reflux, 2h. b) $NH_2OH.HCl$, aq. NaOH,dioxane, 0 °C, 1h. c) *p*-anisaldehyde, anh. $MgSO_4$, DCM, rt, 20h.

Imine **4.17** was characterized using spectral and analytical techniques. The IR spectrum of imine **4.17** displayed peak at 1683 cm^{-1}. In ^{1}H NMR, the protons of the methoxy group resonated as a singlet at 3.79 ppm. The two protons *ortho* to the methoxy group of the PMP ring appeared as a doublet (J = 8.9 Hz) at 6.88 ppm. A multiplet integrating for thirteen protons was seen from 7.29-7.72 ppm. The multiplet corresponded to remaining twelve aromatic protons along with the imine proton (N=C*H*) buried within.

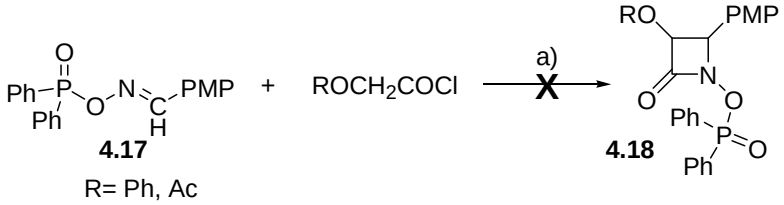


4.17

In ^{13}C NMR spectrum, the methyl carbon from the PMP moiety appeared at 55.3 ppm. A set of seven peaks corresponding to aromatic carbons appeared as a cluster from 114.0-133.7. The quaternary aromatic carbon bearing the methoxy substituent in the PMP ring appeared at 157.7 ppm. The sp^2 imine carbon (H*C*=N) appeared at 164.4 ppm.

With the imine in hand, we proceeded further with our attempts to synthesize β-lactams using the imine. We first tried the reaction with phenoxy acetyl chloride as a ketene precursor, in presence of triethyl amine as a base (Scheme 4.19). The addition of acid chloride to the mixture of imine and triethyl amine in DCM was carried out at -40 °C (Table 1). The reaction, however, yielded no β-lactam product (**4.18**) and the imine was recovered.

Scheme 4.19



4.17 **4.18**

R= Ph, Ac

Reagents and conditions: a) Et_3N, DCM, -40 °C; and various other conditions

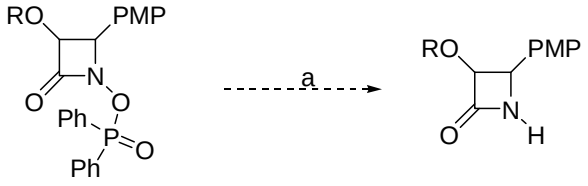
We then tried the same reaction altering the temperature of addition to 0 °C. Even then the β-lactam formation wasn't observed. We tried various things like changing the acid chloride, temperature of addition, base etc., but β-lactam formation still wasn't observed. The results are summarized in Table 1.

Table 1. Attempts made towards synthesis of β-lactams from imine **4.17**

S. no	Starting acid chloride	Base	Solvent	Temperature of addition (°C)	Result
1.	$PhOCH_2COCl$	Et_3N	DCM	-40	No reaction
2.	$PhOCH_2COCl$	Et_3N	DCM	0	No reaction
3.	$PhOCH_2COCl$	Hünig's base	DCM	0	No reaction
4.	$AcOCH_2COCl$	Et_3N	DCM	-40	No reaction
5.	$AcOCH_2COCl$	Et_3N	DCM	0	No reaction

It is known that compound **4.16**, from which we derived our imine **4.17**, is used for electrophilic *C*-amination.[19] It reacts with carbanions and nucleophiles like certain Grignard reagents to *C*-aminate them. Thinking along same lines, we envisaged that the β-lactam derived from imine **4.17** would react with a hydride-reducing agent like sodium borohydride to yield *N*-unsubstituted β-lactam **4.19** (Scheme 4.20). *N*-unsubstituted β-lactams constitute a class of β-lactams which are useful synthons.[20]

Scheme 4.20



4.18 **4.19**

Reagents and conditions: a) $NaBH_4$, MeOH.

4.17: Conclusion

In conclusion, synthesis of phosphorus containing β-lactams was attempted starting with diphenyl phosphinic acid. The imine could be synthesized in good yield, but success in formation of the β-lactam remained elusive.

4.18: Experimental

4.18.1 Diphenyl phosphinyl chloride (4.15):

Diphenyl phosphinic acid (2g, 9.16 mmol) and thionyl chloride (1.33 mL, 18.33 mmol) were dissolved in benzene. The resultant solution was refluxed for 2h. The reaction mixture was then cooled and the volatiles were removed under reduced pressure to obtain crude diphenyl phosphinic chloride which was used as such, without any further purification.

4.18.2 *O*-(Diphenylphosphinyl) hydroxylamine (4.16):

To a stirred aqueous solution of hydroxylamine hydrochloride (6.6M, 25.09 mmol) was added aqueous sodium hydroxide (7.1M, 21.25 mmol), followed by dioxane (12 mL). The resulting solution was cooled in an ice-salt bath, and freshly distilled diphenyl phosphinyl chloride (**4.15**) (2.16g, 9.16 mmol) in dioxan (10 mL) was added in one portion with vigorous stirring. Stirring was continued for 4 min. as copious precipitation ensued. Water (36-40 mL) was added, and the slurry filtered. After drying *in vacuo* (P_2O_5, 3h), the crude product was obtained. This material was purified by stirring with aqueous sodium hydroxide (0.25M, 20 mL) at 0 °C for 30 min, followed by filtration and drying as above, which afforded pure compound **4.16** (1.1g, 52%) as a white solid.

4.18.3 (4-methoxy-benzylidine)-*O*-(Diphenylphosphinyl) hydroxylamine (4.17):

Compound **4.16** (0.200g, 0.858 mmol) and *p*-anisaldehyde (0.117g, 0.858 mmol) were dissolved in DCM (5 mL). To this solution was added anhydrous $MgSO_4$ (2g). The resultant emulsion was stirred at room temperature for 20 h. After this, the solution was filtered and residue was washed with DCM. Combined filtrate and washings were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford crude imine as a colorless semi solid. Crude compound was passed through a short silica gel column (15% ethyl acetate-pet. ether) to obtain pure imine **4.17** (0.18g, 60%) as a colorless semisolid.

IR ($CHCl_3$)	**:**	1683 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	3.79 (3H, s, OCH_3), 6.88 (2H, d, J = 8.9 Hz, Ar), 7.29-7.72 (13H, m, N=C*H*, Ar)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	55.3, 114.0, 114.1, 121.9, 129.6, 130.4, 131.7, 133.7, 157.7, 164.4

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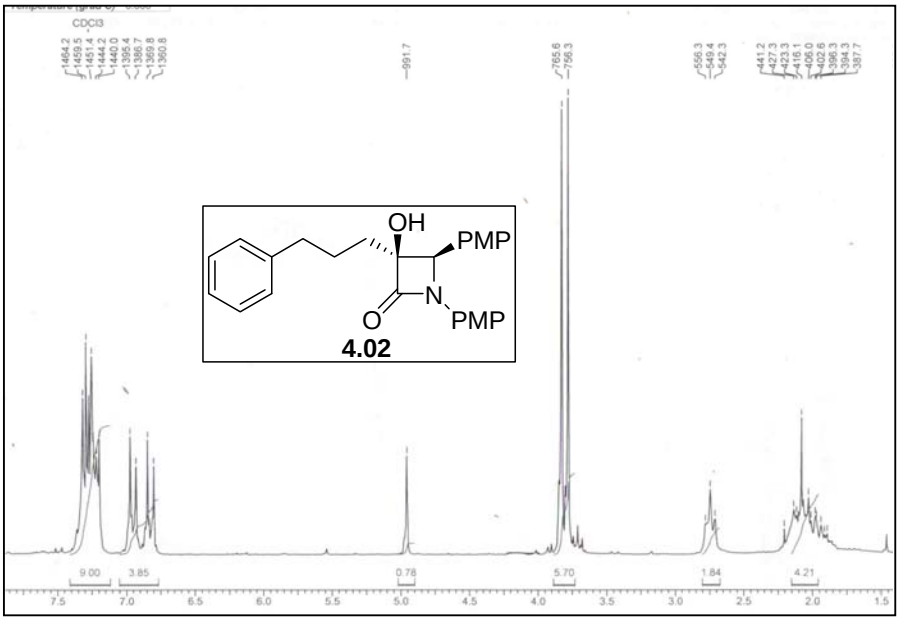
Chapter 4

Spectra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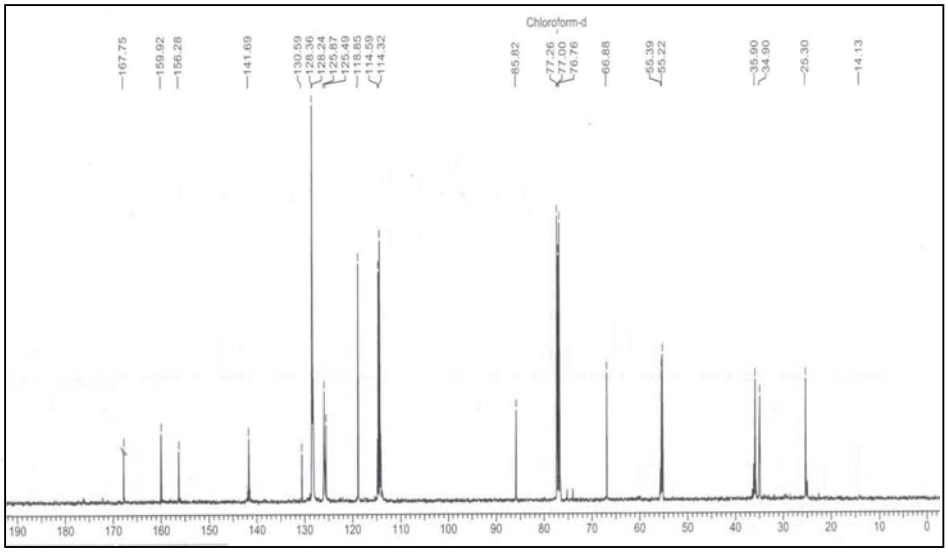
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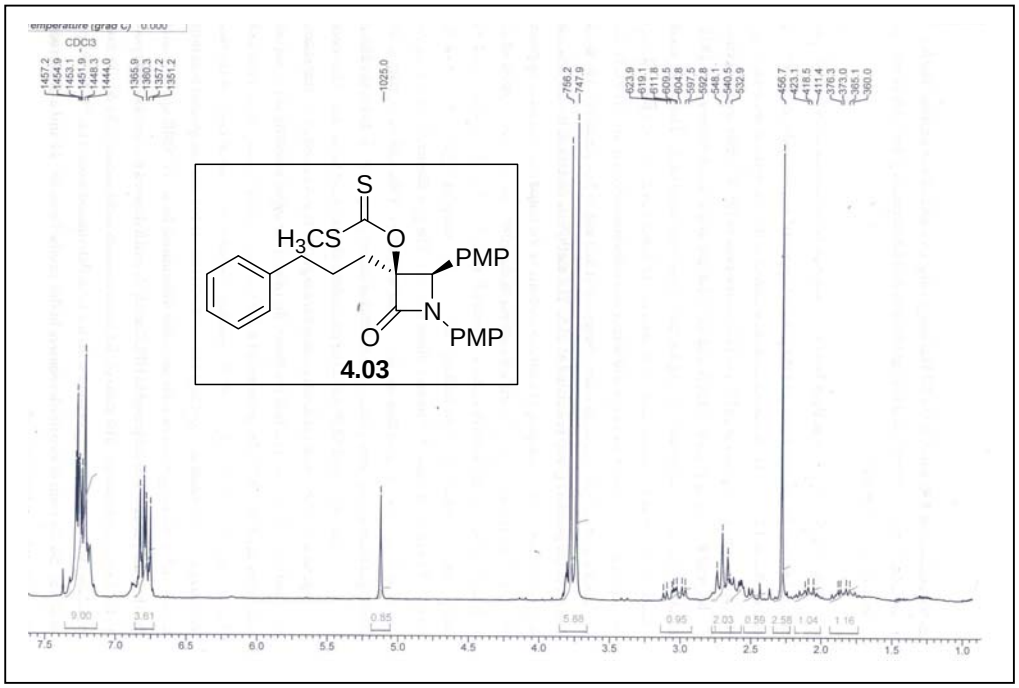
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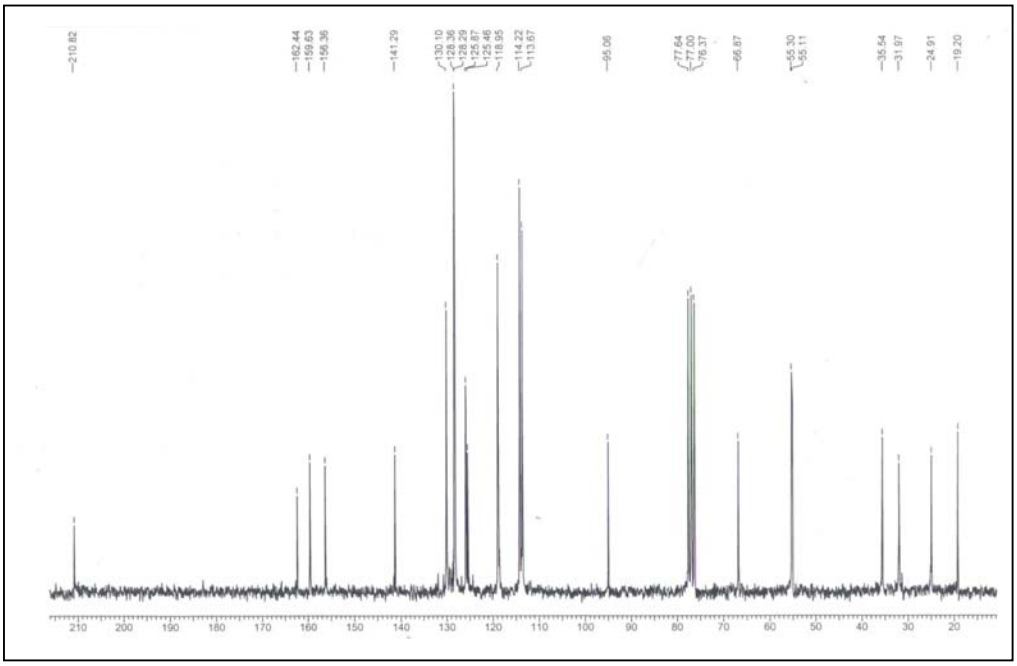
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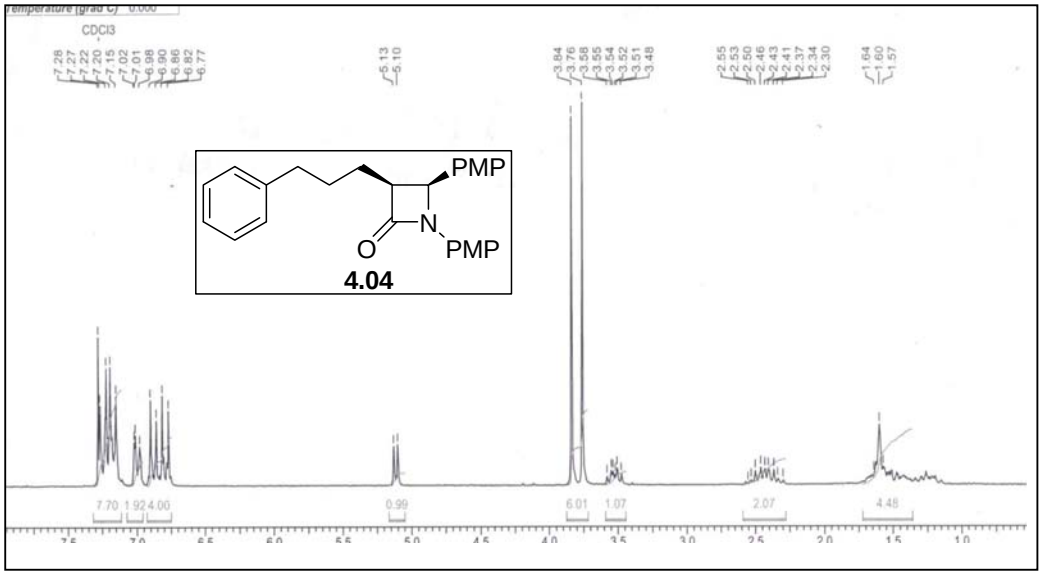
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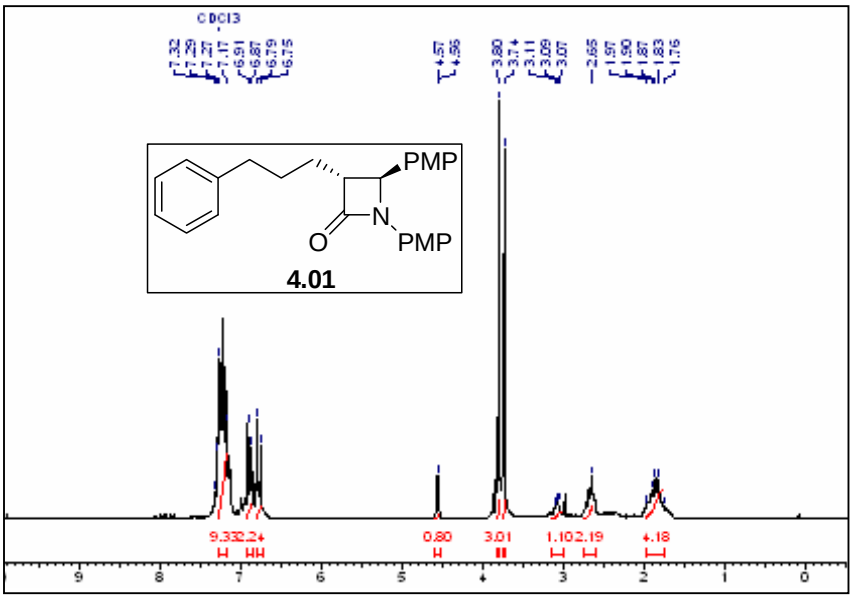
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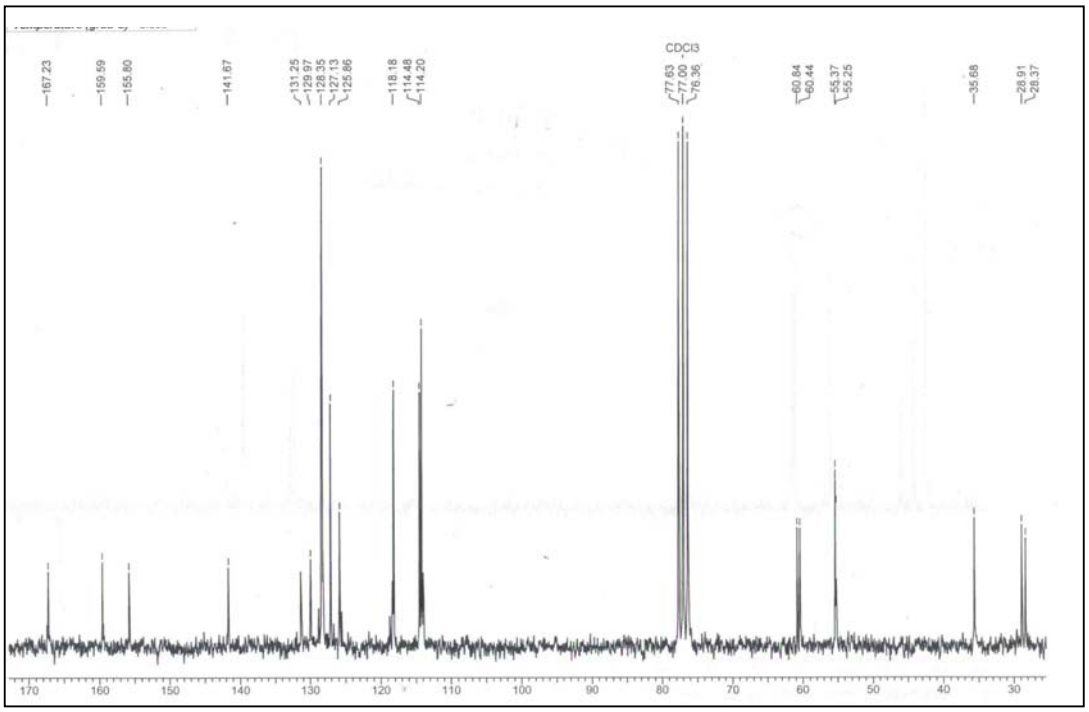
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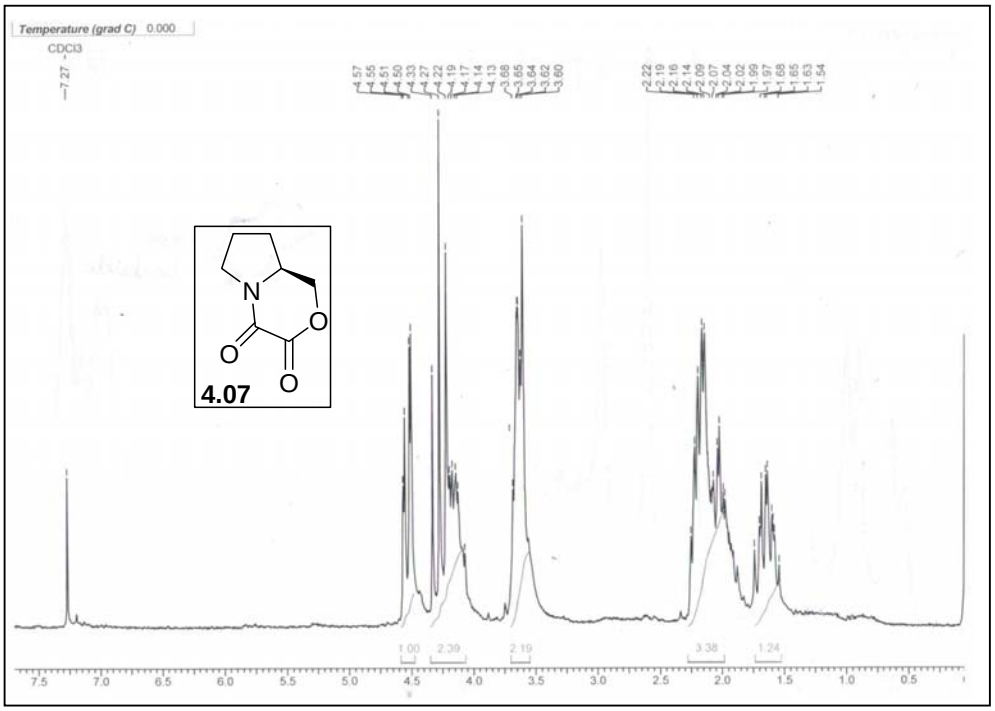
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2.16
2.14
2.09
2.07
2.04
2.02
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O
O
O
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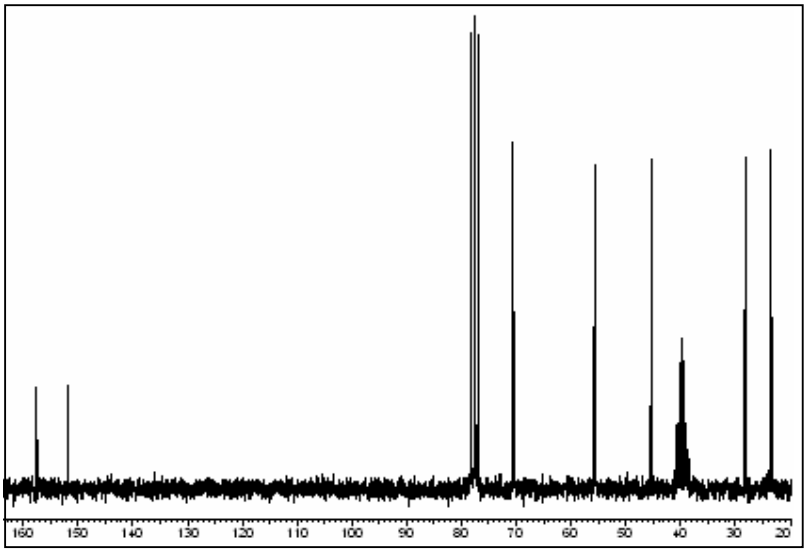
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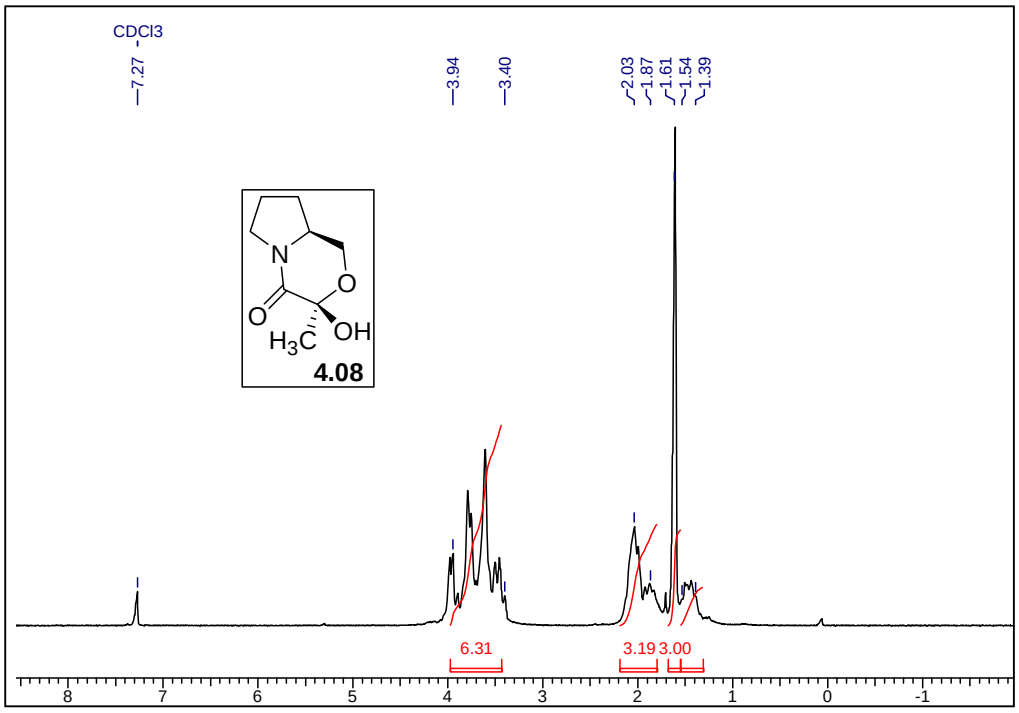
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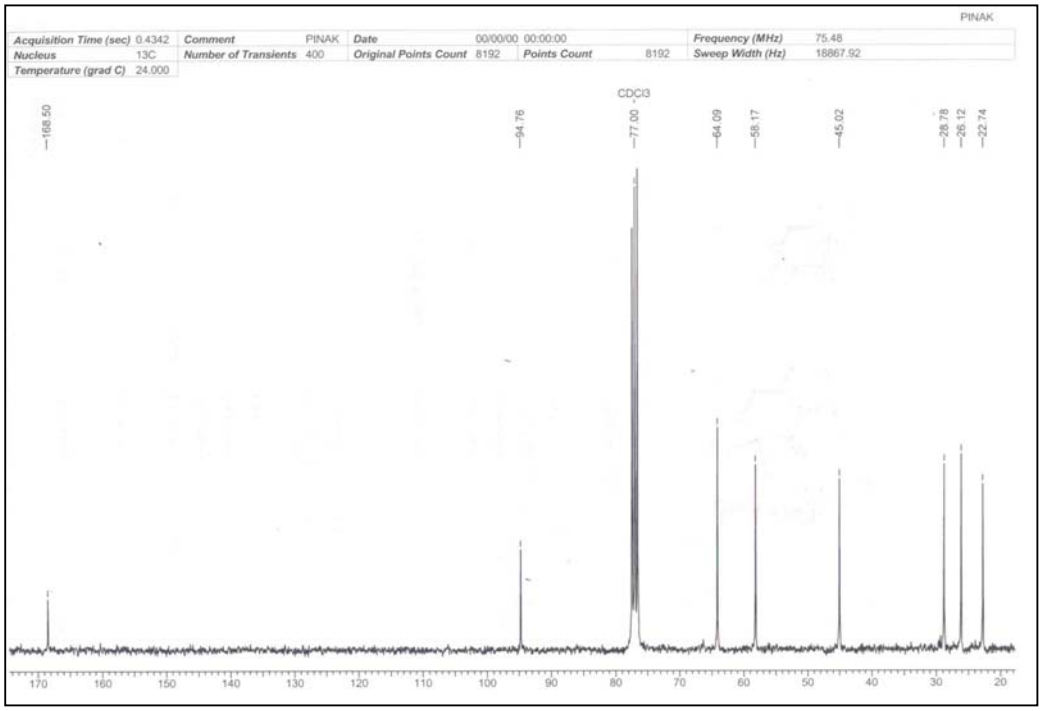
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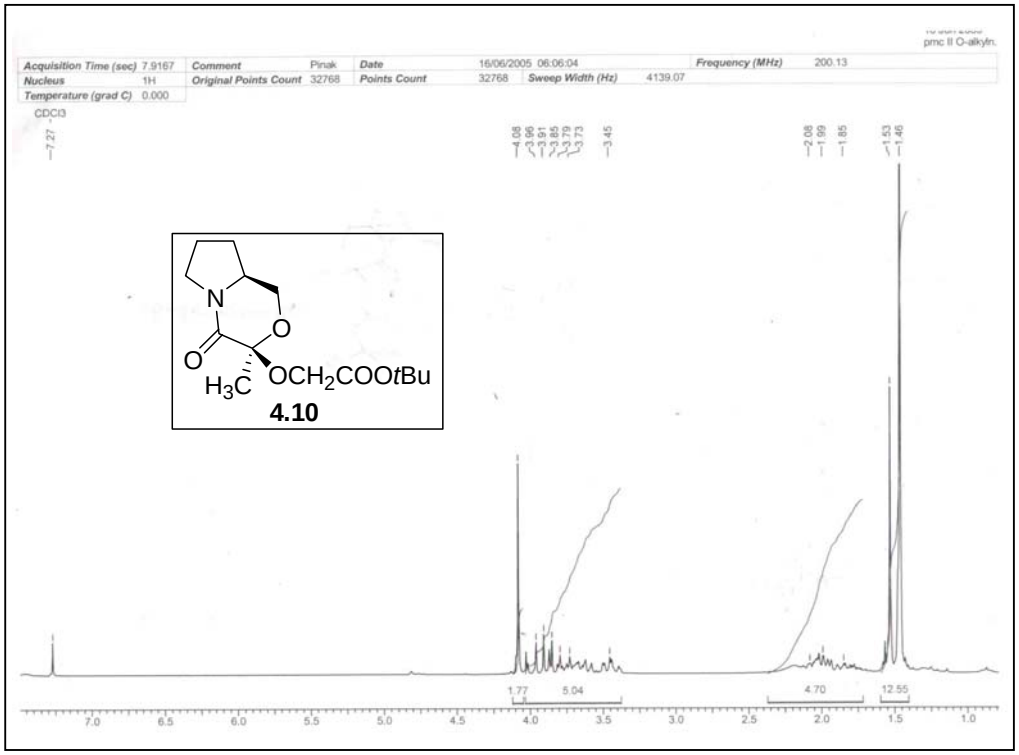
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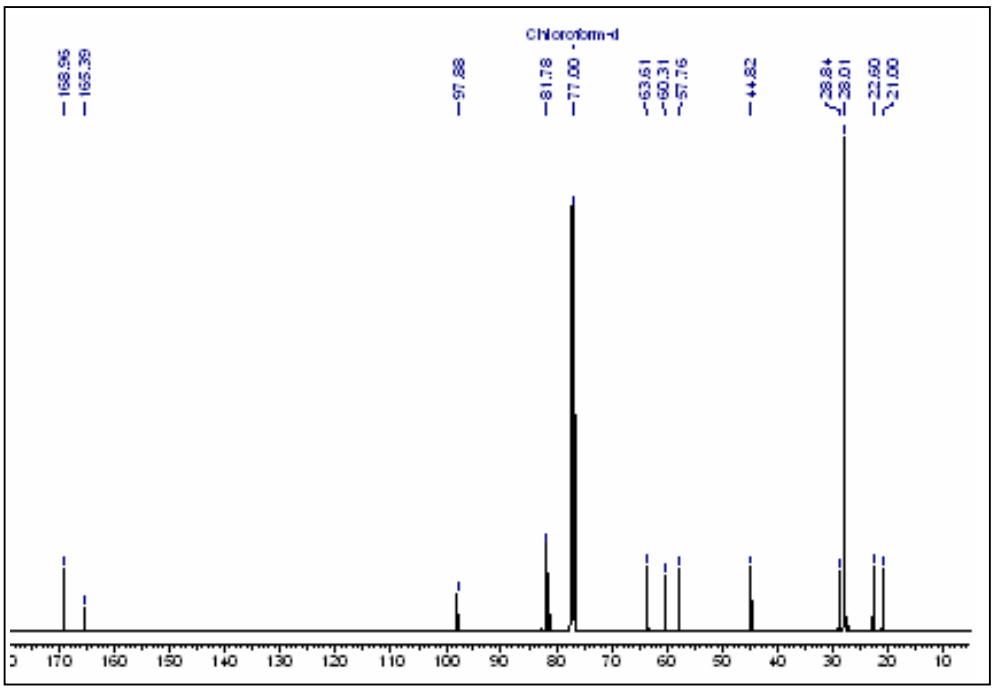
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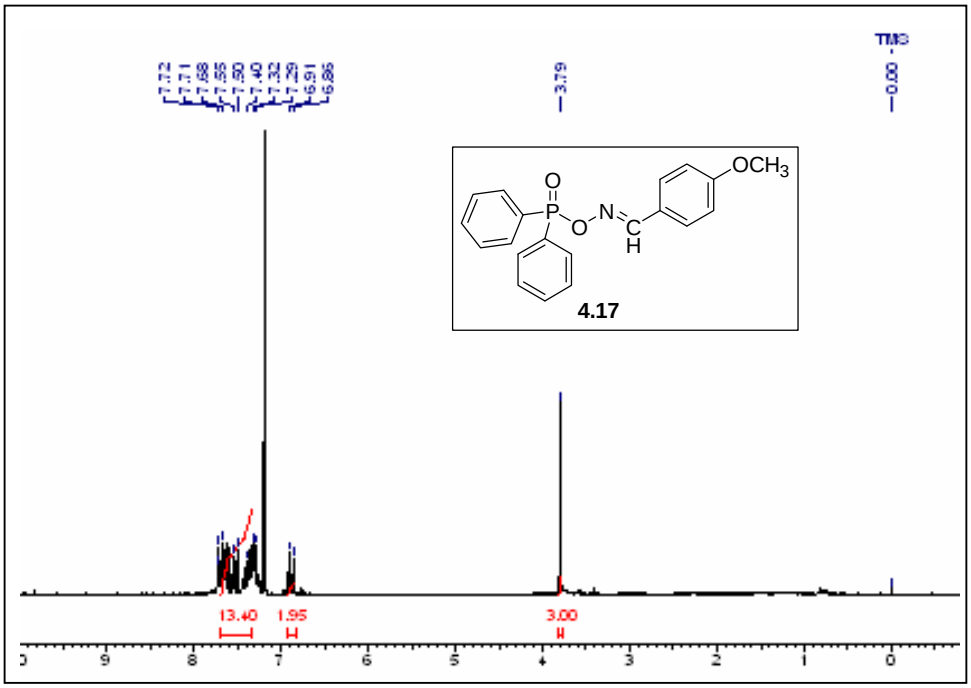
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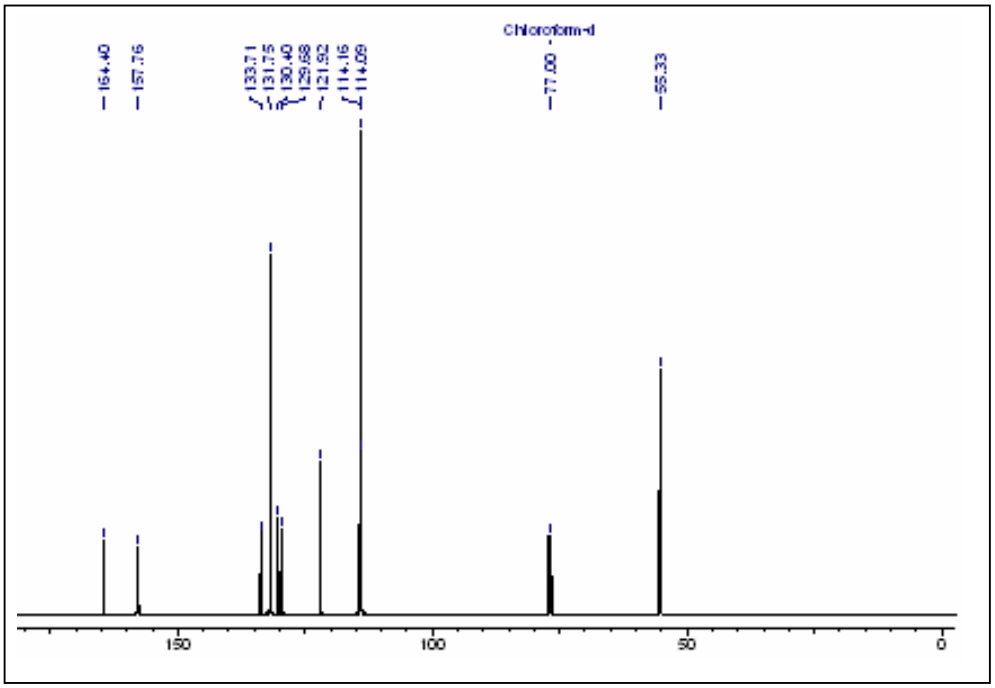
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List of publications

1. Stereoselective synthesis of spiro-β-lactams using D-(+)-glucose derived chiral pool: Remarkable influence of the torquoelectronic effect
   P. M. Chincholkar, Vedavati G. Puranik, A. R. A. S. Deshmukh *Tetrahedron*, **2007**, *63*, 9179.

2. An efficient synthesis of azetidin-2,3-diones from L-(+)-diethyl tartrate
   P. M. Chincholkar, Vedavati G. Puranik, A. R. A. S. Deshmukh *Synlett*, **2007**, *14*, 2242.

3. An efficient formal synthesis of (*S*)-dapoxetine from enantiopure 3-hydroxy azetidin-2-one
   P. M. Chincholkar, A. S. Kale, V. K. Gumaste, A. R. A. S. Deshmukh *Tetrahedron* (in press).

4. Stereoselective synthesis of Sch 48461, a cholesterol absorption inhibitor, from substituted azetidin-2,3-dione
   P. M. Chincholkar, V. K. Gumaste, A. R. A. S. Deshmukh (manuscript under preparation).

Errata