STUDIES IN STEREOSELECTIVE SYNTHESIS OF SUBSTITUED AZETIDIN-2-ONES

BY

AARIF LATIF SHAIKH

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

RESEARCH GUIDE

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DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

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A THESIS

SUBMITTED TO THE

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Dedicated to
My Grandmother

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Studies in Stereoselective Synthesis of Substituted Azetidin-2-ones"** submitted by Mr. Aarif Latif Shaikh 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: .06.2007

National Chemical Laboratory
Pune 411 008

Dr. A. R. A. S. Deshmukh
Research Guide

DECLARATION

I hereby declare that the work incorporated in the thesis entitled "**Studies in Stereoselective Synthesis of Substituted Azetidin-2-ones**" submitted for the degree of Doctor of Philosophy 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: .06.2007

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(Aarif L.shaikh)

CONTENTS

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell 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 FT-IR and ATI Mattason, UK, Model-RS-1 FT-IR, 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 MSL-300, Bruker AC-200 and DRX-500. Chemical shifts were recorded in parts per million (δ). Abbreviations, viz., s = singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300 and Bruker DRX-500 instrument operating at 50 MHz, 75 MHz and 125 MHz.
5. Elemental analysis (C, H, N) was obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Optical rotation was 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 and electron spray ionization method (EI).
8. The progress of the reaction was monitored by analytical thin layer chromatography plates pre-coated with silica gel 60 F_{254} (Merck). Column purification of diastereomeric mixture of β-lactams was carried out with silica gel obtained from Merck (230-400 mesh, 9385 grade and 100-200 mesh) under nitrogen pressure.
9. ^{1}H NMR and ^{13}C NMR spectra of the compounds are attached at the end of the corresponding parts. For all the samples containing methylene and quaternary carbons DEPT spectrum was scanned after scanning ^{13}C NMR spectrum and then the assignment of the peaks in ^{13}C NMR was done.
10. Known compounds were characterized by IR and proton NMR spectroscopy.
11. Petroleum ether refers to the fraction boiling between 60-80 °C.

12. Solvents for chromatography were distilled at their respective constant boiling points.
13. All reactions requiring anhydrous conditions were performed under a positive pressure of Argon using oven-dried glassware (120 °C), which was cooled under nitrogen.
14. Dichloromethane was dried over anhydrous P_2O_5 and stored over 4Å molecular sieves. Ether, THF and dioxane were distilled over sodium benzophenone ketyl.
15. All other solvents were dried following the procedure given in the book "Purification of Laboratory Chemicals" by Armarego and Perin (third edition).
16. Compounds have been named based on nomenclature provided by Chem Draw software.

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azabisisobutyronitrile ($Me_2C(CN)N=N(CN)CMe_2$
BF_3	Boron trifluoride
Bn	Benzyl
Boc	*t*-butoxy carbonyl
Bu_3SnH	Tributyltin hydride
$C_6H_5CH_3$	Toluene
C_6H_6	Benzene
CCl_4	Carbon tetrachloride
COSY	2D-Correlation spectroscopy
CSI	Chlorosulphonyl isocyanate
d	Day(s)
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
ee	Enantiomeric excess
Equiv.	Equivalent(s)
g	Gram(s)
h	Hour(s)
HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide

LUMO	Lowest unoccupied molecular orbital
Me_3SiN_3	Trimethylsilyl azide
mg	Milli gram(s)
mL	Milli litre(s)
mmol	Milli mole(s)
mp	Melting point
MS	Mass spectrum
Ms	Methanesulfonyl
MW	Microwave
NOESY	2D-Nuclear Overhauser Enhancement spectroscopy
Ph	Phenyl
Phth	Phthalimido
PPh_3	Triphenylphosphine
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBS	Tertiarybutyldimethylsilyl
t-Bu	Tertiary butyl
TEA	Triethyl amine
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMANO	Trimethylamine N-oxide
TMSCl	Trimethylsilyl chloride

Abstract of the thesis

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

Name of student: **Mr. Aarif L. Shaikh**

Name of Research Guide: **Dr. A. R. A. S. Deshmukh**

Abstract of thesis entitled: **"Studies in Stereoselective Synthesis of Substituted Azetidin-2-ones**"

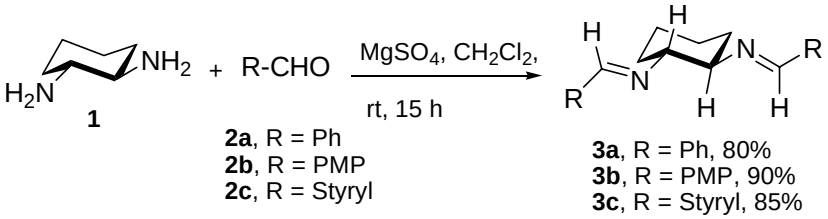
Chapter I

Section A: Stereoslective Synthesis of bis-β-lactams *via* Staudinger cycloaddition reaction

β-Lactams are important part structure of biologically important antibiotics. Also β-lactams has been recognized as a useful precursor to various non-β-lactam derivatives. Although large numbers of β-Lactams derivatives are available this area still attracts many synthetic chemists for the development of new methods and new derivatives. This is mainly due to the fact the bacteria develops resistance to the existing β-lactams antibiotics. The objective of the present investigation was to synthesize bis-β-lactams from ketenes and 1,2 vicinal bisimine using the Staudinger cycloaddition reaction. The Staudinger cycloaddition reaction has distinct advantage over the other methods of construction β-lactams ring. This reaction is operationally simple and large number of imines as well as ketenes can be easily prepared.

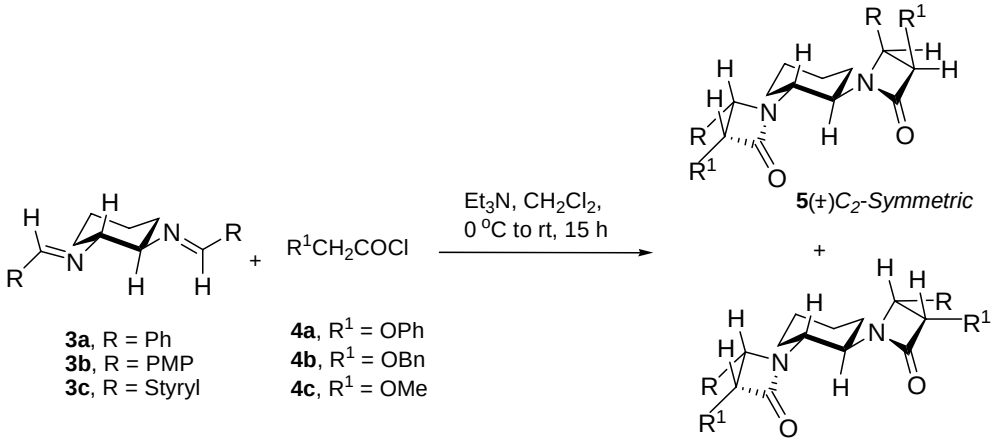
Bis-β-lactams are very useful building block for the synthesis of peptides. Bis-β-lactams serves as an important intermediate for the synthesis of synthetically useful compounds like bis-azetidines, enantiometrically pure diamines, aminoalcochol, polyaminoalcohols, polyaminoethers and polyamines.

Scheme 1



An efficient stereoselective synthesis of *cis*-bis-β-lactams has been achieved in one step by the reaction of bisimines derived from (±) *trans*-1,2-diaminocyclohexane and ketenes. These bis-imines **3a-c** have been easily prepared from aldehyde and (±) *trans*-1,2-diaminocyclohexane as shown in Scheme-1. Bisimines **3a**–**c** on Staudinger reaction cycloaddition reaction with ketenes generated from various acid chlorides in the presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-bis-β-lactams **5a**–**i** and **6a**–**i** in good to excellent yields (Scheme-2). These diastereomers were separated by flash column chromatography. Higher selectivity was observed for *meso* bis-β-lactam **6a** as compared to C_2-symmetric bis-β-lactam **5a** (66:34). The C_2-symmetric bis-β-lactam **5a** and *meso* bis-β-lactam **6a** were established by spectral data and single crystal X-ray analysis (Fig. 1, 2).

Scheme 2



3a, R = Ph
3b, R = PMP
3c, R = Styryl

4a, R^1 = OPh
4b, R^1 = OBn
4c, R^1 = OMe

5a, **6a**, R = Ph, R^1 = OPh
5b, **6b**, R = Ph, R^1 = OBn
5c, **6c**, R = Ph, R^1 = OMe
5d, **6d**, R = PMP, R^1 = OPh
5e, **6e**, R = PMP, R^1 = OBn
5f, **6f**, R = PMP, R^1 = OMe
5g, **6g**, R = Styryl, R^1 = OPh
5h, **6h**, R = Styryl, R^1 = OBn
5i, **6i**, R = Styryl, R^1 = OMe

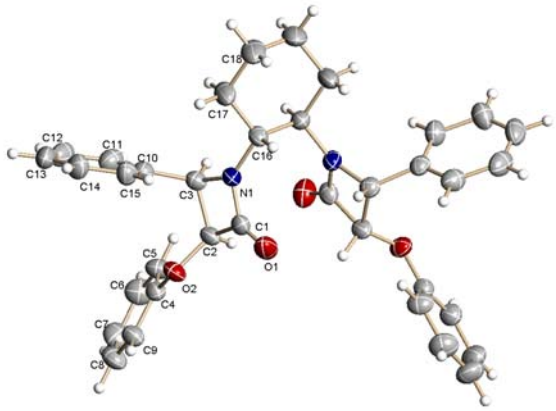


Figure 1. ORTEP diagram of **5a** (C_2-symmetric)

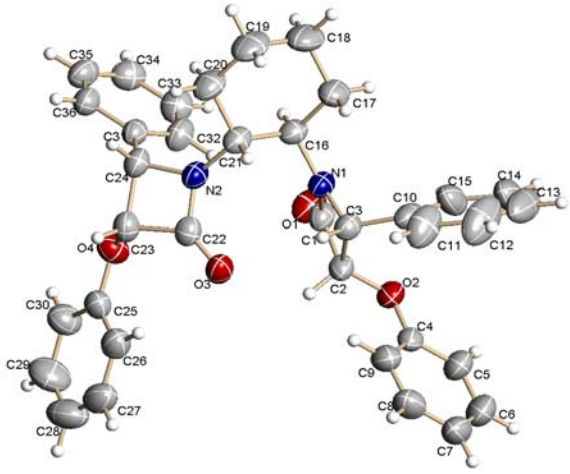
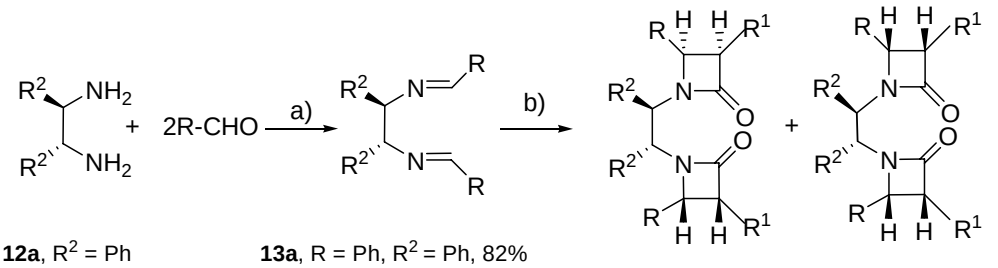


Figure 2. ORTEP diagram of **6a** (*meso*)

Other acyclic C_2-symmetric vicinal diamines, such as 1,2-diphenylethylenediamine **12a** and 2,3-diaminobutane **12b** were also used for the synthesis of bis-imines **13a,b**. These bisimines were used for the Staudinger reaction to get a mixture of C_2-symmetric **14a-d** and *meso* bis-β-lactams **15a-d**, with higher selectivity for *meso* isomer, was obtained in very good yields. Both the diastereomers **14a-d** and **15a-d** were separated by flash column chromatography and characterized by spectral data.

Scheme 3



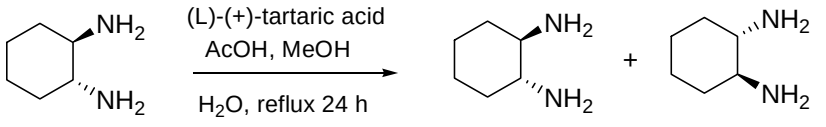
Reagents and conditions: a) $MgSO_4$, CH_2Cl_2, rt, 15 h
b) R^1CH_2COCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 15 h

14a, **15a**, R = Ph, R^1 = OPh, R^2 = Ph
14b, **15b**, R = Ph, R^1 = OBn, R^2 = Ph
14c, **15c**, R = Ph, R^1 = OMe, R^2 = Ph
14d, **15d**, R = Ph, R^1 = OPh, R^2 = Me

Section B: Asymmetric synthesis of *cis* bis-β-lactams via Staudinger cycloaddition reaction using optically pure C_2-symmetric 1, 2-diamines

After establishing the synthetic protocol for racemic bis-β-lactams, we were interested in studying the asymmetric synthesis bis-β-lactams using optically pure 1,2-diamines. Therefore (+)-1*R*, 2*R-trans*-1,2-diaminocyclohexane was resolved using (L)-(+)-tartaric acid. Optically pure (+)-1*R*, 2*R-trans*-1,2-diaminocyclohexane (>99.8% ee) was used for the synthesis of bis-β-lactams. The chiral bis-imine **16** on reaction with ketenes generated form phenoxyacetyl chloride and Et_3N gave a mixture C_2-symmetric **17** and *meso* **18** β-lactams in very good yield. Both the diasteromers were separated by careful flash column chromatography and characterized by spectral data.

Scheme-4

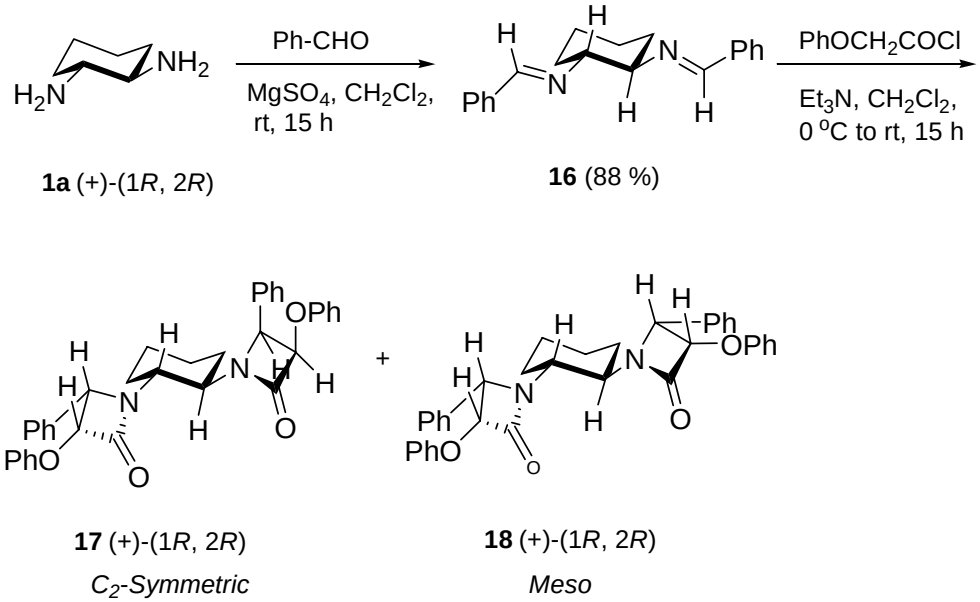


1

1a (+)-(1*R*, 2*R*)

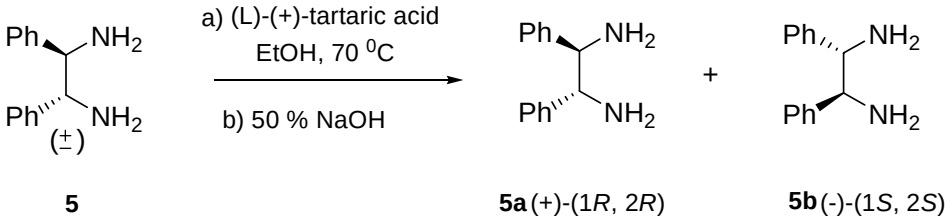
1b (-)-(1*S*, 2*S*)

Scheme-5

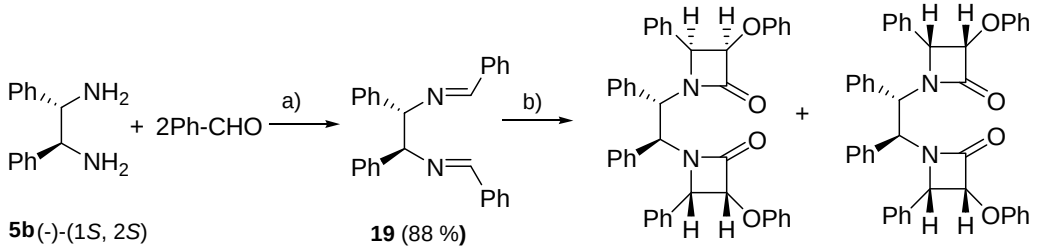


Similarly, racemic 1, 2 diphenylethylenediamine was resolved using (L)-(+)-tartaric acid to get optically pure 1, 2 diphenylethylenediamine **5a** and **5b**. This optically pure 1*S*, 2*S* diphenylethylenediamine **5b** (98% ee) was converted into bisimne **19** by reacting with benzaldehyde. It was further reacted with ketene generated from phenoxyacetyl chloride to get diasteomeric mixture of C_2-symmetric **20** and *meso* **21** β-lactams in very good yield, which were easily separated by flash column chromatography.

Scheme-6



Scheme-7



5b(-)-(1*S*, 2*S*) **19** (88 %**)** **20** *C_2-symmetric* **21** *Meso*

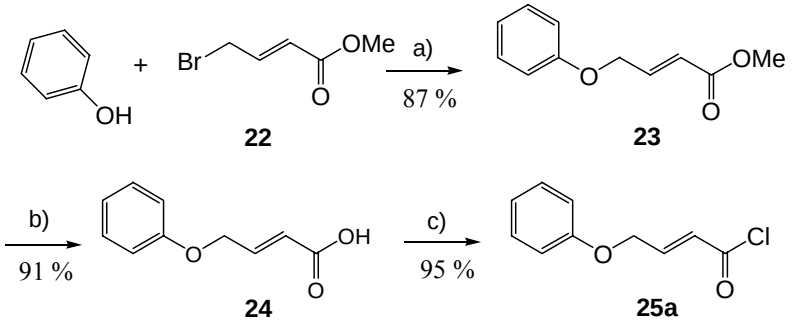
Reagents and conditions: a) $MgSO_4$, CH_2Cl_2, rt, 15 h
b)$PhCH_2COCl$, Et_3N, CH_2Cl_2, 0 ^oC to rt, 15 h

Chapter II

Stereoselctive Synthesis of 3-vinyl-β-lactams via cycloaddition reaction of vinylketenes and imines

3-Vinyl-β-lactams are important intermediates in the synthesis of biomedicinally interesting compounds such as carbapenem, asparenomycin and thienamycin. Normally, these β-lactams are prepared by Staudinger cycloaddition of vinylketenes also referred as Sheehan ketenes and imines. The application of vinylketenes for the synthesis of 3-vinyl-β-lactams has not been fully explored. This chapter describes the synthesis of 3-vinyl-β-lactams and the mechanistic aspects of the cycloaddition reaction of vinylketenes with imines.

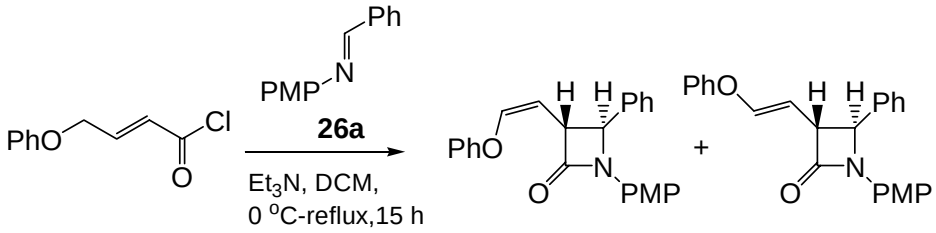
Scheme 8



Reagents and conditions: a) K_2CO_3, PTC, acetone, reflux, 2 h b) 1M NaOH, THF, rt, 15 h c) $(COCl)_2$, DCM, reflux 4 h

In case of normal ketenes, it has been observed that a heteroatom at α-position has pronounced influence on the stereochemical outcome of [2+2] cycloaddition with imines. We envisaged that a heteroatom at the γ-position on vinylketenes would have influence on the diastereoselectivity in the [2+2] cycloaddition reactions with imines. With this idea in mind we prepared 4-phenoxybut-2-enoyl chloride **25a**, a precursor for phenoxyvinyl ketene, from methyl-4-bromo-2-butenoate (Scheme-8). Staudinger reaction of ketenes generated form 4-phenoxybut-2-enoyl chloride **25a** with imine **26a** in presence of triethylamine gave excellent yield of 3-Vinyl-*trans*-βlactams with *Z* geometry of double bond. A small amount of *E*-isomer **28a** was also observed along with Z-isomer **27a**.

Scheme 9



25a **27a** (68 %) **28a** (12 %)

The pure Z-isomer **27a** was obtained by flash column chromatography and the structure was established by spectral data and single crystal X-ray analysis.

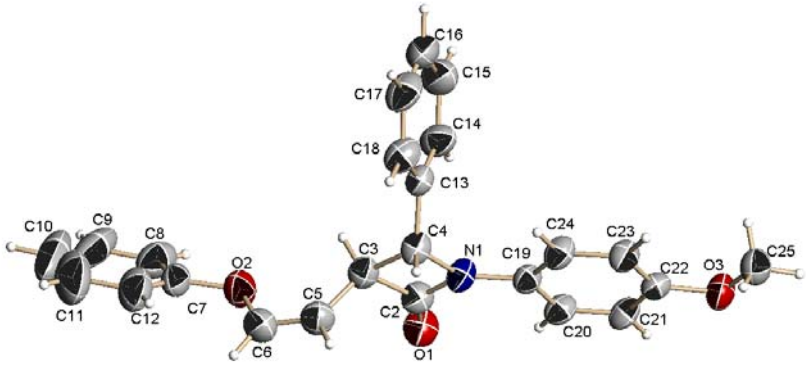
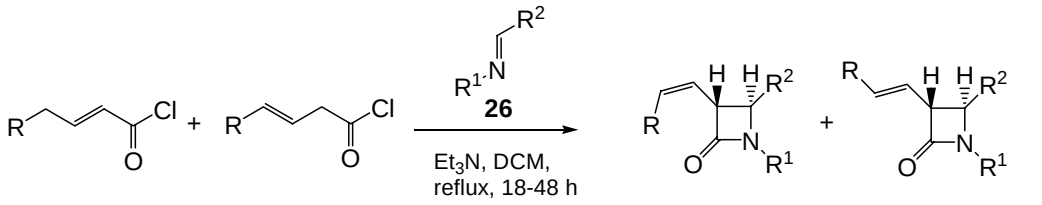


Figure 3. ORTEP diagram of **27a**

Several vinyl-β-lactams were prepared in very good yields from 4-phenoxy-but-2-enoyl chloride (**25a**), 4-methoxy-but-2-enoyl chloride (**25b**) and imines **26a-g** with

various substituents. In all the cases, irrespective of the substituents on the imine, only *trans*-β-lactam formation was observed. We have also synthesized the ketenes generated from acid chloride **25c** and **25d** (R = Phth, N_3) gave *trans*-vinyl-β-lactams **27j-k** and **28j-k**. However, the reaction was slow and gave lower yields of the vinylazetidin-2-one. The thiophenoxyketene generated from **25e** did not undergo the cycloaddition reaction with imine **26a**.

Scheme 10



25b-e (major) **25'b-e** (minor) **27b-k**(major) **28b-k**(minor)

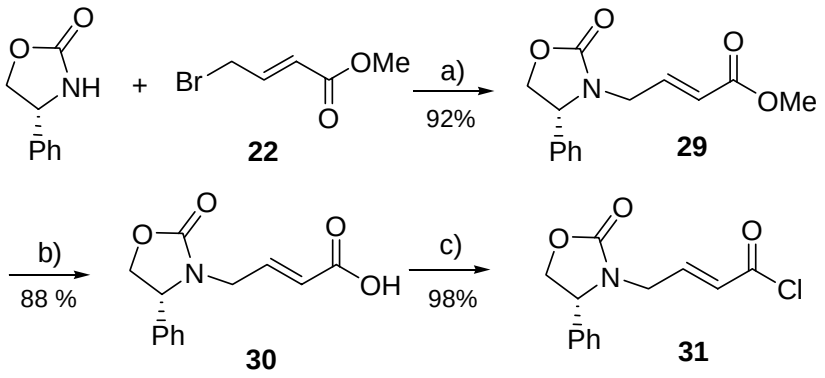
25b, **25'b**, R = OMe
25c, **25'c**, R = Phth
25d, **25'd**, R = N_3
25e, **25'e**, R = SPh

26b, R^1 = PMP, R^2 = PMP
26c, R^1 = Ph, R^2 = Ph
26d, R^1 = Ph, R^2 = PMP
26e, R^1 = 4-ClC_6H_4, R^2 = Ph
26f, R^1 = 4-$CH_3C_6H_4$, R^2 = Ph
26g, R^1 = PMP, R^2 = CO_2Me

Further we have also studied asymmetric Staudinger reaction of the vinylketenes and imines. Optically pure (*R*) (-) 4-*N*-oxazolidinonebut-2-enoyl acid **30** was prepared in very good yield form (*R*) (-) 4-phenyl –2- oxazolidinone. This optically pure acid **30** was further converted into the acid chloride **31** using oxalyl chloride. The acid chloride **31** on Staudinger cycloaddition reaction with imine **26c** in dichloromethane in presence of Et_3N gave a diastereomeric mixture of two compounds **32** (90 %) and **33** (10 %) in 61 % yield.

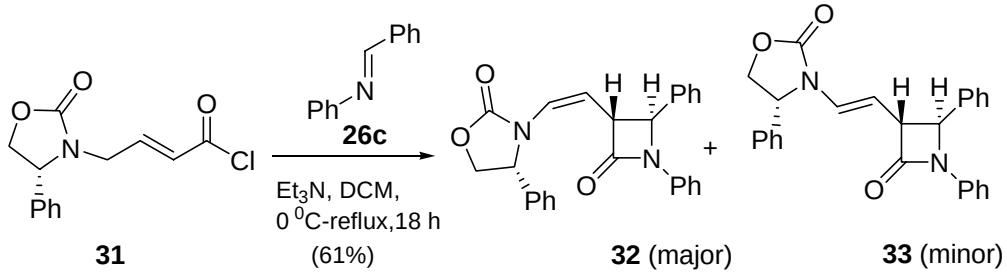
All our efforts to get **32** in pure form by column chromatography were unsuccessful. However we could get pure **32** by recrystallization from methanol. The structure was established by ^1H NMR and IR spectroscopy. The absolute stereochemistry of the newly formed chiral centers was assign as 3R, 4S based on the known stereochemistry of Oxazolidinone.

Scheme 11



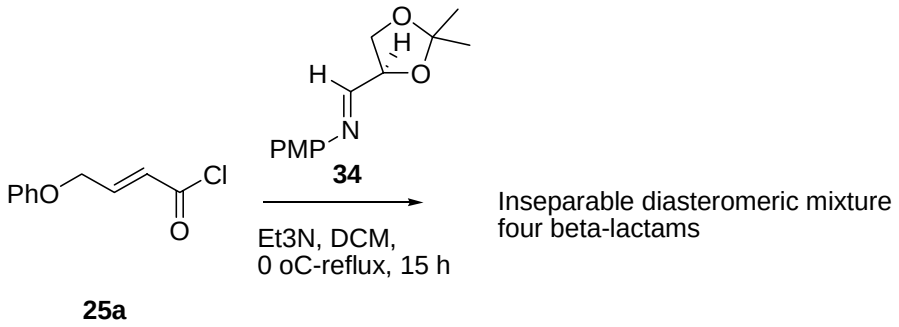
Reagents and conditions: a) NaH, THF, 0 ^{0}C rt, 7h b) 1M NaOH, THF, rt, 15 h c) $(COCl)_2$, CH_2Cl_2, reflux 4 h

Scheme 12



We have also used chiral imine **34** derived from D-glyceraldehyde acetonide and *p*-anisidine for the synthesis of optically pure 3-vinyl-*trans*-β-lactam. The proton NMR of crude product showed mixture of four β-lactams. All our efforts to get pure diastereomer from the mixture were unsuccessful.

Scheme 13



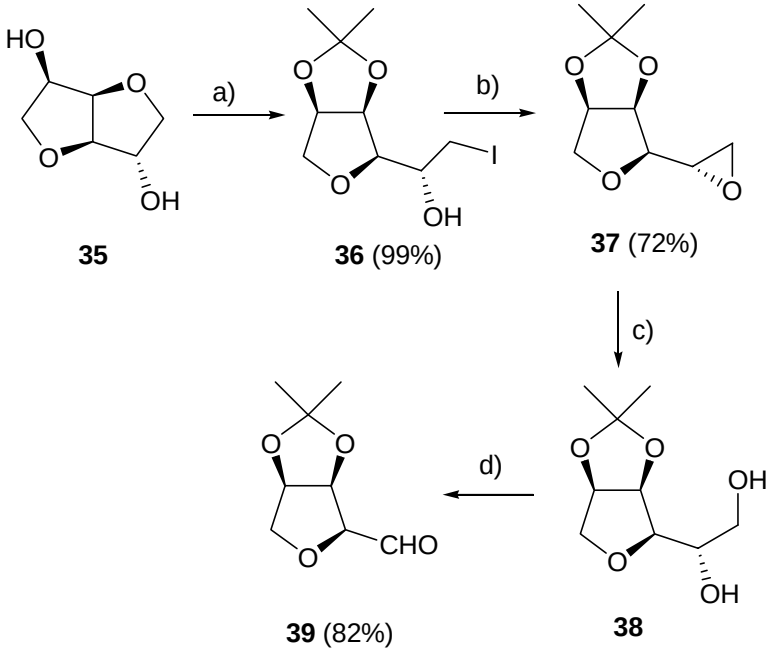
Chapter III

Section A: Asymmetric synthesis of azetidin-2-ones using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral imines

Carbohydrates have attracted considerable attention for their applications as chiral starting materials in the asymmetric syntheses biologically useful organic molecules. Recently they are also used in asymmetric synthesis of β-lactams, which are further transform to antibacterial agents. This chapter describes the synthesis of chiral imine from 1,4:3,6-dianhydro-D-glucitol (isosorbide) and its application in the synthesis of β-lactams. Optically pure (3a*R*,4S,6aR)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde, a bicyclic aldehyde **39** was prepared from isosorbide **35** in 4 steps as shown in scheme 14.

This bicyclic aldehyde **39** on reaction with amines gave imine in excellent yields. These imines on cycloaddition reaction with ketenes gave single diastereomer of *cis*-β-lactam in excellent. One of the β-lactam **43a** was obtained in crystalline form and the absolute stereochemistry of newly form β-lactam ring was established as 3*S*, 4*R* based on the known stereochemistry of bicyclic carbohydrate moiety. Several β-lactams were prepared in excellent yield and very high diastereoselectivity.

Scheme 14

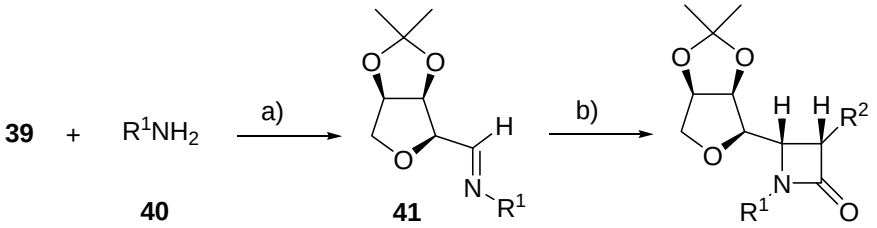


35 **36** (99%) **37** (72%)

38 **39** (82%)

Reagents and conditions: a) TMSCl, NaI, Acetone, 12 h, rt,
b) NaH,THF c) NaOH,THF reflux, 48 h d) $NaIO_4$, SiO_2, CH_2Cl_2

Scheme 15



40 **41**

40a, R^1 = PMP
40b, R^1 = Bn
40c, R^1= 4-Cl-Ph

43a, R^1=PMP, R^2=OCH_3
43b, R^1=PMP, R^2=OBn
43c, R^1=PMP, R^2=OPh
43d, R^1=PMP, R^2=OAc
43e, R^1=CH_2Ph, R^2=OCH_3
43f, R^1=CH_2Ph, R^2=OBn
43g, R^1=CH_2Ph, R^2=OPh
43h, R^1=CH_2Ph, R^2=OAc
43i, R^1=*p*-Cl-Ph, R^2=OCH_3
43j, R^1=*p*-Cl-Ph, R^2=OBn
43k, R^1=*p*-Cl-Ph, R^2=OPh

Reagents and conditions:a) $MgSO_4$, CH_2Cl_2, 15 h, rt
b) R^2OCH_2COCl (**42**), Et_3N, CH_2Cl_2, 0 ^oC to rt, 15 h

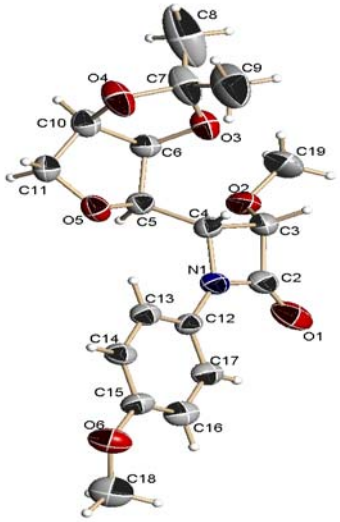


Figure 4. ORTEP diagram for compound **43a**

Table 1. Synthesis of azetidin-2-ones (**43a-k**)

Entry No.	Comp.	R^1	R^2	HPLC[b] Purity	Mp of 42 (° C)	Yield[c] (%)	$[\alpha]_D^{25}$ ($CHCl_3$)
1	**43a**	PMP[a]	OCH_3	98	156-157	74	-138.8 (c, 0.80)
2	**43b**	PMP	OBn	99	Oil	78	-118.1 (c, 1.00)
3	**43c**	PMP	OPh	97	177-178	75	-224.3 (c, 1.20)
4	**43d**	PMP	OAc	97	Thick oil	75	-134.1 (c, 0.90)
5	**43e**	CH_2Ph	OCH_3	95	Thick oil	67	-65.0 (c, 1.00)
6	**43f**	CH_2Ph	OBn	96	Thick oil	70	-58.0 (c, 1.00)
7	**43g**	CH_2Ph	OPh	96	Thick oil	60	-70.0 (c, 1.00)
8	**43h**	CH_2Ph	OAc	96	Thick oil	61	-37.7 (c, 1.10)
9	**43i**	*p*-Cl-Ph	OCH_3	98	Thick oil	68	-128.0 (c, 0.50)
10	**43j**	*p*-Cl-Ph	OBn	98	Thick oil	71	-117.1 (c, 0.70)
11	**43k**	*p*-Cl-Ph	OPh	97	Thick oil	62	-117.9 (c, 0.60)

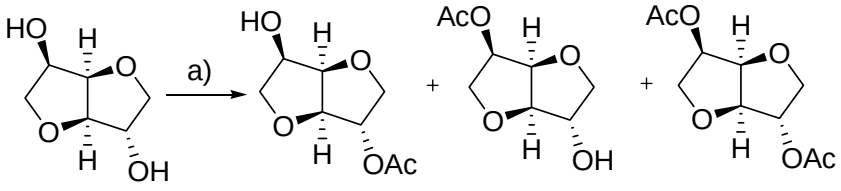
[a] PMP = *p*-Methoxyphenyl [b] Purity was determined by HPLC analysis on Chromsphere Chromsep 5 C-18, 250 x 4.6 mm (5 μm) column; Solvent system (v/v): MeCN:H_2O (60:40), flow rate 1.5 mL/min. [c] Isolated yields

Section B: Asymmetric synthesis of azetidin-2-ones using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral acids

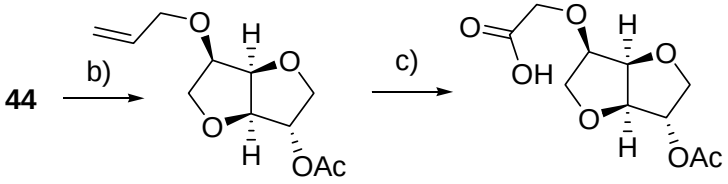
In the earlier section, we have described the application of chiral imines derived from isosorbide in highly diastereoselectivity β-lactams. In this chapter, we have described the application of chiral ketenes derived from isosorbide in asymmetric Staudinger reaction for the synthesis of β-lactams. We have exploited the reactivity differences of *endo* and *exo* hydroxyl group of isosorbide. Two chiral bicyclic acids **48** and **55** were prepared from isosorbide and further used in the synthesis of β-lactams.

The *endo*-chiral bicyclic acid **48** was synthesized from isosorbide in 3 steps in good yield as shown in scheme-16. The isosorbide **35** was converted into monoacetate **44**, which on reaction with ally bromide gave allyl ether **47**. This ally ether was further oxidized to acid **48**. This *endo*-bicylic acid **48** on reaction with imine under Staudinger reaction conditions gave diastereomeric mixtures of two β-lactams (6:4).

Scheme 16



35 **44** (68%) **45** (5%) **46** (12%)

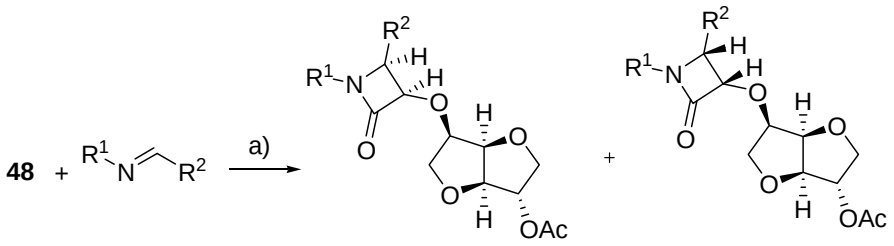


47 (87%) **48** (55%)

Reagents and Conditions: a)CH_3COOH,CH_2Cl_2/DMAP/DCC, rt, 3h, b) Allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark, rt, c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O.

All our efforts to separate these diastereomers by flash column were unsuccessful. However, a single major diastereomer was obtained as white crystalline form **50a** by recrystallization from methanol.

Scheme 17



49a R^1=Ph, R^2=Ph
49b R^1=*p*-ClPh, R^2=Ph

50a R^1=Ph, R^2=Ph (65%)
51a R^1=*p*-ClPh, R^2=Ph (68%)

50b R^1=Ph, R^2=Ph (minor)
51b R^1=*p*-ClPh, R^2=Ph (minor)

Reagents and Conditions: a) triphosgene, Et_3N, DCM, 0 ^{0}C to rt, 15 h

The *cis* stereochemistry of the β-lactam ring was ascertained from the coupling constant of the ring protons (J = 5.4 Hz for *cis*-isomer). The absolute stereochemistry of the newly formed chiral centers was established as 3*R*, 4*S* from the single crystal X-ray analyses of the β-lactam **50a** (Fig. 5).

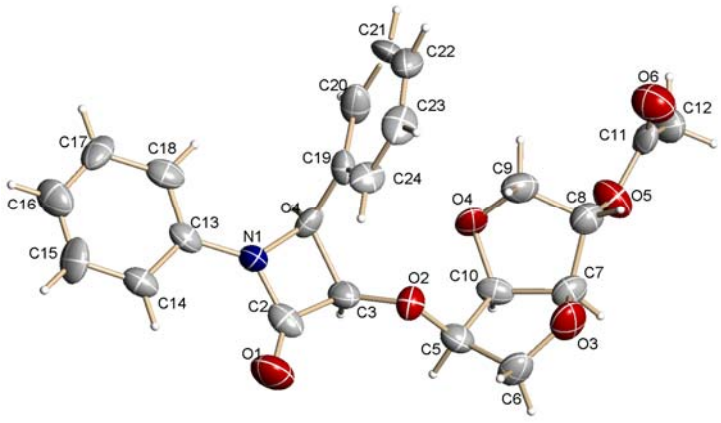
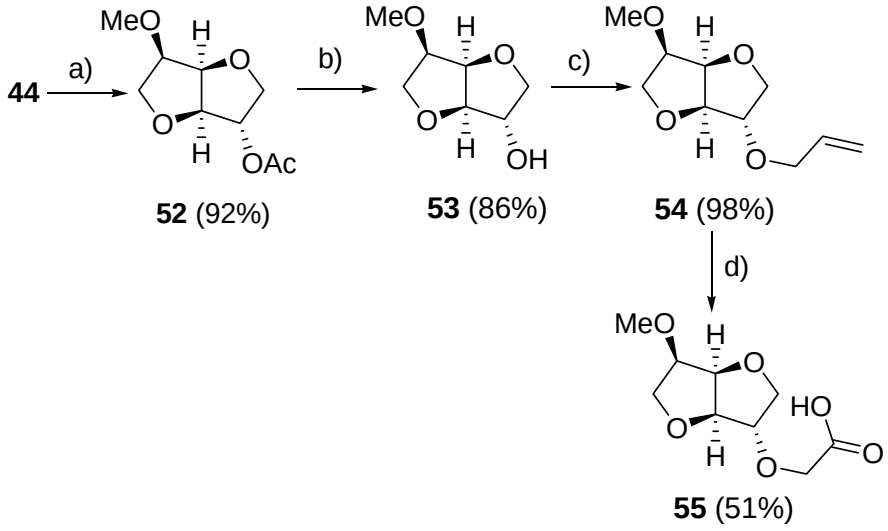


Figure 5. ORTEP diagram for compound **50a**

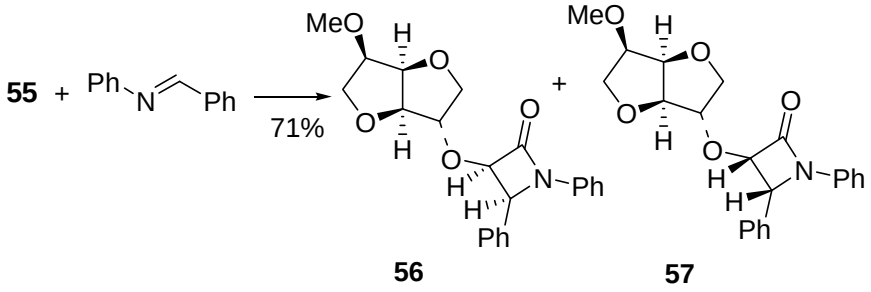
The other *exo*-chiral bicyclic acid **55** was also synthesized from isosorbide in 5 steps in good yield as shown in scheme-18. This acid **55** on cycloaddition reaction with imine **49a** gave an inseparable diastreomeric mixture of two β-lactams **56** and **57** (1:1).

Scheme 18



Reagents and Conditions: a) CH_3I, Ag_2O, $CaSO_4$, 2 days, dark rt, b) KOH, EtOH, 30 min, 50 ^{0}C c) Allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark rt, d) $KMnO_4$, K_2CO_3, Acetone, rt, 3hr.

Scheme 19



Reagents and Conditions:a) triphosgene, Et_3N, DCM, 0 ^{0}C to rt, 15 h

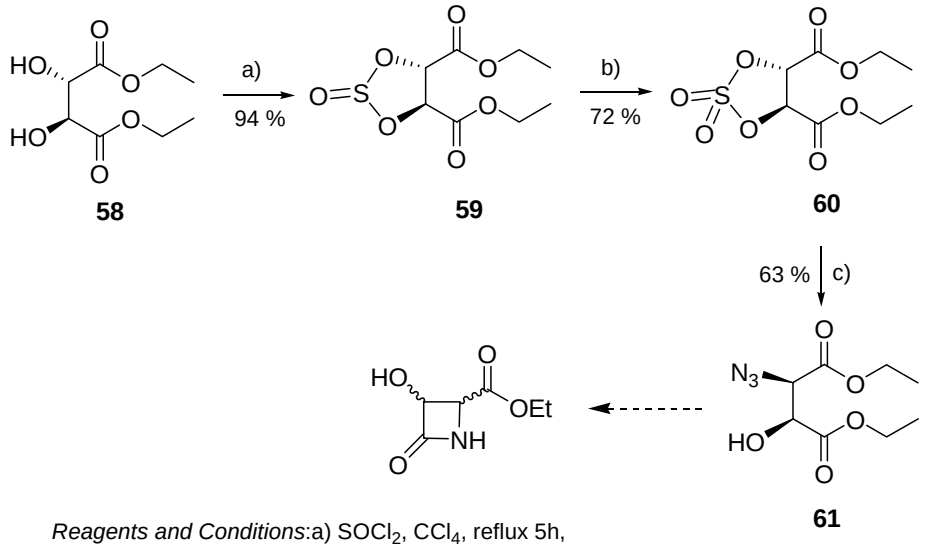
Chapter IV

Study directed towards synthesis of 3-hydroxy-4-carboethoxy azetidin-2-ones from L(+) diethyl tatrate

The synthesis of the β-lactam ring *via* formation of the C_4-N_1 bond is the synthetic route selected by nature for the biosynthesis of azetidinone containing antibiotics. The essential strategy involved in the synthesis of β-lactams through C_4–N_1 bond was the intramolecular displacement of a leaving group attached to carbon 4 with an appropriately activated nitrogen. We were interested in the asymmetric synthesis of 3-hydroxy-4-carboethoxy β-lactams *via* intramolecular cyclization of the C_4-N_1 bond formation starting from optically pure L(+)-diethyl tartarate (**58**).

3-Hydroxy-4-substituted β-lactam is an important synthon in Organic synthesis. It has been shown that a suitably substituted 3-hydroxy-β-lactam can serve as a synthetic equivalent for the phenylisoserine side chain of taxol, a unique complex diterpene, is considered to be the most exciting drug in the anticancer chemotherapy in particular, for the treatment of lung, breast and ovarian cancer.

Scheme 20

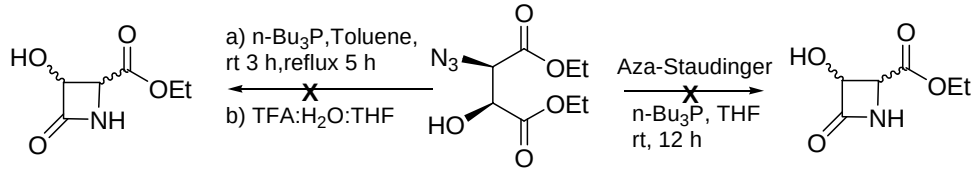


Reagents and Conditions:a) $SOCl_2$, CCl_4, reflux 5h,
b) $RuCl_3$, MeCN, $NaIO_4$, CCl_4/H_2O, 50-60 min c) aq. LiN_3, THF, 6 h

The L(+)-diethyl tartarate (**58**) was reacted with thionyl chloride in refluxing carbon tetrachloride as a solvent for 5 hours to get cyclic sulphite **59** which was further oxidized with $NaIO_4$ and $RuCl_3$ in acetonitrile and carbon tetrachloride mixture (1:1) to

give the cyclic sulfate **60** in 72% yield. The nucleophilic ring opening of cyclic sulfate **60** was carried out with the aq.lithium azide in THF-H_2O mixture (1:1) at room temperature to give the optically pure azido-alcohol **61**, which is a precursor for the intramolecular cyclization reaction of β-lactam ring formation.

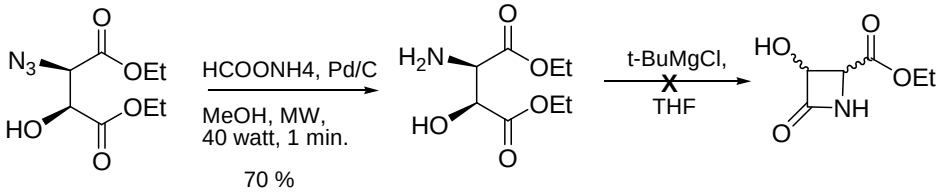
Scheme 21



63

The optically pure azido-alcohol **63** was reacted with n-Bu_3P in THF at room temperature for 12 h (Aza-Staudinger reaction). We did not get the desired intramolecular cyclized 3-hydroxy-4-carboethoxy- β -lactam.

Scheme 22

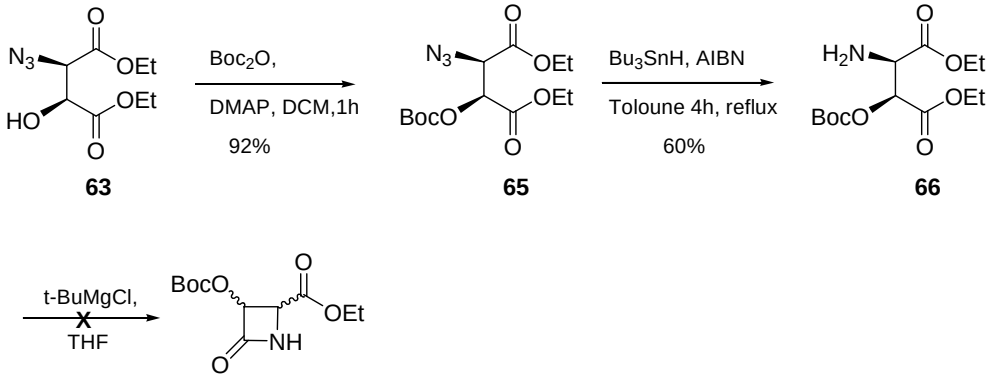


63 **64**

The optically pure azido-alcohol **63** was reduced with $HCOONH_4$, Pd/C into the optically pure amino-alcohol **64** in good yield that was treated with t-BuMgCl in THF in different reaction conditions did not give the desired cyclized product.

The hydroxyl group of optically pure azido-alcohol **63** was protected with Boc-anhydride to give azido-boc tartarate **65** in excellent yield which was reduced into the corresponding amino-boc tartate **66** in good yield. The amino-boc tartate **66** was further treated with t-BuMgCl in THF in different reaction conditions. But, our efforts to cyclized the amino-boc tartate **66** into the desired product was not successful. The work is in under progress.

Scheme 23


N3
OEt
OEt
HO
O
O
Boc2O,
DMAP, DCM,1h
92%
63
N3
OEt
OEt
BocO
O
O
65
Bu3SnH, AIBN
Toloune 4h, reflux
60%
H2N
OEt
OEt
BocO
O
O
66
t-BuMgCl,
X
THF
BocO
O
OEt
NH
O

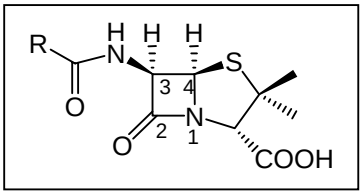
Chapter I

Section A: Stereoselective Synthesis of bis-β-lactams *via* Staudinger cycloaddition reaction

Part of this work has been published in *Tetrahedron*, **2005**, *61*, 2441-2451

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.



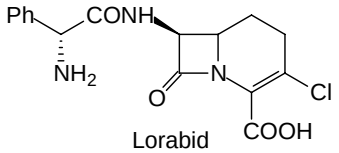
Azetidin-2-one

(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

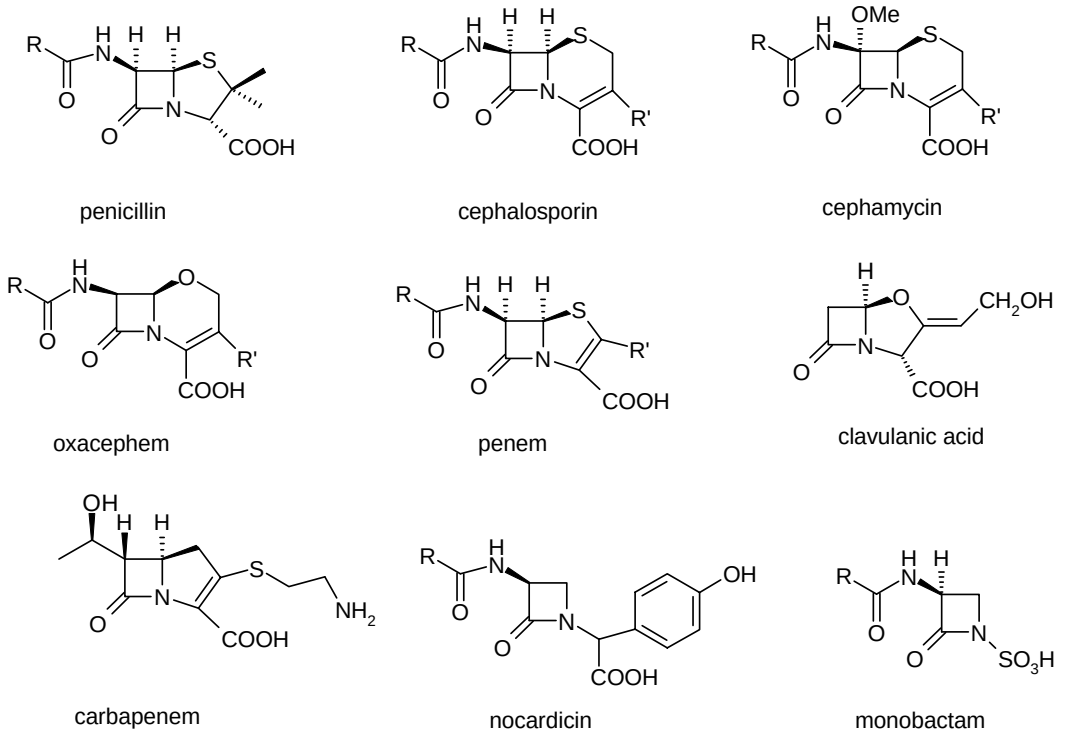


Figure 3. Classification of β-lactam antibiotics based on core structure

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.

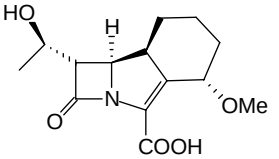


Figure 4

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).

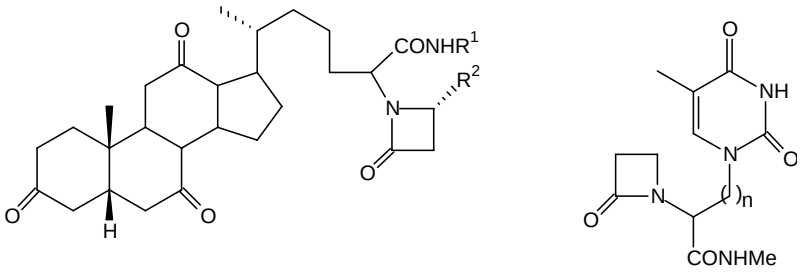


Figure 5

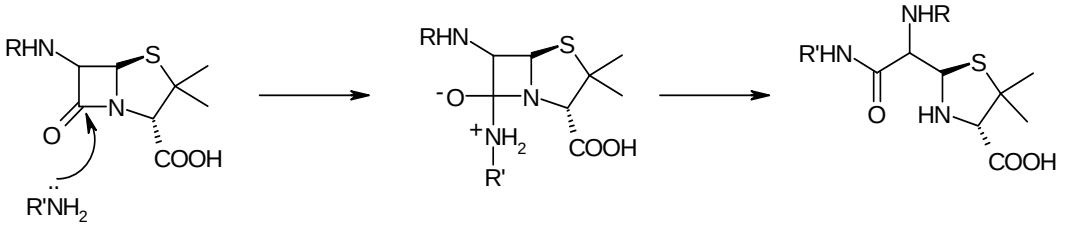
Apart from their antibacterial activities, β-lactams also show other biological activities that include cholesterol absorption inhibition[10] and human leukocyte elastase (HLE).[11]

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

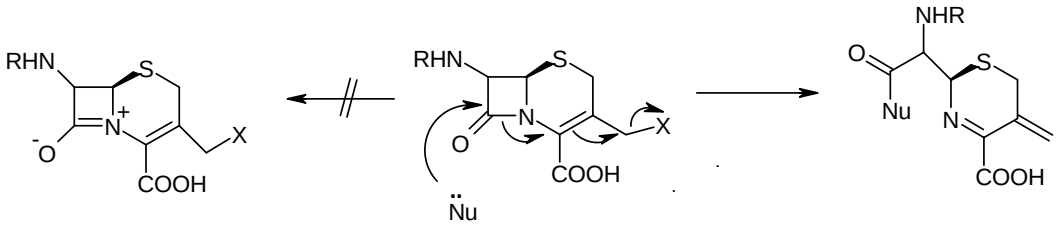


The schematic representation of this phenomenon in the case of penicillin and cephalosporin is shown in Scheme 1.01, 1.02. Penicillin and cephalosporin are entering

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

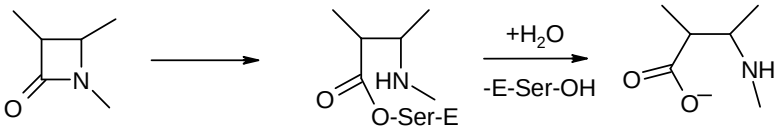


β-lactamases and β-lactamase inhibitors:

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.

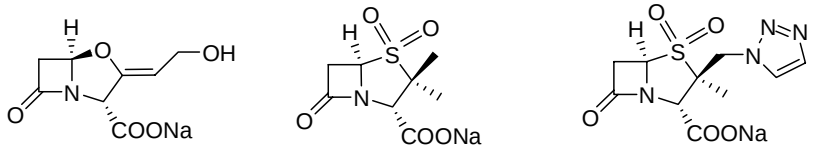


Figure 6

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

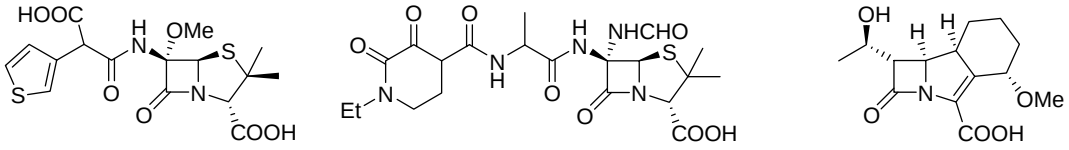


Figure 7

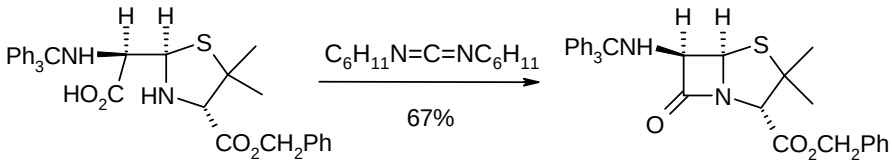
Methods for constructing β-lactam ring:

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

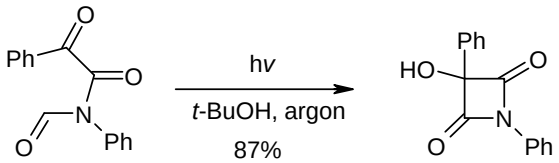


Triphenylphosphine-pyridine disulfide, methanesulfonyl chloride in combination with base and Grignard reagent (RMgX) can also be used instead of DCC to form the amide bond from β-amino acids.

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]

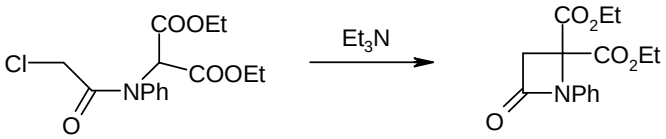
Scheme 1.05



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]

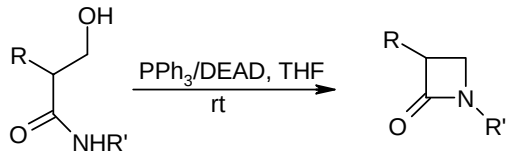
Scheme 1.06



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



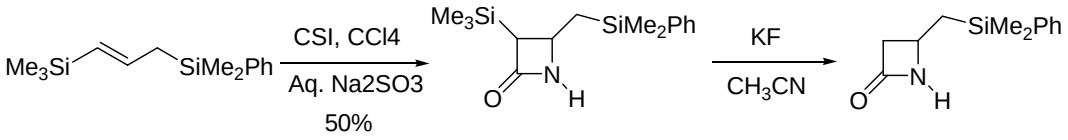
Multiple bond forming reactions:

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

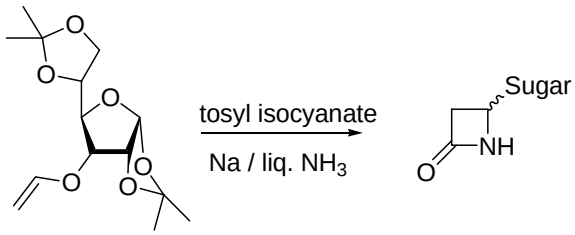
chlorosulfonyl isocyante to various allyl and allenyl silanes to give functionalized β-lactams, which were then converted into synthetically important 3-unsubstituted *NH*-β-lactams by removal of the chlorosulfonyl group followed by silyl deprotection (Scheme 1.08).

Scheme 1.08



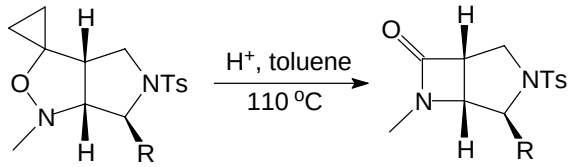
Chmielewski and co-workers have used this cycloaddition reaction between tosyl isocyanate and sugar derived vinyl ethers to obtain good diastereoselectivities in β-lactam formation (Scheme 1.09).[26]

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).

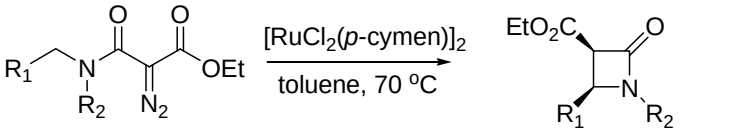
Scheme 1.10



R = Me, *iso*-propyl

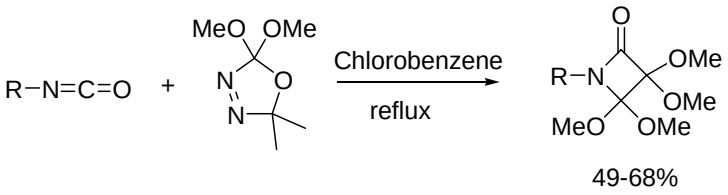
Wing et al.[28a] have developed an operationally simple Ru-catalyzed stereoselective intramolecular carbenoid C-H insertion reaction for the β-lactam formations in excellent yields with *cis*-stereoselectivity (Scheme 1.11).

Scheme 1.11



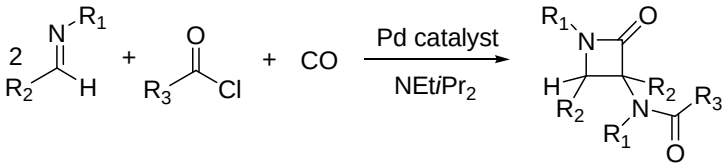
Rigby et al.[28b] have reported a highly substituted β-lactam ring formation *via* a reaction between dimethoxycarebene with selected isocyanates. This reaction offers a new entry into β-lactams and the potential for rapid access into variety of highly functionalized species (Scheme 1.12).

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).

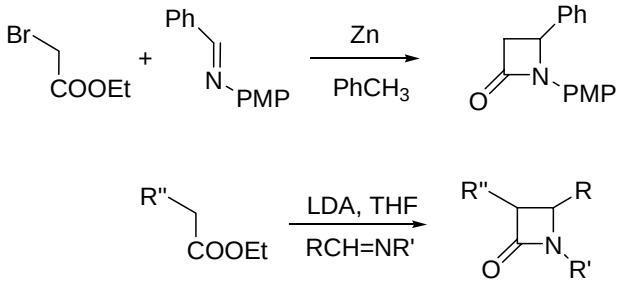
Scheme 1.13



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 disatereoselective synthesis of β-lactams (Scheme 1.14).[29]

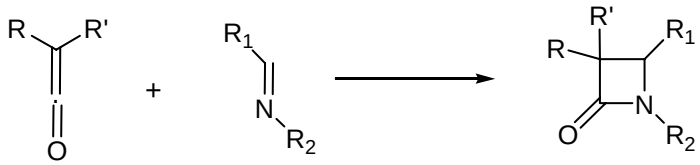
Scheme 1.14



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



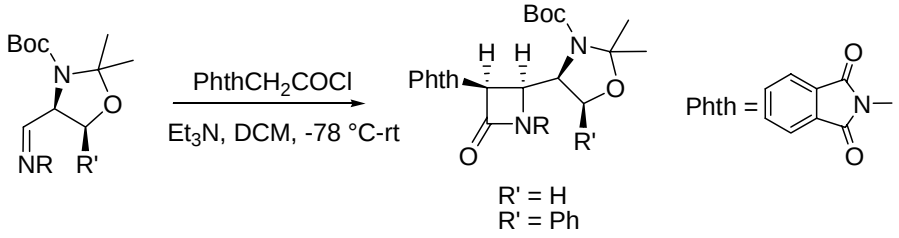
Asymmetric synthesis of β-lactams using Staudinger reaction:

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]

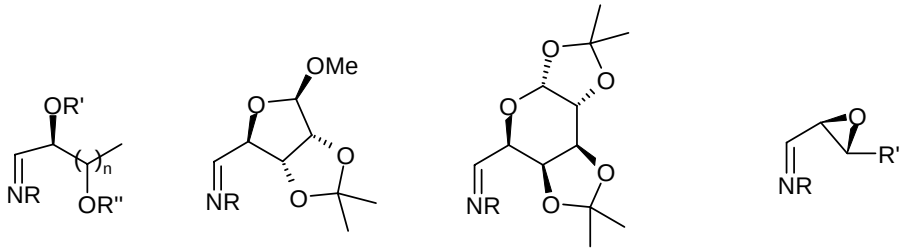
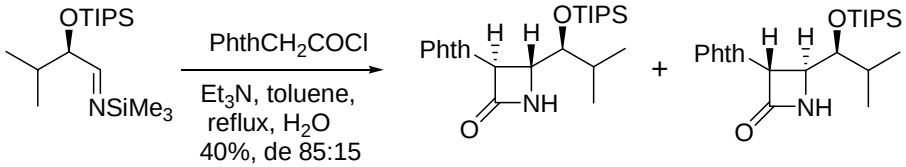


Figure 8

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:

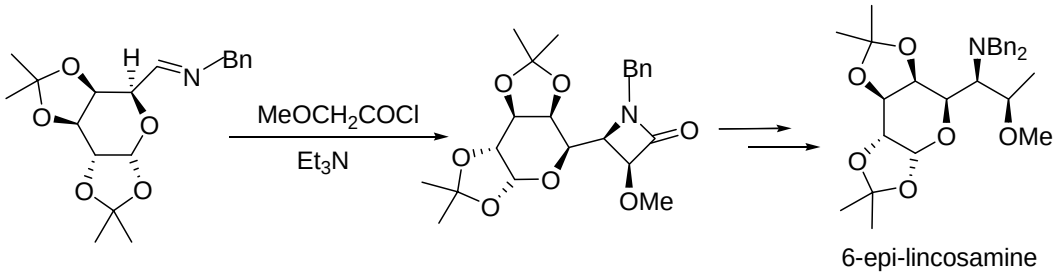
Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[33] The use of carbohydrates in the

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.

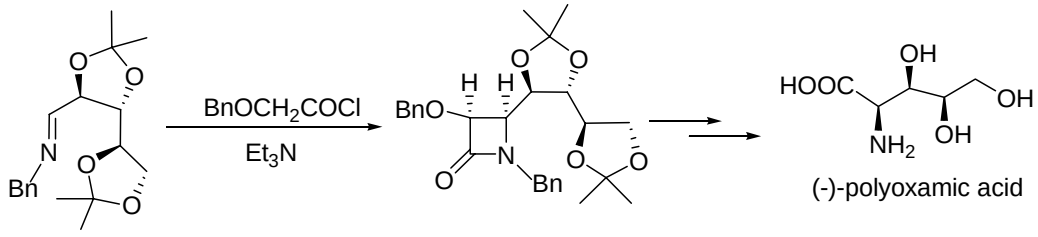
A single *cis*-diastereomer was obtained from the reaction of D-galactopyranose derived chiral imine and methoxy-ketene. On further synthetic transformation this isomer was converted into 6-*epi*-lincosamine (Scheme 1.18).[35]

Scheme 1.18



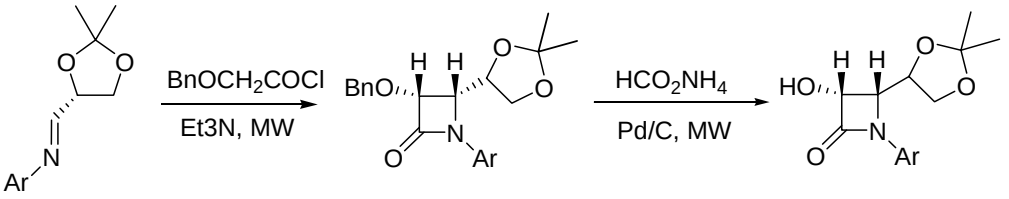
Similarly, the cycloaddition reaction of benzyloxyketene with the imine provided *cis*-β-lactams with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, an antipode of natural (+)-polyoxamic acid (Scheme 1.19).[36]

Scheme 1.19



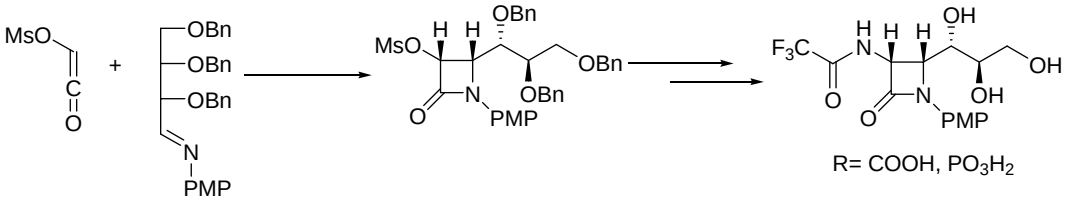
Bose and Manhas have recently reported the enantiospecific synthesis of α-hydroxy-β-lactams using Schiff's bases derived from D-glyceraldehyde under microwave irradiation (Scheme 1.20).[37]

Scheme 1.20



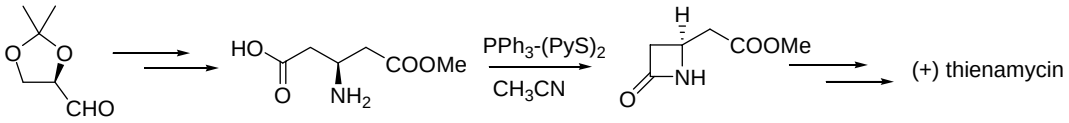
Recently, Stortz et al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-mannonic acid derivatives (Scheme 1.21).[38]

Scheme 1.21



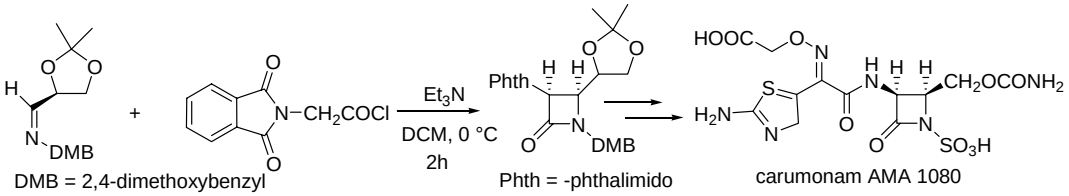
The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into a β-amino ester, which on cyclization with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubstituted β-lactam. This β-lactam has been converted into (+)-thienamycin antibiotic in several steps (Scheme 1.22).[39]

Scheme 1.22



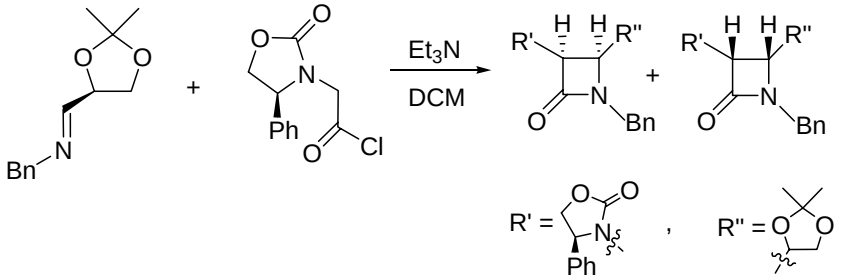
The imine derived from L-(-)-glyceraldehyde and 2,4-dimethoxybenzylamine underwent Staudinger reaction with phthalimidoacetyl chloride to afford the corresponding 3-Phth substituted β-lactam, which is a key intermediate in the synthesis of carumonam antibiotics (Scheme 1.23).[40]

Scheme 1.23



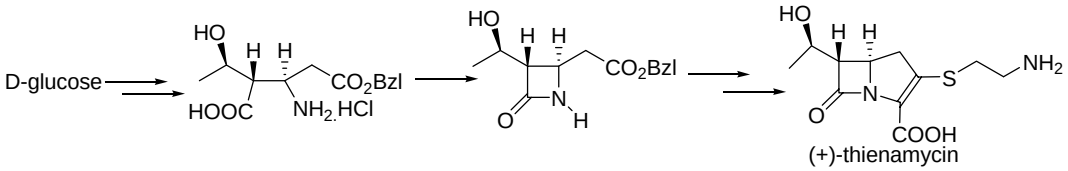
Palomo et al. have treated the imine derived from L-(-)-glyceraldehyde and benzylamine with oxazolidinone derived acid chloride to give *cis*-β-lactams in good yield with 40:60 diastereomeric ratio (Scheme 1.24).[41]

Scheme 1.24



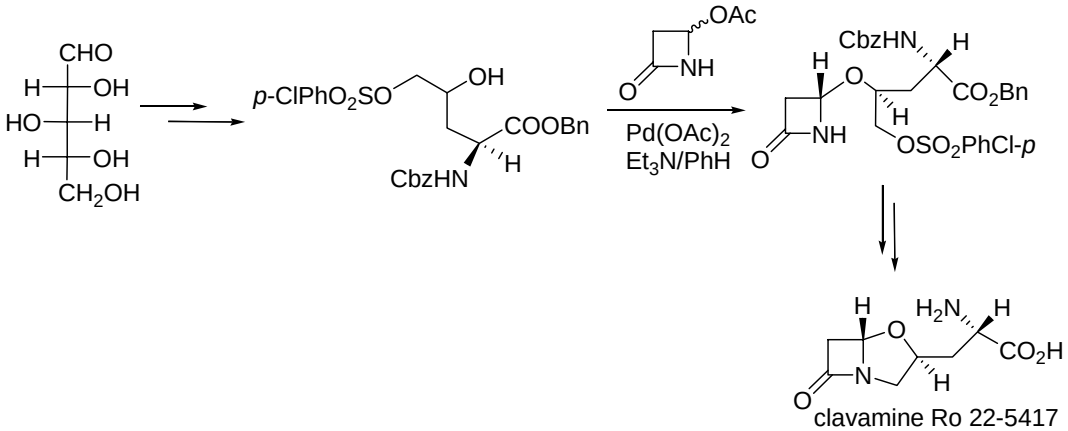
The β-amino acid derived from D-glucose, on cyclization in the presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotic in several steps (Scheme 1.25).[42]

Scheme 1.25



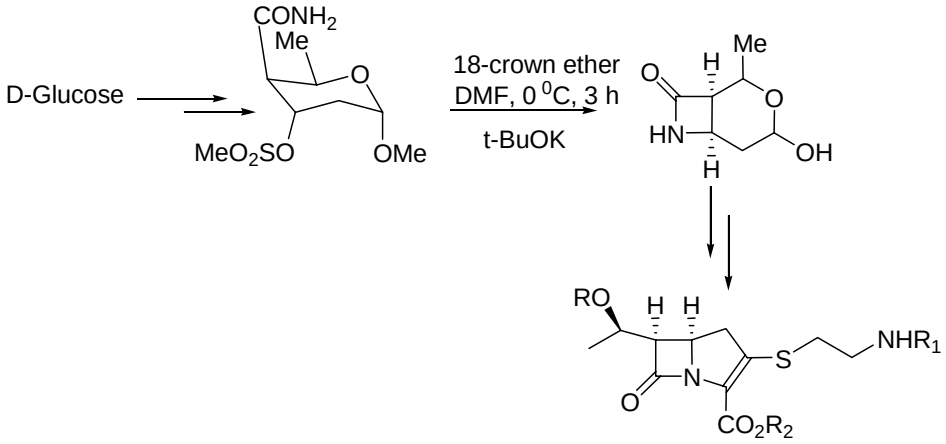
A chiral amino alcohol derived from D-xylose was coupled with racemic 4-acetyloxy-*N*-unsubstiuted-β-lactam in the presence of palladium acetate/ Et_3N to give diastereomeric 70:30 mixture of β-lactams in 65% yield. The major isomer has been converted to the antibiotic clavamine Ro 22-5417 (Scheme 1.26).[43]

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]

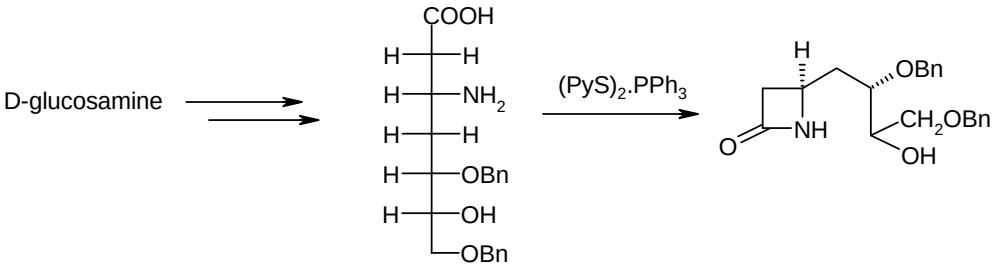
Scheme 1.27



6-epithienamycin

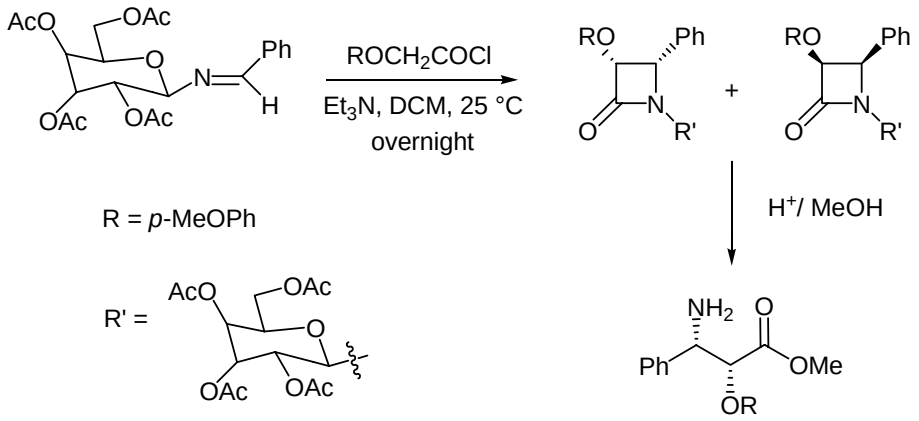
The β-amino acid derived from D-glucosamine has been cyclized to *N*-unsubstituted β-lactam in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. This *N*-unsubstituted β-lactam serves as an intermediate for the synthesis of (+)-thienamycin antibiotic (Scheme 1.28).[45]

Scheme 1.28



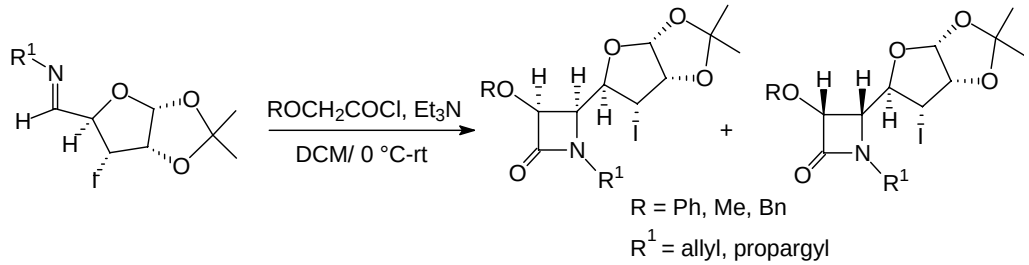
Georg et al. have used the chiral imine derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactose amine for diastereoselective synthesis of β-lactams. They obtained a 60:40 diastereomeric mixture of β-lactams in 90% yield. The α-isomer is transformed to β-amino ester, which is used as a building block for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

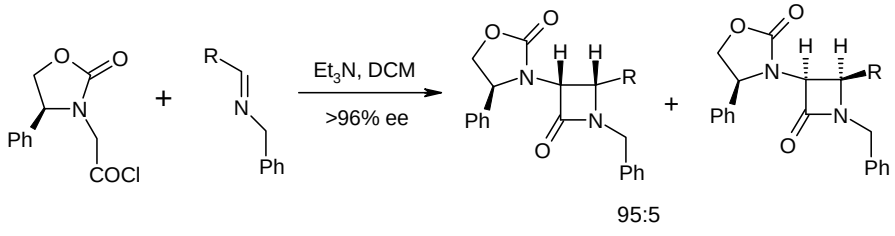
Scheme 1.30



Chiral Ketenes:

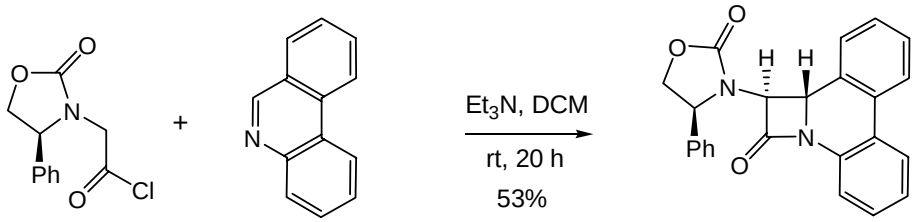
Chiral ketenes have also been used in the Staudinger reaction. However, in most of the cases poor diastereoselectivity has been observed. The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides and triethylamine, with achiral imines afforded optically active β-lactams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

Scheme 1.31



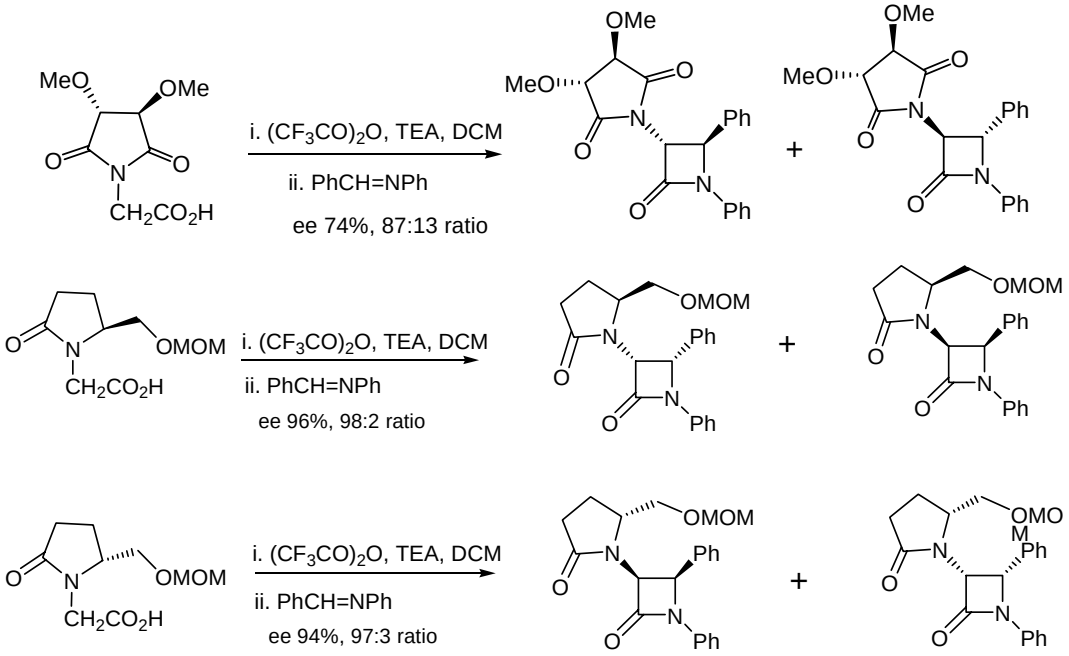
Recently, phenanthridine has been reported to give exclusively *trans* β-lactam with Evans-Sjogren chiral ketene (Scheme 1.32).[49]

Scheme 1.32



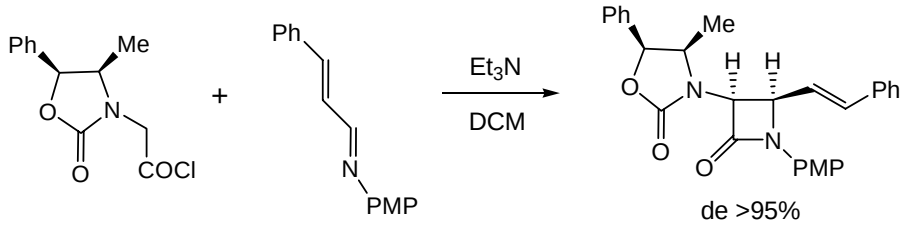
Ikota, in a series of papers, has reported a highly stereoselective β-lactam formation by asymmetric cyclo-condensation employing chiral heterocycles derived from L-(+)-tartaric acid, (*S*)-glutamic acid and (*S*)-serine as ketene precursors.

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]

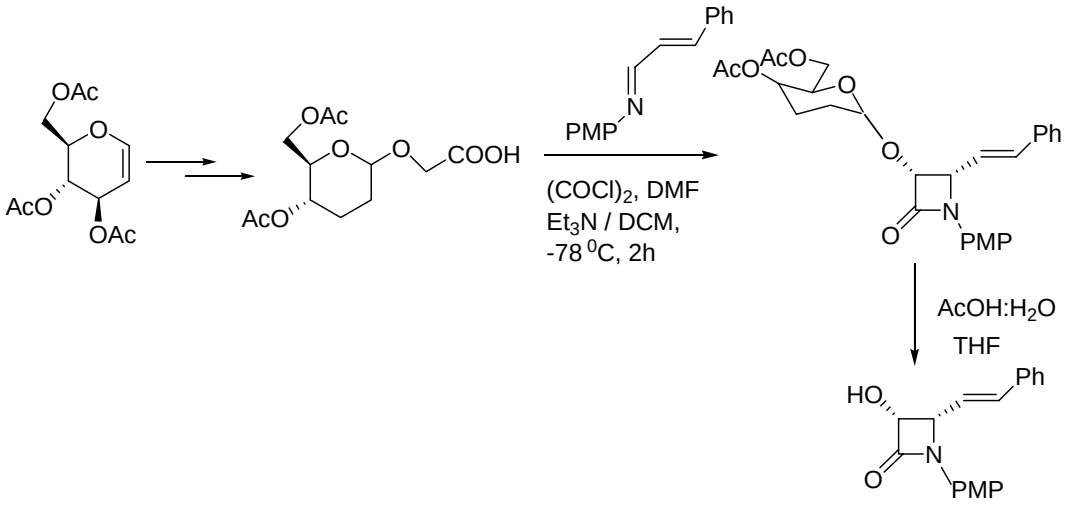
Scheme 1.34



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]

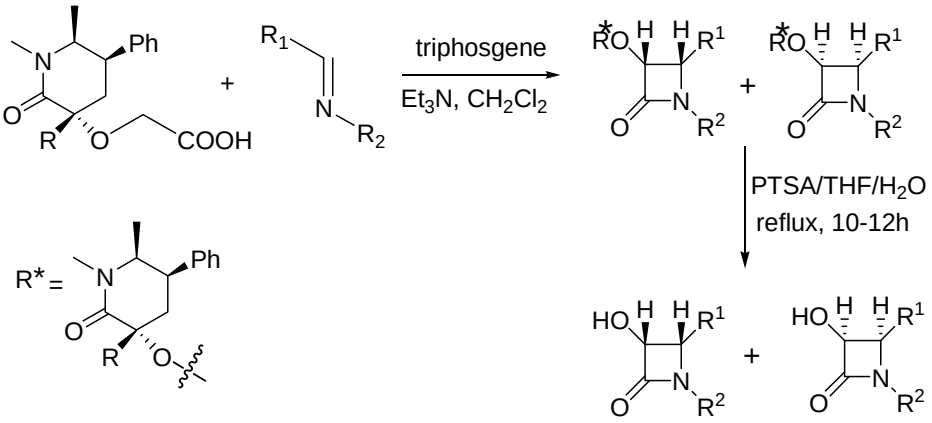
Borer et al. have employed tri-*O*-acetyl-D-glucal derived chiral acid as ketene precursor for diastereoselective synthesis of β-lactams and obtained a diastereoselectivity of 70:30 in this reaction. The sugar moiety was deprotected upon treatment with acetic acid/water to generate 3-hydroxy-β-lactam, 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



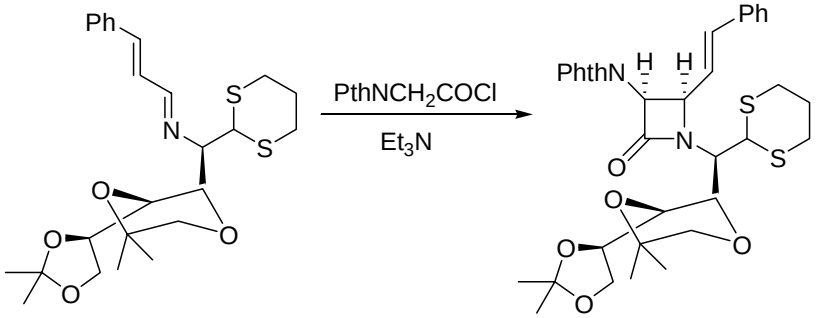
The chiral auxiliary, ephedrine, was removed under acidic hydrolysis and furnished both the enantiomers of 3-hydroxy-4-aryl β-lactams. One of these hydroxy β-lactams (β isomer) is an advanced intermediate for the synthesis of taxol side chain (Scheme 1.36).[50d]

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.

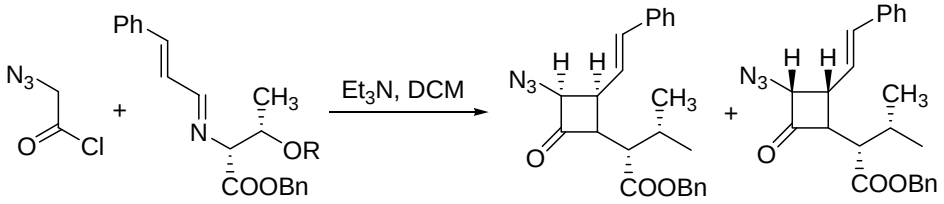
Asymmetric Staudinger reaction using imines derived from D-Glucosamine[52] and cinnamaldehyde have resulted in diastereospecific formation of single *cis* β-lactam (Scheme 1.37).

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]

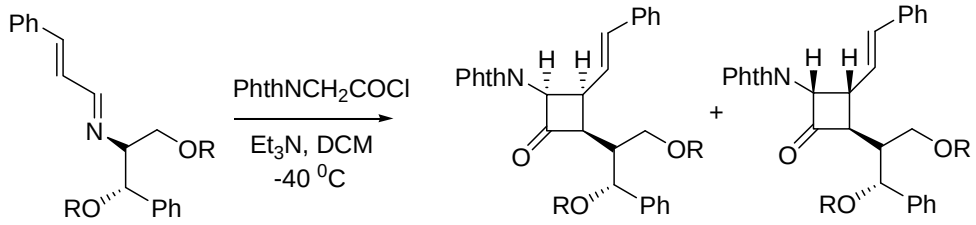
Scheme 1.38



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

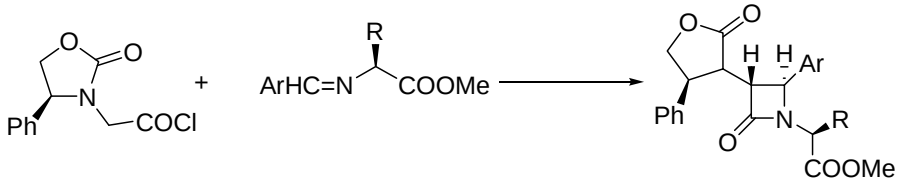


R = TBDMS (ratio 90:10)

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).

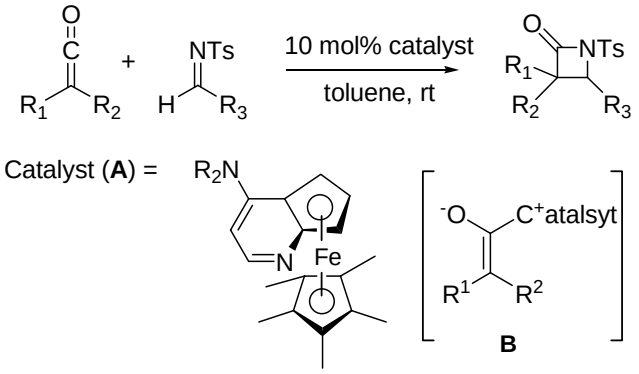
Scheme 1.40



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 over nine decades, the mechanism and the stereochemical course of this reaction are still obscure. Recent efforts in this aspect have resulted in a series of papers by various groups.[58] Based on these results, a two-step zwitterionic mechanism has been preferred to a concerted [2+2] cycloaddition.

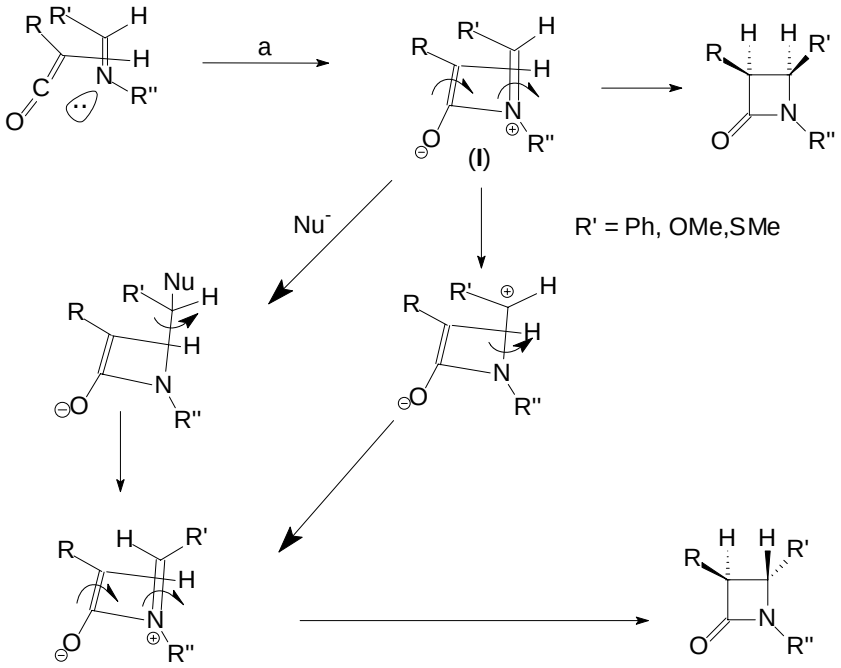
The involvement of a zwitterionic intermediate has been proved by various spectroscopic methods and zwitterion trapping experiments.[59] That the zwitterion intermediate was indeed formed from a ketene precursor was proved by results from Lynch's group[60] wherein, treatment of the acid chloride with 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

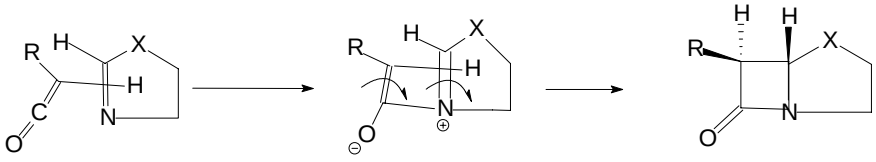
through each other. These stereochemical explanations are in good agreement with the results obtained from many acyclic imines and ketenes.

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).

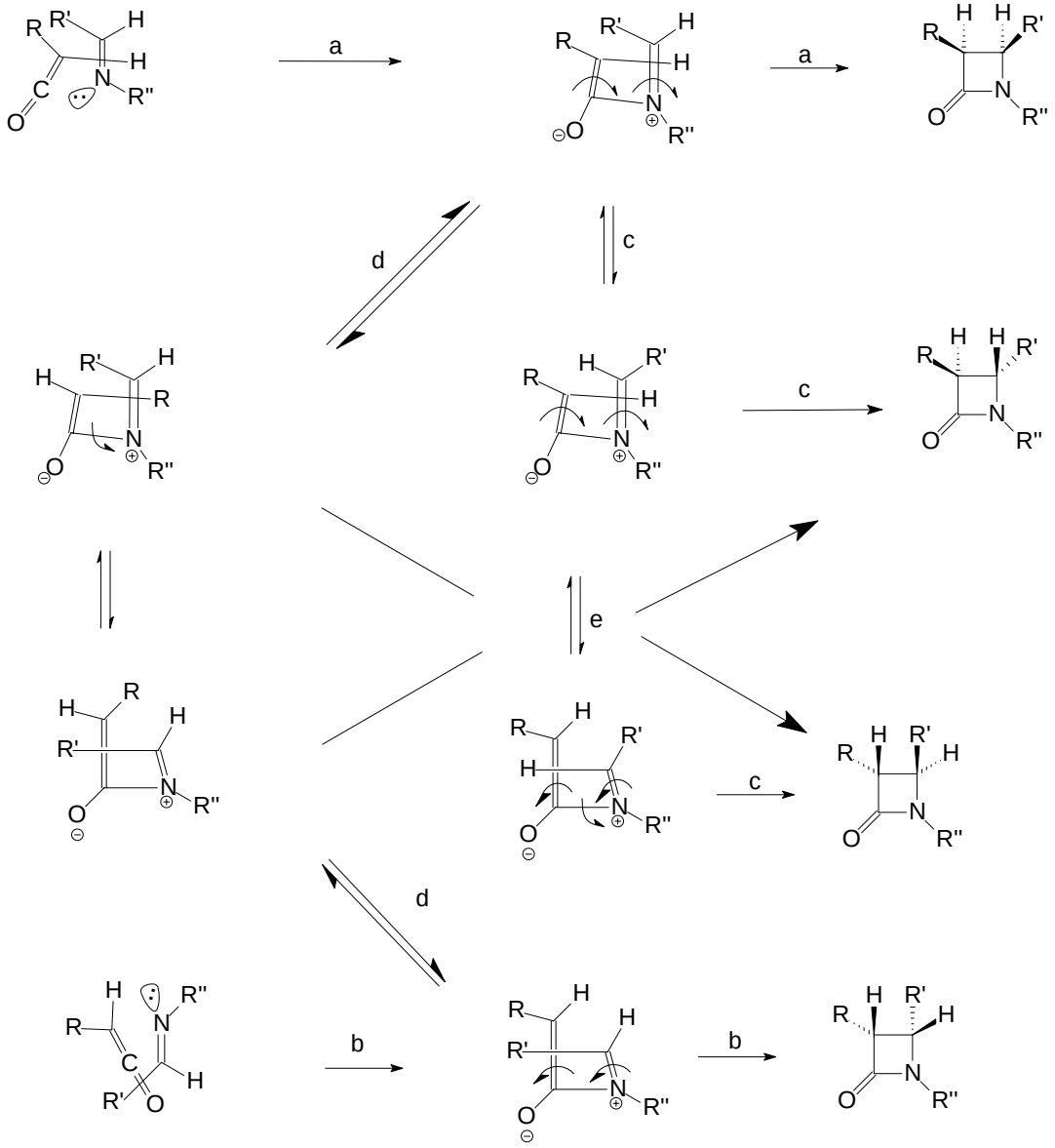
Asymmetric Induction:

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.

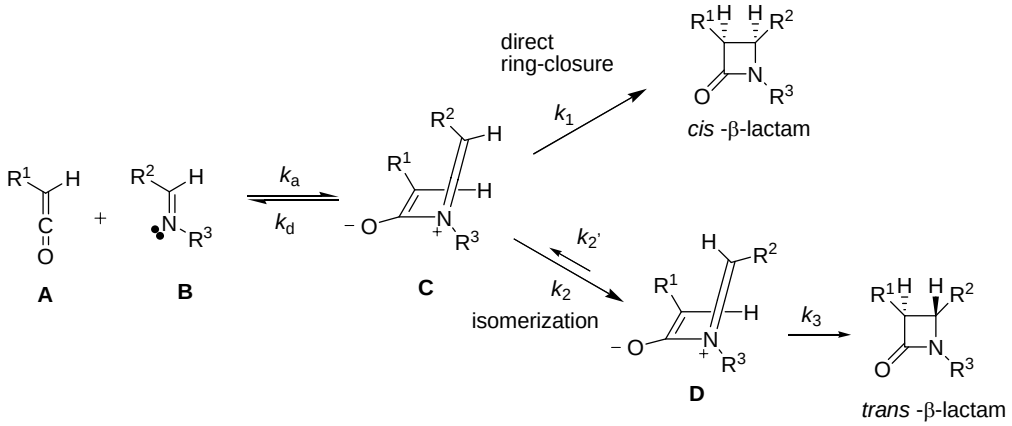
The formation of the thermodynamically more stable *trans* β-lactam from a *trans* imine can only result from isomerization of either the iminium portion (*path c*) or the enolate portion *(path d)* of the zwitterions prior to cyclization. Isomerization should be promoted by substituents that stabilize 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.

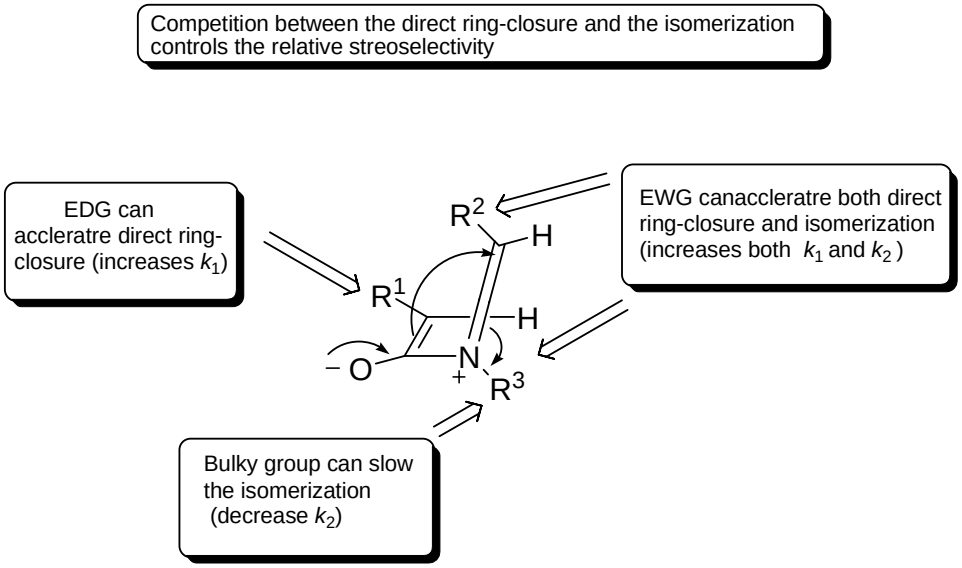


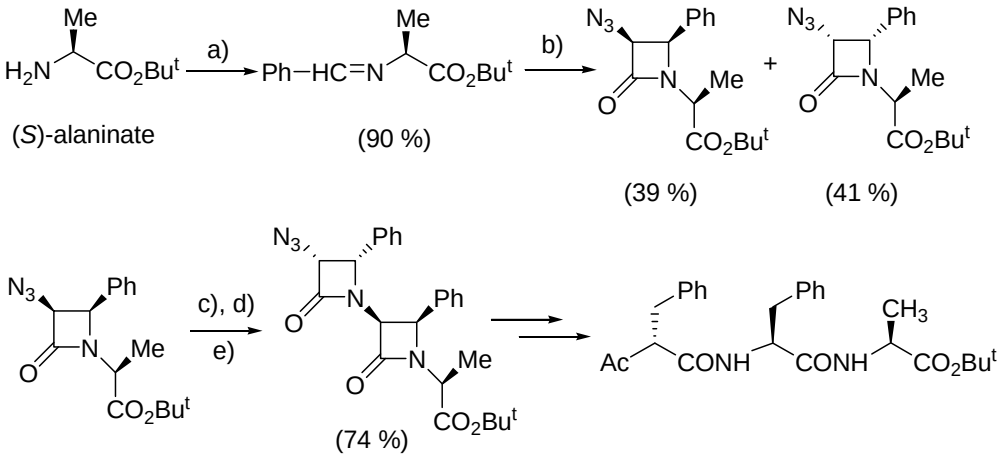
Figure 9

1.2: Background for the present work

Although β-lactam derivatives are well known for their antibiotic activities, [63] they are also emerged as useful intermediates in organic synthesis. Similarly, bis-β-lactams also serves as important intermediates for the synthesis [64] of synthetically useful compounds like bis-azetidines, enantiometrically pure diamines, aminoalcochol, polyaminoalcohols, polyaminoethers and polyamines. It has been proposed that bis-β-lactams may possess more power to attack bacterial targets with two azetidin-2-one rings and penicillin binding proteins (PBP's) that catalyze the peptidoglycan biosynthesis in bacteria.[65] Bis-azetidines are shown to exhibit various biologically activities. Ojima et al.[66] has synthesized bis-β-lactams and used these β-lactams for the synthesis of peptides.[67]

In 1981, Ojima et al. [66a, 68] have investigated the first stepwise synthesis of bis-β-lactams. (*S*)-*N*-Benzylidene1-*t*-butoxycarbonylethylamine was prepared from (*S*)-alaninate and benzaldehyde, and treated with azidoacetyl chloride in presence of triethylamine to get diastereomeric mixture of *cis*-β-lactams. A single diastereomer was further converted into imine *via* reduction followed by reaction with benzaldehyde. This imine on Staudinger reaction with azidoacetyl chloride gave bis-β-lactam in 74% overall yield (Scheme 1.46).

Scheme 1.46

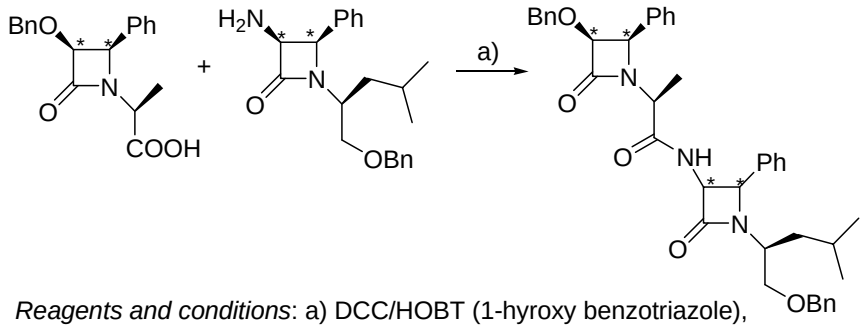


Reagents and conditions: a) PhCHO, An. $MgSO_4$, PhH, rt; b) N_3CH_2COCl, Et_3N, -78 ^oC to rt; c) H_2 (1 atm), 5 % Pd-C, MeOH, rt;d) PhCHO, An. $MgSO_4$, PhH; e) N_3CH_2COCl, Et_3N, -78 ^oC to rt.

In 1991, Ojima et al. [64] have reported the second synthesis of bis-β-lactam *via* coupling of two mono β-lactam rings. The tandem bis-β-lactams were prepared by the coupling of a chiral 3-(benzyloxy)-β-lactam carboxylic acid with a chiral 3-amino-β-

lactam in excellent yield (Scheme 1.47). These bis-β-lactams have been utilized for the synthesis of peptides.

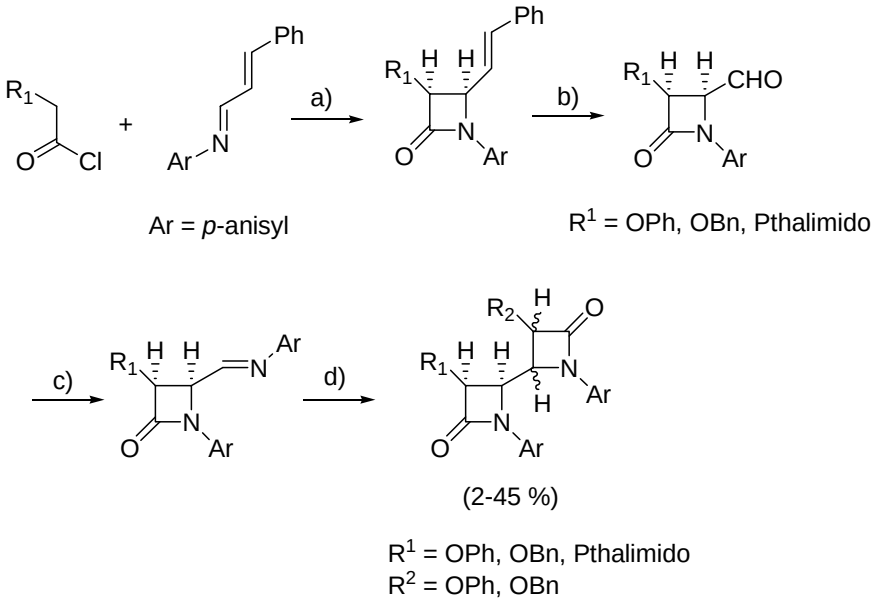
Scheme 1.47



Reagents and conditions: a) DCC/HOBT (1-hyroxy benzotriazole), THF, 0 ^{o}C, Overnight

A step-wise synthesis of bis-β-lactam has been reported by Bose et al.[66b] The β-lactam ring was constructed by ketene-imine cycloaddition (Staudinger reaction) using styryl imine and an acid chloride. The Styryl group at C-4 position was converted to aldehyde by oxidation. The imine derived from this aldehyde on Staudinger reaction with different acid chloride gave bis-β-lactam in 2-45 % over all yields (Scheme 1.48).

Scheme 1.48

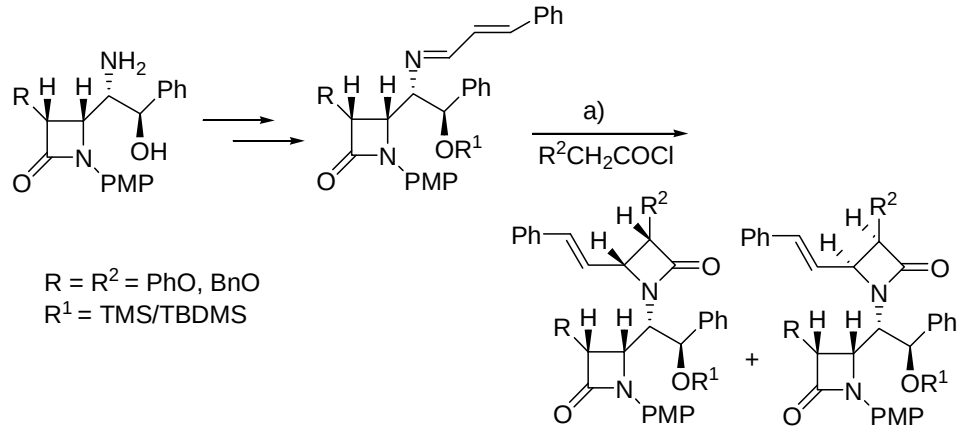


Reagents and conditions: a) Et_3N, dry CH_2Cl_2, 0 ^{o}C to rt, 15h; b) O_3, Me_2S, -78 ^{o}C to rt 15min; c) *p*-anisidine, moleculer sieves, dry CH_2Cl_2, rt 6h; d)Et_3N, dry CH_2Cl_2, 0 ^{o}C to rt, 15.

Jayaraman et al. from our laboratory have used 3-amino substituted optically pure β-lactam [66c] for the step-wise synthesis of bis-β-lactams by converting it to imine followed by cycloaddition reaction with ketene generated from various acid chlorides in

presence of tertiary amines (Scheme 1.49). This methodology gave moderate to high diastereoselectivity (65:35-95:5) in second β-lactam ring construction with good yield (69-96%).

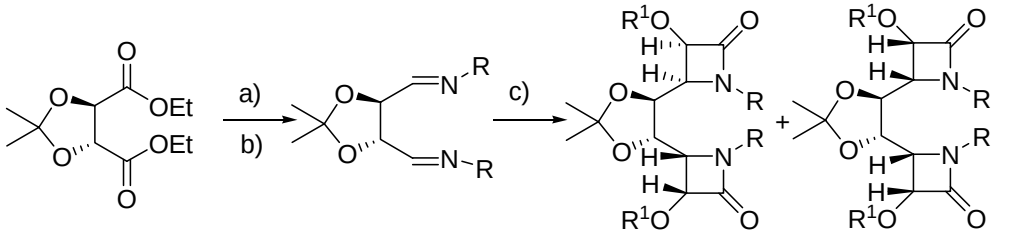
Scheme 1.49



Reagents and conditions: a)Et_3N/DCM, -78 ^oC to rt.

A chiral auxiliary, L(+) tartaric acid [69, 70] was used for one step synthesis of bis-β-lactams in excellent yields. The diester was converted to C_2-symmteric bis-imine *via* reduction followed by reaction with amines. This bis-imine on cycloaddition reaction with ketene gave bis-β-lactams in good yield and diastereoselectivity (Scheme 1.50).

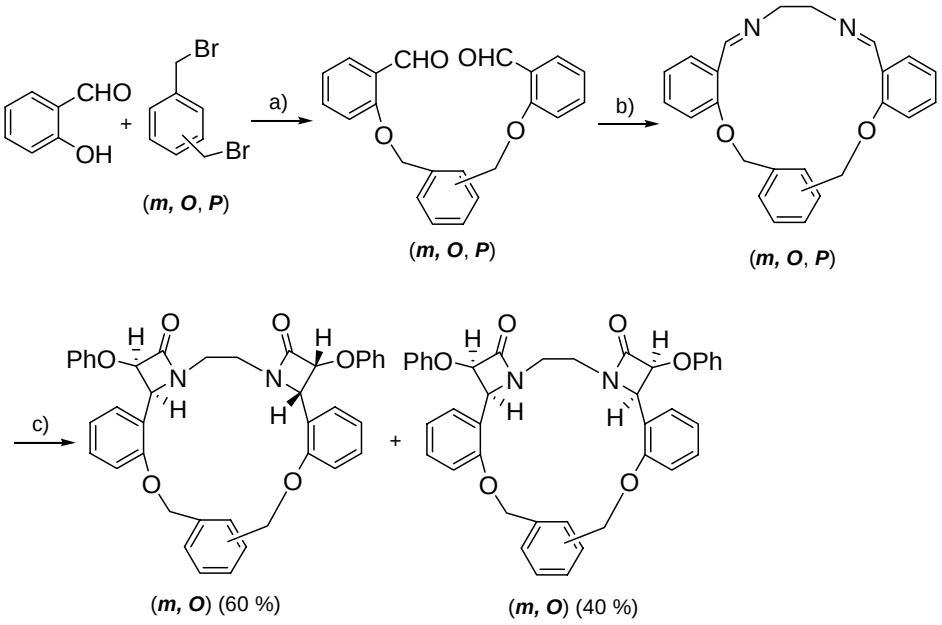
Scheme 1.50



Reagents and conditions: a) DIBALH, toluene, -78 ^oC, 2 h, b) R-NH_2, toluene, rt 15h, c) R^1CH_2COCl, Et_3N, CH_2Cl_2, 0 ^oC- rt, 15h.

Recently, Raghunathan et al.[71] have reported a highly stereoselective synthesis of bis-β-lactam grafted on macrocycles. Incorporation of a β-lactam in a macrocyclic ring was accomplished by Staudinger reaction using appropriate macrocyclic imine (Scheme 1.51).

Scheme 1.51



Reagents and conditions: a) An. K_2CO_3, dry acetone, rt, 3h; b) ethylene diamine, ethanol, rt, 12 h; c) $PhOCH_2COCl$, dry CH_2Cl_2, Et_3N, 0 ^oC-rt, 12 h

1.3: Present work

This section deals with one step synthesis of bis-β-lactam from bis-imines derived from *trans*-1,2-diaminocyclohexane, 1,2-diphenyl-ethylenediamine and 2,3-diaminobutane *via* Staudinger reaction with *in situ* generated ketenes from various acid chlorides.

We selected *trans*-1,2-diaminocyclohexane for the preparation of various bisimines from different aldehydes and these imines were used for the stereoselective construction of bis-β-lactams. *Trans*-1,2-Diaminocyclohexane is one of the few vicinal diamines commercially available in both the enantiomeric forms with wide applications in stereoselective synthesis[72] and chemotherapy.[73] Bisimines derived from *trans*-1,2-diaminocyclohexane have been used as chiral ligands for asymmetric epoxidation, [74] cyclopropanation, [75] Diels-Alder reaction, [76] asymmetric alkylation[77] and several other asymmetric reactions.[78] Garwronski et al.[79] have shown that out of four different conformations of *N*, *N*-dibenzylidine-1, 2-diaminocyclohexane, *syn*-*syn*-bisimine **A** is the most favored conformation (Figure 10). We were interested in studying the effect of this conformational preference on the product formation in [2+2] cycloaddition reaction of bisimine and ketene.

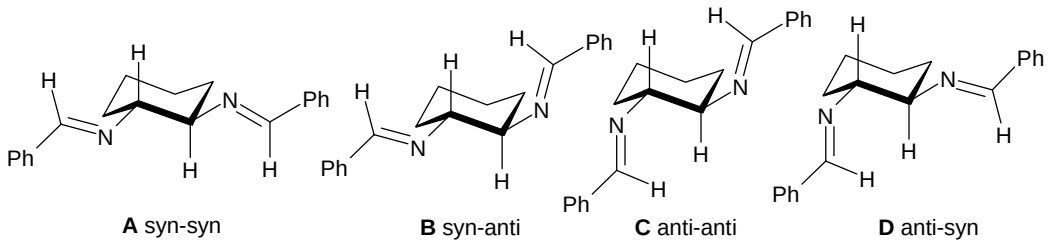


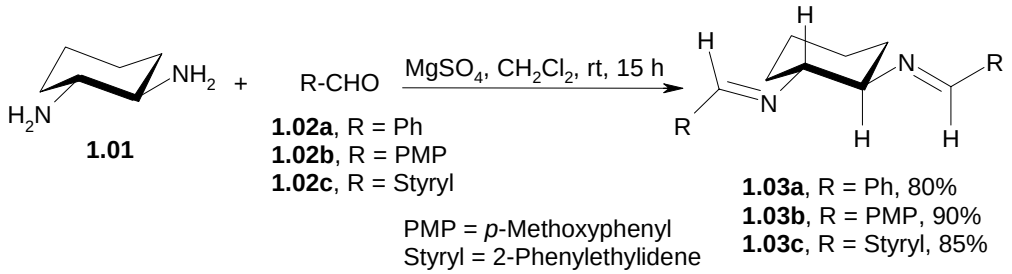
Figure 10 Conformations of *N*, *N´*-dibenzylidinecyclohexane-1, 2-diamine

1.4: Results and Discussion

1.4.1 Preparations of bis-imines 1.03a, 1.03b and 1.03c

The bisimines (**1.03a-c**) were prepared by stirring (±) *trans*-1,2-diaminocyclohexane and freshly distilled excess aromatic aldehydes using a reported procedure in excellent yields (Scheme 1.52).[80]

Scheme 1.52



The imine **1.03a** has been chosen as a representative compound for spectral discussion and characterization. The IR spectrum of **1.03a** showed a strong absorption band at 1641 cm^{-1} for to C=N. The ^{1}H NMR spectrum of **1.03a** showed a multiplet at 1.03 to 2.07 ppm for the cyclohexane CH_2 protons, a multiplet appeared at 3.21 to 3.45 ppm for the cyclohexane C*H* proton. The aromatic protons appeared as multiplet at 7.12 to 7.64 ppm. A sharp singlet appeared at 8.15 ppm was assigned to methyne protons of imine. The ^{13}C NMR spectrum of **1.03a** showed peak at 24.5, 32.9 ppm for the cyclohexane *C*H_2 carbons, which were identified by ^{13}C-DEPT experiment, peak observed at 73.7 ppm for cyclohexane C*H* carbon. The aromatic carbons appeared at 127.9, 128.2, 130.0 and 136.5 ppm. The imine carbon appeared at 160.8 ppm. The mass spectrum of **1.03a** gave M+1 peak at *m*/*z* 290, also supporting the structure of the compound.

1.4.2 Preparations of bis-β-lactams 1.05a-i and 1.06a-i

Bisimines (**1.03a-c**) on cycloaddition reaction (Staudinger reaction) with ketenes generated from various acid chlorides (phenoxyacetyl chloride, benzyloxyacetyl chloride and methoxyacetyl chloride) in the presence of triethylamine gave diastereomeric mixtures of *cis*-bis-β-lactams **1.05a–i** and **1.06a–i** in good to excellent yields (Scheme 1.53, Table 1). The TLC and ^{1}H NMR spectra of the crude reaction mixture showed the presence two diastereomers. These diastereomers were separated by flash column chromatography to give pure bis-β-lactams in very good yield. Higher selectivity for *meso* bis-β-lactam formation was observed in the cycloaddition reaction (Table 1).

Scheme 1.53

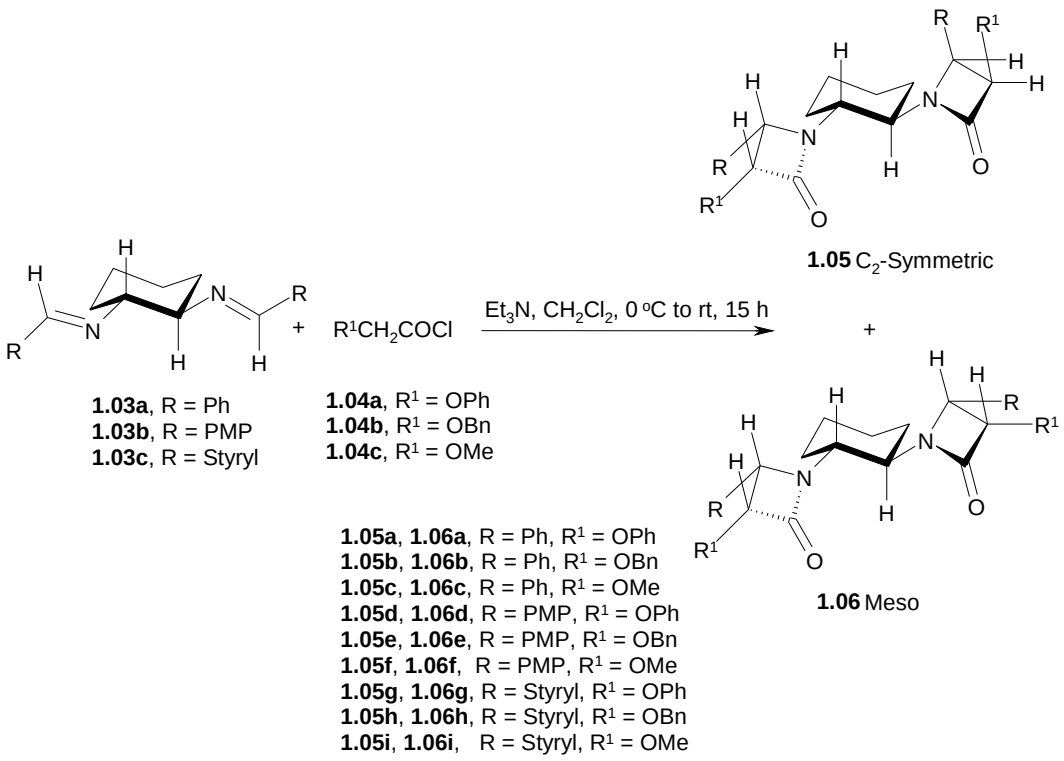
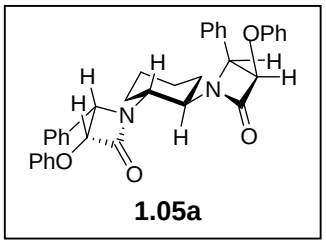


Table 1. Synthesis of bis-β-lactams **1.05a-i** and **1.06a-i**

β-lactams	**R**[a]	**R**[1]	Ratio of **1.05** and **1.06**[b]	Yield (%)[c]	Mp of **1.05** (˚C)[d]	Mp of **1.06** (˚C)[d]
a	-Ph	-OPh	34:66	90	231-232	82-83
b	-Ph	-OBn	34:66	87	111-112	72-73
c	-Ph	-OMe	23:77	86	247-248	191-192
d	-PMP	-OPh	22:78	93	158-159	209-210
e	-PMP	-OBn	28:72	80	194-195	123-124
f	-PMP	-OMe	24:76	73	229-230	84-85
g	-Styryl	-OPh	36:64	88	245-246	175-176
h	-Styryl	-OBn	46:54	81	179-180	61-62
i	-Styryl	-OMe	42:56	86	211-212	79-80

[a] PMP = *p*-Methoxyphenyl; Bn = benzyl.
[b] The ratio of the diastereomers **1.05** and **1.06** was determined by ^{1}H NMR.
[c] Isolated yields of the diastereomeric mixture of **1.05** and **1.06**.
[d] Pure diastereomers were obtained by flash column chromatography.

The compound **1.05a** was chosen as a representative of **1.05** series for spectral discussion and characterization. The structure and stereochemistry of **1.05a** was established by COSY and NOESY 2D NMR techniques and single crystal X-ray crystallography.



1.05a

The IR spectrum of **1.05a** showed a strong absorption at 1745 cm^{-1} indicating the presence of carbonyl group of β-lactam ring. In the ^{1}H NMR spectrum, the methylene protons of cyclohexane ring appeared as multiplet at 0.69 to 1.80 ppm. The methyne protons of cyclohexane ring showed a broad doublet at 3.97 ppm (J = 9 Hz). The four β-lactam protons appeared together as two doublets. The C-4H and C-3H β-lactam protons appeared as two doublets at 5.27 and 5.39 ppm respectively with coupling constant J = 4.7 Hz. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values (J = 4.7 Hz). In general, if the coupling constant range is in between 4-5 Hz, the stereochemistry of the β-lactam ring is *cis* and if the coupling constant range is 2-3 Hz, then the stereochemistry of the β-lactam ring is *trans*. The presence of only two doublets, integrating for two protons each, for β-lactam protons of both the ring and one broad doublet for two protons for methine protons with coupling constant (J = 9 Hz) indicates C_2 symmetry in the molecule. The twenty aromatic protons appeared as a set of multiplets between 6.48 and 7.73 ppm.

In the ^{13}C NMR spectrum, cyclohexane methylene carbons appeared at 24.4, 30.1 ppm, which was identified by ^{13}C-DEPT experiment, cyclohexane methine carbon was seen at 54.0 ppm. The β-lactam ring carbons, C-4 and C-3 appeared at 61.4, 81.6 ppm respectively. The aromatic carbons appeared in the region of 115.7 to 156.8 ppm. The β-lactam carbonyl carbon showed a single peak for both the carbonyl carbons at 167.7 ppm.

COSY experiment was carried out for **1.05a** to further confirm the bond connectivities (Figure 11). The methine proton of cyclohexane moiety showed a strong interaction with the other methine proton of cyclohexane moiety. The β-lactam proton C-3H showed a strong coupling with C-4H proton. The methylene protons of cyclohexane moiety also showed strong interactions.

The NOESY spectrum of **1.05a** gave an idea about the stereo alignment of the newly generated β-lactam protons (Figure 12). The C-4H proton of one β-lactam ring

showed interaction with C-3H proton. The orientation of C-4H and C-3H of one β-lactam ring protons was on the same side.

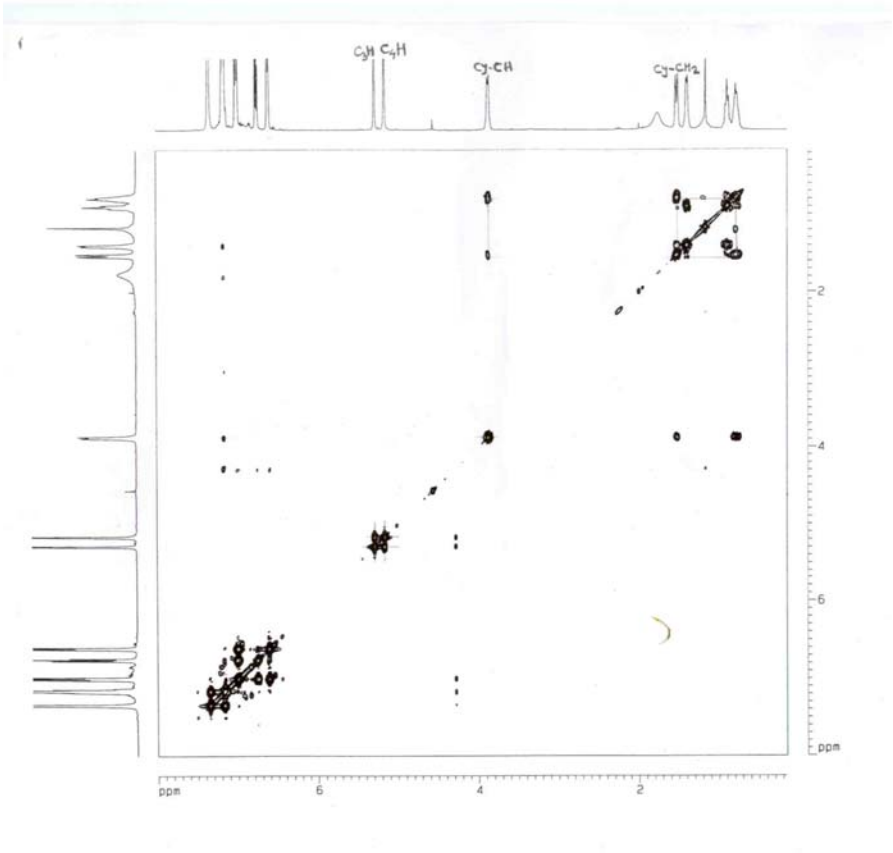


Figure 11 COSY 2D NMR spectrum of **1.05a**

proton	ppm	*J*	^{1}H-^{1}H connectivity
C*H*-Cy	3.97 (d)	9 Hz	CH_2-Cy
C4*H*	5.27 (d)	4.7 Hz	C3*H*
C3*H*	5.39 (d)	4.7 Hz	C4*H*

Other β-lactam ring proton C'-4H showed interaction with C'-3H proton that indicated the β-lactam ring protons was on the same side. The mass spectrum of **1.05a** gave M+1 peak at *m*/*z* 588, also supporting the structure of the compound. The compound **1.05a** also gave a satisfactory elemental analysis. All the other bis-β-lactams showed two characteristics doublets (Table 2) in the range of 4.49 to 5.34 ppm for corresponding protons at C4 and C3 of β-lactam ring with the *J* values range between 4.3 and 4.7 Hz. The coupling constant indicates *cis* stereochemistry of these protons.

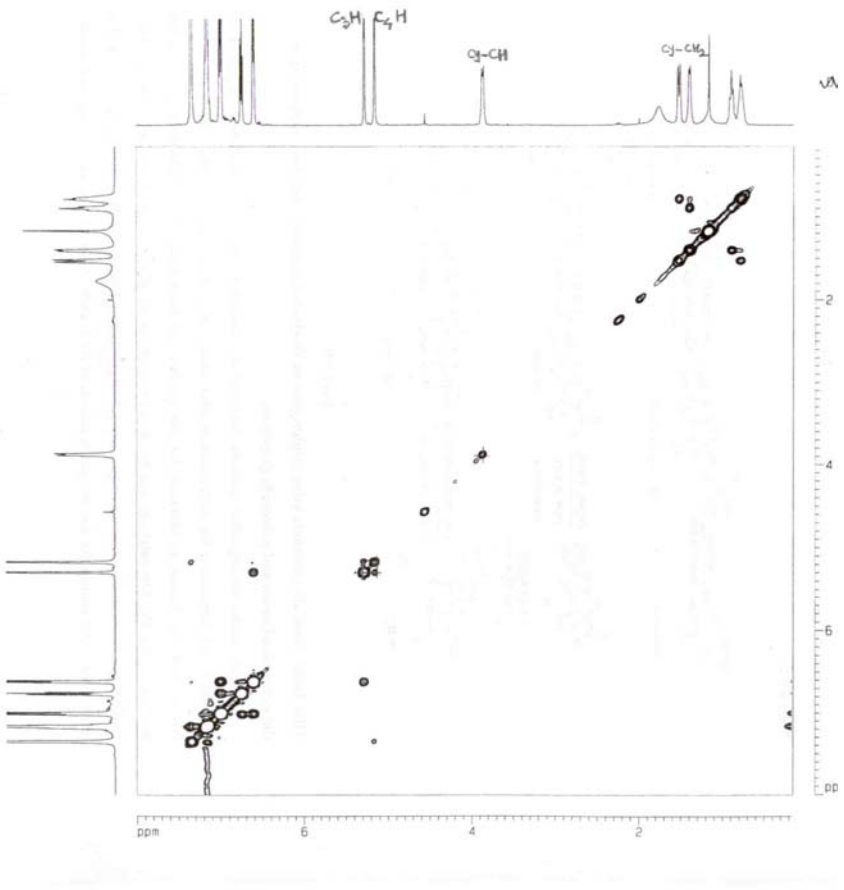


Figure 12 NOESY 2D NMR spectrum of **1.05a**

Table 2. ^{1}H NMR data for bis-β-lactams **1.05.**

Compound No	Chemical Shifts and *J* values for protons at C3 and C4 of β-lactam **1.05**	
	C4-H	C3-H
1.05b	4.89 (d, *J* = 4.3 Hz)	5.11 (d, *J* = 4.3 Hz)
1.05c	4.49 (d, *J* = 4.3 Hz)	4.92 (d, *J* = 4.3 Hz)
1.05d	5.22 (d, *J* = 4.7 Hz)	5.34 (d, *J* = 4.7 Hz)
1.05e	4.78 (d, *J* = 4.3 Hz)	5.01 (d, *J* = 4.3 Hz)
1.05f	4.55 (d, *J* = 4.3 Hz)	4.96 (d, *J* = 4.3 Hz)
1.05g	4.88 (dd, *J* = 4.7, 8.2 Hz)	5.29 (d, *J* = 4.7 Hz)
1.05h	4.65 (dd, *J* = 4.3, 9.4 Hz)	4.73 (d, *J* = 4.3 Hz)
1.05i	4.49 (dd, *J* = 4.3, 9.4 Hz)	4.62 (d, *J* = 4.3 Hz)

The presence of C_2 symmetry in these compounds was further confirmed from X-ray crystal structure analysis of the compound **1.05a** from this series (Figure 15).

1.4.3a. X-ray structure determination of 1.05a

In order to ascertain the relative stereochemistry of the bis-β-lactam **1.05a,** single crystal X-ray analysis was undertaken. X-ray quality crystals of **1.05a** were obtained by careful recrystallization from dichloromethane-petroleum ether. The data for the compounds was collected at T = 295 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. All the data were corrected for Lorentzian, polarisation and absorption effects. The structure was solved by direct methods using SHELX-97 (ShelxTL) [81] and refined by full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

Table 3: Crystal data and structure refinement for **1.05a**

Empirical formula	$C_{36}H_{34}N_2O_4$
Formula weight	558.65
Crystal system, space group	Orthorhombic, Pccn
Unit cell dimensions	a = 24.698(2) Å b = 6.423(1) Å c = 18.595(2) Å
Volume	2949.8(5) $Å^3$
Z, Calculated density	4, 1.258 g cm^{-3}
Absorption coefficient	0.082 mm^{-1}
F(000)	1184
Crystal size	0.69 x 0.57 x 0.06 mm
Reflections collected /unique	2604/13786
Final R indices [I>2σ(I)]	R = 0.0470, Rw = 0.0971
Largest diff. peak and hole	0.142 and -0.145 e. $Å^{-3}$

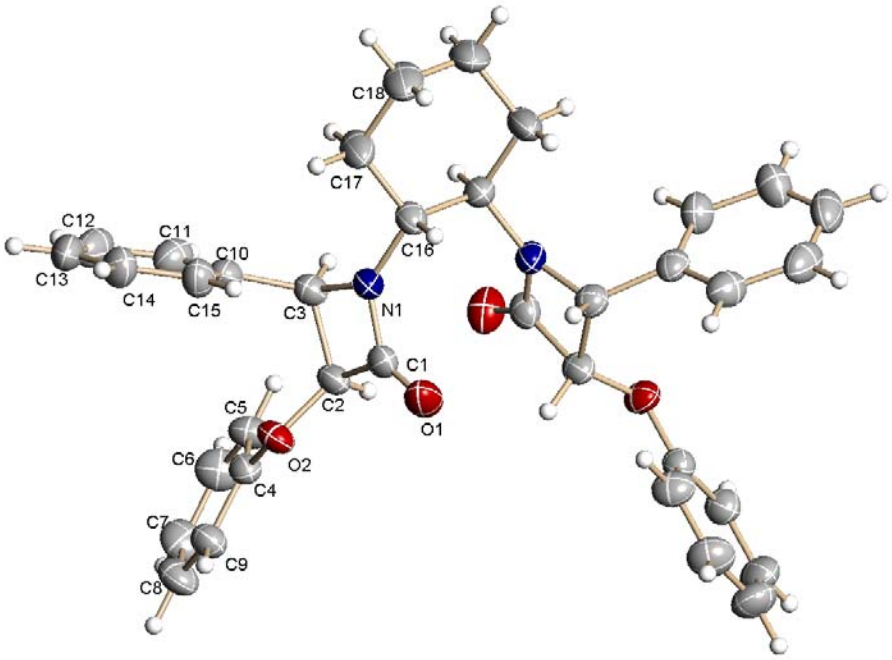
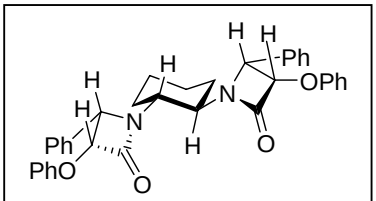


Figure 15 ORTEP diagram of **1.05a**

The compound **1.06a** was chosen as a representative of **1.06** series for spectral discussion and characterization. The structure and stereochemistry of **1.06a** was studied by COSY and NOESY 2D NMR techniques and single crystal X-ray crystallography. The IR spectrum of **1.06a** showed a strong absorption at 1753 cm^{-1} indicating the presence of carbonyl group of β-lactam ring. In the ^{1}H NMR spectrum, the methylene protons of cyclohexane ring appeared as multiplet at 0.83 to 2.06 ppm. The two methine protons of cyclohexane ring showed a set of multiplets at 3.55-3.60 ppm and 3.71-3.76 ppm respectively. The four β-lactam protons appeared as four doublets. The C-4H and C-3H of one β-lactam ring protons appeared as two doublets at 5.05 and 5.40 ppm respectively with coupling constant J = 4.7 Hz. The C'-4H and C'-3H of second β-lactam ring protons appeared as two doublets at 5.47 and 5.56 ppm respectively with coupling constant J = 4.6 Hz. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values. The presence of four doublets, integrating for one proton each, for β-lactam protons of both the ring and two multiplets integrating for one proton each



1.06a

for methine protons indicates unsymmetry (*meso*) in the molecule. The twenty aromatic protons appeared as a set of multiplets between 6.72 and 7.55 ppm.

The ^{13}C NMR spectrum of **1.06a** showed cylcohexane methylene carbons appeared at 24.1, 29.2, 31.3 ppm. Cyclohexane methine carbons showed two peaks at 53.4, 55.2 ppm. Both β-lactam ring carbons of C-3, C'-3 and C-4, C'-4 appeared at 61.2, 62.2 ppm and 81.1, 81.3 ppm respectively. The aromatic carbons appeared in the region of 115.7 to 157.0 ppm. The two β-lactam carbonyl showed two peaks at 166.4, 166.5 ppm. Higher selectivity for *meso* bis-β-lactam formation was observed in the cycloaddition reaction (Table 1).

2D COSY experiment was carried out for **1.06a** to confirm the bond connectivities (Figure 13). The methyne proton of cyclohexane moiety showed a strong interaction with the other methyne proton of cyclohexane moiety, which in turn showed connectivity with the methylene proton of cyclohexane. Both the β-lactam ring protons of C-3H showed a strong interaction with C-4H proton. The methylene protons of cyclohexane also showed strong interactions with methine protons.

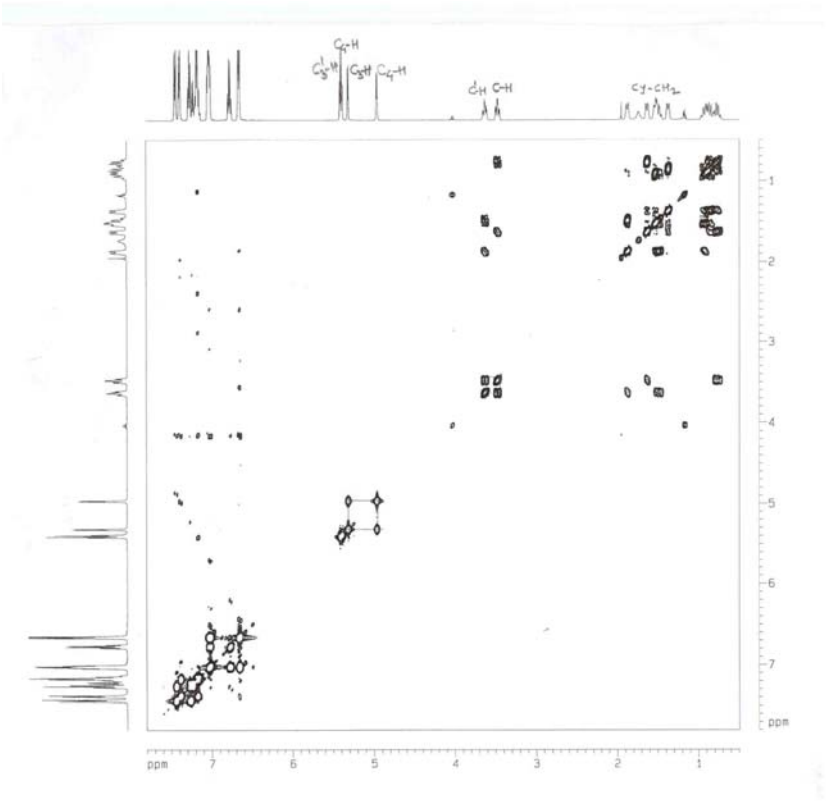


Figure 13 COSY 2D NMR spectrum of **1.06a**

proton	ppm	*J*	^{1}H-^{1}H connectivity
C4*H*	5.05 (d)	4.7 Hz	C3*H*
C3*H*	5.40 (d)	4.7 Hz	C4*H*
C'4*H*	5.47 (d)	4.6 Hz	C'3*H*
C'3*H*	5.56 (d)	4.6 Hz	C'4*H*

The NOESY spectrum of **1.06a** explained the stereochemistry of the newly generated β-lactam protons (Figure 14). Both the β-lactam ring protons C-4H showed NOE interaction with C-3H proton, indicating the *cis* orientation of C-4H and C-3H of both β-lactam ring protons.

The mass spectrum of **1.06a** gave M+1 peak at *m*/*z* 588, also supporting the structure of the compound. The compound **1.06a** also gave a satisfactory elemental analysis.

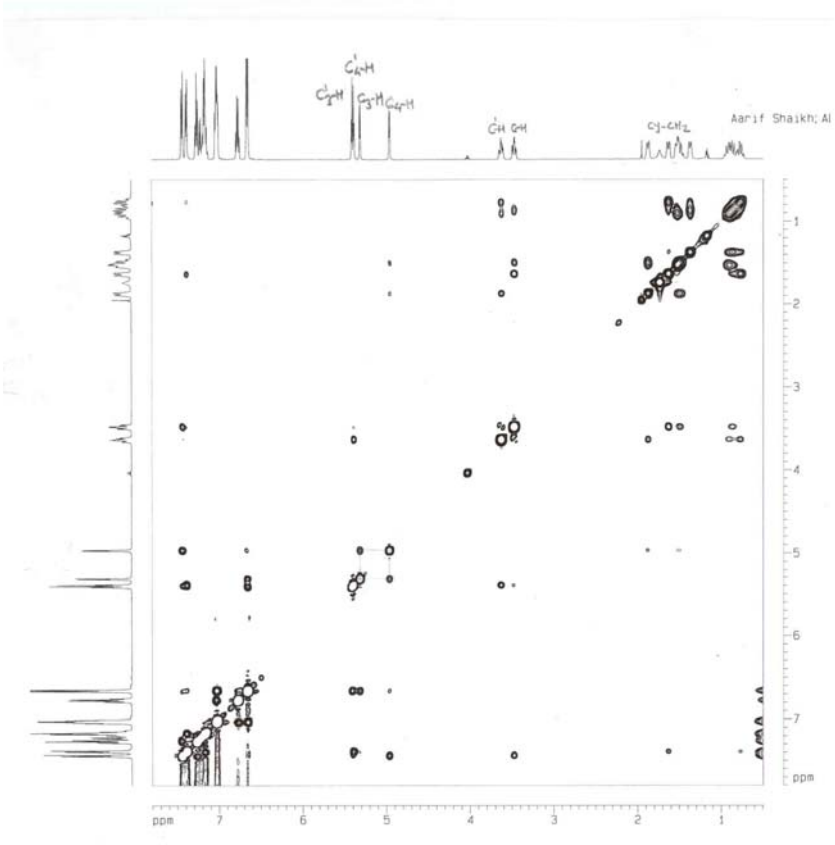


Figure 14 NOESY 2D NMR spectrum of **1.06a**

Table 3. ^{1}H NMR data for bis-β-lactams **1.06.**

Compound No	Chemical Shifts and *J* values for protons at C3 and C4 of β-lactam **1.06**	
	C4-H / C3-H	C'4-H / C'3-H
1.06b	4.85(d), 4.88 (d)(*J* = 4.7 Hz)	4.98(d), 5.29(d) (*J* = 4.3 Hz)
1.06c	4.47(d), 4.56 (d)(*J* = 4.3 Hz)	4.64(d), 5.06(d) (*J* = 4.7 Hz)
1.06d	5.01(d), 5.37 (d)(*J* = 4.7 Hz)	5.46(d), 5.50(d) (*J* = 4.3 Hz)
1.06e	4.76(d), 4.89 (d)(*J* = 4.7 Hz)	4.91(d), 5.21(d) (*J* = 4.3 Hz)
1.06f	4.60(d), 4.70 (d)(*J* = 4.7 Hz)	4.76(d), 5.22(d) (*J* = 4.3 Hz)

All the other bis-β-lactams showed four characteristics doublets (Table 3) in the range of 4.47 to 5.50 ppm for corresponding protons at C4 and C3 of both β-lactam rings with the *J* values range between 4.3 and 4.7 Hz. The coupling constant indicates *cis* stereochemistry of these protons. The presence of two multiplets for the methyne protons of cyclohexane moiety and four doublets for both the β-lactam ring protons suggests unsymmetrical structure for these compounds, which was further confirmed from single X-ray crystal structure analysis of the compound **1.06a** from this series (Figure 16).

1.4.3b. X-ray structure determination of 1.06a

In order to ascertain the relative stereochemistry of the bis-β-lactam **1.06a**, single crystal X-ray analysis was undertaken. X-ray quality crystals of **1.06a** were obtained by careful recrystallization from Methanol. The data for the compounds was collected at *T* = 295 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. All the data were corrected for Lorentzian, polarisation and absorption effects. The structure was solved by direct methods using SHELX-97 (ShelxTL) [81] and refined by full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

Table 4: Crystal data and structure refinement for **1.06a**

Empirical formula	$C_{36}H_{34}N_2O_4$
Formula weight	558.65

Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 13.722 (1) Å b = 18.657 (1) Å c = 12.768 (1) Å β = 111.342(1) Å
Volume	3044.4(4) $Å^3$
Z, Calculated density	4, 1.219 g cm^{-3}
Absorption coefficient	0.079 mm^{-1}
F(000)	1184
Crystal size	0.78 x 0.18 x 0.08mm
Reflections collected /unique	5361/21926
Final R indices [I>2σ(I)]	R = 0.0460, Rw = 0.0970
Largest diff. peak and hole	0.143 and -0.144 e. $Å^{-3}$

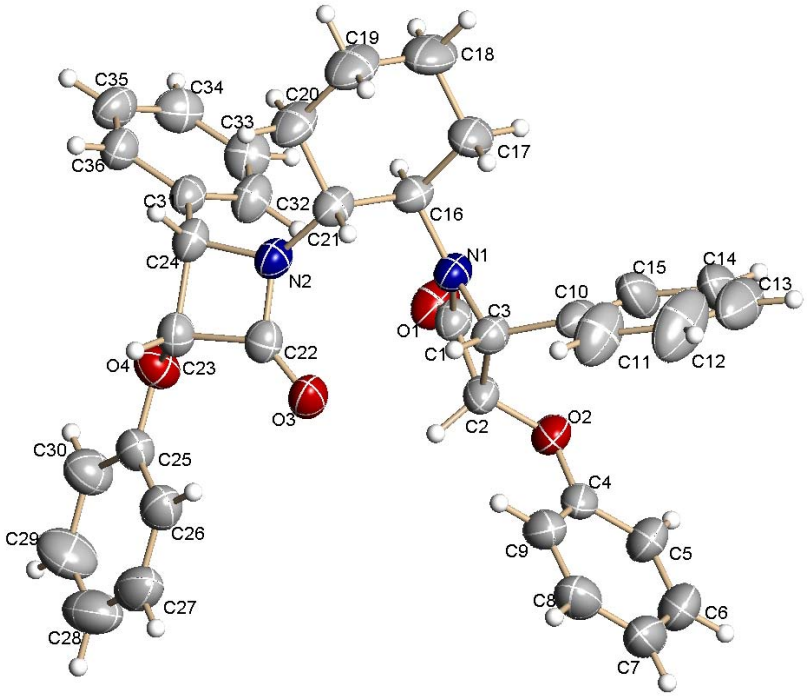
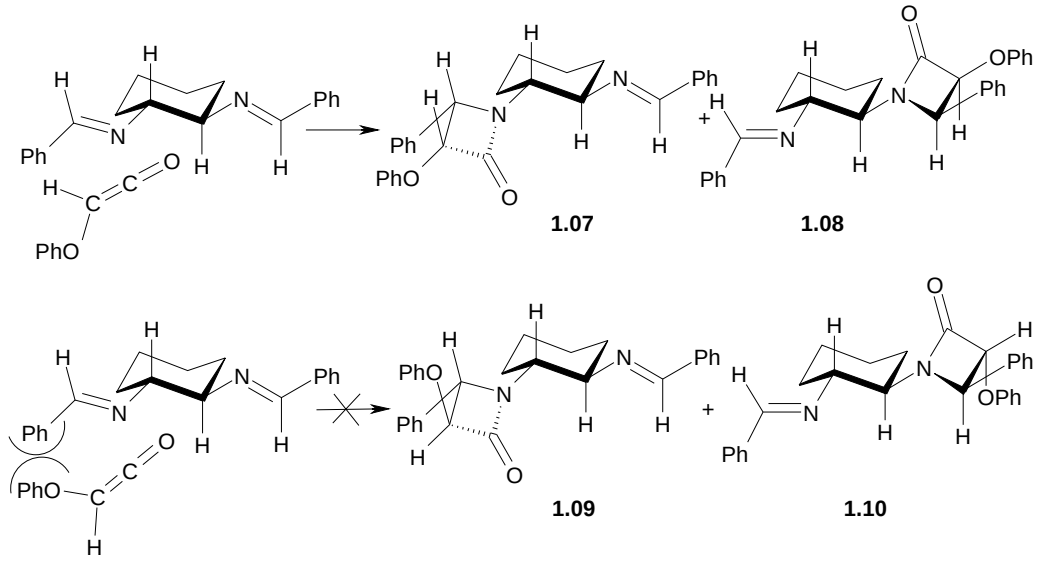


Figure 16 ORTEP diagram of **1.06a**

Mechanism of bis-β-lactams formation:

We believe that mono-β-lactam is initially formed by the reaction of the most stable *syn-syn* bis-imine conformer **A** with ketene. The approach of the ketene in the Staudinger cycloaddition reaction is such that the steric interaction between the aryl group of the imine and phenoxy group of the ketene is minimum in the transition state (Scheme 1.53) resulting in the formation of *cis*-β-lactam **1.07** and **1.08**. However, the formation of *trans*-β-lactam **1.09** and **1.10** is unfavorable due to severe steric interaction between the aryl group of imine and phenoxy group of ketene in the transition state.

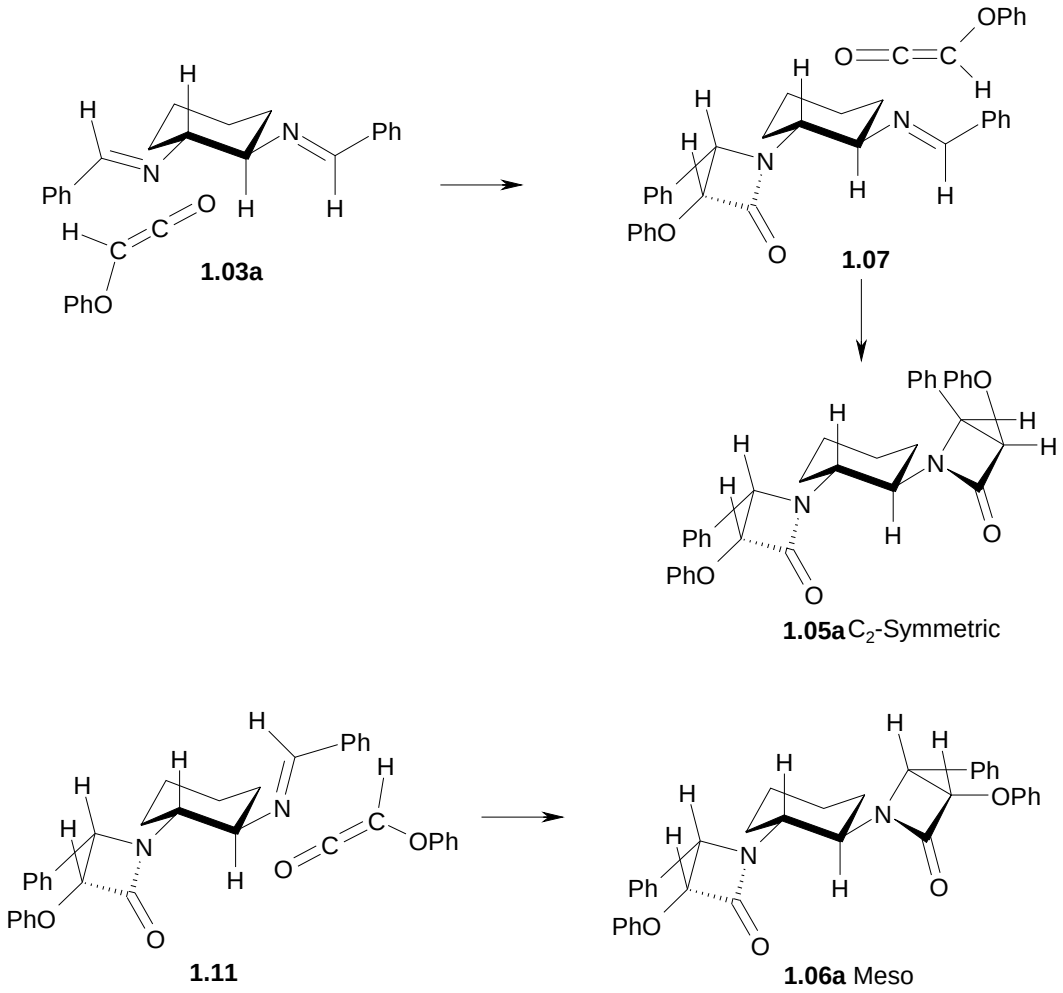
Scheme 1.53



The mono-β-lactam **1.07** further undergoes cycloaddition reaction with the second molecule of ketene to give bis-β-lactam (Scheme 1.54). The approach of the second ketene towards the *syn*-imine **1.07** is from the opposite site of the preformed azetidinone ring to give C_2-symmetric bis-β-lactam **1.05a**. However, *meso* bis-β-lactam **1.06a** is formed by the cycloaddition of *anti*-imine **1.11** with the second molecule of ketene from opposite site of the preformed β-lactam ring as shown in the Scheme 1.53. To substantiate this, cycloaddition reaction of bis-imine **1.03a** with one equivalent of phenoxyketene, generated *in situ* from phenoxyacetyl chloride and triethylamine, was carried out. The ^{1}H NMR of the crude reaction product showed the formation of two diastereomers of mono-β-lactams **1.07** and **1.08** in equal amount along with traces of bis-β-lactams **1.05a** and **1.06a**. However, all our attempts to separate the diastereomers were unsuccessful. This mixture was further subjected to Staudinger reaction with one

equivalent of phenoxyketene to get mixture of bis-β-lactams **1.05a** and **1.06a** in good yield.

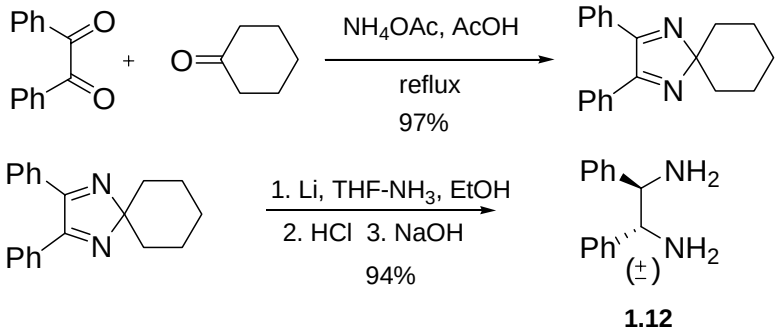
Scheme 1.54



1.4.4 Synthesis of (±) 1,2-diphenyl-1,2-ethylenediamne (1.12)

(±)1,2-Diphenyl-1,2-ethylenediamine **1.12** was synthesized by following reported procedure.[82] A mixture of glacial acetic acid, benzil, ammonium acetate and cyclohexanone was refluxed with stirring for 1.5 hr to get spiroimine in excellent yield which on further Birch reduction to afford (±) 1, 2-diphenyl-1,2-ethylenediamine in 94 % yield (Scheme-1.55).

Scheme 1.55

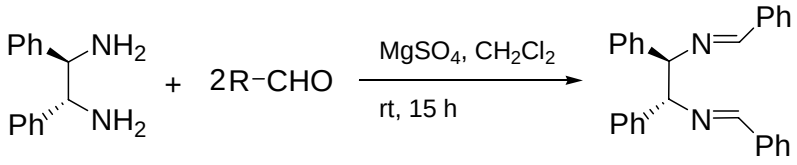


1.12

1.4.5 Preparations of bis-imine 1.13

The bisimine **1.13** was prepared by stirring (±) 1,2-diphenyl-1,2-ethylenediamine and freshly distilled benzaldehyde in excellent yield. The structure of the imine **1.13** has been confirmed by spectroscopic methods (Scheme 1.56).

Scheme 1.56

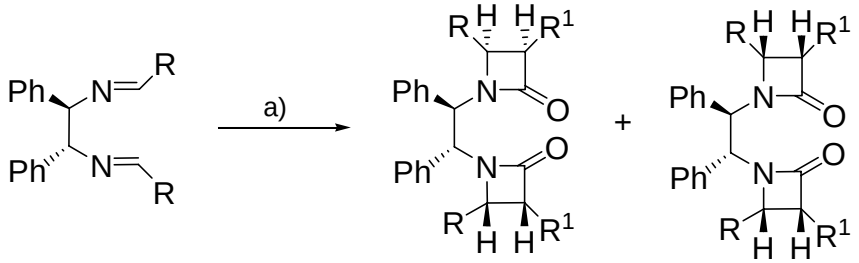


1.12 **1.13**

1.4.6 Preparations of bis-β-lactams 1.14a-c and 1.15a-c

Bisimines **1.13** on cycloaddition reaction (Staudinger reaction) with ketenes generated from various acid chlorides (phenoxyacetyl chloride, benzyloxyacetyl chloride and methoxyacetyl chloride) in the presence of triethylamine gave diastereomeric mixtures of *cis*-bis-β-lactams **1.14a-c** and **1.15a-c** in good to excellent yields (Scheme-1.57, Table 4). The TLC and ^{1}H NMR spectra of the crude reaction mixture showed the presence of two diastereomers. These diastereomers were separated by flash column chromatography. The C_2-symmetric structure for bis-β-lactam **1.14a-c** and the *meso* structure **1.15a-c** were confirmed by spectral and analytical data. Higher selectivity for *meso* bis-β-lactam formation was observed in the cycloaddition reaction.

Scheme 1.57



1.13 **1.14a-c** C_2-Symmetric **1.15a-c** Meso

Reagents and conditions:
a) R^1CH_2COCl, Et_3N,CH_2Cl_2, 0 °C to rt, 15 h

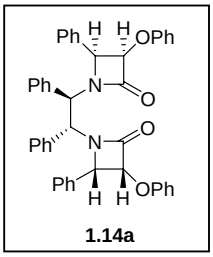
1.14a, **1.15a**, R = Ph, R^1 = OPh
1.14b, **1.15b**, R = Ph, R^1 = OBn
1.14c, **1.15c**, R = Ph, R^1 = OMe

Table 4. Synthesis of bis-β-lactams **1.14a-c** and **1.15a-c**

Compound **1.14** and **1.15**	**R**	**R^1**	Ratio of **1.14** and **1.15**[a]	Yield (%)[b]	Mp of **1.14** (˚C)[c]	Mp of **1.15** (˚C)[c]
a	-Ph	-OPh	42:58	81	197-198	201-202
b	-Ph	-OBn	44:56	84	190-191	79-80
c	-Ph	-OMe	40:60	88	194-195	201-202

[a] The ratio of the diastereomers **1.14** and **1.15** was determined by ^{1}H NMR.
[b] Isolated yields of the diastereomeric mixture of **1.14** and **1.15**.
[c] Pure diastereomers were obtained by flash column chromatography.

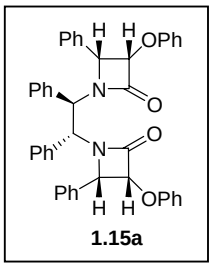
The compound **1.14a** was chosen as a representative of **1.14** series for spectral discussion and characterization. The IR spectrum of **1.14a** showed a strong absorption at 1757 cm^{-1} indicating the presence of carbonyl group of β-lactam ring. In the ^{1}H NMR spectrum, the methyne protons of 1,2 diphenyl moiety appeared as singlet at 5.19 ppm for two protons. The four β-lactam protons appeared together as two doublets. The C-4H and C-3H β-lactam protons appeared as two doublets at 5.34 and 5.55 ppm respectively with coupling constant J = 4.1 Hz. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values (J = 4.1 Hz). The presence of only two doublets, integrating for two protons each, for β-lactam protons of both the ring and one singlet for two protons for methine protons of 1,2 diphenyl moiety indicates C_2 symmetry in the molecule. The thirty aromatic protons appeared as a set of multiplets between 6.69 and 7.70 ppm.



1.14a

In the ^{13}C NMR spectrum, 1,2-diphenyl methine carbon appeared at 59.9 ppm. The β-lactam ring carbons, C-4 and C-3 appeared at 60.9, 73.1 ppm respectively. The aromatic carbons appeared in the region of 111.5 to 152.7 ppm. The β-lactam carbonyl carbon showed a single peak for both the carbonyl carbons at 167.2 ppm. The mass spectrum of **1.14a** indicated M+1 peak at *m*/*z* 608, also supports the structure. The compound **1.14a** also gave satisfactory elemental analysis.

The compound **1.15a** was chosen as a representative of **1.15** series for spectral discussion and characterization. The IR spectrum of **1.15a** showed a strong absorption at 1751 cm^{-1} indicating the presence of carbonyl group of β-lactam ring. The ^{1}H NMR spectrum showed, the methine protons of 1,2 diphenyl moiety appeared as multiplet at 5.24-5.34 ppm for two protons. The four β-lactam protons appeared together as four doublets. The C-4H and C-3H β-lactam protons of one β-lactam ring appeared as two doublets at 4.85 and 5.43 ppm respectively with coupling constant J = 4.7 Hz. The C'-4H and C'-3H β-lactam protons of other β-lactam ring appeared as two doublets at 5.33 and 5.57 ppm respectively with coupling constant J = 4.3 Hz. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values. The presence of four doublets, integrating for one proton each, for β-lactam protons of both the ring and one multiplet for two protons for methine protons of 1,2 diphenyl indicates unsymmetry (*meso*) in the molecule. The thirty aromatic protons appeared as multiplet between 6.67 and 7.40 ppm.



1.15a

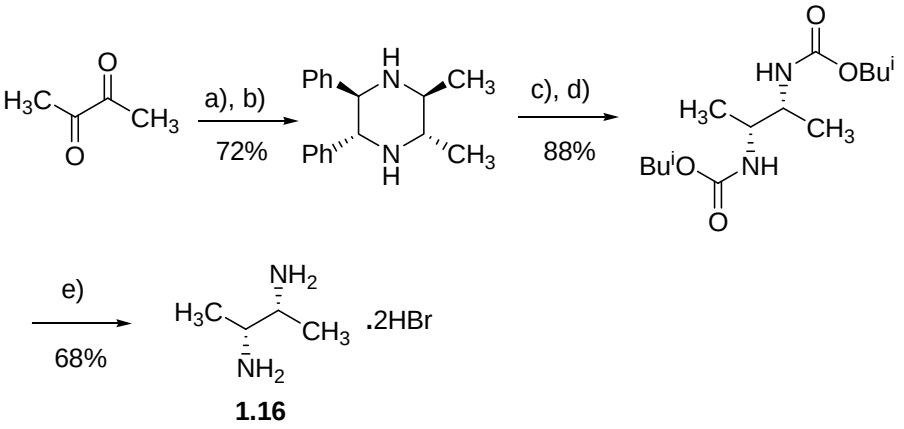
The ^{13}C NMR spectrum showed, 1,2-diphenyl methine carbons appeared at 61.0, 61.8 ppm. Both β-lactam ring carbons, C-3,C'-3 and C-4, C'-4 appeared at 61.9, 64.0 ppm and 81.2, 81.6 ppm respectively. The aromatic carbons appeared in the region of 115.6 to 157.1 ppm. The β-lactam carbonyl showed two peaks at 165.8, 166.9 ppm. The mass spectrum of **1.15a** indicated M+1 peak at *m*/*z* 608, also supports the structure. The compound **1.15a** also gave satisfactory elemental analysis.

1.4.7 Synthesis of (±) 2,3-diaminobutane (1.16)

The (±)2,3-diaminobutane **1.16** was synthesized by following a reported procedure.[83] A solution (±)1,2-diphenyl-1,2-ethylenediamine **1.12** and diacetyl in benzene was heated to reflux under Dean-Stark trap for 12 h to yield the crude dihydropyrazine, which was immediately reduced with pyridinium *p*-toluenesulfonate and $NaBH_3CN$ in MeOH at -30 ^{o}C to give piperazine in 72% yield. The piperazine was protected with isobutylchloroformate/pyridine in CH_2Cl_2 at reflux temperature for 40

min. followed by Birch reduction to afford piperazine bisacetamide in 88% yield. The piperazine bisacetamide was further hydrolysed with 30% HBr in acetic acid to give 2, 3-diaminobutane dihydrobromide **1.16** in 68% yield (Scheme-1.58).

Scheme-1.58



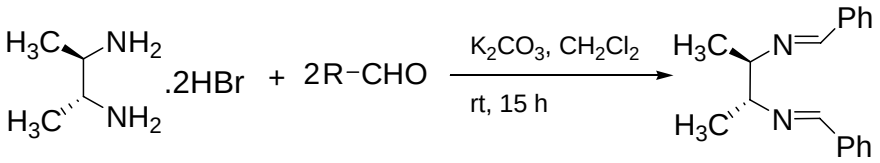
1.16

Reagents and conditions: a) DPEDA, Benzene; b) $NaBH_3CN$, PPTS, MeOH; c) ClC(O)OBui, Pyridine; d) Li^0, NH_3; e) 30% HBr, HOAC, 80 ^{0}C.

1.4.8 Preparations of bis-imine 1.17

The bisimine **1.17** was prepared by stirring (±) 2,3-diaminobutane dihyrobromide and freshly distilled benzaldehyde in excellent yield (Scheme-1.59). The structure of the imine **1.17** has been confirmed by spectroscopic methods.

Scheme 1.59

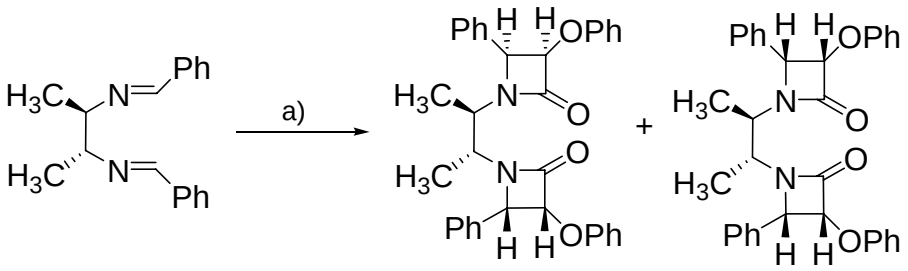


1.16 **1.17**

1.4.9 Preparations of bis-β-lactams 1.18 and 1.19

The bisimines **1.17** on Staudinger cycloaddition reaction with ketene generated from phenoxyacetyl chloride in the presence of triethylamine gave diastereomeric mixtures of *cis*-bis-β-lactams **1.18** and **1.19** in 91% yield (Scheme-1.60). The TLC and ^{1}H NMR spectra of the crude reaction mixture showed the presence of two diastereomers. These diastereomers were separated by flash column chromatography. The C_2-symmetric structure for bis-β-lactam **1.18** and the *meso* structure **1.19** were confirmed by spectral and analytical data. Here too, higher selectivity for *meso* bis-β-lactam formation was observed in the cycloaddition reaction

Scheme 1.60



Reagents and conditions:
a) R^1CH_2COCl, Et_3N,CH_2Cl_2,
0 ^oC to rt, 15 h

The IR spectrum of **1.18** showed a strong absorption at 1755 cm^{-1} indicates the presence of carbonyl group of β-lactam. The ^1H NMR of **1.18** showed a doublet for methyl group at 0.81 ppm (J = 6.6 Hz) integrating for six protons, the methine protons adjacent to 1,2 dimethyl moiety appeared as multiplet at 4.08-4.17 ppm for two protons. The presence of two doublets of C-4H and C-3H of β-lactam ring, integrating for two protons each at 5.26 and 5.40 ppm respectively with coupling constant J = 4.7 Hz. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values (J = 4.7 Hz). The twenty aromatic protons appeared as multiplets between the range 6.62-7.52 ppm. The presence of one carbonyl peak at 167.4 ppm in ^{13}C NMR confirmed the C_2-symmtry in the compound. The mass spectrum of **1.18** indicated M+1 peak at *m*/z 532, also supports the structure. The compound **1.18** also gave a satisfactory elemental analysis.

The IR spectrum of **1.19** showed a strong absorption at 1755 cm^{-1} indicates the presence of β-lactam carbonyl. The ^1H NMR of **1.19** showed two doublet for methyl group at 0.81, 1.32 ppm (J = 6.6 Hz) integrating for three protons each, the methyne protons adjacent to 1,2 dimethyl moiety appeared as multiplet at 3.71-3.90 ppm for two protons. The presence of four separate doublets of C-4H and C-3H of both β-lactam ring, integrating for one proton each at 4.95 and 5.37 ppm (J = 4.7 Hz), at 5.40 and 5.50 ppm (J = 4.3Hz) respectively. The stereochemistry for C-3H and C-4H of both β-lactam rings was assigned as *cis* from coupling constant values. The twenty aromatic protons appeared as multiplet at 6.60-7.57 ppm. The presence of two carbonyl peaks at 166.3, 166.4 ppm in ^{13}C NMR confirmed the unsymmtry (*meso*) in the compound. The mass

spectrum of **1.19** indicated M+1 peak at *m*/z 532, also supports the structure. The compound **1.19** also gave a satisfactory elemental analysis.

1.5: Conclusion

In conclusion, we have developed a one step synthesis of Staudinger reaction for the synthesis of bis-β-lactams from C_2-symmetric 1,2-diamines in excellent yields. The reaction was found to be highly stereoselective giving only *cis*-bis-β-lactams. The reaction gave C_2-symmetric and *meso* bis- β-lactams. Several C_2-symmetric as well as *meso* bis- β-lactams were synthesized in a single operation.

Chapter I

Section B: Asymmetric Synthesis of *cis* bis-β-lactams *via* Staudinger cycloaddition reaction using optically pure C_2-symmetric 1,2-diamines

Part of this work has been published in *Tetrahedron*, **2005**, *61*, 2441-2451

1.6: Present work

After establishing the synthetic protocol for racemic bis-β-lactams, we were interested in studying the asymmetric synthesis bis-β-lactams using optically pure 1,2-diamines. This section deals with one step synthesis of bis-β-lactam with bis-imines derived from optically pure *trans*-1,2-diaminocyclohexane and 1,2-diphenyl-1,2-ethylenediamine *via* Staudinger reaction with *in situ* generated ketenes from various acid chlorides.

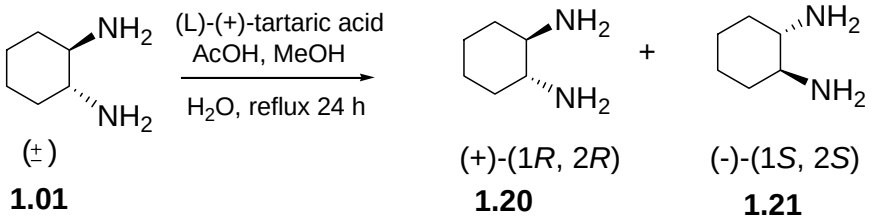
1.7: Results and Discussion

Enantiometrically pure 1,2-diamines and their derivatives are particularly useful as chiral auxiliaries or ligands, and they have found wide applications in stereoselective synthesis.[84] Mageney and Alexakis et al. showed that symmetrical vicinal diamines can be used as resolving agents.[85] We have also planned to use chiral C_2 symmetric 1,2 diamne for the construction of enantiometrically pure bis-β-lactam *via.* asymmetric Staudinger reaction.

1.7.1 Preparation of optically pure *trans*-1,2-diaminocyclohexane 1.20 and 1.21

Racemic *trans*-1,2-diaminocyclohexane has been resolved into optically pure (+)-1*R*,2*R*-*trans*-1,2-diaminocyclohexane and (-)-1*S*,2*S*-*trans*-1,2-diaminocyclohexane by reported procedure.[86a] It was resolved with L(+) tartaric acid and glacial acetic acid to give the corresponding tartrate salts in >99.8 % ee (HPLC).Further tartrate salts was dissociated into enantiometrically pure *trans*-1,2-diaminocyclohexane in 65 % over yield (Scheme 1.61).

Scheme 1.61



(±) **1.01**

(+)-(1*R*, 2*R*) **1.20**

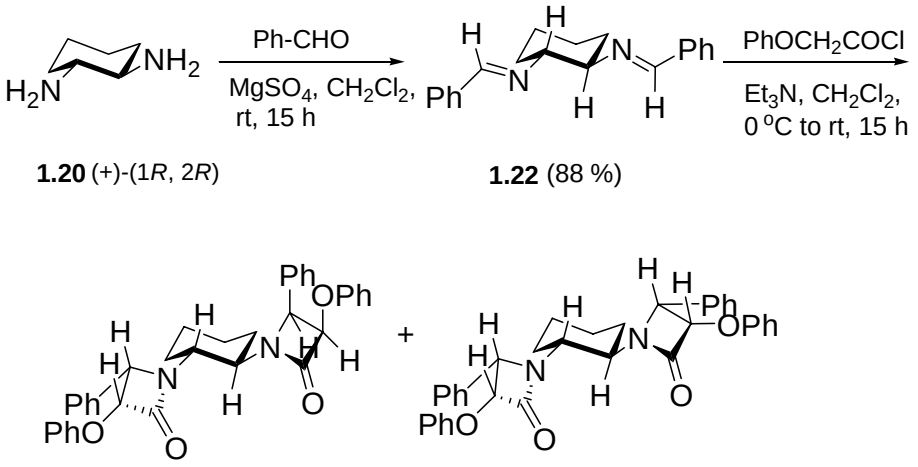
(-)-(1*S*, 2*S*) **1.21**

1.7.2 Preparation of optically pure bis-imine 1.22 and bis-β-lactams 1.23 and 1.24

Optically pure (+)-1*R*,2*R*-*trans*-1,2-diaminocyclohexane **1.20** was reacted with benzaldehye to furnish chiral bis-imine **1.22** in 88% yield. The chiral bis-imine **1.22** on Staudinger reaction with ketenes generated form phenoxyacetyl chloride and Et_3N gave a mixture C_2-symmetric **1.23** (40%) and *meso* **1.24** (60%) bis-β-lactams in 76% yield

(Scheme-1.62). Both the diasteromers were separated by careful flash column chromatography and showed the similar spectral data of that **1.05a** and **1.06a**. The absolute stereochemistry of C_2-symmetric **1.23** and *meso* **1.24** bis-β-lactam was assigned as 1*R*, 2*R*, 3′*S*, 4′*R*, 3″*S*, 4″*R* and 1*R*, 2*R*, 3′*S*, 4′*R*, 3″*R*, 4″*S* respectively by correlating the X-ray structure of **1.05a** and **1.06a**.

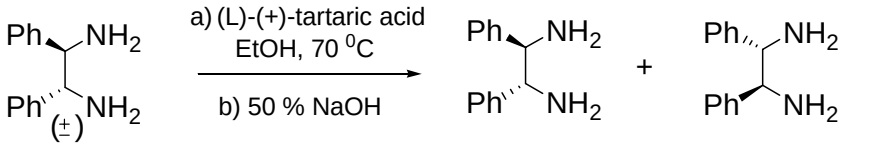
Scheme 1.62



1.7.3 Preparation of optically pure 1,2-diphenyl-1,2-ethylenediamine 1.25 and 1.26

The racemic 1, 2 diphenylethylenediamine was resolved using (L)-(+)-tartaric acid to get optically pure 1,2 diphenyl-1,2-ethylenediamine **1.25** and **1.26** in good yield (>98% ee) by reported procedure [86b] (Scheme-1.63).

Scheme 1.63

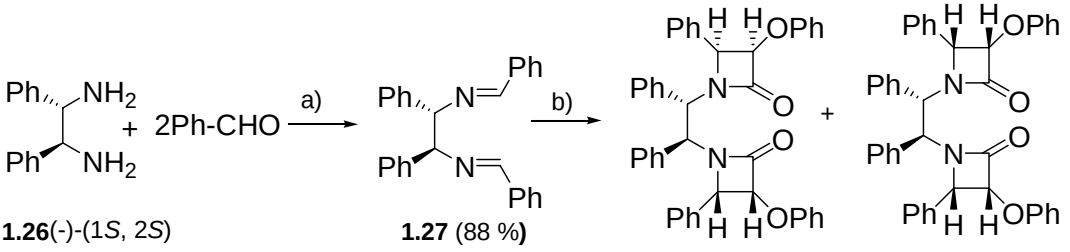


1.7.4 Preparation of optically pure bis-imine 1.27 and bis-β-lactams 1.28 and 1.29

The optically pure (-)-1*S*, 2*S* diphenyl-1,2-ethylenediamine **1.26** (98% ee) was converted into bisimne **1.27** by reacting with benzaldehyde. It was further reacted with ketene generated from phenoxyacetyl chloride to get diasteomeric mixture of C_2-symmetric **1.28** (36%) and *meso* **1.29** (64%) bis-β-lactams in 80% yield (Scheme-1.64),

which were easily separated by flash column chromatography. The structure of C_2-symmetric **1.28** and *meso* **1.29** bis-β-lactam was showed the similar spectral and analytical data as of **1.14a** and **1.15a**. The absolute stereochemistry of C_2-symmetric **1.28** and *meso* **1.29** bis-β-lactam was assigned as 1*S*, 2*S*, 3′*R*, 4′*S*, 3″*R*, 4″*S* and 1*S*, 2*S*, 3′*R*, 4′*S*, 3″*S*, 4″*R* respectively by correlating with the X-ray structure of **1.05a** and **1.06a**.

Scheme 1.64



1.26(-)-(1*S*, 2*S*) **1.27** (88 %**)** **1.28** *C*$_2$-symmetric **1.29** *Meso*

Reagents and conditions: a) $MgSO_4$, CH_2Cl_2, rt, 15 h
b)$PhCH_2COCl$, Et_3N, CH_2Cl_2, 0 ^oC to rt, 15 h

1.8: Conclusion

In conclusion, we have shown the application of Staudinger reaction for the asymmetric synthesis of bis- β-lactams from optically pure C_2-symmetric 1,2-diamines in excellent yields. Both C_2-symmetric as well as *meso* bis- β-lactams were formed in the reaction, which could be easily separated by chromatography.

1.9: Experimental

1.9.1: General procedure for the preparation of imines 1.03a-c

A mixture of freshly distilled aldehyde (26.3 mmol), (±) *trans*-1,2-diaminocyclohexane (8.8 mmol) and anhydrous $MgSO_4$ or anhydrous K_2CO_3 (2.20 g) in dry dichloromethane (30 mL) was stirred for 15 h at room temperature. The reaction mixture was then filtered through a bed of Celite and solvent was removed under reduced pressure. The residue was then treated with 10% solution of ethyl acetate in pet ether to remove unreacted aldehyde and filtered to give required bis-imines **1.03a-c** in excellent yield. Following this procedure bisimines **1.03a-c** were prepared in excellent yield.

1.9.1a Preparation of *N,N´*-Dibenzylidenecyclohexane-1,2-diamine 1.03a

The reaction of freshly distilled benzaldehye (2.78 g, 26.3 mmol), (±) *trans*-1,2-diaminocyclohexane (1.0 g, 8.8 mmol) and anhydrous $MgSO_4$ (2.20 g, 17.5 mmol) gave crude product, which on recrystallization from ethyl acetate: pet ether (90:10) affords pure bisimine **1.03a** (2.0 g, 80 %) as needles.

MP	**:**	129-130 °C
IR (Nujol)	**:**	1462, 1578, 1641 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.03-2.07 (m, 8H, C*H*$_2$, Cyclohexane), 3.21-3.45 (m, 2H, C*H*, Cyclohexane), 7.12-7.64 (m, 10H, Ar-*H*), 8.15 (s, 2H, N=C*H*)
^{13}C NMR (CDCl$_3$) (75.48MHz)	**:**	δ_C 24.5, 32.9, 73.7, 127.9, 128.2, 130.0, 136.5, 160.8
MS (m/z)	**:**	290 (M^+)
Analysis ($C_{20}H_{22}N_2$)	**:**	Calculated: C, 82.72; H, 7.63; N, 9.64 Observed: C, 82.58; H, 7.54; N, 9.53

1.9.1bPreparation of *N,N´*-Bis (4-methoxybenzylidene)cyclohexane-1,2-diamine 1.03b

The reaction of freshly distilled *p*-methoxybenzaldehye (3.58 g, 26.3 mmol), (±) *trans*-1,2-diaminocyclohexane (1.0 g, 8.7 mmol) and anhydrous $MgSO_4$ (2.20 g, 17.5

mmol) gave crude product, which on recrystallization from ethyl acetate: pet ether (90:10) affords pure bisimine **1.03b** (2.8 g, 90 %) as white needles.

MP	**:**	166-167 °C
IR ($CHCl_3$)	**:**	1253, 1512, 1606, 1643 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.20-1.97 (m, 8H, C*H*$_2$, Cyclohexane), 3.27-3.42 (m, 2H, C*H*, Cyclohexane), 3.78 (s, 6H, OC*H*$_3$), 6.82 (d, *J* = 9 Hz, 4H, Ar-*H*), 7.54 (d, *J* = 9 Hz, 4H, Ar-*H*), 8.13 (s, 2H, -N=C*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 24.5, 33.0, 55.2, 73.7, 113.7, 129.2, 129.4, 160.3, 161.2
MS (m/z)	**:**	352 (M^+)
Analysis ($C_{20}H_{26}N_2O_2$)	**:**	Calculated: C, 75.48; H, 7.49; N, 8.00 Observed: C, 75.36; H, 7.38; N, 7.86

1.9.1c Preparation of *N,N´*-Bis (styrylmethylene)cyclohexane-1,2-diamine 1.03c

The reaction of freshly distilled cinnamaldehye (3.47 g, 26.3 mmol), (±) *trans*-1,2-diaminocyclohexane (1.0 g, 8.7 mmol) and anhydrous $MgSO_4$ (2.20 g, 17.5 mmol) affords bisimine **1.03c** (2.20 g, 85 %) as brown oil.

IR (Neat)	**:**	1253, 1448, 1632, 1677, 2854, 2929 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.22-1.84 (m, 8H, C*H*$_2$, Cyclohexane), 3.06-3.23 (m, 2H, C*H*, Cyclohexane), 6.70-6.80 (m, 4H, C*H*-olefin), 7.05-7.55 (m, 10H, Ar), 7.80-7.90 (m, 2H, -N=C*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 24.3, 33.0, 73.7, 127.0, 127.9, 128.3, 128.9, 131.0, 135.7, 141.3, 152.4, 162.4
MS (m/z)	**:**	342 (M^+)
Analysis ($C_{24}H_{26}N_2$)	**:**	Calculated: C, 84.17; H, 7.65; N, 8.18 Observed: C, 84.08; H, 7.57; N, 8.04

1.9.2: A General procedure for the synthesis of β-lactams 1.05a-i and 1.06a-i

A solution of the acid chloride (3.0 mmol) in dry CH_2Cl_2 (10 mL) was added slowly to a solution of the bisimine **1.03a-c** (1.0 mmol) and triethylamine (10.0 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 15 h. The reaction mixture was then washed with water (2 x 10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give the crude diastereomeric mixture. The diastereomers were separated by flash column chromatography to give pure diastereomer of β-lactams (**1.05a-i** and **1.06a-i)**. The less polar C_2-symmteric β-lactam (**1.05a-i**) eluted first followed by more polar *meso* β-lactam (**1.06a-i**).

1.9.2a Synthesis of β-lactams 1.05a and 1.06a

The phenoxyacetyl chloride **1.04a** (0.350 g, 3.0 mmol) on treatment with bisimine **1.03a** (0.200 g, 1.0 mmol) in presence of triethylamine (0.96 mL, 10.0 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.348 g (90%, total yield) of pure β-lactams **1.05a** (minor) and **1.06a** (major) as white solids.

1,2-Bis (3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (1.05a)

It was isolated as a white solid from diastereomeric mixture by flash column chromatography R_f (30% ethyl acetate/pet ether) 0.42 which was recrystallized from dichloromethane: petroleum ether to give white crystalline solid.

MP	**:**	231-232 °C
IR ($CHCl_3$)	**:**	1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.69-1.80 (m, 8H, C*H*$_2$, Cyclohexane), 3.97 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 5.27 (d, *J* = 4.7 Hz, 2H, C4*H*), 5.39 (d, *J* = 4.7 Hz, 2H, C3*H*), 6.48-7.73 (m, 20H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 24.4, 30.1, 54.0, 61.4, 81.6, 115.7, 121.9, 128.0, 128.6, 128.9, 129.1, 134. 9, 156.8, 167.7
MS (m/z)	**:**	588 (M^+)
Analysis ($C_{36}H_{34}N_2O_4$)	**:**	Calculated: C, 77.39, H, 6.13; N, 5.01 Observed: C, 77.19; H, 5.88; N, 4.84

1-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-Phenoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (1.06a)

It was obtained as a white solid; R_f (30% ethyl acetate/pet ether) 0.25, which was recrystallized from methanol to give white needles.

MP	**:**	82-83 °C
IR ($CHCl_3$)	**:**	1753 cm^{-1}
^{1}H NMR ($CDCl_3$) (500 MHz)	**:**	δ_H 0.83-2.06 (m, 8H, C*H*$_2$, Cyclohexane), 3.55-3.60 (m, 1H, C*H*, Cyclohexane), 3.71-3.76 (m, 1H, C*H*, Cyclohexane), 5.05 (d, *J* = 4.7 Hz, 1H, C4*H*), 5.40 (d, *J* = 4.7 Hz, 1H, C3*H*), 5.47 (d, *J* = 4.6 Hz, 1H, C4′*H*), 5.56 (d, *J* = 4.6 Hz, 1H, C3′*H*), 6.72-7.55 (m, 20H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 24.1, 29.2, 31.3, 53.4, 55.2, 61.2, 62.2, 81.1, 81.3, 115.7, 121.8, 122.0,128.0, 128.4, 128.6, 129.0, 129.1, 133.6, 134.8, 157.0, 166.4, 166.5
MS (m/z)	**:**	588 (M^+)
Analysis ($C_{36}H_{34}N_2O_4$)	**:**	Calculated: C, 77.39, H, 6.13; N, 5.01 Observed: C, 77.23; H, 5.96; N, 4.78

1.9.2b Synthesis of β-lactams 1.05b and 1.06b

The benzyloxyacetyl chloride **1.04b** (0.381 g, 2.07 mmol) on treatment with bisimine **1.03a** (0.200 g, 0.69 mmol) in presence of triethylamine (0.96 mL, 6.90 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.350 g (87%, total yield) of pure β-lactams **1.05b** (minor) and **1.06b** (major) as white solids.

1,2-Bis (3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (1.05b)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.48, which was recrystallized from dichloromethane: methanol to afford white crystalline solid.

MP	**:**	111-112 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR ($CDCl_3$)	**:**	δ_H 0.72-1.84 (m, 8H, C*H*$_2$, Cyclohexane), 3.92 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 4.01 (d, *J* = 10.9 Hz, 2H, C*H*$_2$Ph),

(200 MHz)		4.31 (d, J = 10.9 Hz, 2H, CH_2Ph), 4.89 (d, J = 4.3 Hz, 2H,C4H), 5.11 (d, J = 4.3 Hz, 2H, C3H), 6.81-7.68 (m, 20H, Ar)
^{13}C NMR	**:**	δ_C 24.0, 24.4, 29.7, 30.1, 53.4, 61.0, 72.3, 72.5, 83.8, 81.6,
($CDCl_3$)		127.8, 128.1, 128.2, 128.5, 128.8, 129.3, 135.6, 136.3, 167.5,
(75.48 MHz)		168.3
MS (m/z)	**:**	586 (M^+)
Analysis	**:**	Calculated: C, 77.79, H, 6.53; N, 4.77
($C_{38}H_{38}N_2O_4$)		Observed: C, 77.56; H, 6.35; N, 4.87

1-(3′-Benzyloxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-benzyloxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (1.06b)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.35, which was recrystallized from methanol to give white needles.

MP	**:**	72-73 °C
IR ($CHCl_3$)	**:**	1749 cm^{-1}
^{1}H NMR	**:**	δ_H 0.82-2.0 (m, 8H, CH_2, Cyclohexane), 3.41-3.73 (m, 2H,
($CDCl_3$)		CH, Cyclohexane), 4.07 (d, J =11.0 Hz, 1H, CHPh), 4.16 (d, J
(200 MHz)		=11.0 Hz, 1H, CHPh), 4.27 (d, J = 7.8 Hz, 1H, CHPh), 4.33 (d, J = 7.8 Hz, 1H, CHPh), 4.85 (d, J = 4.7 Hz, 1H, C4H), 4.88 (d, J = 4.7 Hz, 1H, C3H), 4.98 (d, J = 4.3 Hz, 1H, C4′H), 5.29 (d, J = 4.3 Hz, 1H, C3′H), 6.88-7.66 (m, 20H, Ar-H)
^{13}C NMR	**:**	δ_C 24.0, 29.3, 31.4, 52.9, 54.7, 60.7, 61.7, 72.3, 82.4, 83.0,
($CDCl_3$)		128.2, 128.5, 129.0, 129.2, 134.2, 135.4, 136.2, 136.4, 167.2,
(125 MHz)		167.5
MS (m/z)	**:**	586 (M^+)
Analysis	**:**	Calculated: C, 77.79, H, 5.33; N, 4.77
($C_{38}H_{38}N_2O_4$)		Observed: C, 77.62; H, 5.40; N, 4.65

1.9.2c Synthesis of β-lactams 1.05c and 1.06c

The methoxyacetyl chloride **1.04c** (0.224 g, 2.07 mmol) on treatment with bisimine **1.03a** (0.200 g, 0.69 mmol) in presence of triethylamine (0.96 mL, 6.90 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.258 g (86%, total yield) of pure β-lactams **1.05c** (minor) and **1.06c** (major) as white solids.

1,2-Bis (3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (1.05c)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.44, which was recrystallized from methanol to furnish white crystalline solid.

MP	**:**	247-248 °C
IR ($CHCl_3$)	**:**	1743 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.52-1.95 (m, 8H, C*H*$_2$, Cyclohexane), 3.01 (s, 6H, OC*H*$_3$), 3.73 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 4.49 (d, *J* = 4.3 Hz, 2H, C4*H*), 4.92 (d, *J* = 4.3 Hz, 2H, C3*H*), 7.16-7.42 (m, 10H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	**:**	δ_C 24.3, 29.9, 53.4, 58.0, 60.8, 85.1, 123.3, 128.1, 128.7, 135.4, 168.5
MS (m/z)	**:**	434 (M^+)
Analysis	**:**	Calculated: C, 71.86, H, 6.96; N, 6.45
($C_{26}H_{30}N_2O_4$)		Observed: C, 71.59; H, 6.71; N, 6.22

1-(3′-Methoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (1.06c)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.33, which was recrystallized from methanol to get white needles.

MP	**:**	191-192 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR ($CDCl_3$)	**:**	δ_H 0.45-1.91 (m, 8H, C*H*$_2$, Cyclohexane), 3.01 (s, 6H, OC*H*$_3$), 3.18-3.54 (m, 2H, C*H*, Cyclohexane), 4.47 (d, *J* = 4.3 Hz, 1H,

(200 MHz)		C4*H*), 4.56 (d, *J* = 4.3 Hz, 1H, C3*H*), 4.64 (d, *J* = 4.7 Hz, 1 H, C4′*H*), 5.06 (d, *J* = 4.7 Hz, 1 H, C3′*H*), 7.04-7.42 (m, 10H, Ar-*H*)
^{13}C NMR	**:**	δ_C 24.0, 29.2, 31.3, 53.1, 55.0, 58.0, 60.5, 61.8, 84.6, 84.8,
($CDCl_3$)		128.0, 128.4, 128.8, 128.8, 129.0,134.1, 135.4, 167.4
(75.48 MHz)		
MS (m/z)	**:**	434 (M^+)
Analysis	**:**	Calculated: C, 71.86, H, 6.96; N, 6.45
($C_{26}H_{30}N_2O_4$)		Observed: C, 71.63; H, 6.73; N, 6.33

1.9.2d Synthesis of β-lactams 1.05d and 1.06d

The phenoxyacetyl chloride **1.04a** (0.290 g, 1.70 mmol) on treatment with bisimine **1.03b** (0.200 g, 0.57 mmol) in presence of triethylamine (0.80 mL, 5.68 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.326 g (93%, total yield) of pure β-lactams **1.05d** (minor) and **1.06d** (major) as white solids.

1,2-Bis [3′-phenoxy-4′- (*p*-methoxyphenyl)azetidin-2′-one-1′-yl]cyclohexane (1.05d)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.59, which was recrystallized from dichloromethane: methanol to give white needles.

MP	**:**	158-159 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR	**:**	δ_H 0.67-1.82 (m, 8H, CH_2, Cyclohexane), 3.76 (s, 6H, OCH_3),
($CDCl_3$)		3.93 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 5.22 (d, *J* = 4.7
(200 MHz)		Hz, 2H, C4*H*), 5.34 (d, *J* = 4.7 Hz, 2H, C3*H*), 6.54 -7.47 (m, 18H, Ar-*H*)
^{13}C NMR	**:**	δ_C 24.3, 29.7, 29.9, 30.1, 53.7, 55.0, 60.9, 81.4, 113.3, 114.6,
($CDCl_3$)		115.5, 121.8, 126.5, 129.1, 129.5, 129.9, 156.7, 159.7, 167.6
(50.32 MHz)		
MS (m/z)	**:**	620 (M^+)
Analysis	**:**	Calculated: C, 73.77, H, 6.19; N, 4.52

($C_{38}H_{38}N_2O_6$) Observed: C, 73.71; H, 6.03; N, 4.52

1-[3′-Phenoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-(*p*-methoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (1.06d)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.47, which was recrystallized from dichloromethane: methanol, white needles.

MP	**:**	209-210 °C
IR ($CHCl_3$)	**:**	1753 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.83-2.06 (m, 8H, C*H*$_2$, Cyclohexane), 3.49-3.71 (m, 2H, C*H*, Cyclohexane), 3.75, 3.79 (s, 6H, OC*H*$_3$), 5.01 (d, *J* = 4.7 Hz, 1H, C4*H*), 5.37 (d, *J* = 4.7 Hz, 1H, C3*H*), 5.46 (d, *J* = 4.3 Hz, 1H, C4′*H*), 5.50 (d, *J* = 4.3 Hz, 1H, C3′*H*), 6.70-7.55 (m, 18H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	**:**	δ_C 23.9, 29.0, 31.4, 53.0, 55.0, 55.1, 60.7, 61.5, 81.0, 81.1, 113.4, 113.8, 115.6, 121.7, 121.9, 125.2, 126.6, 129.1, 130.4, 157.0, 159.7, 160.0, 166.4, 166.5
MS (m/z)	**:**	620 (M^+)
Analysis	**:**	Calculated: C, 73.77, H, 6.19; N, 4.52
($C_{38}H_{38}N_2O_6$)		Observed: C, 73.59; H, 6.07; N, 4.28

1.9.2e Synthesis of β-lactams 1.05e and 1.06e

The benzyloxyacetyl chloride **1.04b** (0.314 g, 1.70 mmol) on treatment with bisimine **1.03b** (0.200 g, 0.57 mmol) in presence of triethylamine (0.80 mL, 5.68 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.299 g (80%, total yield) of pure β-lactams **1.05e** (minor) and **1.06e** (major) as white solids.

1,2-Bis [3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]cyclohexane (1.05e)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.40, which was recrystallized from dichloromethane: methanol to get white needles.

MP	**:**	194-195 °C
IR ($CHCl_3$)	**:**	1755 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.68-1.81 (m, 8H, C*H*$_2$, Cyclohexane), 3.79 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 3.83 (s, 6H, OC*H*$_3$), 3.98 (d, *J* = 10.9 Hz, 2H, C*H*$_2$Ph), 4.24 (d, *J* = 10.9 Hz, 2H, C*H*$_2$Ph), 4.78 (d, *J* = 4.3 Hz, 2H, C4*H*), 5.01 (d, *J* = 4.3 Hz, 2H, C3*H*), 6.83-7.47 (m, 18H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50.32 MHz)	**:**	δ_C 24.4, 30.1, 53.3, 55.3, 60.5, 72.4, 83.6, 113.5, 127.5, 127.8, 128.2, 129.9, 136.4, 159.8, 168.3
MS (m/z)	**:**	648 (M^+)
Analysis ($C_{40}H_{42}N_2O_6$)	**:**	Calculated: C, 74.28, H, 6.54; N, 4.33 Observed: C, 74.14; H, 6.38; N, 4.15

1-[3′-Benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″- (*p*-methoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (1.06e)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.24, which was recrystallized from dichloromethane: methanol to give white crystalline solid.

MP	**:**	123-124 °C
IR ($CHCl_3$)	**:**	1751 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.77-1.92 (m, 8H, C*H*$_2$, Cyclohexane), 3.72-3.86 (m, 2H, C*H*, Cyclohexane), 3.83, 3.85 (s, 6H, OC*H*$_3$), 4.01-4.33 (m, 4H, C*H*$_2$Ph), 4.76 (d, *J* = 4.7 Hz, 1H, C4*H*), 4.89 (d, *J* = 4.7 Hz, 1H, C3*H*), 4.91 (d, *J* = 4.3 Hz, 1H, C4′*H*), 5.21 (d, *J* = 4.3 Hz, 1H, C3′*H*), 6.80-7.49 (m, 18H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 24.0, 29.1, 31.4, 52.6, 54.6, 55.2, 60.2, 61.1, 72.2, 82.3, 82.8, 113.5, 113.9, 125.9, 127.2, 127.7, 127.8, 128.2, 130.2, 130.4, 136.3, 136.5, 159.7, 160.1, 167.3, 167.5
MS (m/z)	**:**	648 (M^+)
Analysis	**:**	Calculated: C, 74.28, H, 6.54; N, 4.33

($C_{40}H_{42}N_2O_6$)		Observed: C, 74.17; H, 6.45; N, 4.28

1.9.2f Synthesis of β-lactams 1.05f and 1.06f

The methoxyacetyl chloride **1.04c** (0.185 g, 1.70 mmol) on treatment with bisimine **1.03b** (0.200 g, 0.57 mmol) in presence of triethylamine (0.80 mL, 5.68 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (60% ethyl acetate/petroleum ether) to give 0.207 g (73%, total yield) of pure β-lactams **1.05f** (minor) and **1.06f** (major) as white solids.

1, 2-Bis [3′-methoxy-4′-(*p*-methoxyphenyl) azetidine-2′-one-1′-yl]cyclohexane (1.05f)

It was obtained as a white solid, R_f (60% ethyl acetate/pet ether) 0.52, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	229-230 °C
IR ($CHCl_3$)	**:**	1743 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.60-1.94 (m, 8H, C*H*$_2$, Cyclohexane), 3.03 (s, 6H, O*CH*$_3$), 3.79 (br d, *J* = 9 Hz, 2H, C*H*, Cyclohexane), 3.82 (s, 6H, PhOC*H*$_3$), 4.55 (d, *J* = 4.3 Hz, 2H, C4*H*), 4.96 (d, *J* = 4.3 Hz, 2H, C3*H*), 6.89 (d, *J* = 8.6 Hz, 4H, Ar-*H*), 7.34 (d, *J* = 8.6 Hz, 4H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (125.76 MHz)	**:**	δ_C 24.5, 30.2, 53.3, 55.2, 58.0, 60.4, 85.2, 113.6, 127.5, 129.8, 159.9, 167.9
MS (m/z)	**:**	496 (M^+)
Analysis	**:**	Calculated: C, 67.99, H, 6.92; N, 5.66
($C_{28}H_{34}N_2O_6$)		Observed: C, 67.88; H, 6.83; N, 5.56

1-[3′-Methoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3″-methoxy-4″-(*p*-methoxyphenyl)azetidin-2″-one-1″-yl]cyclohexane (1.06f)

It was obtained as a white solid, R_f (60% ethyl acetate/pet ether) 0.44, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	84-85 °C
IR ($CHCl_3$)	**:**	1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.72-1.93 (m, 8H, CH_2, Cyclohexane), 3.09 (s, 6H, OCH_3), 3.35-3.65 (m, 2H, C*H*, Cyclohexane), 3.82, 3.84 (s, 6H, PhOCH_3), 4.60 (d, *J* = 4.7 Hz, 1H, C4*H*), 4.70 (d, *J* = 4.7 Hz, 1H, C3*H*), 4.76 (d, *J* = 4.3 Hz, 1 H, C4′*H*), 5.22 (d, *J* = 4.3 Hz, 1 H, C3′*H*), 6.85-7.01 (m, 4 H, Ar-*H*), 7.34-7.48 (m, 4 H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 23.9, 24.0, 28.9, 31.3, 52.7, 54.7, 55.1, 55.2, 57.92, 59.9, 61.0, 84.4, 84.5, 113.4, 113.9, 125.7, 127.1, 130.2, 159.7, 160.0, 167.3, 167.5
MS (m/z)	**:**	496 (M^+)
Analysis ($C_{28}H_{34}N_2O_6$)	**:**	Calculated: C, 67.99, H, 6.92; N, 5.66 Observed: C, 67.86; H, 6.85; N, 5.49

1.9.2g Synthesis of β-lactams 1.05g and 1.06g

The phenoxyacetyl chloride **1.04a** (0.750 g, 4.38 mmol) on treatment with bisimine **1.03c** (0.500 g, 1.46 mmol) in presence of triethylamine (2.03 mL, 14.61 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.780 g (88%, total yield) of pure β-lactams **1.05g** (minor) and **1.06g** (major) as white solids.

1-(3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.05g)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.68, which on recrystallization from methanol to give white needles.

MP	**:**	245-246 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.07-2.01 (m, 8H, CH_2, Cyclohexane), 3.83-3.95 (m, 2H, C*H*, Cyclohexane), 4.88 (dd, *J* = 4.7, 8.2 Hz, 2H, C4*H*), 5.29 (d, *J* = 4.7 Hz, 2H, C3*H*), 6.28 (dd, *J* = 8.2, 16 Hz, 2H, *H*C=CH), 6.77 (d, *J* = 16 Hz, 2H, =C*H*Ph), 6.91-7.44 (m, 20H,

		Ar-*H*)
^{13}C NMR (CDCl$_3$) (75.48 MHz)	**:**	δ_C 24.7, 30.2, 53.5, 60.5, 82.0, 115.8, 122.2, 125.0, 126.7, 128.2, 128.6, 129.4, 136.0, 136.2, 157.4, 166.6
MS (m/z)	**:**	610 (M^+)
Analysis	**:**	Calculated: C, 78.66, H, 6.27; N, 4.58
($C_{40}H_{38}N_2O_4$)		Observed: C, 78.57; H, 6.16; N, 4.51

1-(3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.06g)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.40, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	175-176 °C
IR (CHCl$_3$)	**:**	1753 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.05-2.09 (m, 8H, C*H*$_2$, Cyclohexane), 3.72-3.93 (m, 2H, C*H*, Cyclohexane), 4.67 (dd, *J* = 4.4, 9.4 Hz, 1H, C4*H*), 5.16 (dd, *J* = 4.4, 9.4 Hz, 1H, C3*H*), 5.38 (dd, *J* = 4.7, 9.4 Hz, 2H, C4′*H* and C3′*H*), 6.27 (dd, *J* = 9.4, 16 Hz, 1H, *H*C=CH), 6.67-6.87 (m, 3H, *H*C=CH and =C*H*Ph), 6.89-7.70 (m, 20H, Ar-*H*)
^{13}C NMR (CDCl$_3$) (75.48 MHz)	**:**	δ_C 24.2, 24.4, 28.4, 31.1, 52.2, 54.8, 60.3, 60.6, 81.6, 81.7, 115.6, 115.8, 121.8, 122.0, 124.0, 125.3, 126.6, 127.0, 128.0, 128.2, 128.5, 129.2, 135.8, 136.0, 136.2, 136.5, 157.4, 165.7, 166.2
MS (m/z)	**:**	610 (M^+)
Analysis	**:**	Calculated: C, 78.66, H, 6.27; N, 4.58
($C_{40}H_{38}N_2O_4$)		Observed: C, 78.49; H, 6.27; N, 4.58

1.9.2h Synthesis of β-lactams 1.05h and 1.06h

The benzyloxyacetyl chloride **1.04b** (0.809 g, 4.38 mmol) on treatment with bisimine **1.03c** (0.500 g, 1.46 mmol) in presence of triethylamine (2.03 mL, 14.61 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash

column chromatography (20% ethyl acetate/petroleum ether) to give 0.750 g (81%, total yield) of pure β-lactams **1.05h** (minor) and **1.06h**(major) as white solids.

1-(3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-benzylxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.05h)

It was obtained as a white solid, R_f (20% ethyl acetate/pet ether) 0.54, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	179-180 °C
IR ($CHCl_3$)	**:**	1743 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.01-1.91(m, 8H, C*H*$_2$, Cyclohexane), 3.71-3.82 (m, 2H, C*H*, Cyclohexane), 4.58 (d, *J* = 10.2 Hz, 2H, C*H*$_2$Ph), 4.63 (d, *J* = 10.2 Hz, 2H, C*H*$_2$Ph), 4.65 (dd, *J* = 4.3, 9.4 Hz, 2H, C4*H*), 4.73 (d, *J* = 4.3 Hz, 2H, C3*H*), 6.31 (dd, *J* = 9.4, 16 Hz, 2H, *H*C=CH), 6.72 (d, *J* = 16 Hz, 2H, =C*H*Ph), 7.15-7.51 (m, 20H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 24.6, 30.3, 52.9, 60.3, 73.0, 83.7, 126.0, 126.7, 127.9, 128.2, 128.3, 128.6, 135.1, 136.2, 136.8, 167.5
MS (m/z)	**:**	638 (M^+)
Analysis ($C_{42}H_{42}N_2O_4$)	**:**	Calculated: C, 78.97, H, 6.63; N, 4.39 Observed: C, 78.86; H, 6.55; N, 4.29

1-(3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-benzylxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.06h)

It was obtained as a white solid, R_f (20% ethyl acetate/pet ether) 0.44, which on recrystallization from methanol gave white crystalline solid.

MP	**:**	61-62 °C
IR ($CHCl_3$)	**:**	1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.00-2.10 (m, 8H, C*H*$_2$, Cyclohexane), 3.62-3.73 (m, 2H, C*H*, Cyclohexane), 4.32-4.41 (m, 1H, C4*H*), 4.60 (d, *J* = 11.3 Hz, 2H, C*H*$_2$Ph), 4.66 (d, *J* = 11.3 Hz, 2H, C*H*$_2$Ph), 4.76 (d, *J*

		= 4.7 Hz, 1H, C3*H*), 4.86 (d, *J* = 4.3 Hz, 1H, C4′*H*), 4.93 (dd, *J* = 4.7, 9.4 Hz, 1H, C3′*H*), 6.31 (dd, *J* = 9.4, 15.7 Hz, 1H, *H*C=CH), 6.62-6.85 (m, 3H, *H*C=CH and =C*H*Ph), 7.18-7.65 (m, 20H, Ar-*H*)
^{13}C NMR (CDCl$_3$) (75.48 MHz)	**:**	δ_C 24.3, 24.4, 28.6, 31.3, 51.8, 54.4, 60.1, 60.5, 72.5, 72.8, 82.7, 83.5, 124.9, 126.7, 127.5, 127.9, 128.2, 128.3, 128.6, 135.0, 135.7, 136.2, 136.4, 137.0, 166.9, 167.2
MS (m/z)	**:**	638 (M^+)
Analysis ($C_{42}H_{42}N_2O_4$)	**:**	Calculated: C, 78.97, H, 6.63; N, 4.39 Observed: C, 78.91; H, 6.48; N, 4.32

1.9.2i Synthesis of β-lactams 1.05i and 1.06i

The methoxyacetyl chloride **1.04c** (0.476 g, 4.38 mmol) on treatment with bisimine **1.03c** (0.500 g, 1.46 mmol) in presence of triethylamine (2.03 mL, 14.61 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (40% ethyl acetate/petroleum ether) to give 0.615 g (86%, total yield) of pure β-lactams **1.05i** (minor) and **1.06i** (major) as white solids.

1-(3′-Methoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.05i)

It was obtained as a white solid, R_f (40% ethyl acetate/pet ether) 0.49, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	211-212 °C
IR (CHCl$_3$)	**:**	1741 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.01-1.96 (m, 8H, C*H*$_2$, Cyclohexane), 3.41 (s, 6H, OC*H*$_3$), 3.78-3.81 (m, 2H,C*H*, Cyclohexane), 4.49 (d, *J* = 4.3 Hz, 2H, C4*H*), 4.62 (dd, *J* = 4.3, 9.4 Hz, 2H, C3*H*), 6.27 (dd, *J* = 9.4, 16 Hz, 2H, *H*C=CH), 6.77 (d, *J* = 16 Hz, 2H, =C*H*Ph), 7.25-7.50 (m, 10H, Ar-*H*)
^{13}C NMR (CDCl$_3$) (75.48 MHz)	**:**	δ_C 24.6, 30.3, 52.9, 58.6, 60.0, 85.3, 125.7, 126.6, 128.2, 128.6, 135.2, 136.2, 167.5

MS (m/z)	**:**	486 (M^+)
Analysis	**:**	Calculated: C, 74.05, H, 7.04; N, 5.75
($C_{30}H_{34}N_2O_4$)		Observed: C, 73.92; H, 6.95; N, 5.68

1-(3′-Methoxy-4′-styrylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-styrylazetidin-2″-one-1″-yl)cyclohexane (1.06i)

It was obtained as a white solid, R_f (40% ethyl acetate/pet ether) 0.38, which was recrystallized from methanol to get white needles.

MP	**:**	79-80 °C
IR ($CHCl_3$)	**:**	1749 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.01-1.99 (m, 8H, C*H*$_2$, Cyclohexane), 3.43, 3.44 (s, 6H, OC*H*$_3$), 3.60-3.73 (m, 2H, C*H*, Cyclohexane), 4.34-4.45 (m, 1H, C4*H*), 4.60 (dd, *J* = 4.7, 9.4 Hz, 2H, C3*H* and C4′*H*), 4.92 (dd, *J* = 4.7, 9.4 Hz, 1H, C3′*H*), 6.28 (dd, *J* = 9.4, 16 Hz, 1H, *H*C=CH), 6.62-6.89 (m, 3H, *H*C=CH and =C*H*Ph), 7.24-7.67 (m, 10H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 24.3, 24.4, 28.5, 31.2, 51.8, 54.3, 58.4, 58.5, 59.9, 60.3, 84.8, 85.1, 124.6, 126.1, 126.6, 127.1, 128.0, 128.1, 128.6, 135.1, 135.8, 136.1, 136.3, 166.6, 167.3
MS (m/z)	**:**	486 (M^+)
Analysis	**:**	Calculated: C, 74.05, H, 7.04; N, 5.75
($C_{30}H_{34}N_2O_4$)		Observed: C, 73.88; H, 6.92; N, 5.65

1.9.3: Procedure for the preparation of mono-β-lactams (1.07 and 1.08)

Phenoxyacetyl chloride **1.04a** (0.1 mL, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added slowly to a solution of the bis-imine **1.03a** (0.20 g, 1.0 mmol) and triethylamine (0.96 mL, 10.0 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 15 h. The reaction mixture was then washed with water (2 x 10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The organic layer

was then dried over anhydrous Na_2SO_4 and concentrated to give the crude diastereomeric mixture **1.07** and **1.08** (0.22 g).

Data for diastereomeric mixture of mono-β-lactams 1.07 and 1.08

It was obtained as white solid.

IR ($CHCl_3$)	**:**	1645, 1749 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.28-2.25 (m, 16H), 3.10-3.95 (m, 4H), 4.73 (d, *J* = 4.7 Hz, 2H), 4.83 (d, *J* = 4.3 Hz, 1H), 5.04 (d, *J* = 4.3 Hz, 2H), 5.18 (d, *J* = 4.7 Hz, 1H), 6.58-7.83 (m, 30H), 8.33 (s, 1H), 8.45 (s, 1H)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 23.9, 24.3, 24.7, 25.2, 29.7, 29.9, 33.5, 33.8, 53.8, 58.2, 59.4, 61.3, 64.1, 69.9, 72.2, 96.0, 115.5, 121.7

1.9.4: *N,N´*-Dibenzylidene-1,2-diphenylethane-1,2-diamine (1.13)

The bis-imine **1.13** was prepared from (±)1,2-diphenylethylenediamine (0.50 g, 2.35 mmol) and benzaldehyde (0.75 g, 7.06 mmol) following the same procedure as described for **1.03a-c**. It was isolated as a white solid and recrystallized from ethyl acetate: petroleum ether (90:10) to give white needles (0.750 g, 82%).

MP	**:**	158-159 °C
IR ($CHCl_3$)	**:**	1643 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 4.67 (s, 2H, C*H*Ph), 7.03-7.90 (m, 20H, Ar), 8.22 (s, 2H, -N=C*H*)
^{13}C NMR ($CDCl_3$) (75.48 MHz)	**:**	δ_C 81.3, 126.8, 127.8, 128.1, 128.3, 128.4, 130.3, 136.4, 141.1, 161.7
MS (m/z)	**:**	388 (M^+)
Analysis ($C_{28}H_{24}N_2$)	**:**	Calculated: C, 86.56; H, 6.22; N, 7.21 Observed: C, 86.43; H, 6.13; N, 7.06

1.9.5a Synthesis of β-lactams 1.14a and 1.15a

Following the optimized procedure for bis-β-lactams, the phenoxyacetyl chloride **1.04a** (0.395 g, 2.31 mmol) on treatment with bisimine **1.13** (0.300 g, 0.77mmol) in presence of triethylamine (1.07 mL, 7.7 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.380 g (81%, total yield) of pure β-lactams **1.14a** (minor) and **1.15a** (major) as white solids.

1,2-Diphenyl-1,2-bis(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (1.14a)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.63, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	197-198 °C
IR ($CHCl_3$)	**:**	1757 cm^{-1}
^{1}H NMR ($CDCl_3$) (500 MHz)	**:**	δ_H 5.19 (s, 2H, C*H*Ph), 5.34 (d, *J* = 4.1 Hz, 2H, C4*H*), 5.55 (d, *J* = 4.1 Hz, 2H, C3*H*), 6.69-7.30 (m, 30H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 59.9, 60.9, 73.1, 111.5, 118.0, 123.3, 123.6, 124.0, 124.1, 124.2, 125.0, 125.1, 125.7,125.8, 125.9, 152.7, 167.2
MS (m/z)	**:**	608 (M^+)
Analysis	**:**	Calculated: C, 78.92, H, 5.96; N, 4.60
($C_{40}H_{36}N_2O_4$)		Observed: C, 78.81; H, 5.78; N, 4.50

1,2-Diphenyl-1-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″yl)ethane (1.15a)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.52, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	209-210 °C
IR ($CHCl_3$)	**:**	1751 cm^{-1}
^{1}H NMR ($CDCl_3$)	**:**	δ_H 5.24 -5.34 (m, 2H, C*H*Ph), 4.85 (d, *J* = 4.7 Hz, 1H, C4*H*), 5.43 (d, *J* = 4.7 Hz, 1H, C4′*H*), 5.33 (d, *J* = 4.3 Hz, 1H, C3*H*),

(200 MHz)		5.57 (d, *J* = 4.3 Hz, 1H, C3′*H*), 6.67-7.40 (m, 30H, Ar-*H*)
^{13}C NMR	**:**	δ_C 61.0, 61.8, 61.9, 64.0, 81.2, 81.6, 115.6, 115.8, 121.8,
($CDCl_3$)		122.0, 127.2, 127.6, 127.9, 128.3, 128.5, 128.6, 129.1, 129.2,
(75 MHz)		129.4, 132.4, 133.2, 136.4, 137.2, 157.0, 157.1, 165.8, 166.9
MS (m/z)	**:**	608 (M^+)
Analysis	**:**	Calculated: C, 78.92, H, 5.96; N, 4.60
($C_{40}H_{36}N_2O_4$)		Observed: C, 78.85; H, 5.74; N, 4.53

1.9.5b Synthesis of β-lactams 1.14b and 1.15b

Following the optimized procedure for bis-β-lactams, the benzyloxyacetyl chloride **1.04b** (0.427 g, 2.31 mmol) on treatment with bisimine **1.13** (0.300 g, 0.77mmol) in presence of triethylamine (1.07 mL, 7.7 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (20% ethyl acetate/petroleum ether) to give 0.410 g (84%, total yield) of pure β-lactams **1.14b** (minor) and **1.15b** (major) as white solids.

1,2-Diphenyl-1,2-bis(3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)ethane (1.14b)

It was obtained as a white solid, R_f (20% ethyl acetate/pet ether) 0.56, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	190-191 °C
IR ($CHCl_3$)	**:**	1741 cm^{-1}
^{1}H NMR	**:**	δ_H 5.19 (s, 2H, C*H*Ph), 5.34 (d, *J* = 4.1 Hz, 2H, C4*H*), 5.55 (d,
($CDCl_3$)		*J* = 4.1 Hz, 2H, C3*H*), 6.69-7.30 (m, 30H, Ar-*H*)
(200 MHz)		
^{13}C NMR	**:**	δ_C 59.2, 61.5, 62.9, 63.8, 72.2, 72.8, 82.2, 82.8, 127.7, 127.9,
($CDCl_3$)		128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 130.7,
(50 MHz)		136.0, 136.4, 138.0, 138.3, 138.6, 139.5, 141.0, 166.8
MS (m/z)	**:**	636 (M^+)
Analysis	**:**	Calculated: C, 79.21, H, 6.33; N, 4.39
($C_{42}H_{40}N_2O_4$)		Observed: C, 79.05; H, 6.23; N, 4.28

1,2 Diphenyl-1-(3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-benzyloxy-4″-phenylazetidin-2″-one-1″yl)ethane (1.15b)

It was obtained as a white solid, R_f (20% ethyl acetate/pet ether) 0.44, which on recrystallization from methanol gave white crystalline solid.

MP	**:**	79-80 °C
IR ($CHCl_3$)	**:**	1753 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 4.02- 4.32 (m, 2H, C*H*Ph), 4.61 (d, *J* = 4.3 Hz, 1H, C4*H*), 4.84 (d, *J* = 4.3 Hz, 1H, C3*H*), 4.98 (d, *J* = 4.7 Hz, 1H, C4′*H*), 5.12 (d, *J* = 4.7 Hz, 1H, C3′*H*), 5.14-5.23 (q, *J* = 11.8 Hz, 4H, CH_2Ph), 6.72-7.55 (m, 30H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 60.8, 61.5, 63.8, 63.9, 72.2, 72.3, 82.9, 83.1, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.7, 128.9, 129.1, 129.4, 133.3, 134.1, 136.4, 136.8, 137.5, 167.0, 167.8
MS (m/z)	**:**	636 (M^+)
Analysis ($C_{42}H_{40}N_2O_4$)	**:**	Calculated: C, 79.21, H, 6.33; N, 4.39 Observed: C, 79.09; H, 6.20; N, 4.30

1.9.5c Synthesis of β-lactams 1.14c and 1.15c

Following the optimized procedure for bis-β-lactams, the methoxyacetyl chloride **1.04c** (0.243 g, 2.31 mmol) on treatment with bisimine **1.13** (0.290 g, 0.74 mmol) in presence of triethylamine (1.08 mL, 7.4 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.350 g (88%, total yield) of pure β-lactams **1.14c** (minor) and **1.15c** (major) as white solids.

1,2-Diphenyl-1,2-bis(3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (1.14c)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.55, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	194-195 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR	**:**	δ_H 3.01 (s, 6H, OCH_3), 4.47 (d, *J* = 5.1 Hz, 2H, C4*H*), 4.53 (d,

($CDCl_3$)		*J* = 5.1 Hz, 2H, C3*H*), 5.60 (d, *J* = 10.3 Hz, 2H, C*H*Ph), 7.00-
(200 MHz)		7.68 (m, 20H, Ar-*H*)
^{13}C NMR	**:**	δ_C 57.9, 61.3, 67.2, 85.0, 127.2, 127.7, 127.9, 128.0, 128.2,
($CDCl_3$)		128.3, 128.5, 128.6, 129.1, 130.7, 133.6, 136.4, 138.2, 140.9,
(50 MHz)		162.3
MS (m/z)	**:**	532 (M^+)
Analysis	**:**	Calculated: C, 76.67, H, 6.05; N, 5.26
($C_{34}H_{32}N_2O_4$)		Observed: C, 76.49; H, 5.88; N, 5.10

1,2-Diphenyl-1-(3′-methoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-methoxy-4″-phenylazetidin-2″-one-1″yl)ethane (1.15c)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.47, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	201-202 °C
IR ($CHCl_3$)	**:**	1743 cm^{-1}
^{1}H NMR	**:**	δ_H 3.06, 3.09 (s, 6H, OCH_3), 4.66 (d, *J* = 4.3 Hz, 2H, C4*H* and
($CDCl_3$)		C4′*H*), 4.80 (d, *J* = 4.7 Hz, 1H, C3*H*), 5.08 (d, *J* = 4.7 Hz, 1H,
(200 MHz)		C3′*H*), 5.22 (q, *J* = 11.8 Hz, 2H, C*H*Ph), 6.76-7.47 (m, 20H, Ar-*H*)
^{13}C NMR	**:**	δ_C 57.9, 58.1, 60.6, 61.2, 61.4, 63.4, 84.7, 85.0, 127.5, 127.8,
($CDCl_3$)		127.9, 128.1, 128.3, 128.5, 128.8, 129.1, 132.8, 133.7, 136.5,
(50 MHz)		137.2, 167.0, 167.8
MS (m/z)	**:**	532 (M^+)
Analysis	**:**	Calculated: C, 76.67, H, 6.05; N, 5.26
($C_{34}H_{32}N_2O_4$)		Observed: C, 76.53; H, 5.83; N, 5.07

1.9.6: *N,N′*-Dibenylidenebutane-2, 3-diamine (1.17)

This bis-imine **1.17** was prepared from (±) 2,3-diaminobutane (0.10 g, 0.430 mmole) and benzaldehyde (0.128 g, 1.61 mmole) following the same procedure as described for **1.03a-c**. It was isolated as an oil (0.089 g, 83%); IR($CHCl_3$) 1583, 1596,

1643 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (d, *J* = 5.8 Hz, 6H, C*H*$_3$), 3.38-3.53 (m, 2H, C*H*), 7.17-7.92 (m, 10H, Ar), 8.16 (s, 2H, -N=C*H*).

1.9.7 Synthesis of β-lactams 1.18 and 1.19

Following the optimized procedure for bis-β-lactams, the phenoxyacetyl chloride **1.04a** (0.243 g, 2.31 mmol) on treatment with bisimine **1.17** (0.260 g, 0.98 mmol) in presence of triethylamine (1.37 mL, 9.84 mmol) at 0 °C gave mixtures of two β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.480 g (91%, total yield) of pure β-lactams **1.18** (minor) and **1.19** (major) as white solids.

2,3-Bis [3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]butane (1.18)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.50, which was recrystallized from methanol to get white crystalline solid.

MP	**:**	69-70 °C
IR ($CHCl_3$)	**:**	1755 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 0.81 (d, *J* = 6.6 Hz, 6H, C*H*$_3$), 4.08-4.17 (m, 2H, C*H*CH_3), 5.26 (d, *J* = 4.7 Hz, 2H, C4*H*), 5.40 (d, *J* = 4.7 Hz, 2H, C3*H*), 6.62-7.52 (m, 20H, Ar-*H*)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 15.9, 51.2, 61.3, 81.3, 111.5, 127.9, 128.0, 128.6, 128.9, 129.1, 134.4, 156.6, 167.4
MS (m/z)	**:**	532 (M^+)
Analysis	**:**	Calculated: C, 76.67, H, 6.05; N, 5.26
($C_{34}H_{32}N_2O_4$)		Observed: C, 76.55; H, 6.05; N, 5.16

2-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-3-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)butane (1.19)

It was obtained as a white solid, R_f (30% ethyl acetate/pet ether) 0.35, which was crystallized from methanol to get white crystalline solid.

MP	**:**	175-176 °C
IR ($CHCl_3$)	**:**	1755 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 0.88 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.32 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 3.71-3.90 (m, 2H, C*H*CH$_3$), 4.95 (d, *J* = 4.7 Hz, 1H, C4*H*), 5.37 (d, *J* = 4.7 Hz, 1H, C4′*H*), 5.40 (d, *J* = 4.3 Hz, 1H, C3*H*), 5.50 (d, *J* = 4.3 Hz, 1H, C3′*H*), 6.60-7.57 (m, 20H, Ar)
^{13}C NMR (CDCl$_3$) (125 MHz)	**:**	δ_C 15.8, 17.1, 51.7, 52.4, 61.5, 62.6, 80.9, 115.6, 121.8, 122.0, 128.0, 128.4, 128.7, 129.2, 133.0, 134.4, 156.8, 166.3, 166.4
MS (m/z)	**:**	532 (M^+)
Analysis ($C_{34}H_{32}N_2O_4$)	**:**	Calculated: C, 76.67, H, 6.05; N, 5.26 Observed: C, 76.48; H, 6.03; N, 5.08

1.9.8 Asymmetric synthesis of bis-β-lactams 1.23 and 1.24

Following the optimized procedure described for the bis-β-lactams, the phenoxyacetyl chloride **1.04a** (0.352 g, 2.06 mmol) on treatment with chiral bisimine **1.22** (0.200 g, 0.69 mmol) in presence of triethylamine (0.96 mL, 6.90 mmol) at 0 °C gave mixtures of two optically pure β-lactams. This mixture was separated by flash column chromatography (30% ethyl acetate/petroleum ether) to give 0.290 g (76%, total yield) of pure β-lactams **1.23** (minor) and **1.24** (major) as white solids.

(1*R*,2*R*,3′*S*,4′*R*,3″*S*,4″*R*)-1,2-Bis(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)cyclohexane (1.23)

It was obtained as a white crystalline solid; mp 231-232 °C; $[\alpha]^{25}_{D}$ = -146.9 (*c*, 0.80, $CHCl_3$); spectral data same as for **1.05a**.

(1*R*,2*R*,3′*S*,4′*R*,3″*R*,4″*S*)-1-(3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″-yl)cyclohexane (1.24)

It was obtained as a white crystalline solid, mp 82-83 °C; $[\alpha]^{25}_{D}$ = -53.83 (*c*, 1.00, $CHCl_3$); spectral data same as for **1.06a**.

1.9.9 Asymmetric synthesis of bis-β-lactams 1.28 and 1.29

Following the optimized procedure described for the bis-β-lactams, the phenoxyacetyl chloride **1.04a** (0.395 g, 2.31 mmol) on treatment with chiral bisimine

1.27 (0.300 g, 0.77 mmol) in presence of triethylamine (1.07 mL, 7.7 mmol) at 0 °C gave mixtures of two optically pure β-lactams. This mixture was separated by flash column chromatography (20% ethyl acetate/petroleum ether) to give 0.376 g (80%, total yield) of pure β-lactams **1.28** (minor) and **1.29** (major) as white solids.

(1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-1,2-Diphenyl-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)ethane (1.28)

It was obtained as a white amorphous solid, mp 197-198 °C; $[\alpha]^{25}_{D}$ = +3.03 (*c*, 0.99, $CHCl_3$); spectral data same as for **1.14a**.

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-1,2-Diphenyl-1-(3′-phenoxy-4′-phenylazetidin-2′-one-1′-yl)-2-(3″-phenoxy-4″-phenylazetidin-2″-one-1″yl)ethane (1.29)

It was obtained as a white amorphous solid, mp 209-210 °C; $[\alpha]^{25}_{D}$ = +6.15 (*c*, 0.80, $CHCl_3$); spectral data same as for **1.15a**.

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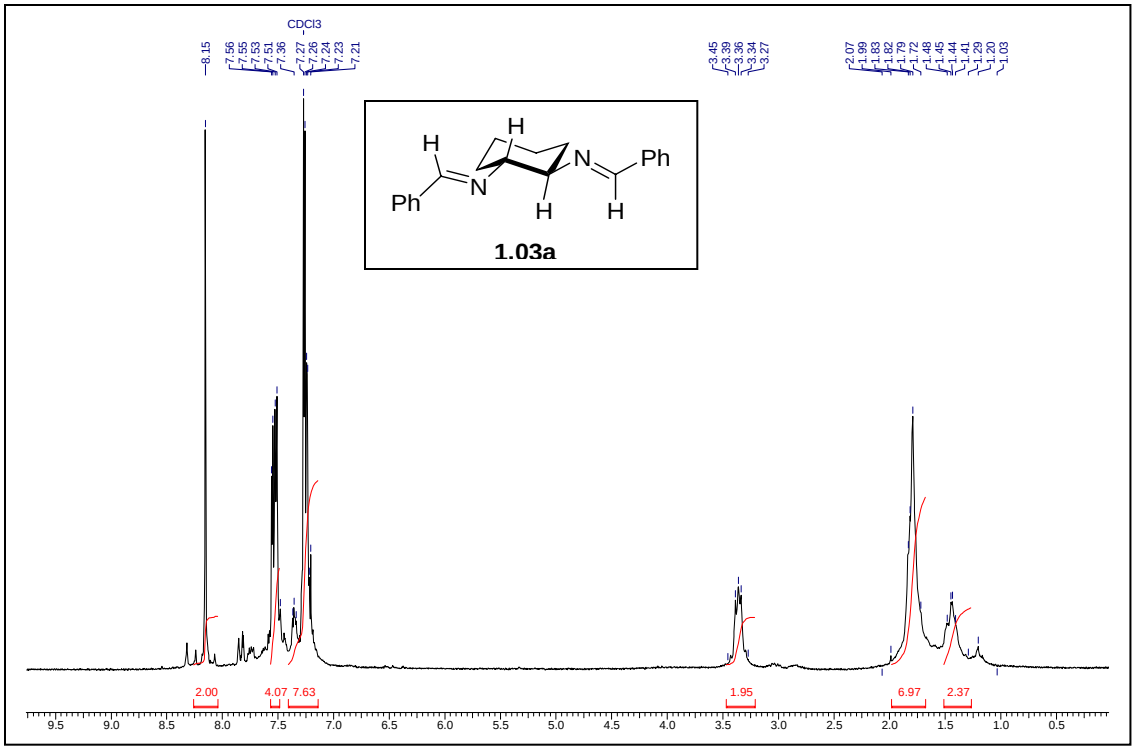
Chapter I

Spectra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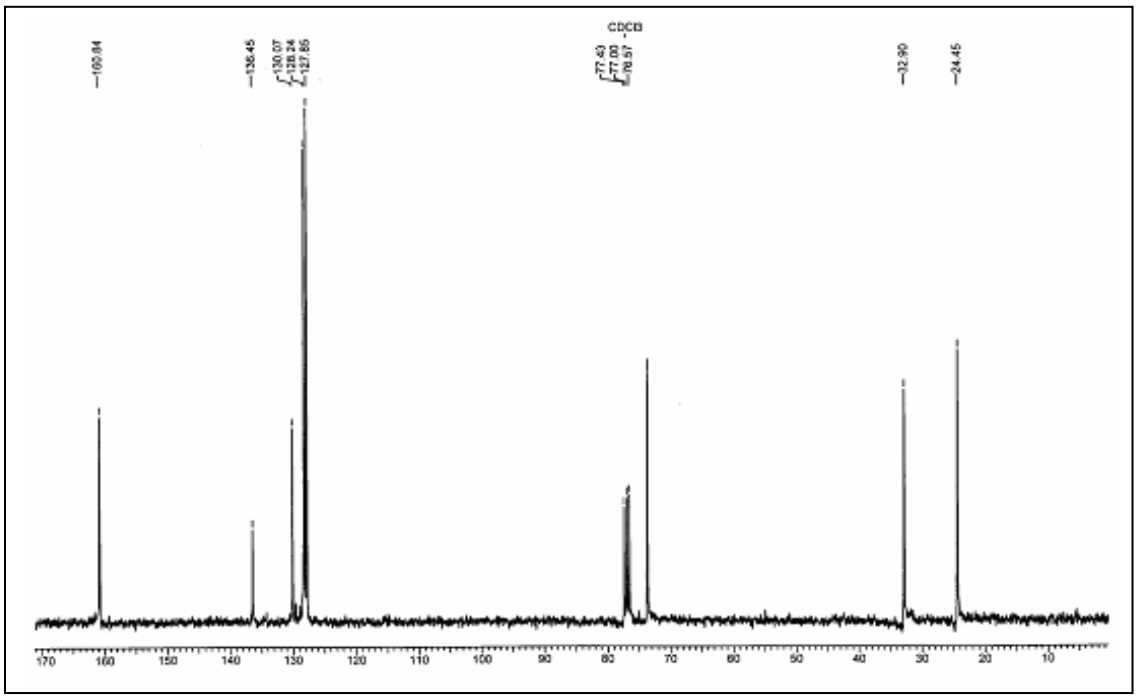
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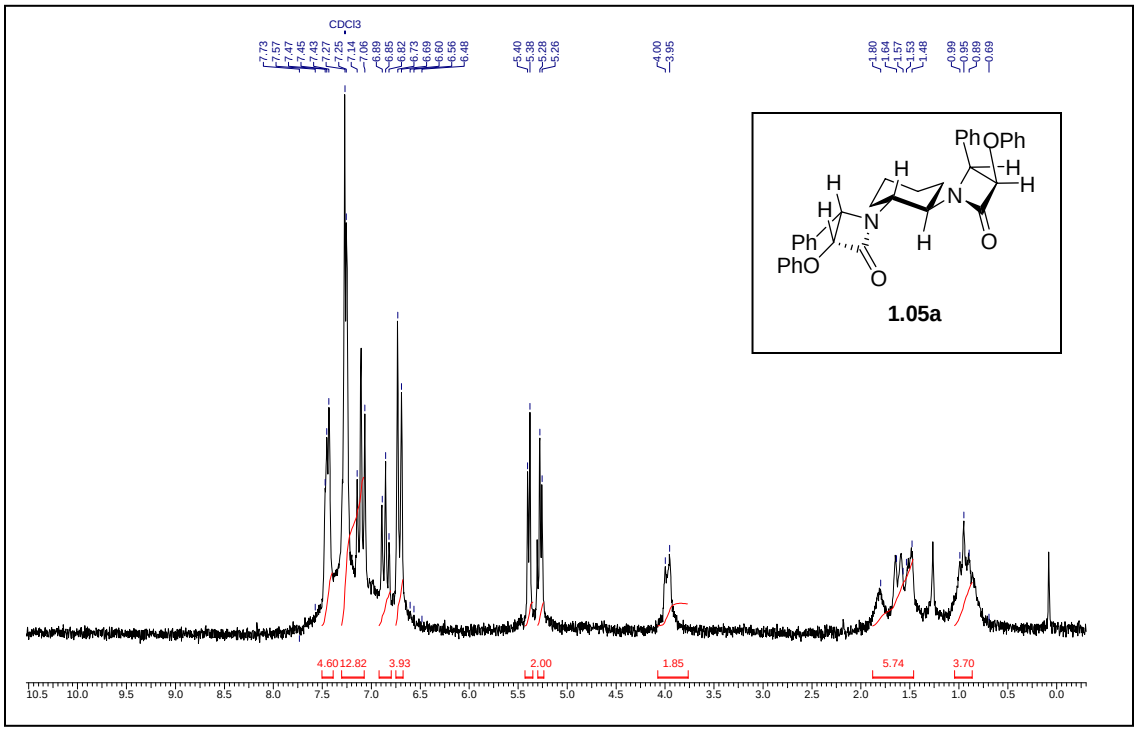
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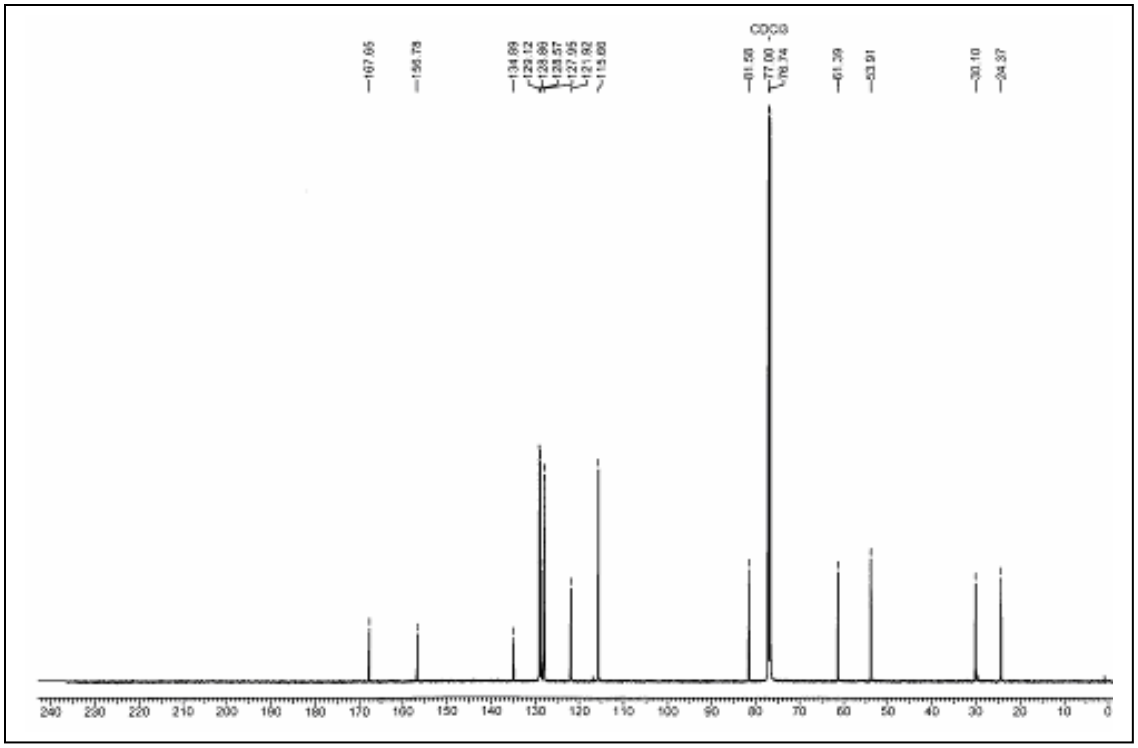
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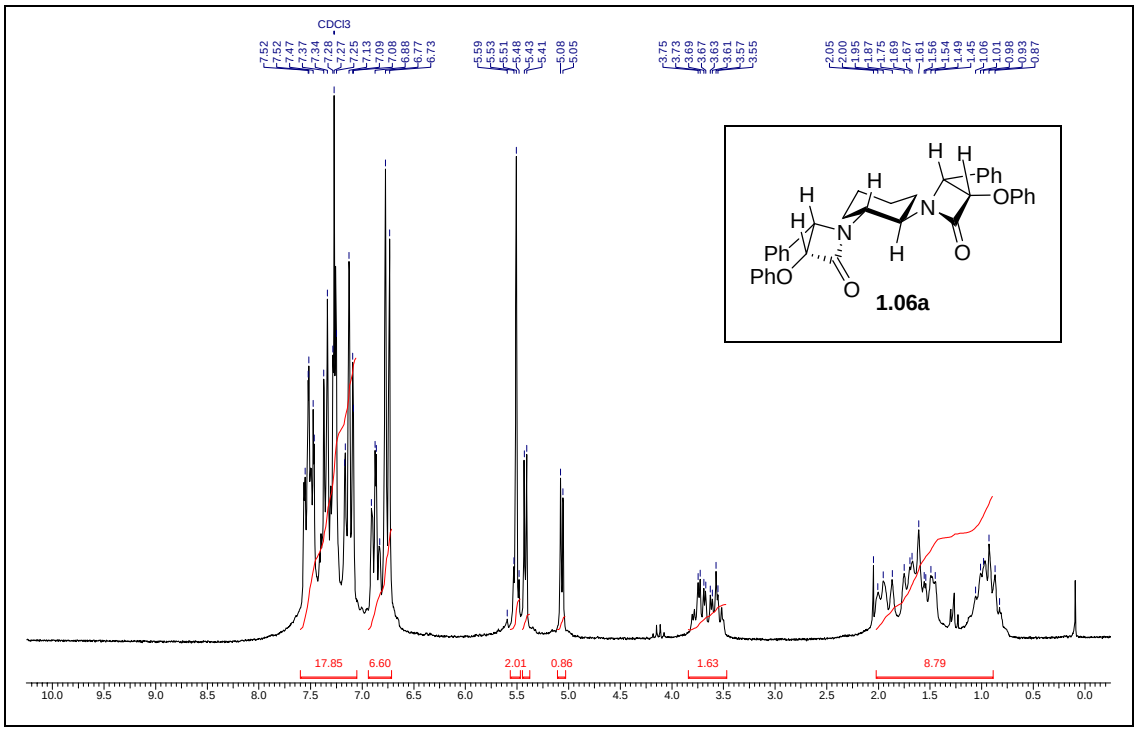
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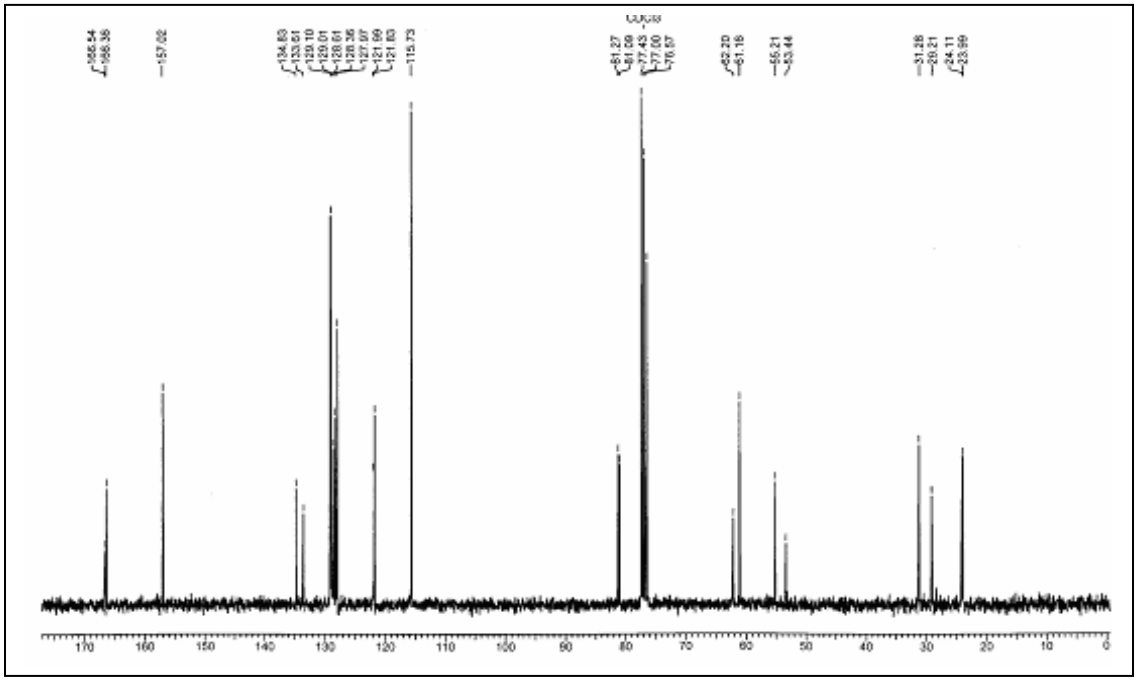

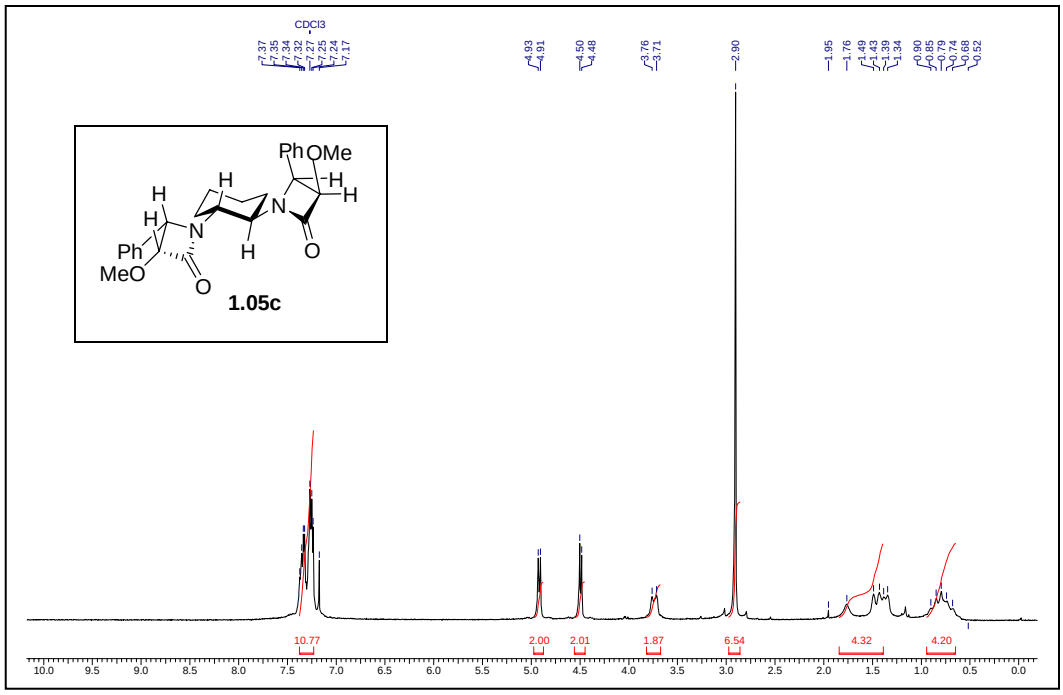
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H
H
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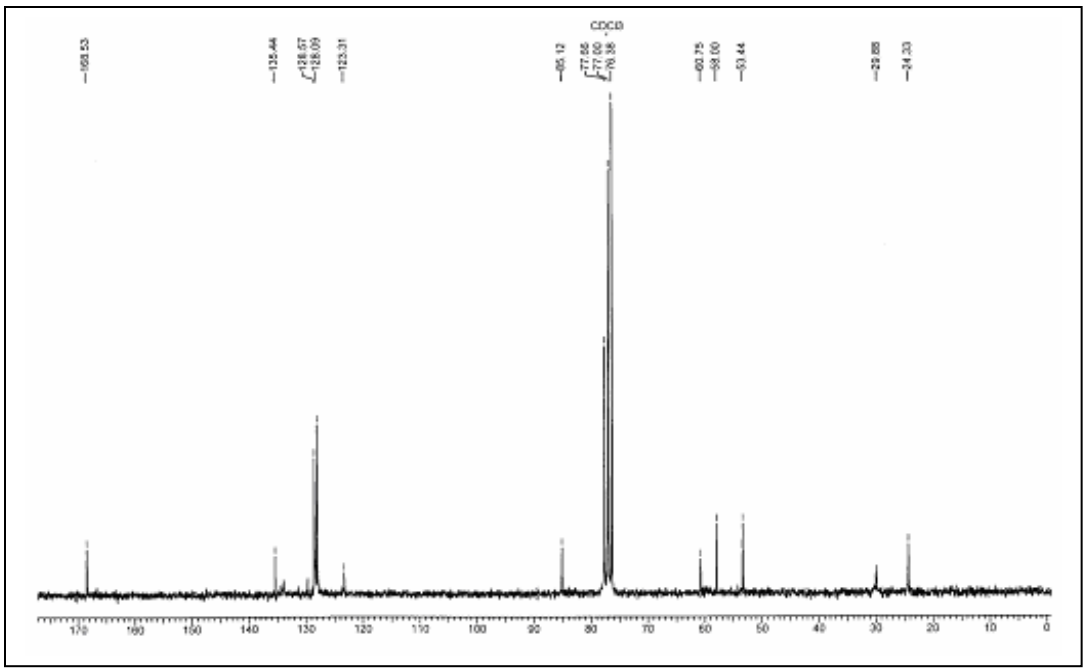
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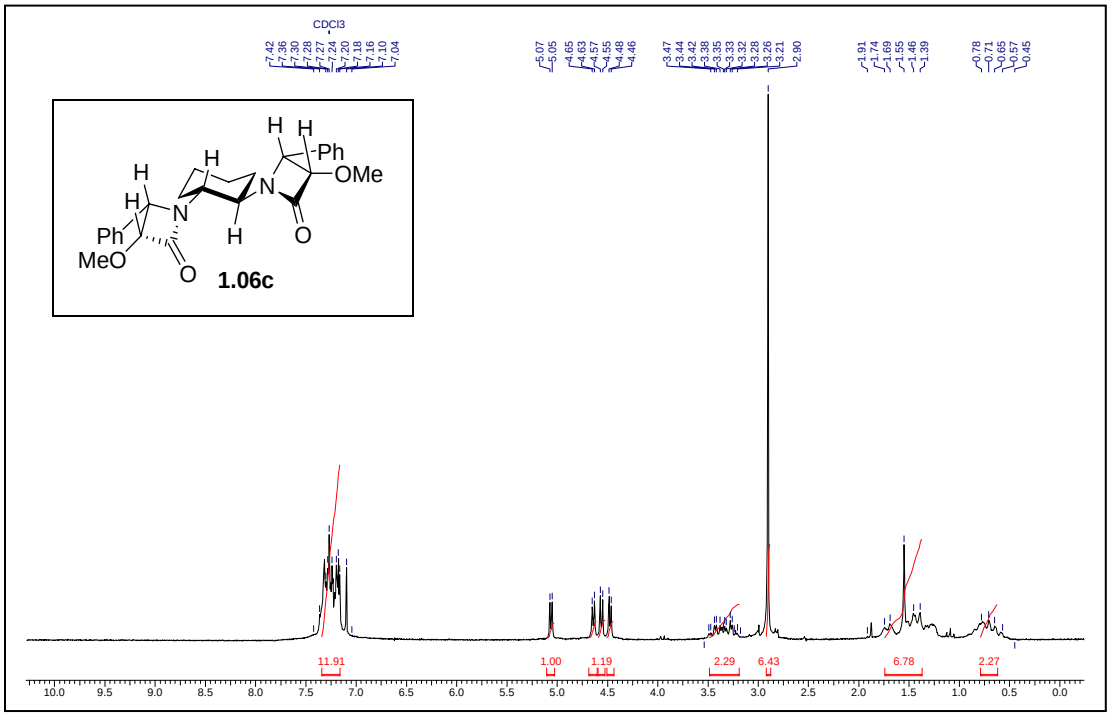
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4.55
4.48
4.46
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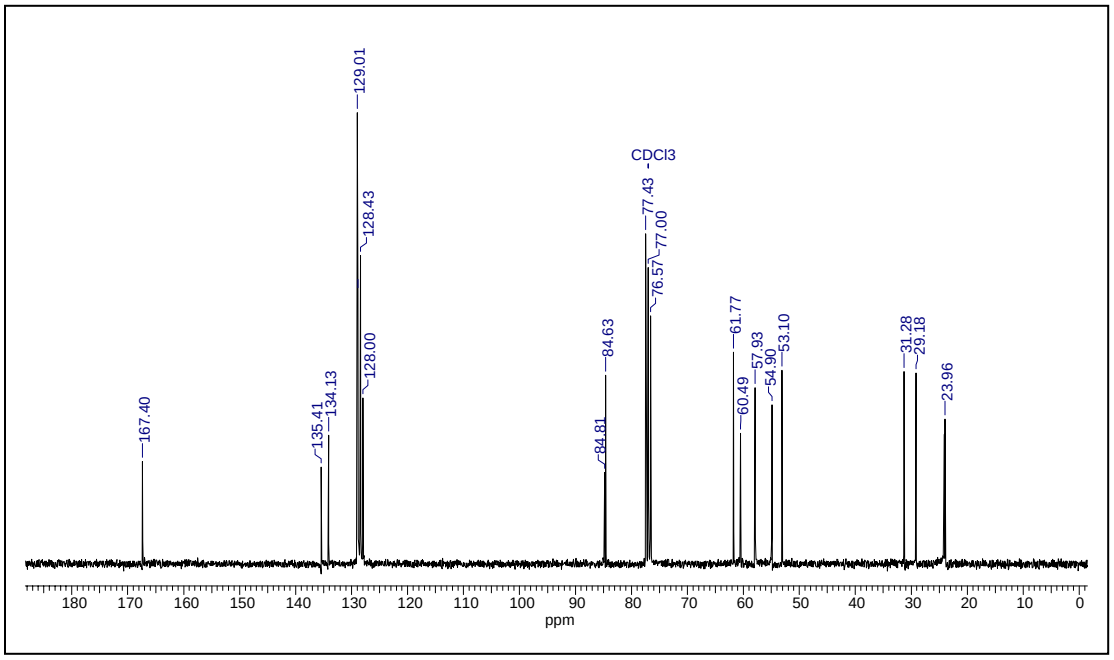
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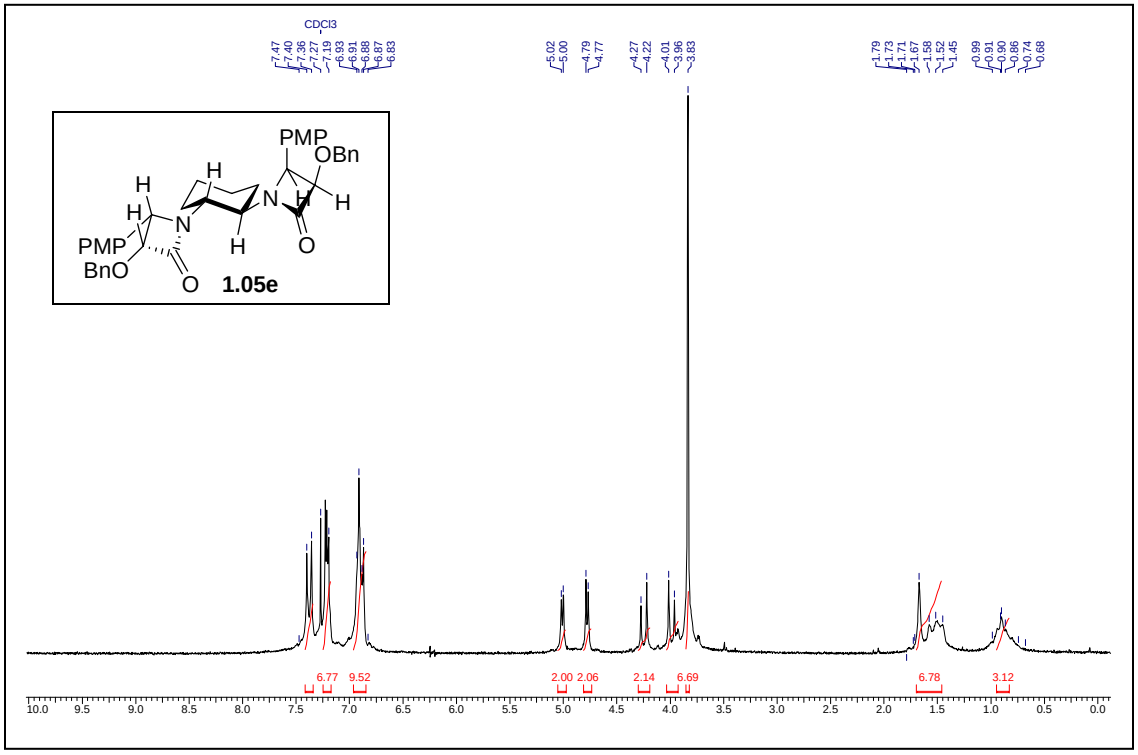
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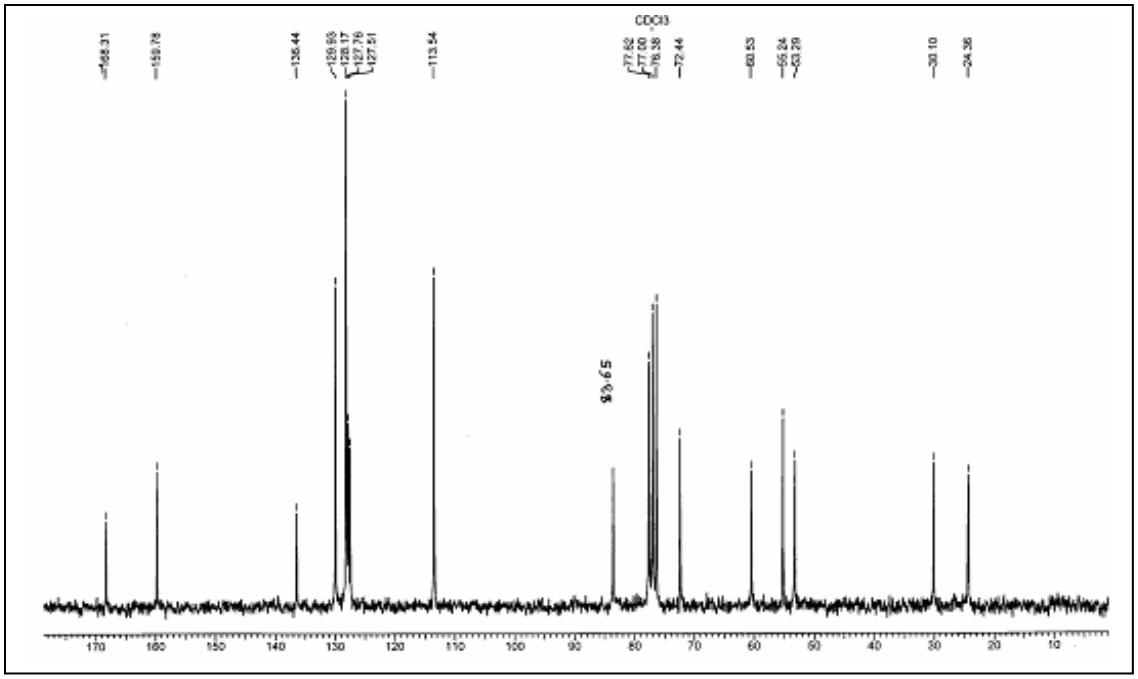
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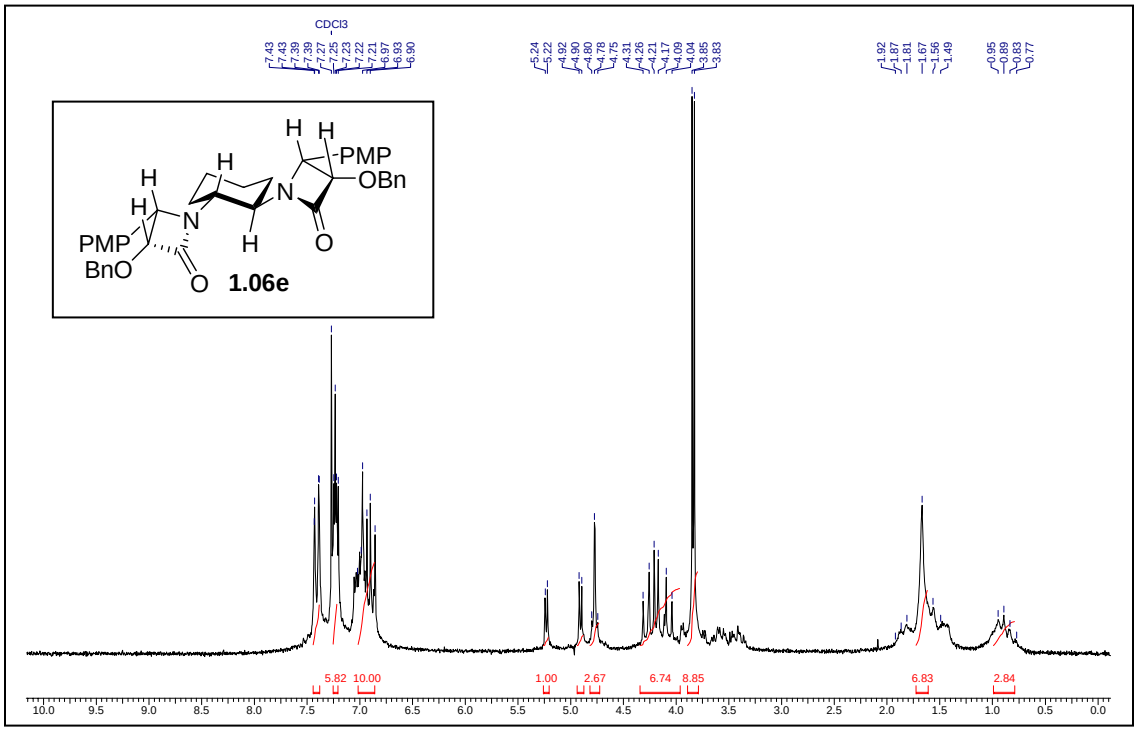
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4.80
4.78
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H
H
H
H
H
N
N
PMP
OBn
PMP
BnO
O
O
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1.00
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9.5
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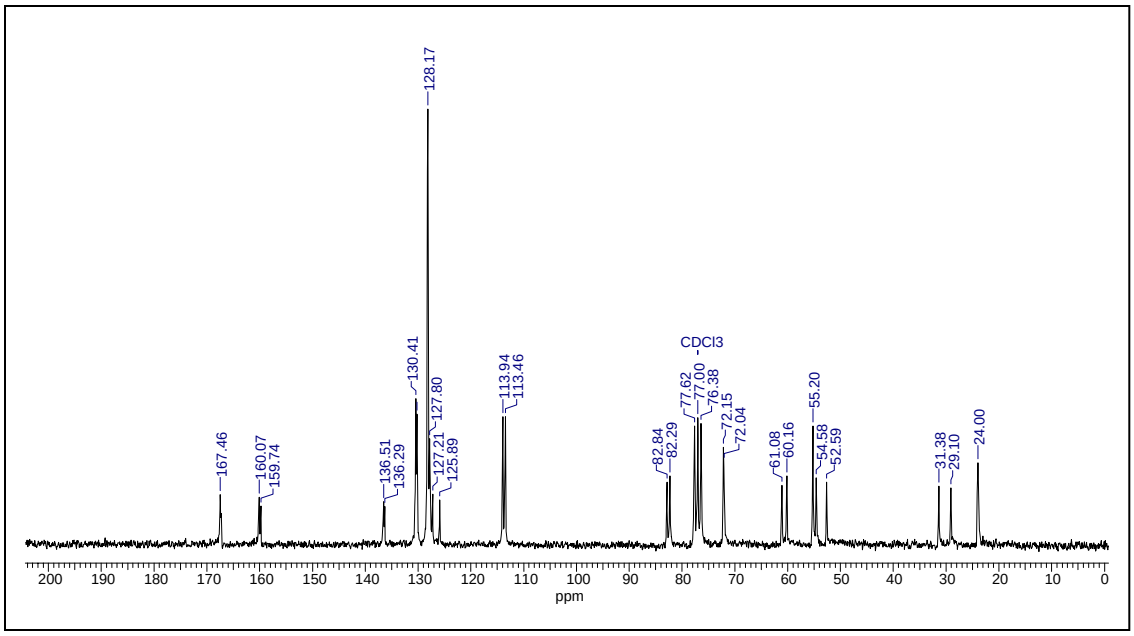
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82.29
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52.59
31.38
29.10
24.00
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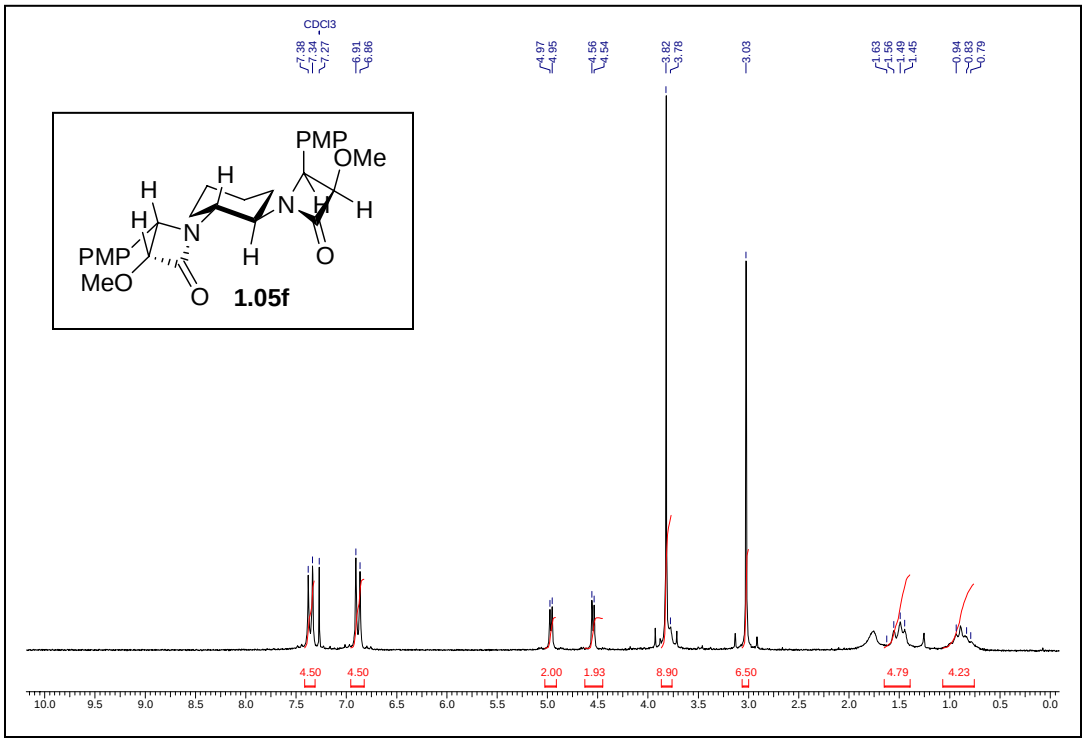
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1.55
1.49
1.45
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H
H
N
N
H
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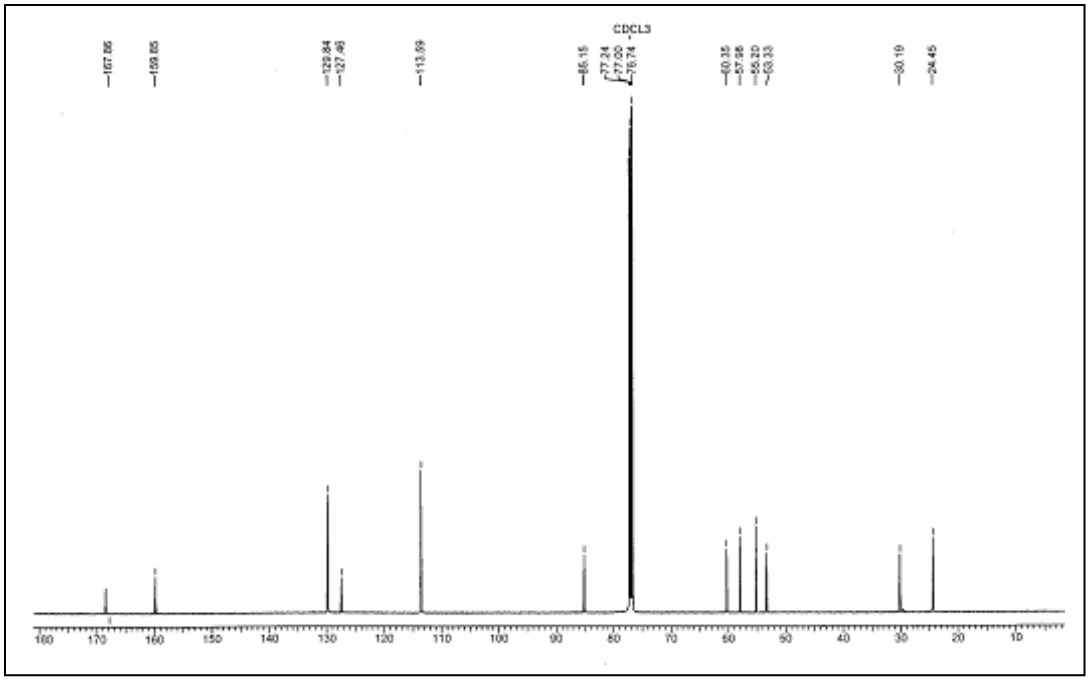
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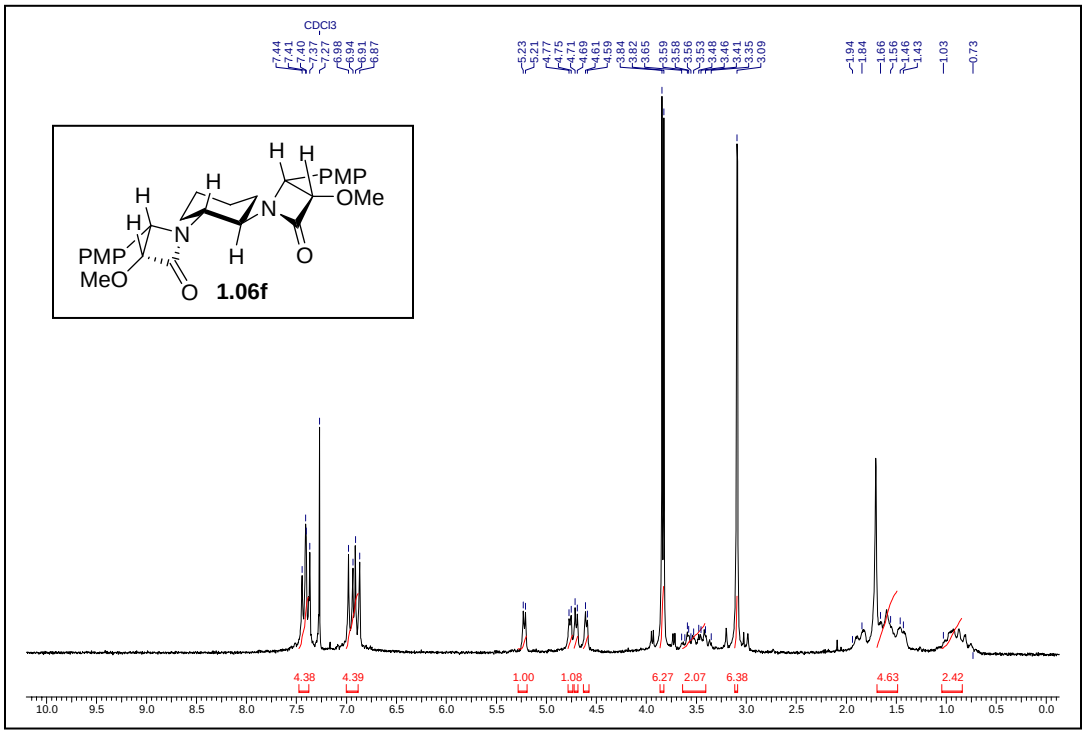
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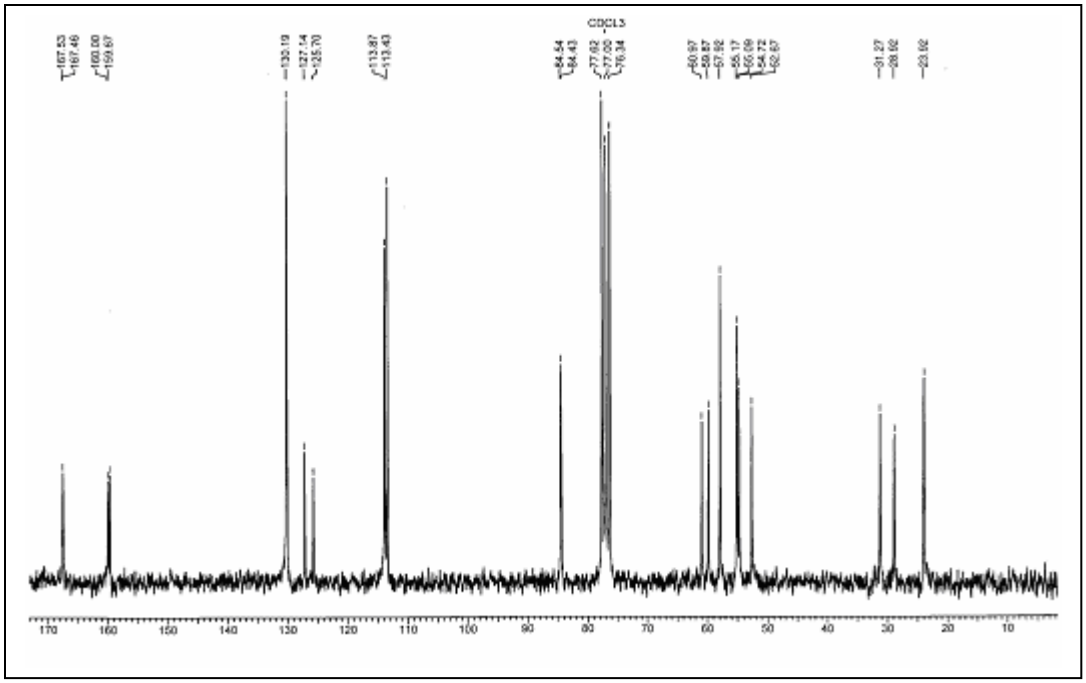
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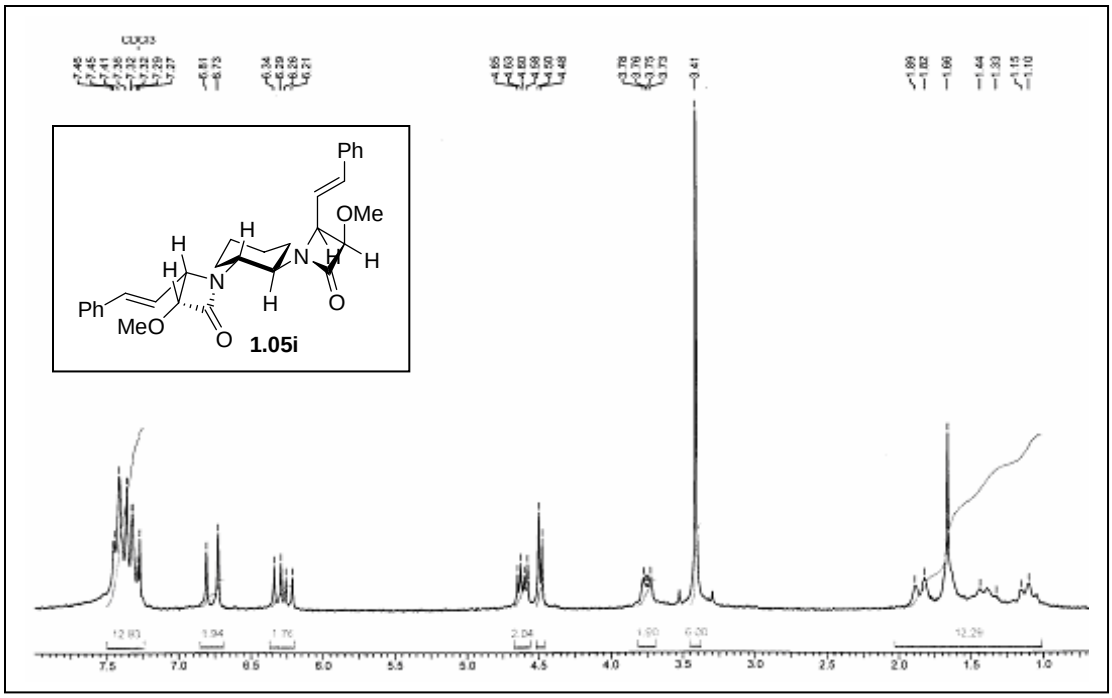
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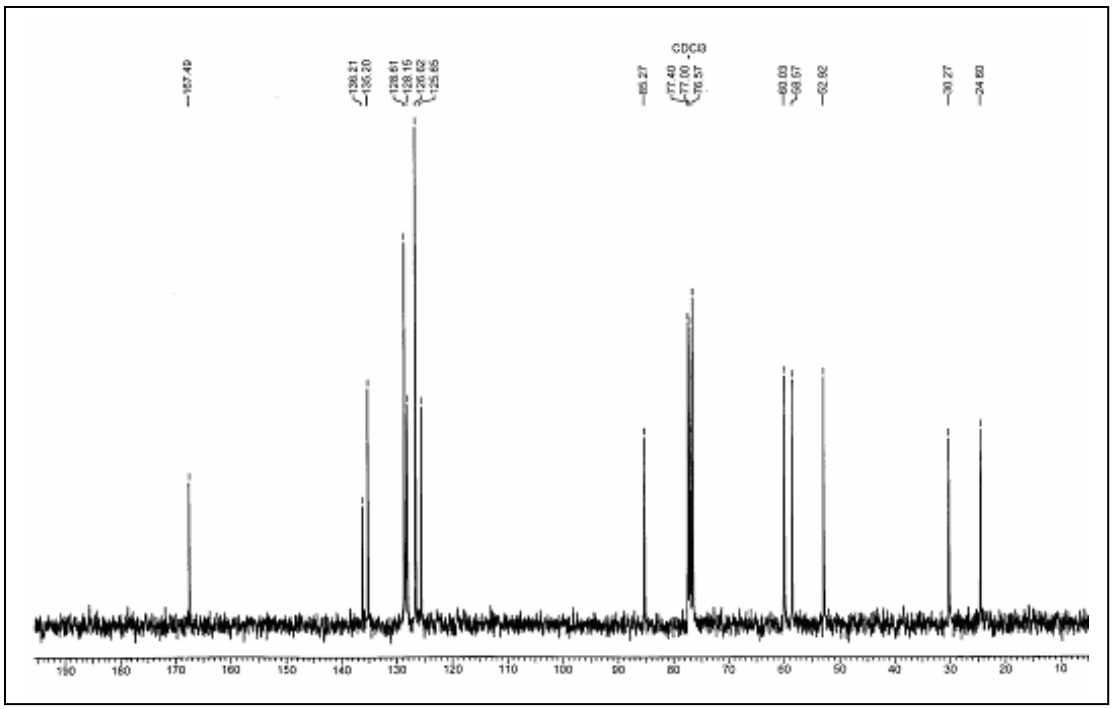
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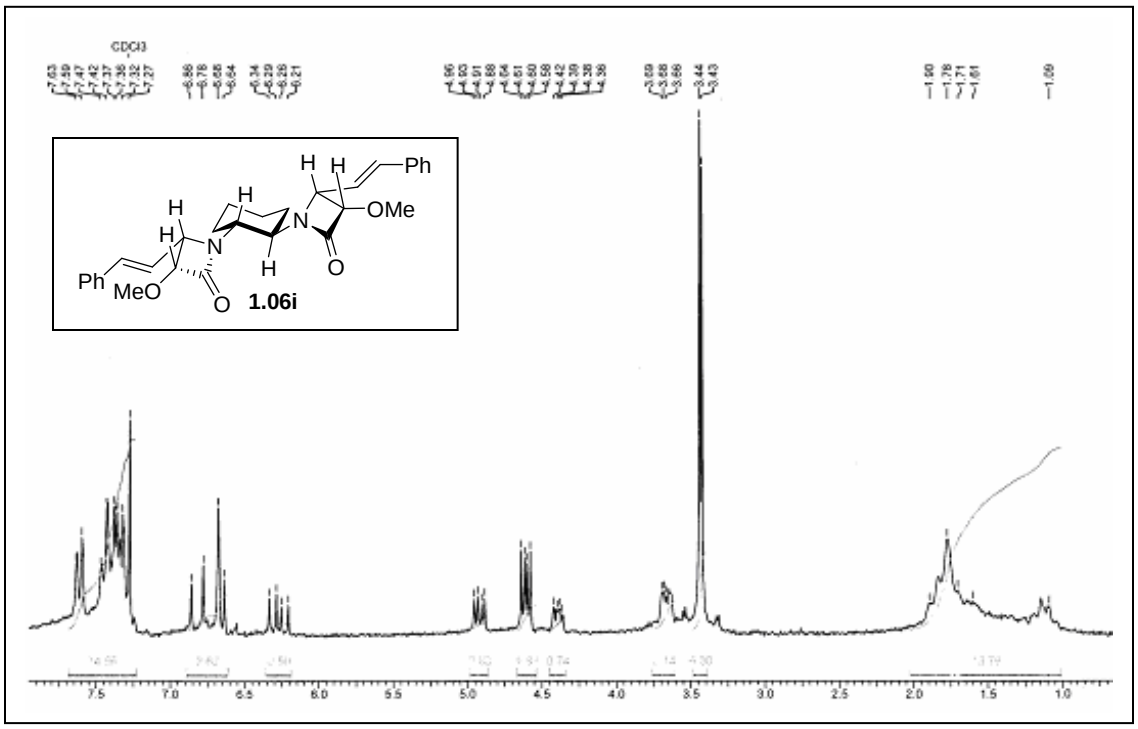
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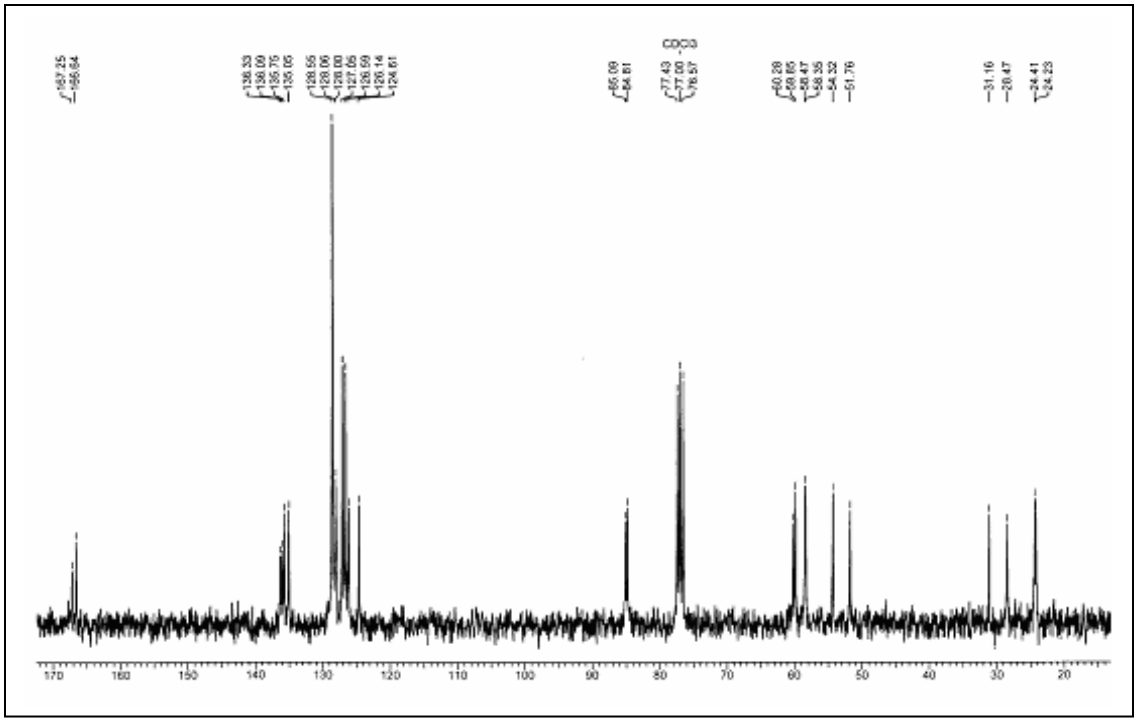
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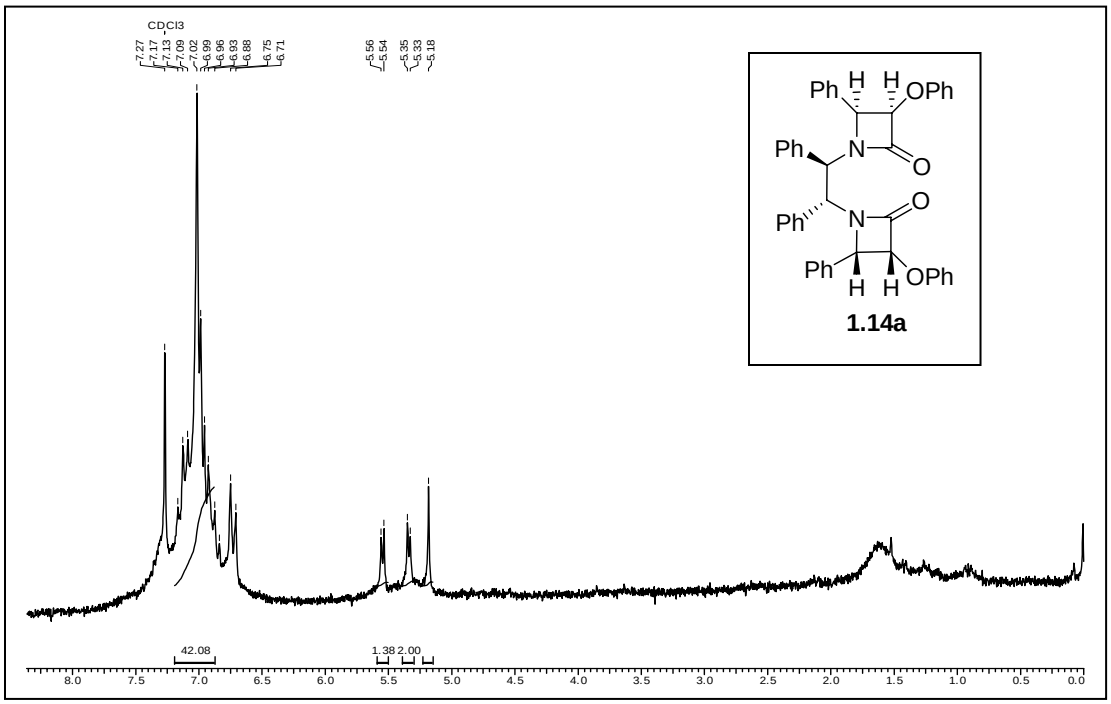
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5.33
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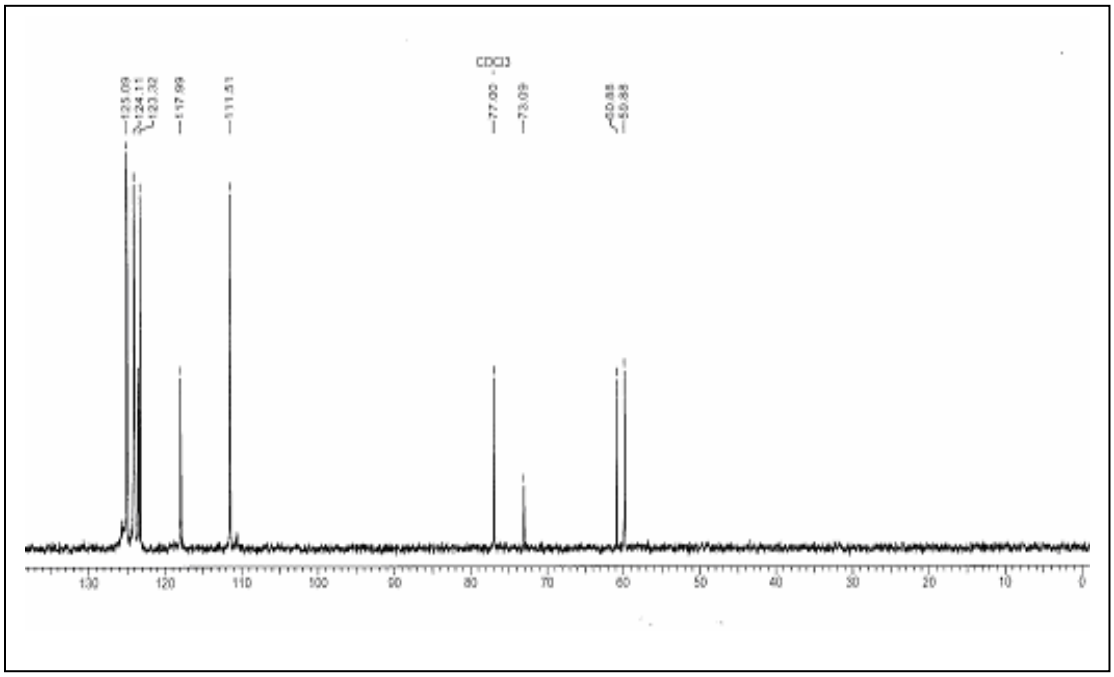
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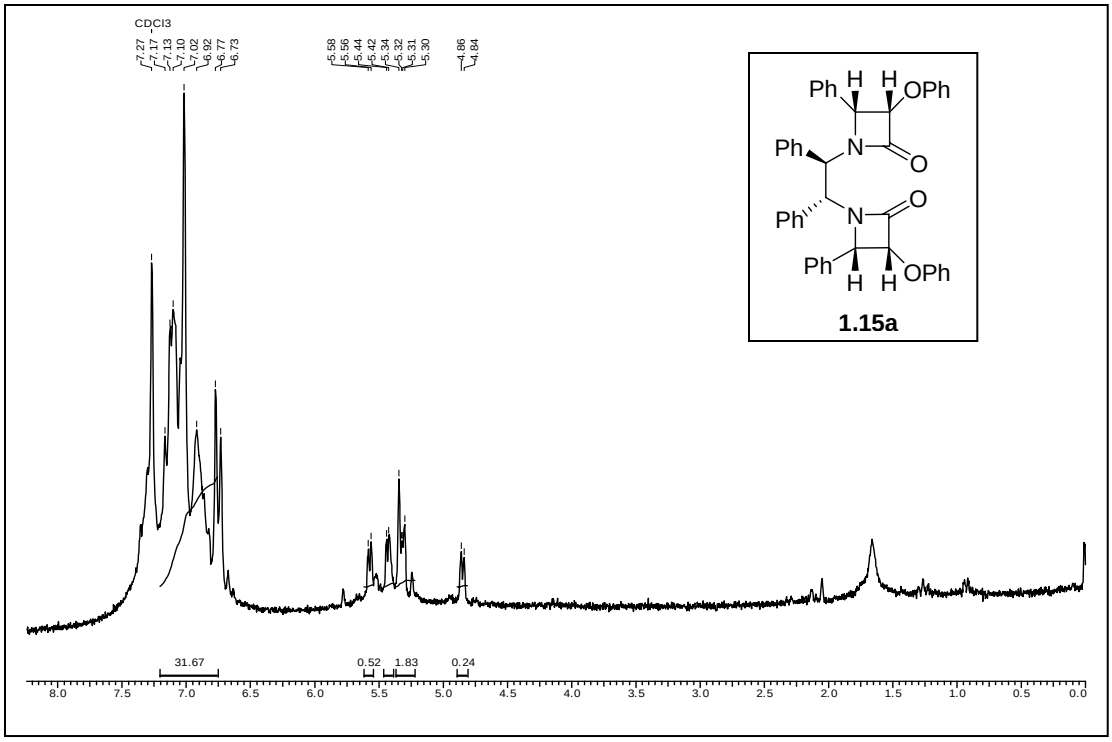
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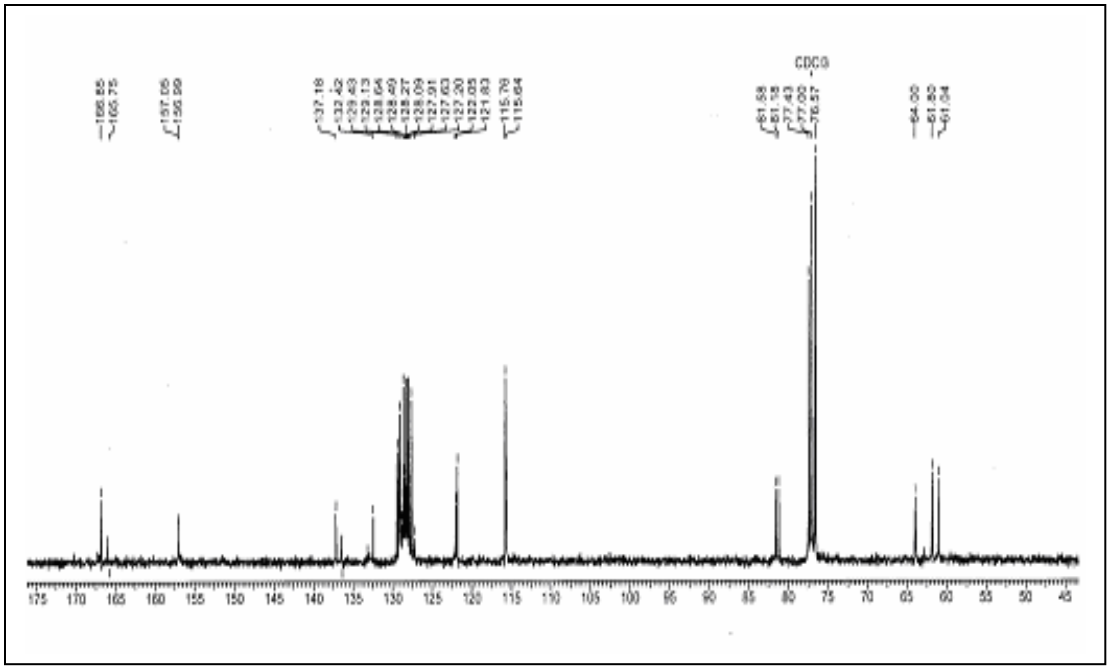
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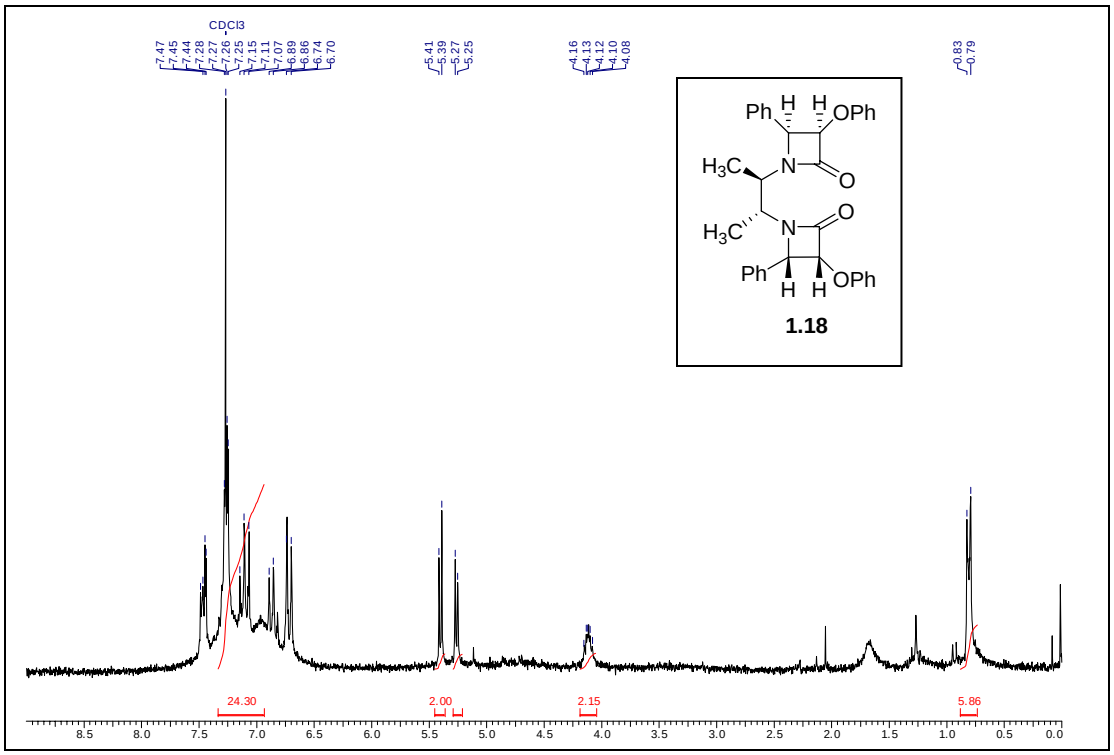
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H3C N O
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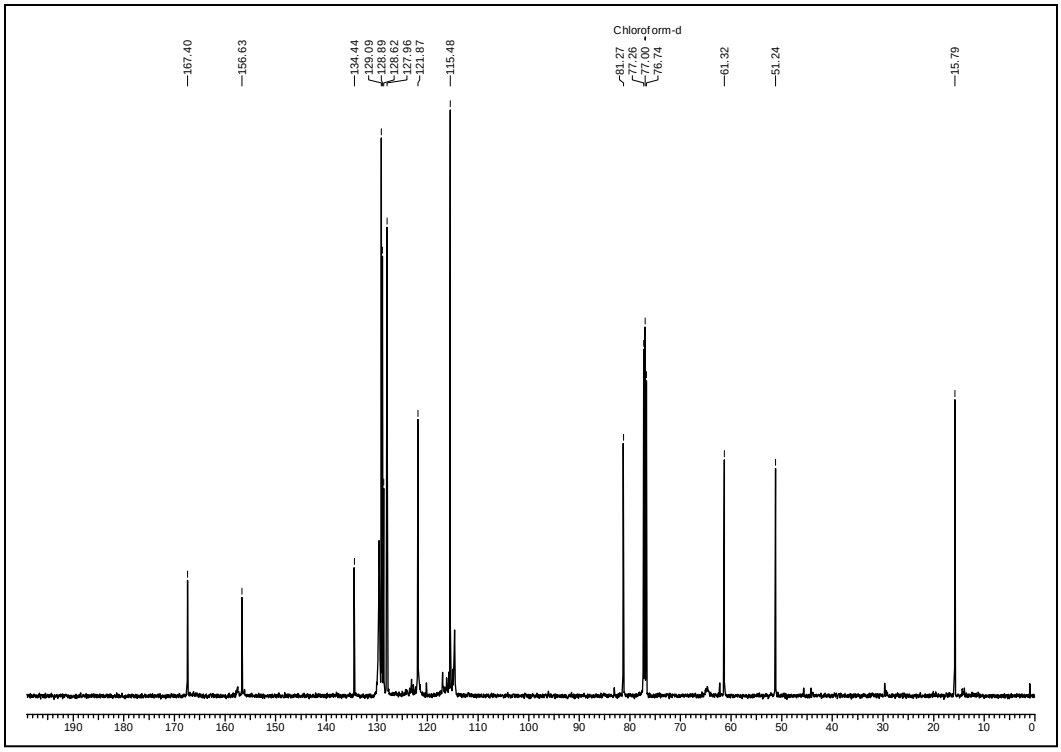
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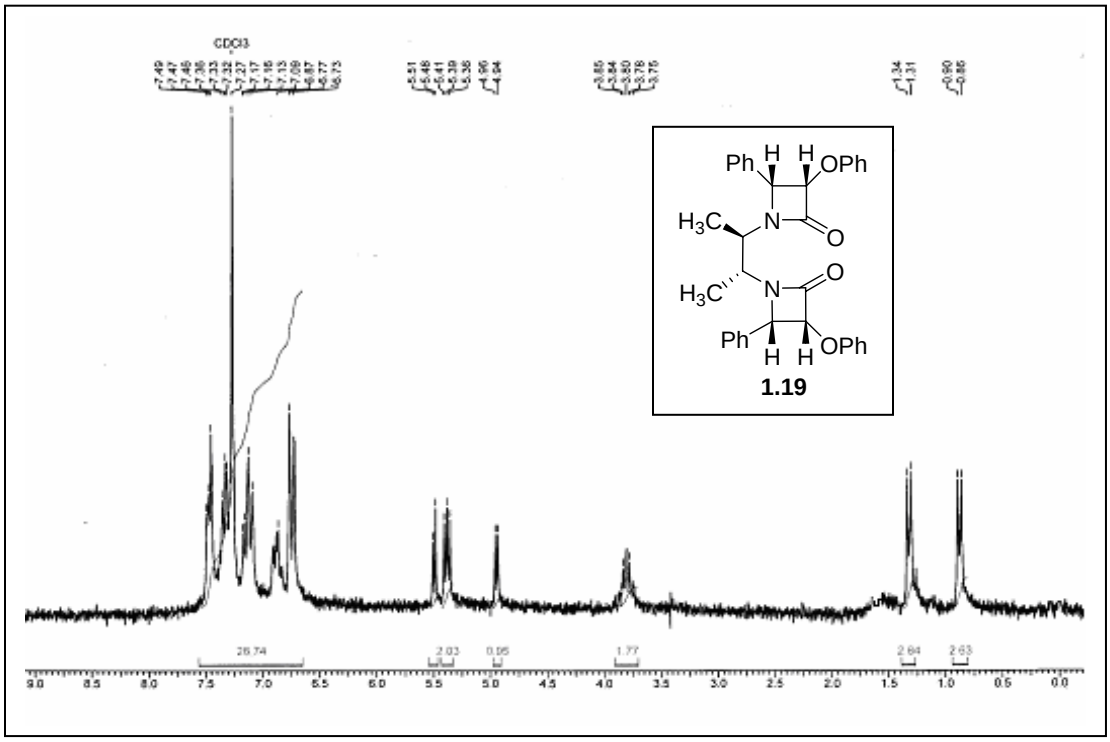
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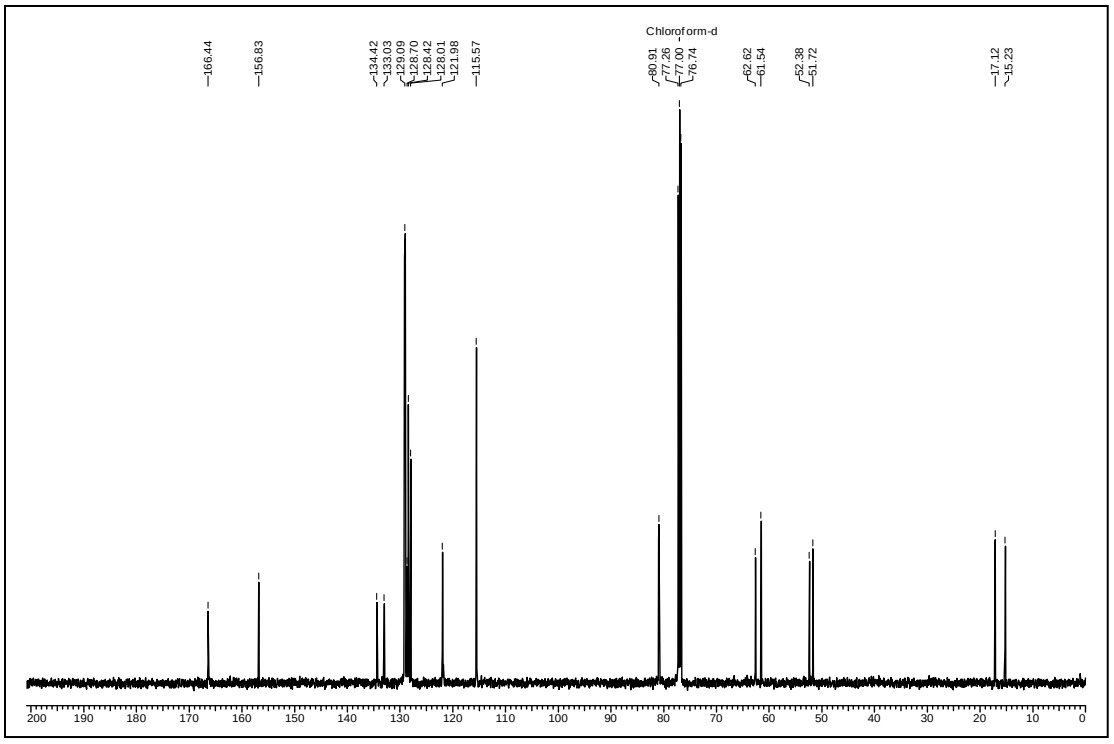
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77.00
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61.54
52.38
51.72
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15.23

Chapter II

Stereoselective Synthesis of 3-vinyl-β-lactams *via* cycloaddition reaction of vinylketenes and imines

Part of this work has been published in *Tetrahedron Lett*, **2006**, *47*, 5993-5996

2.1: Introduction

3-Vinyl-β-lactams are important intermediates in the synthesis of biomedicinally interesting compounds such as carbapenem, [1] asparenomycin[2] and thienamycin.[3] Normally, these β-lactams are prepared by Staudinger cycloaddition of vinylketenes also referred as Sheehan's ketenes[4] and imines. Although Sheehan's ketenes are known for long time, the synthetic utility of these ketenes are not fully explored. This may be due to lower yields and variable diastereoselectivities of the β-lactam formation.[5] This chapter describes the synthesis of 3-vinyl-β-lactams and some of the mechanistic aspects of the cycloaddition reaction of vinylketenes with imines.

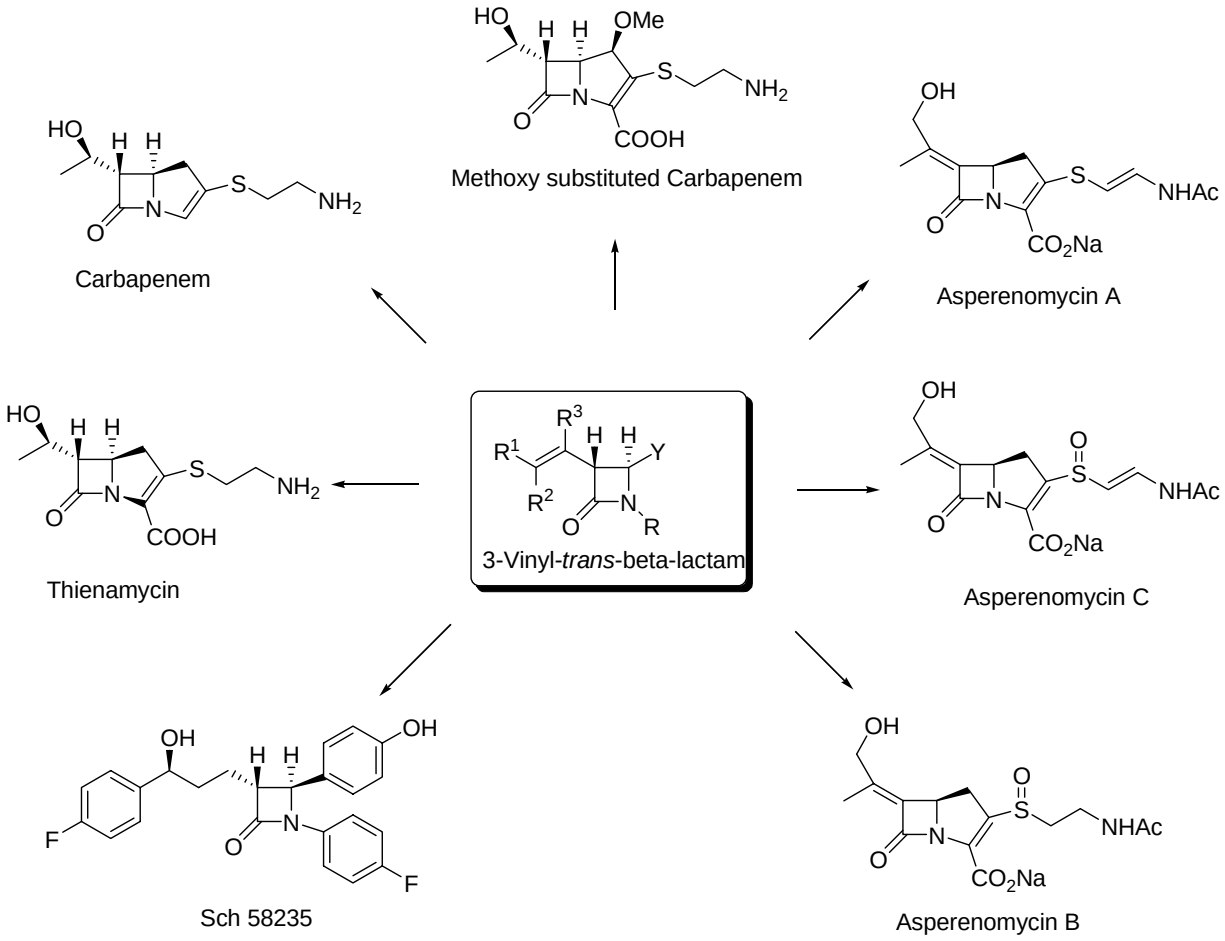
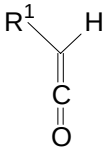
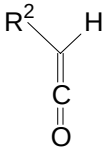
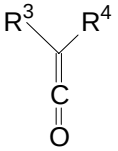
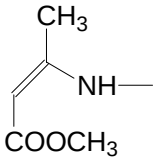
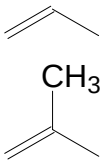
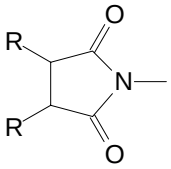


Figure 1: Application of 3-vinyl-β-lactams

Classification of ketenes and stereochemical out come of cycloaddition reaction with imines:

It appears that the stereochemical results (*cis* or *trans* product formation) obtained in the Staudinger reaction can be correlated well with the steric demands of the ketene in the formation of the zwitterionic intermediate.[4] Ketenes are classified into three groups according to the size of substituents as shown in the following Table 1.

Bose-Evans Ketenes	Sheehan Ketenes	Moore Ketenes
		
R^1	R^2	R^3
OCOR *O*-alkyl *O*-aryl *N*-alkylaryl NHCOR  N_3 F	 Phth 	Cl Br Alkyl Aryl SR SOR SO_2R R^4= H, CN

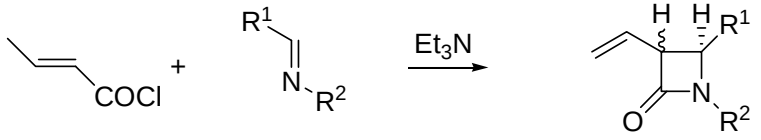
Bose-Evans Ketenes: Bose-Evans ketenes, possessing small substituents or substituents that have dipole interactions such as F, have a distinct preference for *cis*-β-lactam formation with diaryl imines and alkylaryl imines.

Moore Ketenes: Moore ketenes with large substituents have preference for *trans* product formation with diaryl and alkylaryl imines.

Sheehan Ketenes: Sheehan ketenes with medium-size substituents have a strong preference for *cis* product formation with alkylaryl imines, but diaryl imines give *trans* products. The reaction between crotonyl chloride and dimethylacryloyl chloride with imines was investigated by several research groups.[5,6,7] A few other methods are also known in the literature and will be discussed briefly below.

In 1971, Bose et al. [5a] devised a direct synthesis of 3-vinyl-β-lactams by the reaction of crotonyl chloride with Schiff's bases in the presence of triethylamine in refluxing dichloromethane. Exclusive formation of *trans*-β-lactams in low yield was observed (Scheme 1.65). Schiff bases derived from aromatic aldehydes and substituted aniline gave only *trans*-β-lactams while the Schiff bases derived from aromatic aldehydes and aliphatic amine produced a mixture of *cis* and *trans*-β-lactams with ranging ratio depending on the temperature of the reaction mixture.

Scheme 1.65

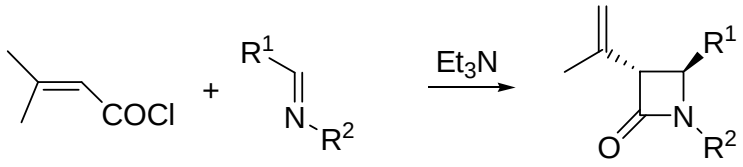


R^1 = Ph, R^2 = Ph
R^1 = -CO-Ph, R^2 = PMP
R^1 = -CO-Ph, R^2 = -CH(CH_3)Ph
R^1 = PMP, R^2 = PMP
R^1 = Ph, R^2 = PMP

R^1 = Ph, R^2 = Ph, *trans* (65%)
R^1 = -CO-Ph, R^2 = PMP *cis*/*trans* (80%)
R^1 = -CO-Ph, R^2 = -CH(CH_3)Ph *cis* (55%)
R^1 = PMP, R^2 = PMP, *trans* (55%)
R^1 = Ph, R^2 = PMP, *trans* (50%)

Zamboni and Just [5b] synthesized number of *trans*-3-vinyl-β-lactams as a potential synthons for β-lactam antibiotics in 1979 using ketene derived from β,β-dimethylacryloyl chloride and Schiff base (Scheme 1.66).

Scheme 1.66



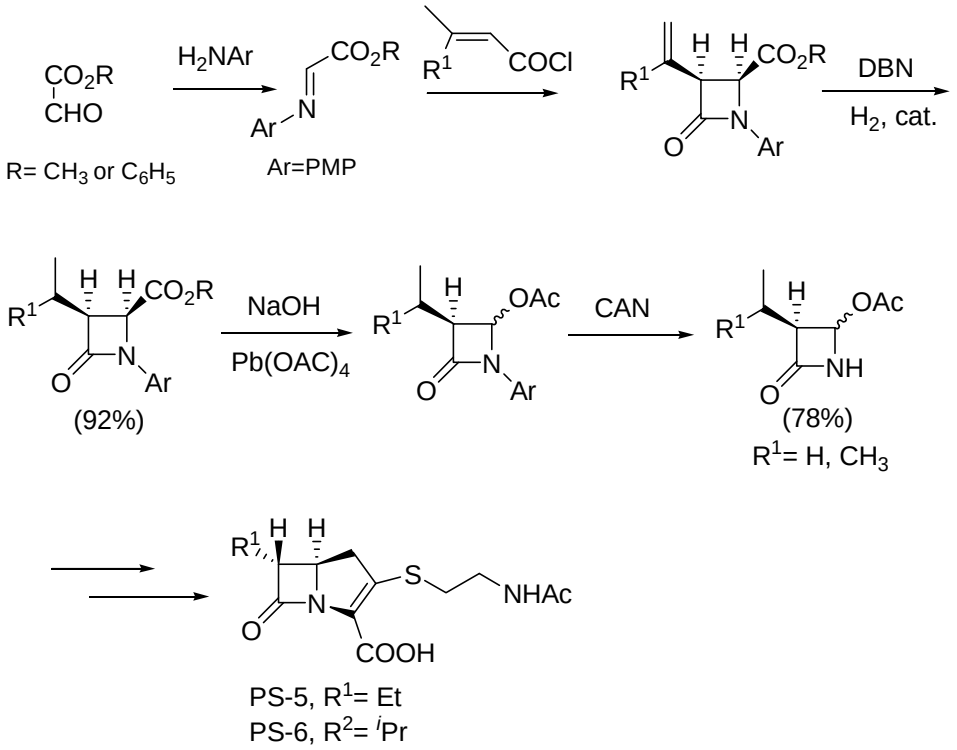
R^1 = Ph, R^2 = Ph

R^1 = Ph, R^2 = Ph, *trans* (52%)

They have also showed that the ketene obtained from crotonyl chloride and β,β-dimethylacryloyl chloride behave in the same way to produce *trans*-3-vinyl-β-lactams. The *cis* isomer predominates at room temperature however, higher temperature favors the *trans* product.

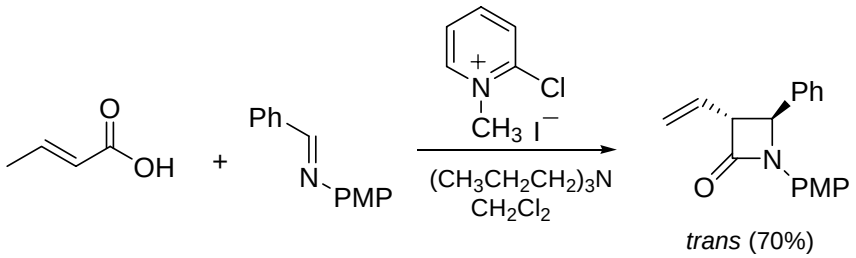
In 1990, Manhas et al.[7] have reported stereocontrolled synthesis of 3-vinyl-β-lactams and their transformations to useful intermediates for PS-5, PS-6, asparenomycin and thinemaycin. Interestingly, only *cis* 3-vinyl-β-lactams were obtained in the reaction of β,β-dimethylacryloyl chloride and Schiff bases derived from glyoxalic esters or phenyl glyoxal (Scheme 1.67).

Scheme 1.67



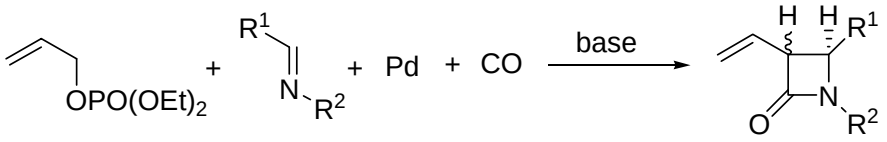
In 1991, George et al. [8] used crotonic acid and Mukaiyama's reagent [9] in place of crotonyl chloride for the synthesis of *trans*-3-vinyl-β-lactams (Scheme 1.68).

Scheme 1.68



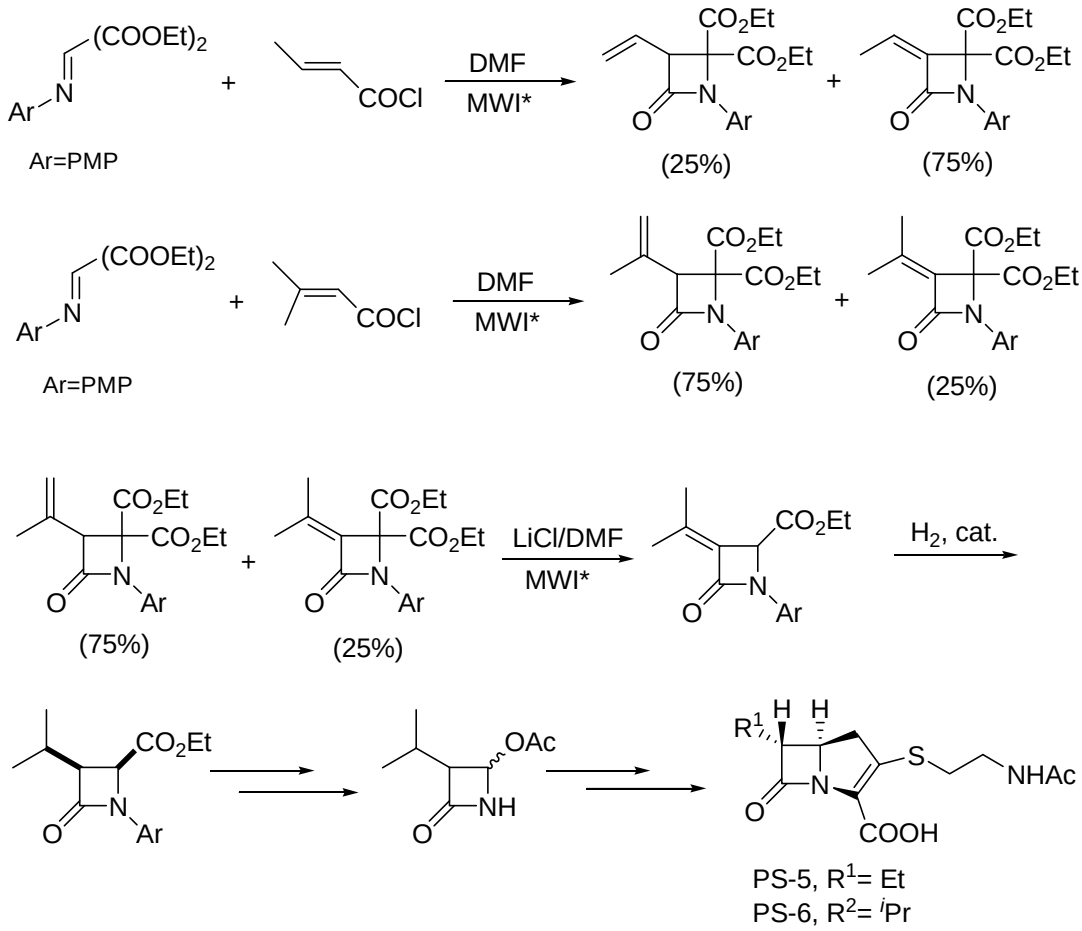
Torii et al. [10] have described a novel method for the synthesis of 3-vinyl-β-lactams, which involves palladium catalyzed corbonylation of allyl diethylphosphate in the presence of imines in an atmosphere of carbon monoxide under pressure. The stereochemistry of the product depends on the nature of the substituents on imines (Scheme 1.69).

Scheme 1.69



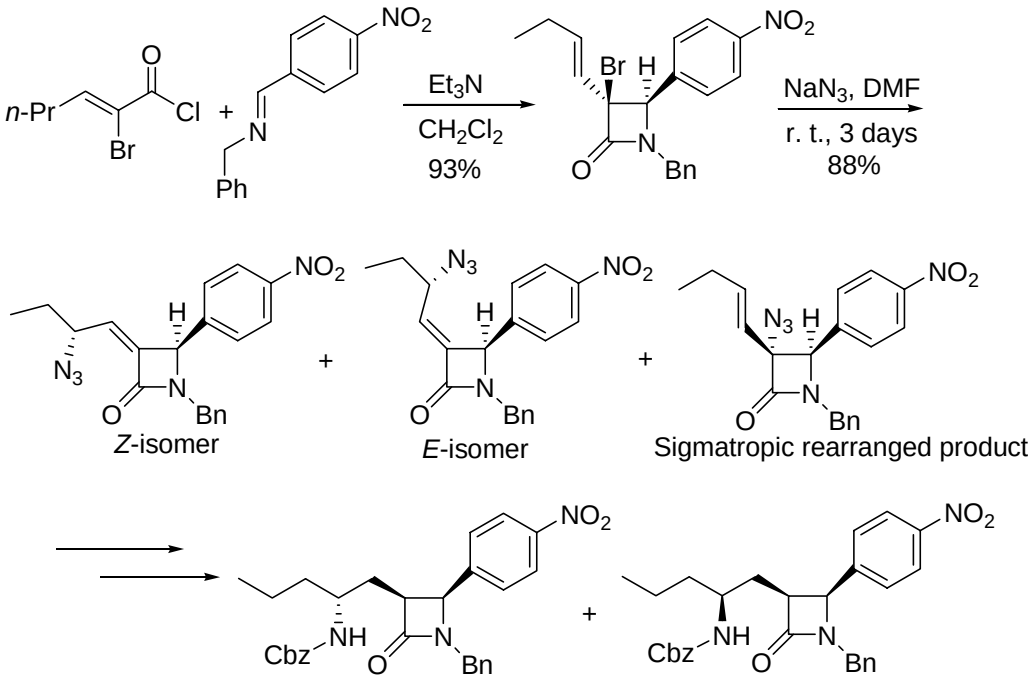
Synthesis of 3-vinyl-β-lactams became of interest after the discovery of PS-5, PS-6, theinamycin and asparenomycin. 3-Vinyl-β-lactams were also employed [11] as a synthons for the synthesis of carbapenem antibiotics intermediates; the key steps were a combination of dealkoxycarbonylation-hydrogenation experiments under microwave irradiation [12] (Scheme 1.70).

Scheme 1.70



Recently, Cardillo G. et al. [13] have used Staudinger reaction of vinylketene with a Schiff base for the synthesis of 3-(2'-amino)-β-lactams in excellent yields. They have synthesized 3-alkenyl-3-bromo-azetidin-2-ones starting from α-bromo-β,γ-unsaturated ketenes and a variety of Schiff bases in moderate to good yields, affording preferentially the *cis* diastereomers. It was further utilized for the transformations to get the 3-(2'-amino)-β-lactams derivatives in moderate yield (Scheme 1.71). The 3-(2'-amino)-β-lactams derivatives are very useful precursors in the synthesis of various biologically important compounds.

Scheme 1.71



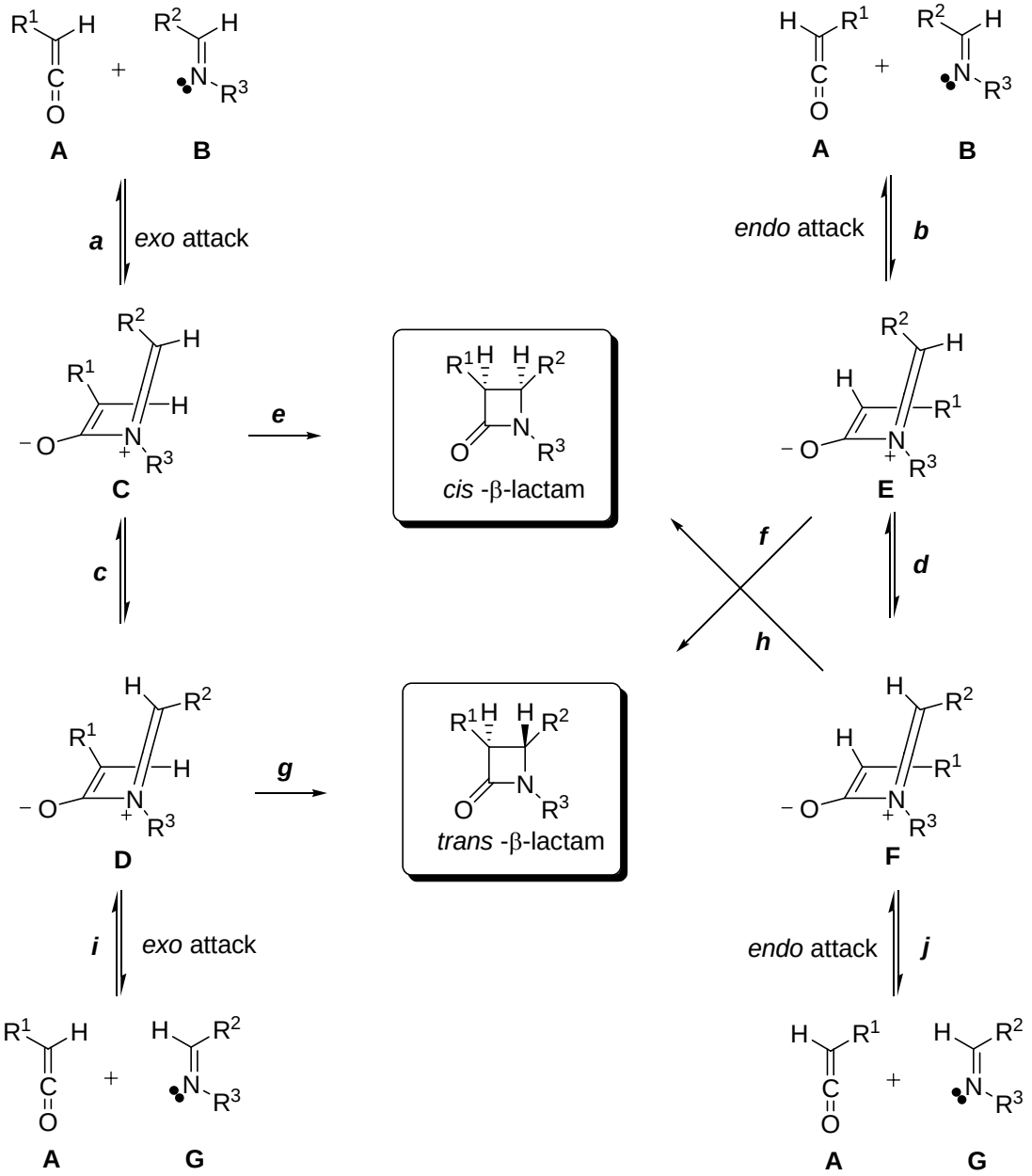
Pathways for the formation of *cis* and *trans*-β-lactams:

The relative stereoselectivity of β-lactam formation (*cis*, *trans*) is one of the critical issues in the Staudinger reaction. [4] Although many attempts have been made to explain and to predict the stereochemical outcomes, the origin of the stereoselectivity remains obscure. The stereochemical results obtained in Staudinger reaction can be explained on the basis of the mechanistic study presented in this chapter.

There are many possible stereochemical processes proposed by several investigators [14a-e, 4] (Scheme 1.69). The simplest explanation was that the stereochemistry of the product is determined by the configuration (*Z* or *E*) of the starting imines.[14d] *E*-imines on *exo* attack led preferentially to *cis*-β-lactams (pathway **a** to **e**) and *Z*-imines on *exo* attack gives predominately the corresponding *trans* isomer (pathway **i** to **g**). There are two other possibilities: (a) the stereochemistry is decided by the different approaches of the imine to the monosusbstitued ketene [14a] (*cis*-β-lactams, pathway **a** to **e**; *trans*-β-lactams, pathway **b** to **f**); and (b) the stereochemistry is decided by the competition between the direct ring closure (pathway **e**) and the isomerization of the imine moiety in the zwitterionic intermediate (pathway **c**). The observed variation of *cis*/*trans* ratios of β-lactams formation

could be explained by the electronic effect of the imine substituents. For imine with a strong electron donating group, the product is predominately *trans* β-lactam, while, for imine with a strong electron-withdrawing substituents, the product is mainly *cis* β-lactam. It is found that the electronic effect of the substituents plays an important role in the streoselectivity.[15]

Scheme 1.72



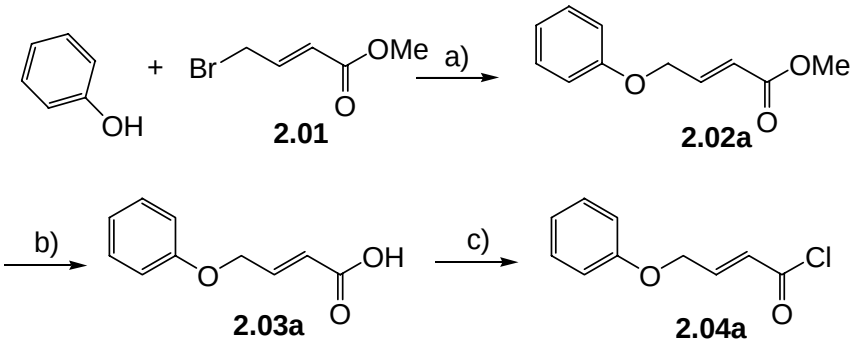
2.2: Present work

The present work describes the synthesis of *trans*-3-vinyl-β-lactams employing the Staudinger cycloaddition reaction of vinylketenes (Sheehan ketenes) with imines. A plausible mechanism of this β-lactam is discussed. Vinylketenes possessing a γ-heteroatom on Staudinger cycloaddition reaction with imines, gave *trans*-3-vinyl-β-lactams in very good yields. The vinyl side chain stereoselectively adopts the *Z*-configuration in the transition state to stabilize the vinylketene and produces, exclusively, *trans* 3-vinyl-β-lactams.

2.3: Results and discussion

Bose et al. have shown that ketenes generated from an acid chloride with a heteroatom, such as oxygen or nitrogen at the α-position, in general, give moderate to good yields of β-lactams with a preference for the *cis* product.[16] We envisaged that vinylketenes with a heteroatom at the γ-position would also have some influence on the diastereoselectivity in [2+2] cycloaddition reactions with imines. With this idea in mind we prepared 4-phenoxybut-2-enoyl chloride (**2.04a**), a precursor for phenoxyvinyl ketene, from methyl-4-bromo-2-butenoate (Scheme 1.73).

Scheme 1.73



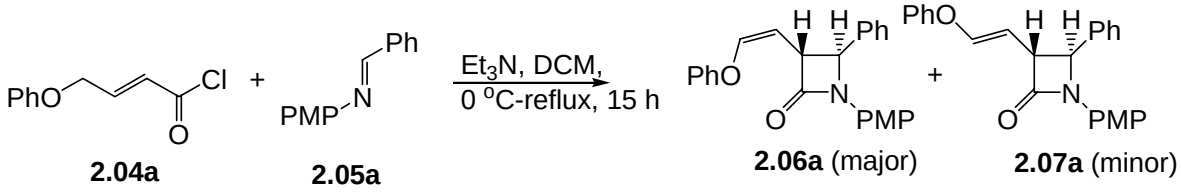
Reagents and conditions: a) K_2CO_3, PTC, acetone, reflux, 2 h; b) 1M NaOH, THF, rt, 15 h; c) $(COCl)_2$, DCM, reflux 4 h

Phenol was alkylated with methyl-4-bromo-2-butenoate (**2.01**) in presence of anhydrous K_2CO_3 in dry acetone to give 4-phenoxybut-2-enoyl ester (**2.02a**) in 87% yield.

The 4-phenoxybut-2-enoyl ester (**2.02a**) was further hydrolysed with aqueous NaOH to give phenoxy-olefinic acid (**2.03a**) in 91% yield. The phenoxy-olefinic acid (**2.03a**) was transformed to the corresponding phenoxy-olefinic chloride **(2.04a**) in quantitive yield by using oxalyl chloride. The structure of **2.02a** and **2.03a** were established by IR, ^{1}H NMR and ^{13}C NMR data.

The phenoxy-olefinic chloride **(2.04a**) was subjected to Staudinger reaction with different imines in presence of triethyl amine to give 3-vinyl-β-lactams (Scheme 1.74). This reaction was found to be highly stereoselective and gave only *trans*-β-lactams in excellent yield. Initially imine **2.05a** was reacted with the ketene, generated from 4-phenoxybut-2-enoyl chloride (**2.04a**) and triethylamine, at -40 ºC for 30 min and then further stirred at room temperature for 15h. A small amount of *trans*-vinyl-β-lactam **2.06a** (10%) was isolated from the reaction mixture. An excellent yield of *Z*-isomer **2.06a** along with a small amount of the *E*-isomer **2.07a** was obtained (*Z*/*E* = 9/1) when a solution of acid chloride **2.04a** in dichloromethane was added to a solution of imine **2.05a** and triethylamine at 0 ºC and then refluxed for 15h. Both the isomers (**2.06a** and **2.07a**) were separated by flash column chromatography. The ^{1}H NMR spectrum of the crude product revealed the formation of only the *trans*-β-lactam and no trace of the *cis*-β-lactam was detected.

Scheme 1.74

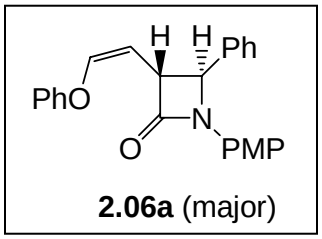


2.04a **2.05a** **2.06a** (major) **2.07a** (minor)

The structure of *Z*-isomer **2.06a** was established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **2.06a** showed an absorption at 1741 cm^{-1} for the β-lactam carbonyl group. The sharp peak at 1664 cm^{-1} corresponds to the vinyl double bond.

The ^{1}H NMR spectrum of **2.06a** showed a singlet at 3.75 ppm which was attributed to the methyl group attached to the aromatic ring. The C-3 proton of β-lactam ring appeared as multiplet at 4.13-4.19 ppm and the C-4 proton of β-lactam ring appeared as a characteristics doublet at 4.87 ppm (*J* = 2.5 Hz for the ring protons). The coupling constant of 2.5 Hz is typical of a *trans* β-lactam. A doublet of doublet at 5.10 ppm (*J* = 6.0 Hz, *J* =

8.0 Hz) appeared for the vinyl proton attached with C-3 carbon of β-lactam. The other vinyl proton attached with phenoxy group appeared as doublet of doublet at 6.67 ppm (J = 6.0 Hz, J = 1.3 Hz). The coupling constant of J = 6.0 Hz confirmed a Z geometry of the double bond at the C3 vinyl side chain. All other aromatic protons appeared as a multiplet in the range of 6.77-7.38 ppm.



2.06a (major)

The ^{13}C NMR spectrum of **2.06a** showed a peak at 55.4 ppm which is attributed for the methyl carbon of the PMP group. The C-3 and C-4 carbons of β-lactam ring appeared at 55.6 and 62.3 ppm respectively. The peaks were seen at 103.9 and 144.3 ppm corresponds to the vinyl side chain carbons. The aromatic carbons appeared at 114.3, 116.5, 118.3, 123.2, 126.0, 128.4, 128.9, 129.6, 131.4, 137.8, 155.9 and 156.8. The characteristic peak of β-lactam carbonyl appeared at 165.6 ppm. The mass spectrum of *Z*-isomer **2.06a** gave M+1 peak at m/z 372, also supporting the structure. This compound gave satisfactory elemental data.

X-ray structure determination of 2.06a:

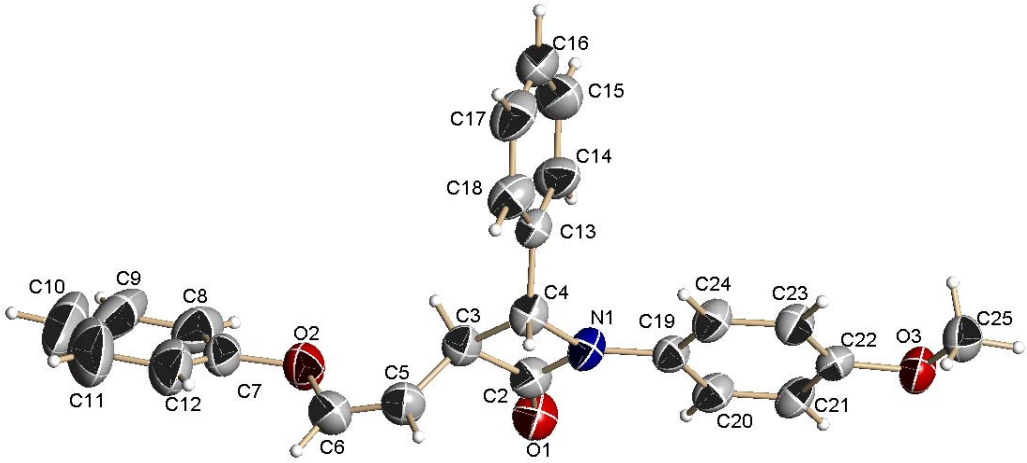


Figure 2 ORTEP diagram of **2.06a**

The structure **2.06a** was further confirmed by single crystal X-ray analysis (Figure 2). An X-ray quality crystal of **2.06a**, Colorless needles were obtained by careful recrystallization from methanol. The data for this compound was collected at T = 295 K, on

SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. All the data were corrected for Lorentzian, polarisation and absorption effects. The structure was solved by direct methods using SHELX-97 (ShelxTL) [17] and refined by full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

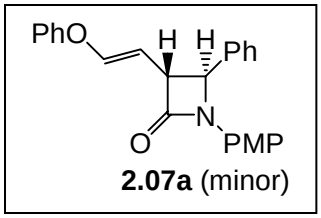
Table 2: Crystal data and structure refinement for **2.06a**

Empirical formula	$C_{24}\ H_{21}\ N\ O_3$
Formula weight	371.42
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	*a* = 11.3472(2) Å *b* = 5.9741(8) Å *c* = 29.163(4) Å β = 91.397 (2) ^{0}
Volume	1976.3(5) $Å^3$
Z, Calculated density	4, 1.248 mg cm^{-3}
Absorption coefficient	0.082 mm^{-1}
F(000)	784
Crystal size	0.39 x 0.05 x 0.02 mm
Reflections collected /unique	3476
Final R indices [I>2σ(I)]	R = 0.0654, Rw = 0.1112
Largest diff. peak and hole	0.148and -0.113 e. $Å^{-3}$

The structure of *E*-isomer **2.07a** was also established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectrum of *E*-isomer **2.07a** showed an absorption at 1743 cm^{-1} for the β-lactam carbonyl group. The sharp peak at 1658 cm^{-1} corresponds to the vinyl double bond.

The ^{1}H NMR spectrum of *E*-isomer **2.07a** showed a singlet at 3.75 ppm which was attributed to the methyl group attached to the aromatic ring. The C-3 proton of β-lactam ring appeared as multiplet at 3.68-3.80 ppm and the C-4 proton of β-lactam ring appeared

as a characteristics doublet at 4.72 ppm (J = 2.5 Hz for the ring protons) indicated *trans* stereochemistry of β-lactam ring. A doublet of doublet at 5.53 ppm (J = 9.3 Hz, J = 12.0 Hz) appeared for the vinyl proton attached with C-3 carbon of β-lactam. The coupling constant of J = 9.3 Hz confirmed an *E* geometry of the double bond at the C3 vinyl side chain. The other vinyl proton attached with phenoxy group and all other aromatic protons appeared as a multiplet in the range of 6.71-7.38 ppm.

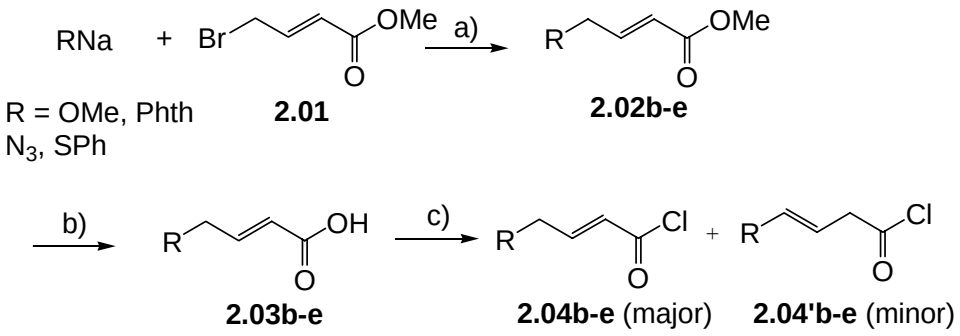


2.07a (minor)

The ^{13}C NMR spectrum of *E*-isomer **2.07a** showed a peak at 55.5 ppm which is attributed for the methyl carbon of the PMP group. The C-3 and C-4 carbons of β-lactam ring appeared at 59.4 and 62.7 ppm respectively. The peaks were seen at 104.8 and 146.4 ppm corresponds to the vinyl side chain carbons. The aromatic carbons appeared at 114.4, 117.1, 118.5, 123.4, 125.9, 128.6, 129.2, 129.7, 137.5, 156.2 and 156.7 respevitley. The characteristic peak of β-lactam carbonyl appeared at 163.1 ppm. The mass spectrum of *E*-isomer **2.07a** gave M+1 peak at m/z 372, also confirming the structure. This compound gave satisfactory elemental data.

We have also synthesis γ-methoxy olefinic acid chloride (**2.04b**), γ- azido olefinic acid chloride (**2.04c**) and γ- phthalimido olefinic acid chloride (**2.04d**) in quantitatve yields (Scheme 1.75).

Scheme 1.75

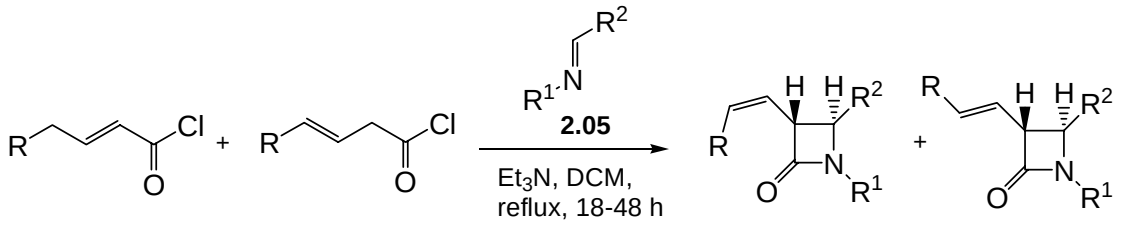


Reagents and conditions: a) K_2CO_3, PTC, acetone and nethanol, reflux;
b) 1M NaOH, THF, rt, 15 h; c) $(COCl)_2$, DCM, reflux 4 h

Several vinyl-β-lactams were prepared in very good yields from 4-phenoxy-but-2-enoyl chloride (**2.04a**) and imines **2.05a-g** with various substituents (Scheme 1.76, Table

3). In all the cases, irrespective of the substituents on the imine, only *trans*-β-lactam formation was observed. The *trans* stereochemistry for all β-lactams (**2.06b-g** and **2.07b-g**) was established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

Scheme 1.76



2.04b-e (major) **2.04'b-e** (minor) **2.06** (major) **2.07** (minor)

2.04b, **2.04'b**, R = OMe
2.04c, **2.04'c**, R = Phth
2.04d, **2.04'd**, R = N_3
2.04e, **2.04'e**, R = SPh

2.05b, R^1 = PMP, R^2 = PMP
2.05c, R^1 = Ph, R^2 = Ph
2.05d, R^1 = Ph, R^2 = PMP
2.05e, R^1 = 4-ClC_6H_4, R^2 = Ph
2.05f, R^1 = 4-$CH_3C_6H_4$, R^2 = Ph
2.05g, R^1 = PMP, R^2 = CO_2Me

Similar results were obtained with ketenes having γ-methoxy, azido and phthalimido groups on Staudinger reaction with various imines in good to excellent yields (Scheme 1.76, Table 3). In all the cases, irrespective of the substituents on the imine, only *trans* 3-vinyl-β-lactam with *Z*-stereochemistry at the vinyl side chain was formed. A small amount of the *E*-isomer possibly arose from thermal isomerization of the *Z*-vinyl side chain.

In case of the ketenes generated from **2.04c** and **2.04d** (R = Phth, N_3) gave *trans*-β-lactams **2.06j-k** and **2.07j-k**. However, the reaction was slow and gave lower yields of the vinylazetidin-2-one. All the *trans*-vinyl-β-lactams (**2.06j-k** and **2.07j-k**) were purified on flash column chromatography and the structures were established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The thiophenoxyketene generated from **2.04e** did not undergo the cycloaddition reaction with imine **2.05a**.

Table 3: Synthesis of *trans*-3-vinyl-β-lactams **2.06a-k** and **2.07a-k**

β-lactams **2.06** and **2.07**	R	R^1	R^2	Ratio of **2.06** : **2.07**[b]	Yield[c] (%)	Mp of **2.06** (° C)	Mp of **2.07** (° C)
a	OPh	PMP[a]	Ph	90 : 10	80	128-129	Thick oil
b	OPh	PMP	PMP	92 : 8	77	125-126	Thick oil
c	OPh	Ph	Ph	91 : 9	75	131-132	Thick oil
d	OPh	Ph	PMP	93 : 7	73	139-140	Thick oil
e	OPh	4-ClC_6H_4	Ph	89 : 11	78	112-113	Oil
f	OPh	4-$CH_3C_6H_4$	Ph	90 : 10	83	122-123	Oil
g	OPh	PMP	CO_2Me	100 : 0	70	Oil	-
h	OMe	Ph	Ph	92 : 8	75	88-89	Oil
i	OMe	PMP	Ph	90 : 10	85	95-96	Oil
j	Phth[a]	Ph	Ph	85 : 15	61	109-110	Oil
k	N_3	Ph	Ph	80 : 20	66	Oil	Oil

[a] Phth = Phthalimido, PMP = 4-$MeOC_6H_4$

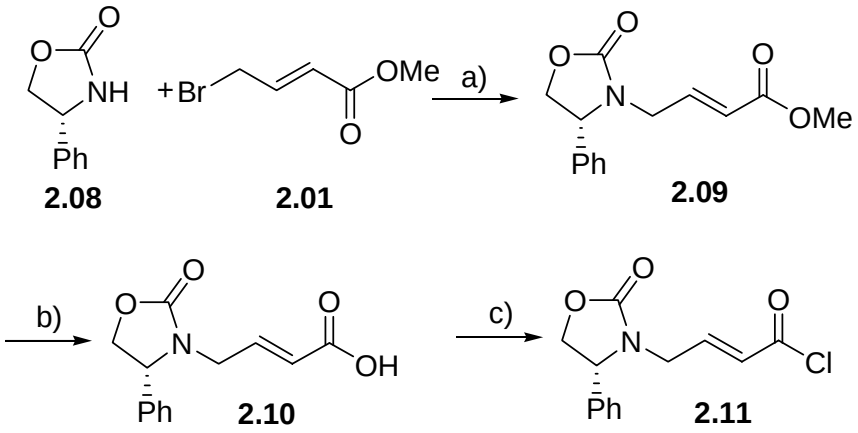
[b] The ratio of the diastereomers **2.06** and **2.07**, from ^{1}H NMR

[c] Isolated yields of the diastereomeric mixture of **2.06** and **2.07**

Asymmetric Synthesis of 3-vinylazetidin-2-ones:

We have already elaborated about the asymmetric Staudinger reaction in Chapter 1. The chirality can be introduced in Staudinger reaction either by chiral ketene or chiral imine precursors. We were interested to see the effect of chiral auxiliary attached to the vinyl ketene and study the stereoselectivity in the cycloaddition reaction with imines. With this idea in mind, we prepared oxazolidone derived chiral acid (**2.10**) in very good yield by *N*-alkylation of chiral oxazolidone (**2.08**) with methyl-4-bromo-2-butenoate (**2.01**) followed by hydrolysis of the ester (**2.09**) using a reported procedure. [18] The optically pure chiral acid (**2.10**) was converted into the acid chloride (**2.11**) using oxalyl chloride in quantitive yield (Scheme 1.77).

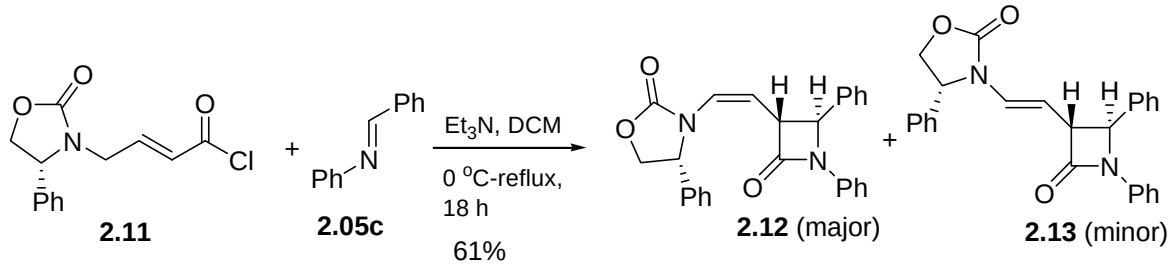
Scheme 1.77



Reagents and conditions: a) NaH, THF, 0 ^{0}C to rt,7 h b) 1M NaOH, THF, rt, 15 h c) $(COCl)_2$, DCM, reflux 4 h

An anhydrous solution of acid chloride **2.11** in dichloromethane was slowly added to a cooled (0 ^{o}C) solution of imine **2.05c** in presence of triethylamine. After completion of addition, the reaction mixture was allowed to come to room temperature and refluxed for 18 h. The usual work-up of the reaction gave crude product as brownish oil in 61% yield (Scheme 1.78). The IR spectrum of the brownish oil showed a band at 1751 cm^{-1} characteristic of β-lactam. The ^{1}H NMR of crude product showed the presence of two diastereomers **2.12** (90 %) and **2.13** (10 %).

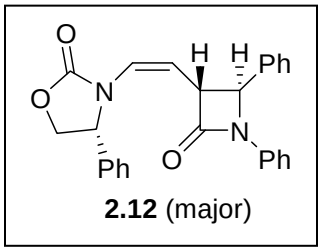
Scheme 1.78



All our efforts to get a single diastereomer **2.12** in pure form by flash column chromatography were unsuccessful. However, we could get pure white solid of **2.12** by recrystallization from methanol. The structure of **2.12** was established by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

The IR spectrum of **2.12** showed a band at 1751 cm^{-1} corresponding to the β-lactam carbonyl. The peak at 1666 cm^{-1} corresponds to the vinyl double bond.

The ^{1}H NMR spectrum of **2.12** showed a doublet of doublet at 3.58 ppm (J = 5.1 Hz, J = 8.7 Hz) corresponding to the –CH proton of oxazolidone group. The C3*H* proton of β-lactam ring appeared as doublet of doublet at 4.16 ppm (J = 2.4 Hz, J = 7.0 Hz) and C4*H* proton of β-lactam ring appeared as doublet at 4.32 ppm (J = 2.4 Hz). The J value (2.4 Hz) showed that β-lactam protons are *trans* to each other. The methylene protons of oxazolidone appeared as multiplet between 4.73 to 4.80 ppm. The C3 substituted vinyl proton NCH=C*H* appeared as doublet of doublet at 5.06 ppm (J = 5.1 Hz, J = 7.0 Hz). The J value (7.0 Hz) showed that the vinyl double bond has Z geometry. The aromatic protons including other vinyl proton (sixteen protons) appeared as multiplet in the range 6.80-7.48 ppm.

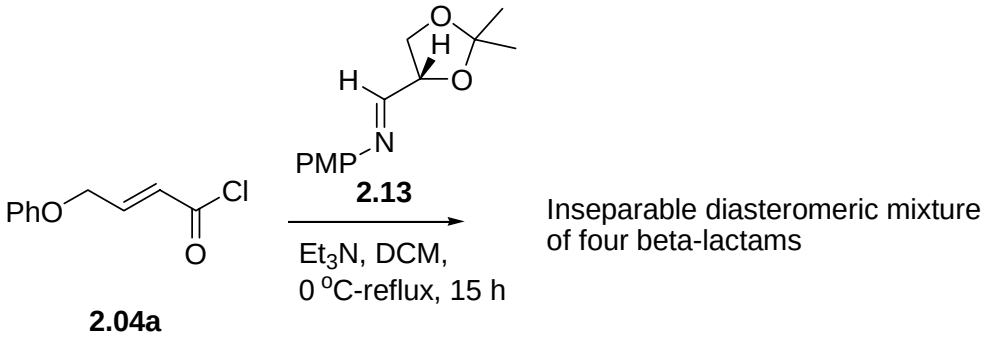


2.12 (major)

The ^{13}C NMR spectrum of **2.12** showed a peak at 61.8 ppm for –*C*H carbon of oxazolidone group. The C-3 and C-4 carbons of β-lactam ring appeared at 62.3 and 77.2 ppm respectively. The methylene carbon of oxazolidone group appeared at 70.6 ppm, which was identified by ^{13}C-DEPT experiment. The peaks were seen at 104.9 and 137.6 ppm corresponds to the vinyl side chain carbons. The aromatic carbons appeared at 117.0, 124.0, 125.6, 125.9, 127.6, 128.6, 129.0, 129.2, 129.5, 136.8 and 137.4 ppm. The characteristic peak of β-lactam carbonyl appeared at 165.7 ppm and a peak at 155.4 ppm corresponding to the oxazolidone carbonyl. The mass spectrum of **2.12** gave M+1 and M+Na peak at m/z 411 and 433, also confirming the structure. This compound gave satisfactory elemental data.

We have also used chiral imine **2.13** derived from D-glyceraldehyde acetonide and *p*-anisidine for the synthesis of optically pure 3-vinyl-*trans*-β-lactam. The phenoxy olefinic chloride (**2.04a**) on (2+2) Staudinger cycloaddition reaction with an imine (**2.13**) in presence of triethylamine in refluxing dichloromethane for 15h gave brown oil (Scheme 1.79). The IR spectrum of the crude product showed a band at 1737 cm^{-1} indicated the formation of β-lactam.

Scheme 1.79



The proton NMR of crude product showed mixture of four β-lactams. All our efforts to get pure diastereomer from the mixture were unsuccessful. The same reaction we tried under different reaction conditions however, we did not get the selectivity in the Staudinger reaction.

Plausible mechanism for the formation of a *trans*-β-lactam:

We believe that the phenoxyvinyl side chain stereoselectively adopts the *Z*-configuration to stabilize the ketene via participation of the oxygen lone pair of electrons (Figure 3).

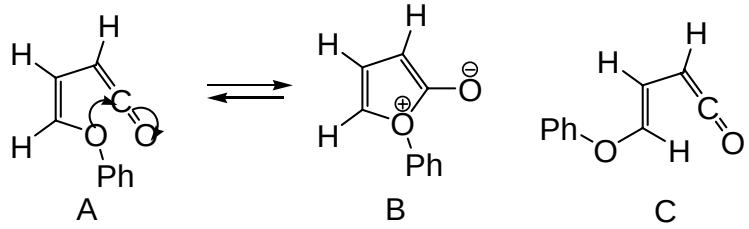


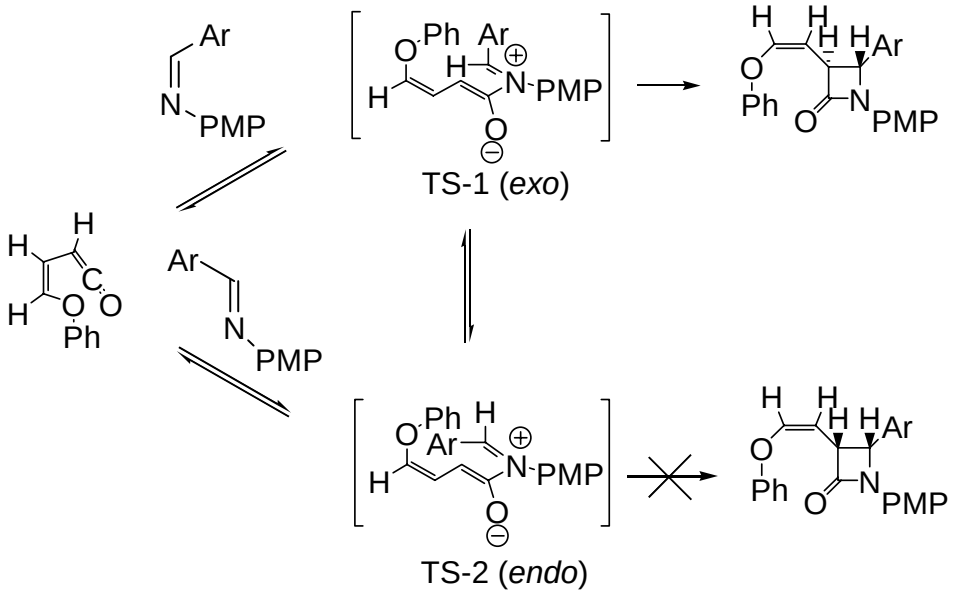
Figure 3. Conformations of phenoxyvinyl ketene

In the cycloaddition reaction the approach of the imine is normally orthogonal to the ketene and the stereochemical outcome depends upon the configuration of the imine.[14d] The *Z*-imine can react with the ketene in an *exo*-mode to give the zwitterionic transition state TS-1. Similarly the *E*-imine can react only in an *endo*-mode to give TS-2 (Scheme 1.80).

TS-1, on *con*rotatory ring closure would provide a *trans*-β-lactam, while TS-2 should give a *cis*-β-lactam. Although, the *E*-imine is more stable compare to the corresponding *Z*-imine, it is less reactive due to severe steric interaction between the phenoxy group and the aryl group of the imine in the transition state TS-2. This steric interaction is absent in TS-1, which arises from the *exo* attack of the *Z*-imine to the

vinylketene Therefore, TS-1 is preferentially formed, which on *con*rotatory ring closure gives *trans*-β-lactams. The rate of the reaction depends upon the rate of equilibrium of the *E* and *Z*-imines.

Scheme 1.80



The formation of the *trans*-β-lactams can also be explained by the isomerization of TS-2 to a more favorable TS-1 followed by the *con*rotatory ring closure. However, this seems to be less likely as this would provide, in some cases, depending up on the nature of the substituents present on the imine[15] a mixture of *cis* and *trans*-β-lactams. In fact, irrespective of the substituents on the imine, only *trans*-3-vinyl-β-lactam formation was observed in the cycloaddition reaction.

Conclusion:

In conclusion we have shown that the γ-heteroatom on a vinylketene directs imine approach in the Staudinger cycloaddition reaction. The reaction was found to be highly stereoselective. Irrespective of the substituents on the imine, only *trans*-3-vinyl-β-lactam formation was observed. Several *trans*-3-vinyl-β-lactams are synthesized which can be useful building blocks in organic synthesis. We have also synthesized chiral ketene and chiral imine precursors for asymmetric Staudinger reaction, which gave mixtures of 3-vinyl-β-lactams.

2.4: Experimental

2.4.1 Preparation of 4-phenoxy-but-2-enoic acid methyl ester (2.02a)

To a solution of phenol (0.200 g, 2.1 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_3 (1.50 g, 10.6 mmol) and 1-2 drops of aliquot as a phase transfer catalyst at 0 ^oC. After stirring for 20 min, 4-bromomethylcrotonate **2.01** (0.74 mL, 6.4 mmol) was added to the reaction mixture at 0 ^oC and the reaction mixture was then refluxed for 2 h. The solvent was distilled off under reduced pressure from the reaction mixture and the residue was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (15 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate 9:1) to give **2.02a** as a colourless oil (0.351 g, 87%).

IR (Neat)	**:**	3039, 2950, 1724, 1664, 1598, 1589, 1494, 1436, 1242, 1220 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.77 (3H, s, COOC*H*$_3$), 4.70 (2H, dd, *J* = 2.1 Hz, *J* = 4.2 Hz, C*H*$_2$), 6.18-6.28 (1H, m, *H*C-CH$_2$), 6.90-7.35 (6H, m, Ar-*H* and *H*C-OPh)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 51.6, 66.3, 114.6, 121.3, 121.5, 129.5, 142.7, 157.9, 166.5
MS (m/z)	**:**	193 (M+1), 215 (M+Na)
Analysis ($C_{11}H_{12}O_3$)	**:**	Calculated: C, 68.74; H, 6.29 Observed: C, 68.69; H, 6.20

2.4.2 Preparation of 4-phenoxy-but-2-enoic acid (2.03a)

To a solution of phenoxy olefinic ester **2.02a** (0.500 g, 2.60 mmol) in THF (10 mL) was added aqueous NaOH solution (1M, 5 mL) and the reaction mixture was stirred at room temperature for 15 h. The solvent THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The aqueous layer was then

acidified with Conc. HCl and the solution was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give phenoxy olefinic acid **2.03a** as a pale yellow solid (0.420 g, 91%).

MP	**:**	104-105 °C
IR ($CHCl_3$)	**:**	3020, 1719, 1664, 1596, 1220 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 4.73 (2H, dd, *J* = 2.1 Hz, *J* = 4.2 Hz, C*H*$_2$), 6.19-6.29 (1H, m, *H*C-CH$_2$), 6.90-7.35 (6H, m, Ar-*H* and *H*C-OPh), 7.87 (1H, bs, O*H*)
^{13}C NMR ($CDCl_3$) (125 MHz)	**:**	δ_C 66.2, 114.6, 121.0, 121.4, 129.6, 145.4, 157.9, 171.2
MS (m/z)	**:**	179 (M+1), 201 (M+Na)
Analysis ($C_{10}H_{10}O_3$)	**:**	Calculated: C, 67.40; H, 5.65 Observed: C, 67.33; H, 5.57

2.4.3 Preparation of 4-phenoxy-but-2-enoyl chloride (2.04a)

To a solution of phenoxy olefinic acid **2.03a** (0.580 g, 3.25 mmol) in dry dichloromethane (5 mL) was added oxalyl chloride (0.43 mL, 4.88 mmol) in dry dichloromethane (5 mL) drop-wise at 0 ^oC. After the addition was complete, the reaction mixture was refluxed for 4 h. Then excess oxalyl chloride was removed under reduced pressure to give phenoxy olefinic chloride **2.04a** (0.610 g, 95%) as brown oil. The olefinic acid chloride **2.04a** was used for the synthesis of *trans*-3-vinyl-β-lactams **2.06a-g** and **2.07a-g**.

IR ($CHCl_3$)	**:**	3055, 1753, 1637, 1490, 1265 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.76 (1H, d, *J* = 3.4 Hz, =*H*C-CO), 4.74 (2H, dd, *J* = 2.0 Hz, *J* = 3.6 Hz, C*H*$_2$), 6.20-6.29 (1H, m, CH2C*H*=), 6.91-7.36 (5H, m, Ar-*H*).

2.4.4 General procedure for the synthesis of *trans*-3-vinyl-β-lactams 2.06a-g and 2.07a-g

A solution of olefinic acid chloride **2.04a** (1.42 mmol) in dry dichloromethane (20 mL) was added slowly to a mixture of imine **2.05a-g** (0.94 mmol) and triethylamine (4.26 mmol) in dry dichloromethane (20 mL) at 0 ºC. After addition was complete, the reaction mixture was refluxed with stirring for 15 h. The reaction mixture was washed with water (2 x 10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The combined organic layer was then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give a thick brown oil. ^{1}H NMR of the crude product showed, it is a mixture of *trans*-β-lactams **2.06a-g** and **2.07a-g** (*Z* and *E* isomers 90:10), which were separated by flash column chromatography (petroleum ether-ethyl acetate 8:2) in good to excellent yield. The less polar *E*-isomer **2.07a-g** eluted first followed by more polar *Z*-isomer **2.06a-g**.

2.4.4a Synthesis of *trans*-3-vinyl-β-lactams 2.06a and 2.07a

The phenoxyolefinic chloride **2.04a** (0.280 g, 1.42 mmol) on treatment with imine **2.05a** (0.200 g, 0.94 mmol) in presence of triethylamine (0.430 g, 4.26 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.280 g, 80%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 8:2) to give pure *Z*-isomer **2.06a** (major) as white solid and *E*-isomer **2.07a** (minor) as thick oil.

***Trans*-1-(4-Methoxyphenyl)-3-(*Z*-2-phenoxyvinyl)-4-phenylazetidin-2-one (2.06a)**

It was obtained as white needles (recrystallized from MeOH) in 68% yield.

MP	**:**	128-129 °C
IR ($CHCl_3$)	**:**	3018, 1741, 1664, 1595, 1512, 1245, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.75 (3H, s, Ph-OC*H*$_3$), 4.13-4.19 (1H, m, C3*H*), 4.87 (1H, d, *J* = 2.5 Hz, C4*H*), 5.10 (1H, dd, *J* = 6.0 Hz, *J* = 8.0 Hz, C*H*=CHOPh), 6.67 (1H, dd, *J* = 6.0 Hz, *J* = 1.3 Hz, CH=C*H*OPh), 6.77-7.38 (14H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$)	**:**	δ_C 55.4, 55.6, 62.3, 103.9, 114.3, 116.5, 118.3, 123.2, 126.0, 128.4, 128.9, 129.6, 131.4, 137.8, 144.3, 155.9, 156.8, 165.6

(125 MHz)

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

Analysis : Calculated: C, 77.60; H, 5.69; N, 3.77

($C_{24}H_{21}NO_3$) Observed: C, 77.54; H, 5.62; N, 3.70

***Trans*-1-(4-Methoxyphenyl)-3-(*E*-2-phenoxyvinyl)-4-phenylazetidin-2-one (2.07a)**

It was isolated as thick oil; yield 12%.

IR ($CHCl_3$) : 3016, 2360, 1743, 1658, 1512, 1240 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.75 (3H, s, Ph-OC*H*$_3$), 3.68-3.80 (1H, m, C3*H*), 4.72 (1H, d, *J* = 2.5 Hz, C4*H*), 5.53 (1H, dd, *J* = 9.3 Hz, *J* = 12.0 Hz, C*H*=CHOPh), 6.71-7.38 (15H, m, Ar-*H* and CH=C*H*OPh)

^{13}C NMR ($CDCl_3$) (75 MHz) : δ_C 55.5, 59.4, 62.7, 104.8, 114.4, 117.1, 118.5, 123.4, 125.9, 128.6, 129.2, 129.7, 137.5, 146.4, 156.2, 156.7, 163.1

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

Analysis : Calculated: C, 77.60; H, 5.69; N, 3.77

($C_{24}H_{21}NO_3$) Observed: C, 77.51; H, 5.60; N, 3.69

2.4.4b Synthesis of *trans*-3-vinyl-β-lactams 2.06b and 2.07b

The phenoxyolefinic chloride **2.04a** (0.238 g, 1.21 mmol) on treatment with imine **2.05b** (0.200 g, 0.80 mmol) in presence of triethylamine (0.368 g, 3.64 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.194 g, 77%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 8:2) to give pure *Z*-isomer **2.06b** (major) as white solid and *E*-isomer **2.07b** (minor) as thick oil.

***Trans*-1,4-Bis-(4-methoxyphenyl)-3-(*Z*- 2-phenoxyvinyl)-azetidin-2-one (2.06b)**

It was obtained as white solid (MeOH); yield 64 %.

MP	**:**	125-126 °C
IR ($CHCl_3$)	**:**	3016, 2956, 2837, 1741, 1668, 1598, 1512, 1245, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.74 (3H, s, Ph-OC*H*$_3$), 3.80 (3H, s, Ph-OC*H*$_3$), 4.10-4.15 (1H, m, C3*H*), 4.81 (1H, d, *J* = 2.3 Hz, C4*H*), 5.08 (1H, dd, *J* = 6.0 Hz, *J* = 8.0 Hz, C*H*=CHOPh), 6.65 (1H, dd, *J* = 6.0 Hz, *J* = 1.1 Hz, CH=C*H*OPh), 6.76-7.35 (13H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 55.3, 55.4, 56.7, 61.9, 104.0, 114.2, 114.4, 116.5, 118.4, 123.2, 127.3, 129.7, 131.3, 144.2, 155.9, 156.8, 159.6, 165.7
MS (m/z)	**:**	402 (M+1), 424 (M+Na)
Analysis ($C_{25}H_{23}NO_4$)	**:**	Calculated: C, 74.79; H, 5.77; N, 3.48 Observed: C, 74.68; H, 5.71; N, 3.42

***Trans*-1,4-Bis-(4-methoxyphenyl)-3-(*E*- 2-phenoxyvinyl)-azetidin-2-one (2.07b)**

It was isolated as thick oil; yield 13 %.

IR ($CHCl_3$)	**:**	3016, 2956, 2835, 1740, 1654, 1610, 1510, 1244, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.71-3.77 (1H, m, C3*H*), 3.75 (3H, s, Ph-OC*H*$_3$), 3.80 (3H, s, Ph-OC*H*$_3$), 4.67 (1H, d, *J* = 2.4 Hz, C4*H*), 5.51 (1H, dd, *J* = 9.3 Hz, *J* = 12.2 Hz, C*H*=CHOPh), 6.64-7.49 (14H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 55.3, 55.6, 56.8, 61.8, 104.8, 114.4, 115.2, 115.8, 123.9, 127.3, 129.8, 131.9, 137.0, 141.9, 153.8, 154.2, 159.5, 164.7
MS (m/z)	**:**	402 (M+1), 424 (M+Na)
Analysis ($C_{25}H_{23}NO_4$)	**:**	Calculated: C, 74.79; H, 5.77; N, 3.48 Observed: C, 74.71; H, 5.69; N, 3.39

2.4.4c Synthesis of *trans*-3-vinyl-β-lactams 2.06c and 2.07c

The phenoxyolefinic chloride **2.04a** (0.330 g, 1.68 mmol) on treatment with imine **2.05c** (0.202 g, 1.11 mmol) in presence of triethylamine (0.507 g, 5.02 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.287 g, 75%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06c** (major) as white solid and *E*-isomer **2.07c** (minor) as thick oil.

***Trans*-3-(*Z*- 2-phenoxyvinyl)-1, 4-diphenyl-azetidin-2-one (2.06c)**

It was obtained as white solid (MeOH), yield 64 %.

MP	**:**	131-132 °C
IR ($CHCl_3$)	**:**	3018, 1749, 1662, 1595, 1500, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 4.15-4.20 (1H, m, C3*H*), 4.91 (1H, d, *J* = 2.4 Hz, C4*H*), 5.11 (1H, dd, *J* = 6.2 Hz, *J* = 8.1 Hz, C*H*=CHOPh), 6.67-7.40 (16H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 56.7, 62.2, 103.7, 116.5, 117.0, 123.3, 123.8, 126.0, 128.4, 129.0, 129.7, 137.7, 144.4, 156.8, 166.2
MS (m/z)	**:**	342 (M+1), 364 (M+Na)
Analysis ($C_{23}H_{19}NO_2$)	**:**	Calculated: C, 80.91; H, 5.60; N, 4.10 Observed: C, 80.88; H, 5.55; N, 4.03

***Trans*-3-(*E*-2-phenoxyvinyl)-1, 4-diphenyl-azetidin-2-one (2.07c)**

It was isolated as thick oil; yield 11 %.

IR ($CHCl_3$)	**:**	3026, 1749, 1666, 1596, 1492, 1220 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.68-3.75 (1H, m, C3*H*), 4.76 (1H, d, *J* = 2.5 Hz, C4*H*), 5.53 (1H, dd, *J* = 9.2 Hz, *J* = 12.2 Hz, C*H*=CHOPh), 6.71-7.54 (16H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$)	**:**	δ_C 59.4, 62.5, 104.6, 114.6, 117.1, 123.5, 124.0, 125.9, 128.5, 128.6, 129.1, 137.5, 144.7, 156.6, 165.9

(75 MHz)

MS (m/z) : 342 (M+1), 364 (M+Na)

Analysis : Calculated: C, 80.91; H, 5.60; N, 4.10

($C_{23}H_{19}NO_2$) Observed: C, 80.94; H, 5.52; N, 4.07

2.4.4d Synthesis of *trans*-3-vinyl-β-lactams 2.06d and 2.07d

The phenoxyolefinic chloride **2.04a** (0.350 g, 1.78 mmol) on treatment with imine **2.05d** (0.250 g, 1.18 mmol) in presence of triethylamine (0.540 g, 5.34 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.257 g, 73%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06d** (major) as white solid and *E*-isomer **2.07d** (minor) as thick oil.

***Trans*-4-(4-methoxyphenyl)-3-(*Z*- 2-phenoxyvinyl)-1-phenyl-azetidin-2-one (2.06d)**

It was obtained as white solid (MeOH); yield 64 %.

MP : 139-140 °C

IR ($CHCl_3$) : 3016, 2358, 1743, 1662, 1595, 1512, 1247, 1225 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.75 (3H, s, Ph-OC*H*$_3$), 4.11-4.18 (1H, m, C3*H*), 4.88 (1H, d, *J* = 2.5 Hz, C4*H*), 5.11 (1H, dd, *J* = 6.0 Hz, *J* = 8.3 Hz, C*H*=CHOPh), 6.67 (1H, dd, *J* = 6.0 Hz, *J* = 1.2 Hz, CH=C*H*OPh), 6.73-7.41 (14H, m, Ar-*H*)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 55.4, 55.6, 62.2, 103.9, 114.2, 116.5, 118.3, 123.2, 126.0, 128.4, 129.0, 129.6, 131.3, 137.8, 144.3, 155.9, 156.8, 165.6

MS (m/z) : 372 (M+1), 394 (M+Na)

Analysis : Calculated: C, 77.60; H, 5.69; N, 3.77

($C_{24}H_{21}NO_3$) Observed: C, 77.49; H, 5.57; N, 3.71

***Trans*-4-(4-methoxyphenyl)-3-(*E*- 2-phenoxyvinyl)-1-phenyl-azetidin-2-one (2.07d)**

It was isolated as thick oil; yield 9 %.

IR ($CHCl_3$)	**:**	3028, 2931, 1745, 1666, 1595, 1512, 1244 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.75 (3H, s, Ph-OC*H*$_3$), 3.71-3.81 (1H, m, C3*H*), 4.72 (1H, d, *J* = 2.2 Hz, C4*H*), 5.53 (1H, dd, *J* = 9.1 Hz, *J* = 12.0 Hz, C*H*=CHOPh), 6.66-7.65 (15H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 55.4, 59.4, 62.6, 104.7, 114.4, 117.1, 118.4, 123.5, 125.9, 128.7, 129.2, 129.7, 130.9, 136.9, 143.7, 154.7, 155.8, 165.5
MS (m/z)	**:**	372 (M+1), 394 (M+Na)
Analysis	**:**	Calculated: C, 77.60; H, 5.69; N, 3.77
($C_{24}H_{21}NO_3$)		Observed: C, 77.52; H, 5.61; N, 3.68

2.4.4e Synthesis of *trans*-3-vinyl-β-lactams 2.06e and 2.07e

The phenoxyolefinic chloride **2.04a** (0.300 g, 1.53 mmol) on treatment with imine **2.05e** (0.220 g, 1.02 mmol) in presence of triethylamine (0.461 g, 4.57 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.298 g, 78%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06e** (major) as white solid and *E*-isomer **2.07e** (minor) as thick oil.

***Trans*-1-(4-chlorophenyl)-3-(*Z*- 2-phenoxyvinyl)-4-phenyl-azetidin-2-one (2.06e)**

It was obtained as white solid (MeOH); yield 70 %.

MP	**:**	112-113 °C
IR ($CHCl_3$)	**:**	3031, 2923, 1755, 1662, 1492, 1371, 1222 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 4.14-4.20 (1H, m, C3*H*), 4.89 (1H, d, *J* = 2.5 Hz, C4*H*), 5.10 (1H, dd, *J* = 6.1 Hz, *J* = 8.1 Hz, C*H*=CHOPh), 6.67 (1H, dd, *J* = 6.1 Hz, *J* = 1.3 Hz, CH=C*H*OPh), 6.92-7.40 (14H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 57.1, 62.4, 103.5, 116.6, 118.3, 123.4, 126.0, 128.6, 129.0,

($CDCl_3$)		129.1, 129.7, 136.4, 137.4, 144.7, 156.8, 166.0
(50 MHz)		
MS (m/z)	**:**	376 (M+1), 398 (M+Na)
Analysis	**:**	Calculated: C, 73.50; H, 4.82; N, 3.72; Cl, 9.43
($C_{23}H_{18}NO_2Cl$)		Observed: C, 73.42; H, 4.80; N, 3.68; Cl, 9.40

***Trans*-1-(4-chlorophenyl)-3-(*E*-2-phenoxyvinyl)-4-phenyl-azetidin-2-one (2.07e)**

It was isolated as oil; yield 8 %.

IR ($CHCl_3$)	**:**	3031, 2923, 1755, 1666, 1593, 1492, 1380, 1230 cm^{-1}
^{1}H NMR	**:**	δ_H 3.71-3.77 (1H, m, C3*H*), 4.73 (1H, d, *J* = 2.5 Hz, C4*H*),
($CDCl_3$)		5.52 (1H, dd, *J* = 9.2 Hz, *J* = 12.0 Hz, C*H*=CHOPh), 6.74 (1H,
(200 MHz)		dd, *J* = 12.0 Hz, *J* = 1.0 Hz, CH=C*H*OPh), 6.98-7.44 (14H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 59.8, 62.8, 102.9, 117.2, 118.5, 121.5, 125.8, 128.8, 129.2,
($CDCl_3$)		129.4, 129.7, 136.1, 137.0, 146.0, 156.6, 167.2
(75 MHz)		
MS (m/z)	**:**	376 (M+1), 398 (M+Na)
Analysis	**:**	Calculated: C, 73.50; H, 4.82; N, 3.72; Cl, 9.43
($C_{23}H_{18}NO_2Cl$)		Observed: C, 73.44; H, 4.78; N, 3.66; Cl, 9.38

2.4.4f Synthesis of *trans*-3-vinyl-β-lactams 2.06f and 2.07f

The phenoxyolefinic chloride **2.04a** (0.322 g, 1.63 mmol) on treatment with imine **2.05f** (0.200 g, 1.09 mmol) in presence of triethylamine (0.496 g, 4.91 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.320 g, 83%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06f** (major) as white solid and *E*-isomer **2.07f** (minor) as thick oil.

***Trans*-3-(*Z*-2-phenoxyvinyl)-4-phenyl-1-*p*-tolyl-azetidin-2-one (2.06f)**

It was obtained as white solid (MeOH); yield 77 %.

MP	**:**	122-123 °C
IR ($CHCl_3$)	**:**	3016, 1745, 1664, 1595, 1492, 1373, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 2.28 (3H, s, Ph-C*H*$_3$), 4.14-4.19 (1H, m, C3*H*), 4.89 (1H, d, *J* = 2.4 Hz, C4*H*), 5.11 (1H, dd, *J* = 6.0 Hz, *J* = 8.0 Hz, C*H*=CHOPh), 6.67 (1H, dd, *J* = 6.0 Hz, *J* = 1.3 Hz, CH=C*H*OPh), 6.94-7.41 (14H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 20.8, 56.7, 62.1, 103.9, 116.5, 117.0, 123.2, 126.0, 128.3, 129.5, 129.6, 133.3, 135.4, 137.9, 144.3, 156.8, 165.8
MS (m/z)	**:**	356 (M+1), 378 (M+Na)
Analysis	**:**	Calculated: C, 81.10; H, 5.95; N, 3.94
($C_{24}H_{21}NO_2$)		Observed: C, 81.05; H, 5.91; N, 3.87

***Trans*-3-(*E*-2-phenoxyvinyl)-4-phenyl-1-*p*-tolyl-azetidin-2-one (2.07f)**

It was isolated as thick oil; yield 6 %.

IR ($CHCl_3$)	**:**	3016, 2956, 1741, 1668, 1596, 1514, 1490, 1386, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 2.28 (3H, s, Ph-C*H*$_3$), 3.42-3.75 (1H, m, C3*H*), 4.75 (1H, d, *J* = 2.4 Hz, C4*H*), 5.54 (1H, dd, *J* = 9.0 Hz, *J* = 12.0 Hz, C*H*=CHOPh), 6.71-7.66 (15H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 20.8, 59.4, 62.4, 104.7, 117.0, 123.4, 125.8, 128.6, 128.9, 129.6, 129.7, 133.7, 135.0, 137.3, 146.4, 156.6, 165.5
MS (m/z)	**:**	356 (M+1), 378 (M+Na)
Analysis	**:**	Calculated: C, 81.10; H, 5.95; N, 3.94
($C_{24}H_{21}NO_2$)		Observed: C, 81.02; H, 5.87; N, 3.84

2.4.4g Synthesis of *trans*-3-vinyl-β-lactams 2.06g

The phenoxyolefinic chloride **2.04a** (0.305 g, 1.55 mmol) on treatment with imine **2.05g** (0.200 g, 1.03 mmol) in presence of triethylamine (0.470 g, 4.66 mmol) at 0 ºC and refluxed for 15h gave a crude product of *trans*-β-lactams as thick brown oil (0.388 g, 70%). The crude product was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give only pure *Z*-isomer **2.06g** as thick oil in 70% yield.

***Trans*-1-(4-methoxyphenyl)-4-oxo-3-(*Z*-2-phenoxyvinyl)-azetidin-2-carboxylic acid methyl ester (2.06g)**

IR ($CHCl_3$)	**:**	3024, 2954, 1751, 1733, 1672, 1595, 1490, 1388, 1222 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.36-3.49 (1H, m, C3*H*), 3.48 (3H, s, COOCH_3), 3.76 (3H, s, Ph-OCH_3), 4.99 (1H, dd, *J* = 6.0 Hz, *J* = 8.0 Hz, C*H*=CHOPh), 5.91 (1H, d, *J* = 2.0 Hz, C4*H*), 6.49-7.31 (10H, m, Ar-*H* and CH=C*H*OPh)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 52.8, 57.1, 93.3, 102.5, 110.0, 116.4, 117.0, 123.0, 124.0, 124.8, 129.6, 143.0, 154.9, 156.9, 166.0, 170.9
MS (m/z)	**:**	354 (M+1), 376 (M+Na)
Analysis	**:**	Calculated: C, 67.97; H, 5.41; N, 3.96
($C_{20}H_{19}NO_5$)		Observed: C, 67.90; H, 5.33; N, 3.91

2.4.5 Preparation of 4-methoxy-but-2-enoic acid methyl ester (2.02b)

To a solution of sodium methoxide (0.181 g, 3.35 mmol) in dry methanol (10 mL) was added 4-bromomethylcrotonate **2.01** (0.32 mL, 2.79 mmol) at 0 ^oC and 1 drop of aliquot as a phase transfer catalyst. The reaction mixture was then refluxed for 12 h. Reaction mixture was neutralized with acetic acid and most of the methanol was removed under reduced pressure and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (10 mL), brine solution (10 mL) and dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography (petroleum ether-ethyl acetate 8:2) to give **2.02b** as a colourless oil (0.290 g, 80%).

IR (Neat)	**:**	3018, 2933, 1732, 1662 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 2.66 (2H, m, C*H*$_2$COOMe), 3.38 (3H, s, OC*H*$_3$), 3.48 (3H, s, OC*H*$_3$), 3.67 (3H, s, COOC*H*$_3$), 3.72 (3H, s, COOC*H*$_3$), 3.96- 4.06 (2H, m, C*H*$_2$OMe), 5.98-6.08 (2H, m, C*H*-olefin), 6.86-7.02 (2H, m, C*H*-olefin)
^{13}C NMR (CDCl$_3$) (75 MHz)	**:**	δ_C 38.0, 51.5, 51.8, 57.6, 58.6, 76.5, 109.0, 140.5, 120.7, 144.4, 166.7, 171.2.

2.4.6 Preparation of 4-methoxy-but-2-enoic acid (2.03b)

Following the similar procedure for the compounds (**2.03a**), we have synthesized acid **2.03b** as colorless oil; yield 98 %.

IR (Neat)	**:**	3200, 1714, 1662 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 2.59-2.67 (2H, m, C*H*$_2$COOH), 3.34 (3H, s, OC*H*$_3$), 3.44 (3H, s, OC*H*$_3$), 4.11-4.38 (2H, m, C*H*$_2$OMe), 6.03-6.12 (2H, m, C*H*-olefin), 6.99-7.11 (2H, m, C*H*-olefin), 8.81(2H, bs, O*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 34.5, 56.5, 58.7, 75.9, 109.0, 120.4, 145.0, 146.9, 171.5, 177.6

2.4.7 Preparation of 4-methoxy-but-2-enoyl chloride (2.04b):

Following the similar procedure for the compound (**2.04a**), we have synthesized methoxyolefinic chloride **2.04b** as colorless oil, yield 98 %. The IR spectrum showed peak at 3025, 1760, 1644, 1230 cm^{-1} confirmed the presence of acid chloride **2.04b**. Further it was used as such for the synthesis of *trans*-3-vinyl-β-lactams **6h-i** and **7h-i**.

2.4.8 Synthesis of *trans*-3-vinyl-β-lactams 2.06h and 2.07h

The methoxyolefinic chloride **2.04b** (0.222 g, 1.65 mmol) on treatment with imine **2.05c** (0.200 g, 1.10 mmol) in presence of triethylamine (0.50 g, 4.97 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.231 g, 75%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 8:2) to give pure *Z*-isomer **2.06h** (major) as white solid and *E*-isomer **2.07h** (minor) as thick oil.

***Trans*-3-(*Z*-2-methoxyvinyl)-1,4-diphenyl-azetidin-2-one (2.06h)**

It was obtained as white solid (MeOH); yield 68 %.

MP	**:**	88-89 °C
IR ($CHCl_3$)	**:**	3031, 1747, 1660, 1598, 1500, 1371 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.51 (3H, s, OC*H*$_3$), 3.85-3.94 (1H, m, C3*H*), 4.53 (1H, dd, *J* = 6.1 Hz, *J* = 8.7 Hz, C*H*=CHOMe), 4.71 (1H, d, *J* = 2.5 Hz, C4*H*), 6.06 (1H, dd, *J* = 1.1 Hz, *J* = 6.1 Hz, CH=C*H*OMe), 6.89-7.33 (10H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 56.6, 59.9, 62.2, 98.0, 116.9, 123.6, 125.9, 128.2, 128.9, 137.8, 137.9, 150.3, 166.9
MS (m/z)	**:**	280 (M+1), 302 (M+Na)
Analysis	**:**	Calculated: C, 77.39; H, 6.13; N, 5.01
($C_{18}H_{17}NO_2$)		Observed: C, 77.35; H, 6.09; N, 4.91

***Trans*-3-(*E*-2-methoxyvinyl)-1,4-diphenyl-azetidin-2-one (2.07h)**

It was isolated as thick oil; yield 7 %.

IR ($CHCl_3$)	**:**	3018, 1749, 1652, 1600, 1502, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.60 (3H, s, OC*H*$_3$), 3.57-3.63 (1H, m, C3*H*), 4.70 (1H, d, *J* = 2.5 Hz, C4*H*), 4.95 (1H, dd, *J* = 9.4 Hz, *J* = 12.7 Hz, C*H*=CHOMe), 6.52 (1H, d, *J* = 12.7 Hz, CH=C*H*OMe), 7.03-7.46 (10H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 56.2, 59.8, 62.1, 97.8, 116.1, 123.2, 125.3, 127.7, 128.1,

($CDCl_3$)		137.2, 137.4, 149.8, 166.4
(50 MHz)		
MS (m/z)	**:**	342 (M+1), 364 (M+Na)
Analysis	**:**	Calculated: C, 77.39; H, 6.13; N, 5.01
($C_{18}H_{17}NO_2$)		Observed: C, 77.31; H, 6.07; N, 4.98

2.4.9 Synthesis of *trans*-3-vinyl-β-lactams 2.06i and 2.07i

The methoxyolefinic chloride **2.04b** (0.286 g, 2.13 mmol) on treatment with imine **2.05a** (0.300 g, 1.42 mmol) in presence of triethylamine (0.64 g, 6.39 mmol) at 0 ºC and refluxed for 15h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.376 g, 85%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 8:2) to give pure *Z*-isomer **2.06i** (major) as white solid and *E*-isomer **2.07i** (minor) as thick oil.

***Trans*-1-(4-methoxyphenyl)-3-(*Z*-2-methoxyvinyl)-4-phenyl-azetidin-2-one (2.06i)**

It was obtained as white solid (MeOH); yield 78 %.

MP	**:**	95-96 °C
IR ($CHCl_3$)	**:**	2935, 1743, 1660, 1512, 1377, 1244 cm^{-1}
^{1}H NMR	**:**	δ_H 3.51 (3H, s, OC*H*$_3$), 3.65 (3H, s, Ph-OC*H*$_3$), 3.87-3.93 (1H,
($CDCl_3$)		m, C3*H*), 4.58 (1H, dd, *J* = 6.0 Hz, *J* = 8.6 Hz, C*H*=CHOMe),
(200 MHz)		4.67 (1H, d, *J* = 2.4 Hz, C4*H*), 6.05 (1H, dd, *J* = 1.0 Hz, *J* =
		6.0 Hz, CH=C*H*OMe), 6.67-7.28 (9H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 55.4, 56.6, 59.9, 62.3, 98.3, 114.2, 118.3, 125.9, 126.9,
($CDCl_3$)		127.9, 128.2, 128.4, 128.9, 131.4, 135.6, 138.0, 150.3, 155.8,
(50 MHz)		166.3
MS (m/z)	**:**	310 (M+1), 332 (M+Na)
Analysis	**:**	Calculated: C, 73.76; H, 6.19; N, 4.52
($C_{19}H_{19}NO_3$)		Observed: C, 73.71; H, 6.12; N, 4.44

***Trans*-1-(4-methoxyphenyl)-3-(*E*-2-methoxyvinyl)-4-phenyl-azetidin-2-one (2.07i)**

It was isolated as thick oil; yield 7 %.

IR ($CHCl_3$)	**:**	2954, 1743, 1649, 1512, 1240 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.60 (3H, s, OC*H*$_3$), 3.75 (3H, s, Ph-OC*H*$_3$), 3.71-3.77 (1H, m, C3*H*), 4.67 (1H, d, *J* = 2.5 Hz, C4*H*), 4.95 (1H, dd, *J* = 9.5 Hz, *J* = 12.5 Hz, C*H*=CHOMe), 6.49-7.44 (10H, m, Ar-*H* and CH=C*H*OMe)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 55.7, 56.2, 60.1, 63.1, 96.0, 113.9, 114.3, 114.7, 117.0, 118.4, 120.7, 125.8, 128.4, 129.1, 137.4, 138.6, 151.4, 155.9, 166.3
MS (m/z)	**:**	310 (M+1), 332 (M+Na)
Analysis	**:**	Calculated: C, 73.76; H, 6.19; N, 4.52
($C_{19}H_{19}NO_3$)		Observed: C, 73.68; H, 6.09; N, 4.48

2.4.10 Preparation of 4-phthalimido-but-2-enoic acid methyl ester (2.02c)

To a solution of pthalimido potassium salt (0.500 g, 2.70 mmol) in dry methanol (20 mL) was added 4-bromomethylcrotonate **2.01** (0.63 mL, 5.40 mmol) at 0 ^oC and 1 drop of aliquot as a phase transfer catalyst. The reaction mixture was then refluxed for 15h. Reaction mixture was neutralized with acetic acid and most of the methanol was removed under reduced pressure and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with water (10 mL), brine solution (10 mL) and dried over anhydrous Na_2SO_4 and concentrated to give the yellowish solid **2.02c** (0.988 g, 75%).

MP	**:**	175-176 °C
IR (Nujol)	**:**	2941, 1730, 1664, 1460, 1377, 1288 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.76, 3.77 (6H, s, COOC*H*$_3$), 4.37 (2H, dd, *J* = 2.7 Hz, *J* = 4.0 Hz, OC*H*$_2$), 4.98 (2H, dd, *J* = 2.0 Hz, *J* = 4.7 Hz, NC*H*$_2$), 6.07-6.17 (2H, m, C*H*-olefin), 6.98-7.12 (2H, m, C*H*-olefin), 7.69-7.96 (8H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 51.6, 52.7, 61.8, 63.6, 119.7, 122.2, 123.6, 128.7, 129.0,

($CDCl_3$) (50 MHz)		130.9, 131.2, 131.5, 132.6, 134.3, 140.9, 147.1, 166.9, 168.1.

2.4.11 Preparation of 4- phthalimido-but-2-enoic acid (2.03c)

Following the similar procedure for the compound (**2.03a**), we have synthesized acid **2.03c** as yellow solid; yield 80 %.

MP	**:**	136-137 °C
IR (Nujol)	**:**	2924, 2854,1715, 1666, 1460, 1377, 1290 cm^{-1}
^{1}H NMR ($CDCl_3$ + DMSO-d_6) (200 MHz)	**:**	δ_H 3.60-3.63 (2H, m, OCH_2), 4.61-4.77 (2H, m, NCH_2), 5.50-5.68 (2H, m, C*H*-olefin), 6.16-6.52 (10H, m, Ar-*H* and C*H*-olefin)
^{13}C NMR ($CDCl_3$ + DMSO-d_6) (50 MHz)	**:**	δ_C 60.0, 62.8, 119.2, 120.9, 122.4, 127.5, 128.3, 129.4, 129.7, 132.6, 143.1, 147.4, 166.4, 166.7, 168.8, 172.1.

2.4.12 Preparation of 4- phthalimido-but-2-enoyl chloride (2.04c)

It was obtained as colorless oil (yield 98 %) following the similar procedure for the compound **2.04a**. The IR spectrum appeared a band at 1757, 1670 cm^{-1} confirmed the presence of acid chloride **2.04c** and used as such for the synthesis of *trans*-3-vinyl-β-lactams **2.06j** and **2.07j**.

2.4.13 Synthesis of *trans*-3-vinyl-β-lactams 2.06j and 2.07j

The pthalimido-olefinic chloride **2.04c** (0.793 g, 3.18 mmol) on treatment with imine **2.05c** (0.384 g, 2.12 mmol) in presence of triethylamine (0.96 g, 9.54 mmol) at 0 ºC and refluxed for 48h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.516 g, 61%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06j** (major) as white solid and *E*-isomer **2.07j** (minor) as thick oil.

***Trans*-2-[*Z*- 2-(2-oxa-1, 4-diphenyl-azetidin-3-yl)-vinyl]-isoindole-1, 3-dione (2.06j)**

It was obtained as white solid (MeOH); yield 51 %.

MP	**:**	109-110 °C
IR ($CHCl_3$)	**:**	3016, 1747, 1662, 1600, 1500, 1217 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.87-3.94 (1H, m, C3*H*), 4.53 (1H, dd, *J* = 6.1 Hz, *J* = 8.6 Hz, C*H*=CHPhth), 4.71 (1H, d, *J* = 2.7 Hz, C4*H*), 6.07 (1H, dd, *J* = 1.0 Hz, *J* = 6.1 Hz, CH=C*H*Phth), 6.89-7.90 (14H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 56.7, 61.5, 103.0, 117.0, 120.2, 123.6, 123.7, 124.0, 126.0, 128.6, 128.9, 137.1, 137.9, 138.0, 150.3, 165.9, 167.2
MS (m/z)	**:**	395 (M+1), 417 (M+Na)
Analysis	**:**	Calculated: C, 76.13; H, 4.60; N, 7.10
($C_{25}H_{18}N_2O_3$)		Observed: C, 76.07; H, 4.51; N, 7.03

***Trans*-2-[*E*- 2-(2-oxa-1, 4-diphenyl-azetidin-3-yl)-vinyl]-isoindole-1, 3-dione (2.07j)**

It was isolated as thick oil; yield 10 %.

IR ($CHCl_3$)	**:**	3018, 1745, 1652, 1600, 1500, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.56-3.64 (1H, m, C3*H*), 4.70 (1H, d, *J* = 2.5 Hz, C4*H*), 4.93 (1H, dd, *J* = 9.4 Hz, *J* = 12.6 Hz, C*H*=CHPhth), 6.53 (1H, d, *J* = 12.6 Hz, CH=C*H*Phth), 7.03-8.00 (14H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 59.0, 62.3, 103.5, 116.8, 120.0, 123.1, 123.5, 124.2, 125.9, 128.2, 128.5, 137.4, 137.5, 138.2, 149.0, 166.9, 167.4
MS (m/z)	**:**	395 (M+1), 417 (M+Na)
Analysis	**:**	Calculated: C, 76.13; H, 4.60; N, 7.10
($C_{25}H_{18}N_2O_3$)		Observed: C, 76.09; H, 4.55; N, 7.05

2.4.14 Preparation of 4-azido-but-2-enoic acid methyl ester (2.02d)

To a solution of 4-bromomethyl crotonate **2.01** (0.66 mL, 5.6 mmol) in dry acetone (30 mL) was added anhydrous NaI (1.67 g, 11.2 mmol), NaN_3 (1.09 g, 16.8 mmol) and catalytic Tetrabutyl ammonium iodide as a phase transfer catalyst at room temperature. The reaction mixture was then refluxed for 18 h. The solvent was distilled off under reduced pressure and residue was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with water (15 mL), brine solution (30 mL) and dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography (petroleum ether-acetone, 9.5:0.5) to give **2.02d** as a pale yellow oil (0.620 g, 78%).

IR (Neat)	**:**	2109, 1724, 1663 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 3.76 (3H, s, OC*H*$_3$), 3.99-4.02 (2H, m, C*H*$_2$N$_3$), 6.04-6.14 (1H, m, C*H*-olefin), 6.84-6.97 (1H, m, C*H*-olefin)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 51.1, 51.8, 123.2, 140.7, 166.0

2.4.15 Preparation of 4-azido-but-2-enoic acid (2.03d)

Following the similar procedure for the compound (**2.03a**), we have synthesized acid **2.03d** as colourless oil; yield 97 %.

IR (Neat)	**:**	3200, 1716, 1650 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 4.07-4.18 (2H, m, C*H*$_2$N$_3$), 4.99-5.10 (1H, m, C*H*-olefin), 6.33-6.38 (1H, m, C*H*-olefin), 10.27 (1H, O*H*, bs)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 58.5, 110.7, 126.1, 171

2.4.15 Preparation of 4-azido-but-2-enoyl chloride (2.04d)

It was obtained as colourless oil (yield 95 %) following the similar procedure for the compound **2.04a**. The IR spectrum showed a peak 1763, 1665 cm^{-1} confirmed the presence of acid chloride **2.04d** and used as such for the synthesis of *trans*-3-vinyl-β-lactams **2.06k** and **2.07k**.

2.4.16 Synthesis of *trans*-3-vinyl-β-lactams 2.06k and 2.07k

The azido-olefinic chloride **2.04d** (0.423 g, 2.90 mmol) on Staudinger reaction with imine **2.05c** (0.350 g, 1.93 mmol) in presence of triethylamine (0.88 g, 8.72 mmol) at 0 ºC and refluxed for 48h gave a diastereomeric mixture of two *trans*-β-lactams as thick brown oil (0.350 g, 66%). This mixture was separated by flash column chromatography (petroleum ether-ethyl acetate 9:1) to give pure *Z*-isomer **2.06k** (major) and *E*-isomer **2.07k** (minor) as thick oil.

***Trans*-3-(*Z*-2-azidovinyl)-1,4-diphenylazetidin-2-one (2.06k)**

It was isolated as thick oil; yield 57 %.

IR ($CHCl_3$)	**:**	3029, 2109, 1747, 1640, 1600, 1500, 1371 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 3.89-3.95 (1H, m, C3*H*), 4.71 (1H, d, *J* = 2.5 Hz, C4*H*), 5.00 (1H, dd, *J* = 7.5 Hz, *J* = 9.0 Hz, C*H*=CHN_3), 6.35 (1H, dd, *J* = 1.1 Hz, *J* = 7.5 Hz, CH=C*H*N_3), 6.90-7.29 (10H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 57.5, 61.7, 111.3, 117.1, 124.0, 125.9, 128.6, 129.0, 130.5, 137.3, 137.5, 165.3
MS (m/z)	**:**	291 (M+1), 314 (M+Na)
Analysis ($C_{17}H_{14}N_4O$)	**:**	Calculated: C, 70.33; H, 4.86; N, 19.30 Observed: C, 70.25; H, 4.81; N, 19.21

***Trans*-3-(*E*-2-azidovinyl)-1,4-diphenylazetidin-2-one (2.07k)**

It was isolated as thick oil; yield 9 %.

IR ($CHCl_3$)	**:**	3018, 2111, 1747, 1647, 1600, 1502, 1371 cm^{-1}

^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 3.69-3.75 (1H, m, C3*H*), 4.75 (1H, d, *J* = 2.5 Hz, C4*H*), 5.29-5.39 (1H, m, C*H*=CHN$_3$), 6.44-7.55 (11H, m, Ar-*H* and CH=C*H*N$_3$)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 58.9, 62.4, 112.5, 117.1, 123.7, 127.0, 128.7, 129.7, 130.4, 137.4, 137.8, 166.5
MS (m/z)	**:**	291 (M+1), 314 (M+Na)
Analysis	**:**	Calculated: C, 70.33; H, 4.86; N, 19.30
(C$_{17}$H$_{14}$N$_4$O)		Observed: C, 70.28; H, 4.79; N, 19.25

2.4.17 Preparation of (*R*, *E*)-methyl 4-(2-oxo-4-phenyloxazolidin-3-yl) but-2-enoate (2.09)

To a solution of (*R*) (-) 4-phenyl-2-oxazolidinone (**2.08**) (0.50 g, 3.06 mmol) in dry THF (20 mL), a suspension to NaH (0.183 g, 7.66 mmol) in THF (10 mL) was added with stirring at 0 ^oC. After stirring for 30 min, 4-bromomethylcrotonate **2.01** (0.54 mL, 4.59 mmol) was added to the reaction mixture at 0 ^oC. The reaction mixture was then stirred at room temperature for 7h. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL). The solvent was distilled off under reduced pressure and the residue was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with water (15 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate 1:1) to give **2.09** as a pale yellow oil (0.737 g, 92%).

IR (CHCl$_3$)	**:**	3028, 2952, 1734, 1655, 1479, 1433, 1228 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 2.95 (1H, dd, *J* 16.1, 7.1 Hz, m, N-C*H*$_a$H$_b$), 3.22 (1H, dd, *J* = 10.2, 5.9 Hz, m, N-CH$_a$*H*$_b$), 3.59 (3H, s, OC*H*$_3$), 3.68 (1H, t, *J* = 8.6, C*H*-Ph), 4.15-4.23 (2H, m, OC*H*$_2$CH), 4.65 (1H, t, *J* = 8.8, =C*H*COOMe), 4.99 (1H, dd, *J* 8.8, 7.01 Hz, C*H*=CHCOOMe), 7.26-7.43 (5H, m, Ar-*H*)
^{13}C NMR	**:**	δ_C 35.8, 52.0, 61.3, 70.2, 123.1, 125.9, 126.8, 129.1, 136.8,

($CDCl_3$) (50 MHz)		141.0, 157.2, 170.5
MS (m/z)	**:**	262 (M+1), 284 (M+Na)
Analysis ($C_{14}H_{15}NO_4$)	**:**	Calculated: C, 64.34; H, 5.79; N, 5.36 Observed: C, 64.23; H, 5.71; N, 5.22
Optical Rotation	**:**	$[\alpha]^{25}_D$ -54.05 (*c*, 0.44, $CHCl_3$)

2.4.18 Preparation of (*R, E*)-4-(2-oxo-4-phenyloxazolidin-3-yl) but-2-enoic acid (2.10)

To a solution of oxazolidone olefinic ester **2.09** (0.300 g, 1.14 mmol) in THF (5 mL) was added aqueous NaOH solution (1M, 3 mL) and the reaction mixture was stirred at 25 ^oC for1h. The solvent THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The aqueous layer was then acidified with conc. HCl and the solution was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give oxazolidone olefinic acid **2.10** as pale yellow oil (0.250 g, 88%).

IR ($CHCl_3$)	**:**	3423, 1714, 1693, 1419, 1242 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 2.41-2.72 (2H, m, N-CH_2), 3.32 (1H, dd, *J* 11.5, 5.41 Hz, OCH_aH$_b$), 3.53 (1H, dd, *J* 11.5, 7.5 Hz, OCH$_a$$H_b$), 3.98-4.11 (1H, m, *H*C-Ph), 4.49-4.61 (1H, m, =C*H*COOMe), 4.83 (1H, dd, *J* 9.0, 7.0 Hz, C*H*=CHCOOMe), 6.02 (1H, bs, OH), 7.15-7.31 (5H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 31.6, 61.0, 70.6, 126.8, 127.3, 128.8, 129.2, 129.6, 137.7, 157.7, 176.5
MS (m/z)	**:**	248 (M+1), 270 (M+Na)
Analysis	**:**	Calculated: C, 63.14; H, 5.30; N, 5.67

($C_{13}H_{13}NO_4$) Observed: C, 63.04; H, 5.20; N, 5.56

Optical Rotation : $[\alpha]^{25}_D$ -26.08 (*c*, 0.23, $CHCl_3$)

2.4.19 Preparation of (*R, E*)-4-(2-oxo-4-phenyloxazolidin-3-yl) but-2-enoyl chloride (2.11)

It was obtained as pale yellow oil (yield 97 %) following the same procedure as for compound **2.04a**. The IR spectrum of **2.11** showed peak at 1758, 1685 cm^{-1} indicated the presence of acid chloride and was used for the synthesis of *trans*-3-vinyl-β-lactams **2.12** and **2.13**.

2.4.20 Synthesis of optically pure 3-vinylazetidi-2ones 2.12 and 2.13

The oxazolidone-olefinic chloride **2.11** (0.280 g, 1.05 mmol) on Staudinger reaction with imine **2.05c** (0.130 g, 0.71 mmol) in presence of triethylamine (0.326 g, 3.23 mmol) at 0 ºC and refluxed for 18h gave a diastereomeric mixture of two *trans*-β-lactams (**2.12** and **2.13)** as thick yellow oil (0.180 g, 61%). Our all attempts to separate the two diastereomers by flash column chromatography were unsuccessful but recrystallization from methanol gave a single pure *Z*-isomer **2.12** (major) as a white solid.

(*R*)-3-((Z)-2-((3*R, 4S*)-2-oxo-1, 4-diphenylazetidin-3-yl)vinyl)-4-phenyloxazolidin-2-one (2.12)

MP : 259-260 °C

IR ($CHCl_3$) : 3028, 1743, 1666, 1598, 1494 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 3.58 (1H, dd, *J* = 5.1 Hz, *J* = 8.7 Hz, CH_2CHPh), 4.16 (1H, dd, *J* = 2.4 Hz, *J* = 7.0 Hz, C3*H*), 4.32 (1H, d, *J* = 2.4 Hz, C4*H*), 4.73-4.80 (2H, m, CH_2CHPh), 5.06 (1H, dd, *J* = 5.1 Hz, *J* = 7.0 Hz, NCH=C*H*), 6.80-7.48 (16H, m, Ar-*H* and NC*H*=CH)

^{13}C NMR ($CDCl_3$) (50 MHz) : δ_C 61.8, 62.3, 70.6, 77.2, 104.9, 117.0, 124.0, 125.6, 125.9, 127.6, 128.6, 129.0, 129.2, 129.5, 136.8, 137.4, 137.6, 155.4, 165.7

MS (m/z)	**:**	411(M+1), 433 (M+Na)
Analysis	**:**	Calculated: C, 76.07; H, 5.40; N, 6.83
($C_{26}H_{22}N_2O_3$)		Observed: C, 75.98; H, 5.28; N, 6.77
Optical Rotation	**:**	$[\alpha]^{25}_D$ -14.28 (*c*, 1.4, $CHCl_3$)

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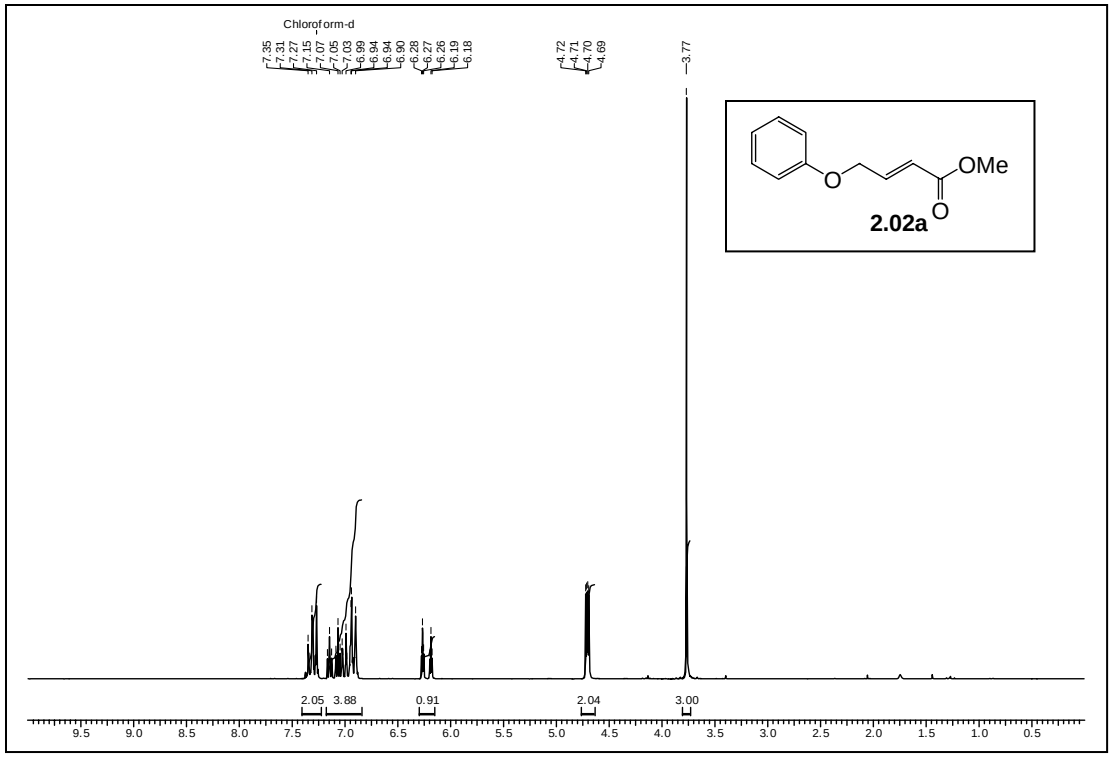
Chapter II

Spectra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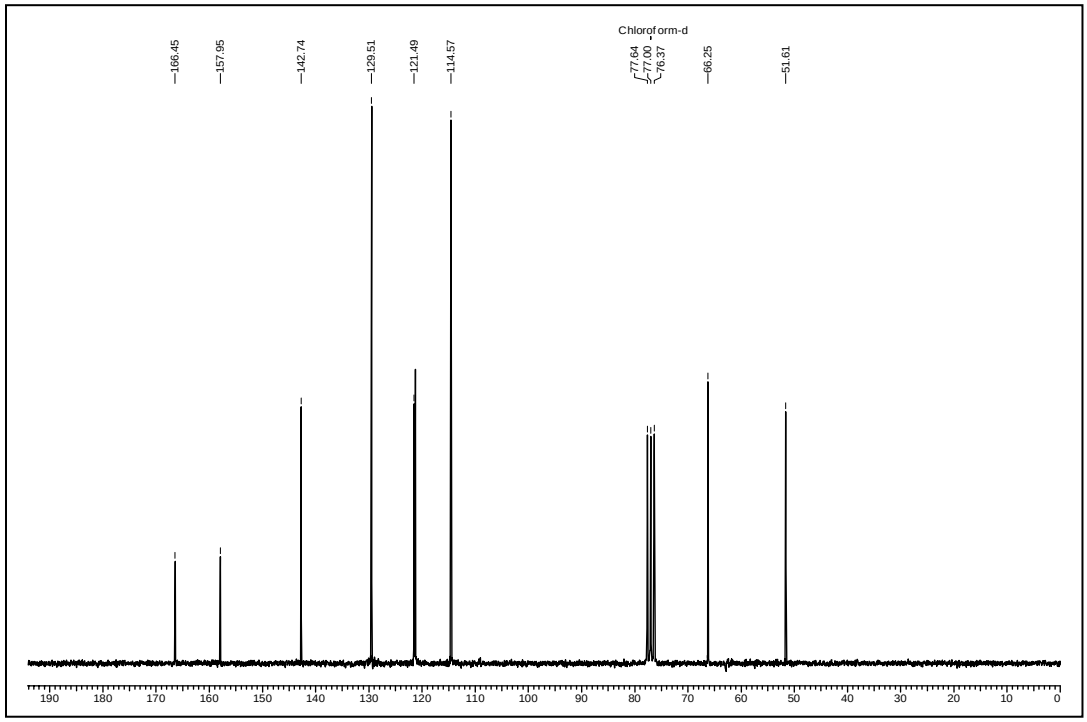
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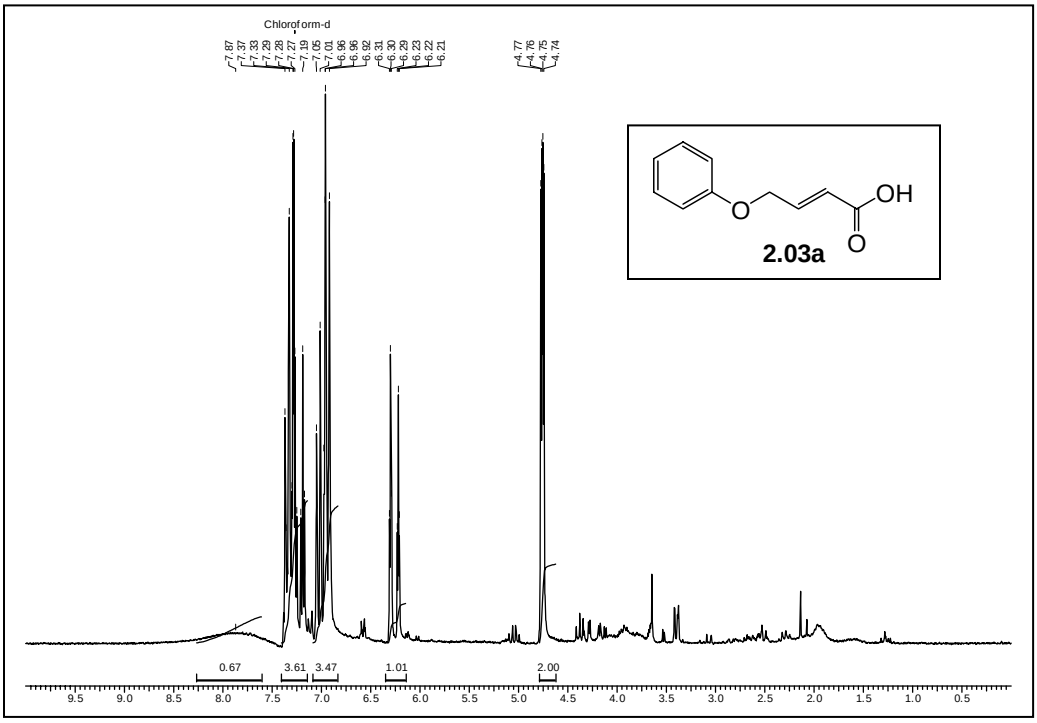
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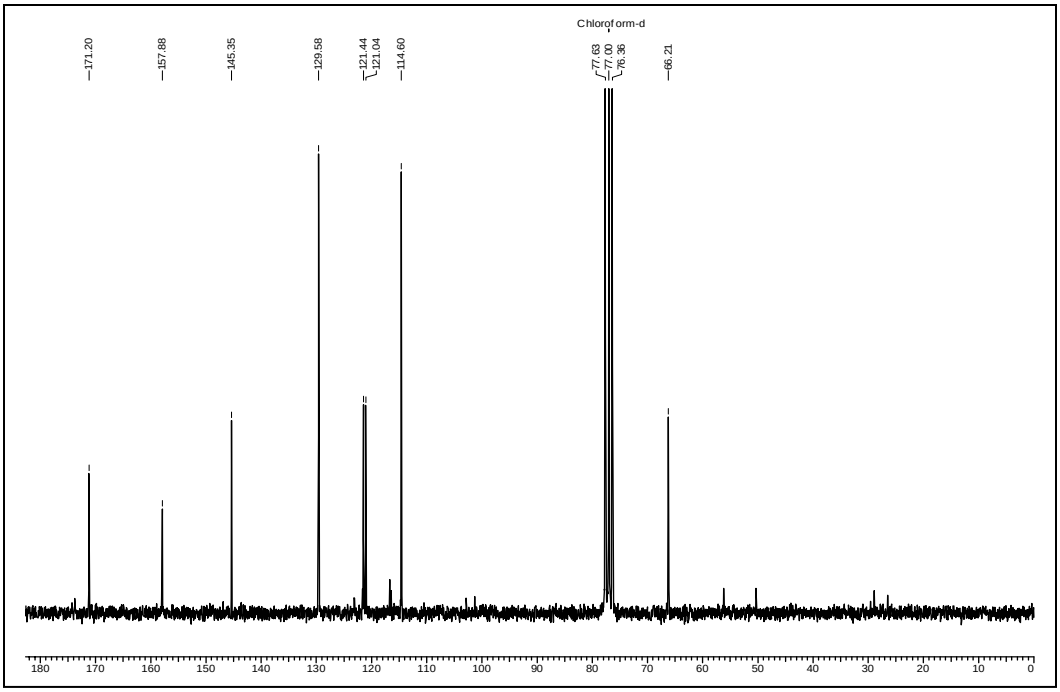
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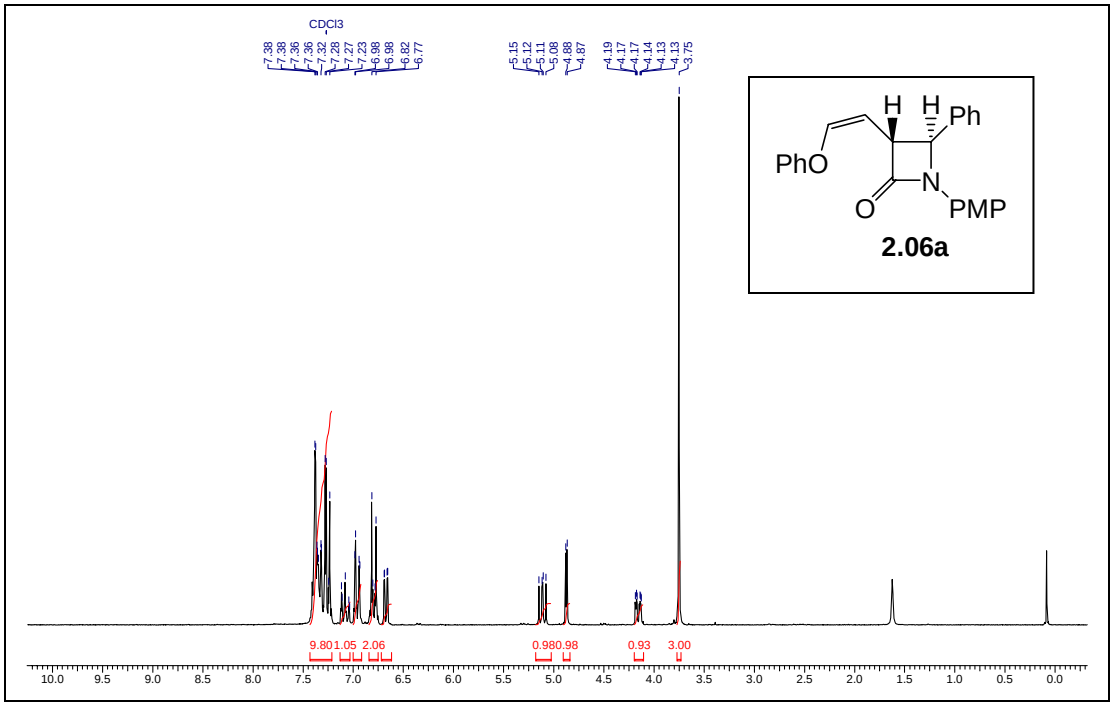
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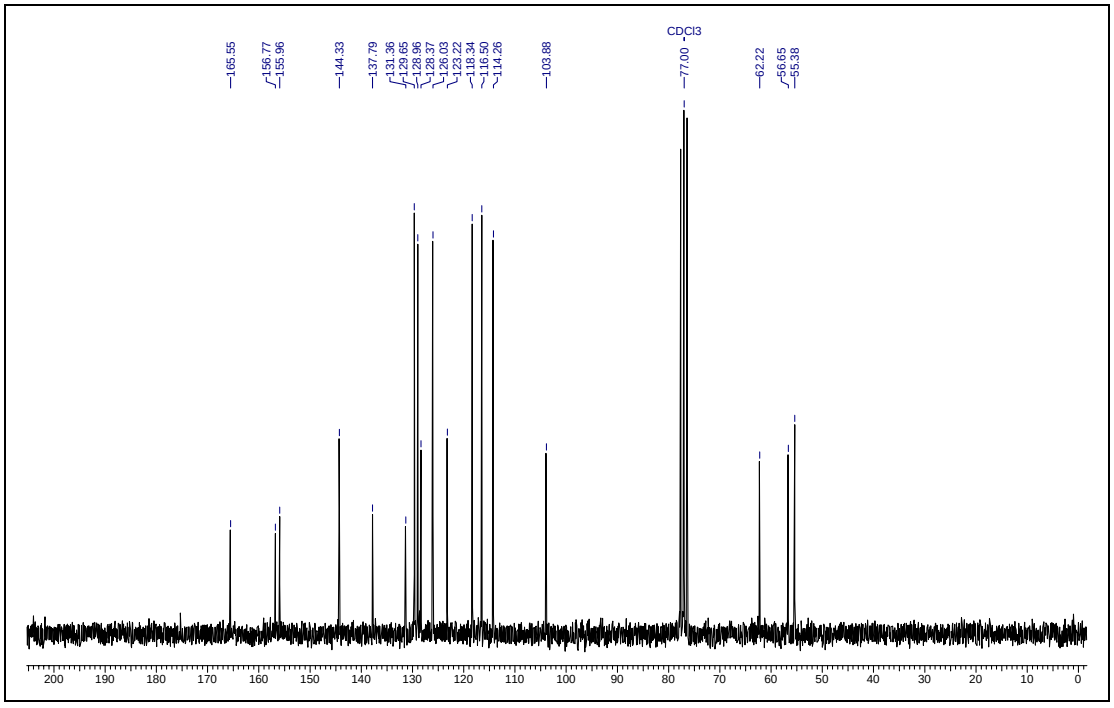
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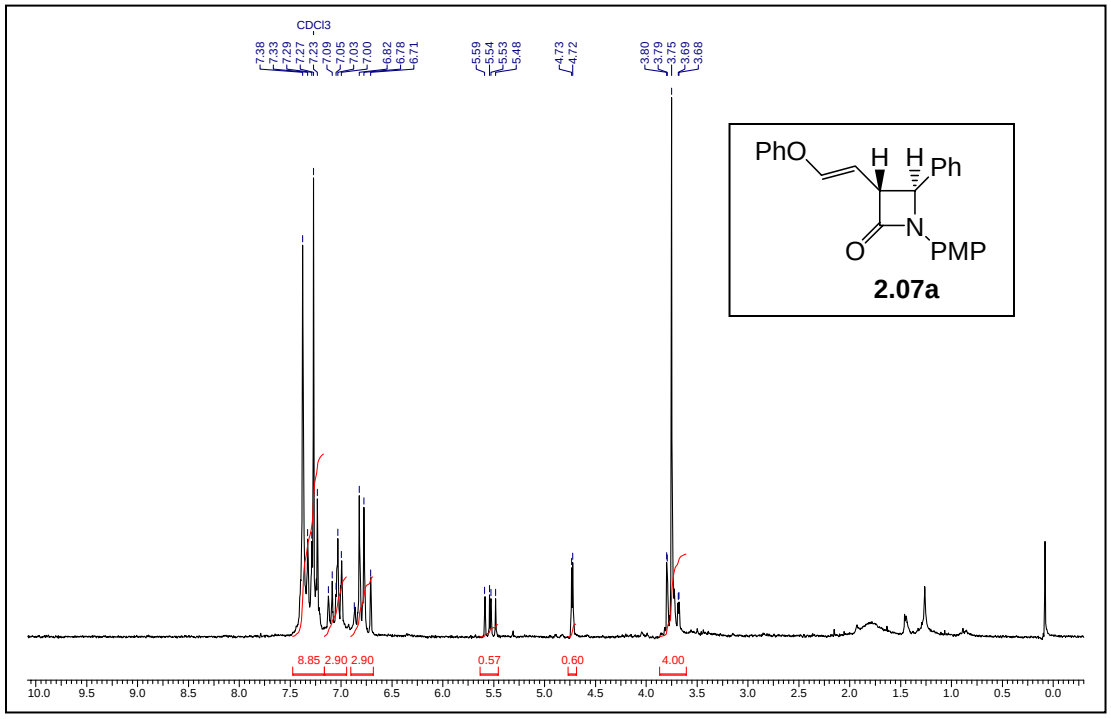
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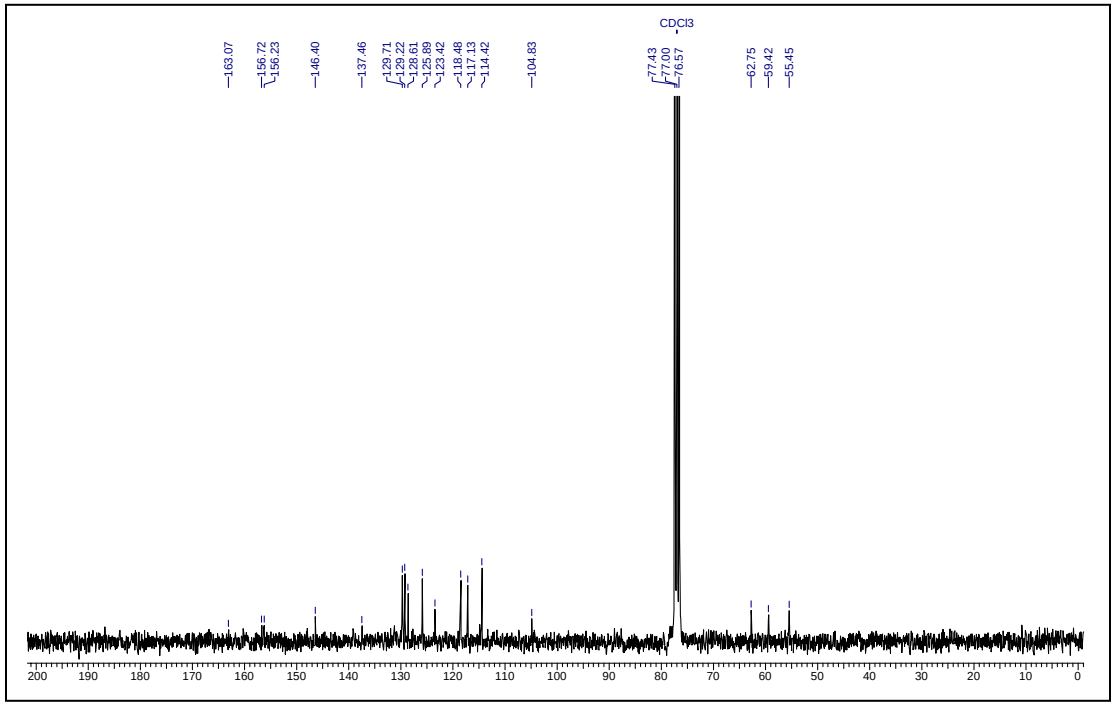
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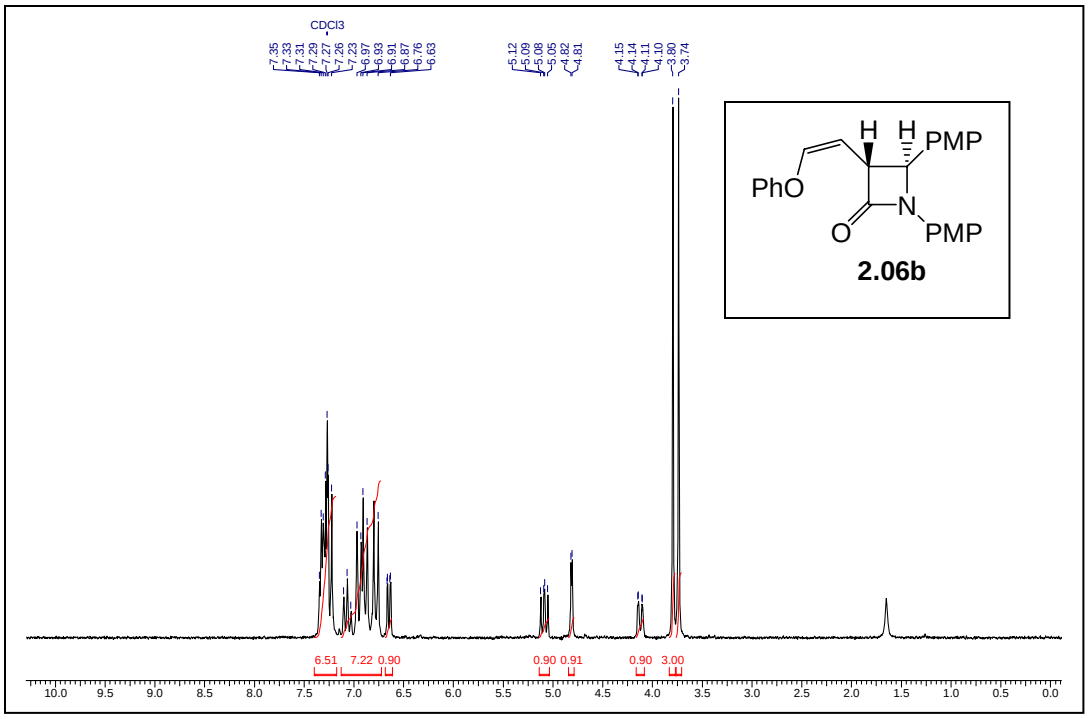
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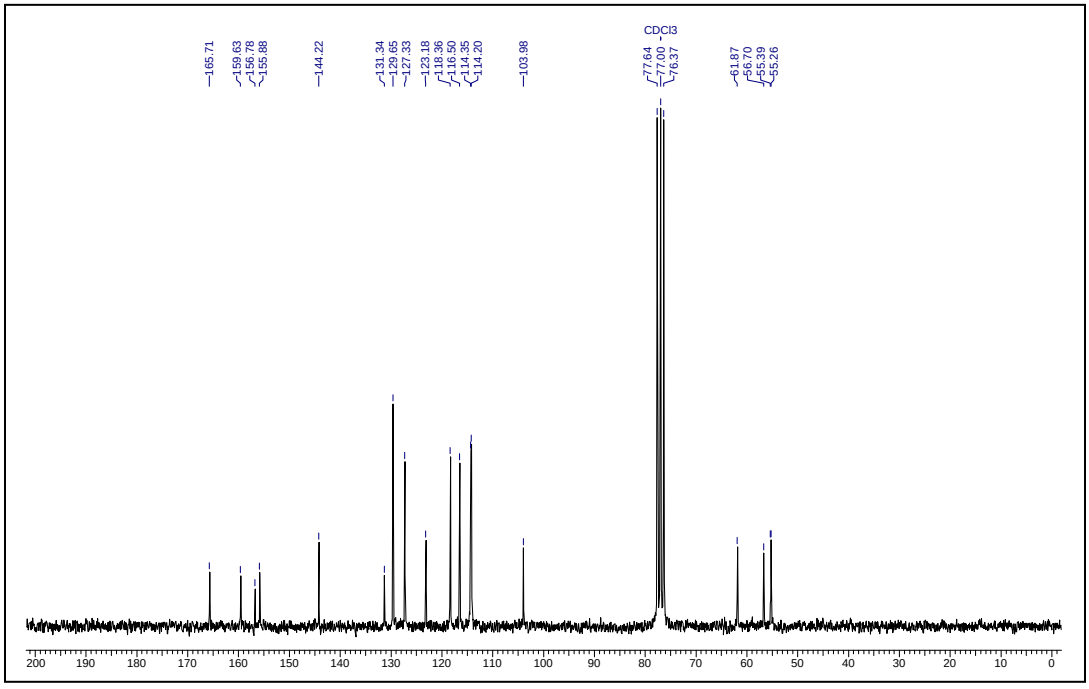
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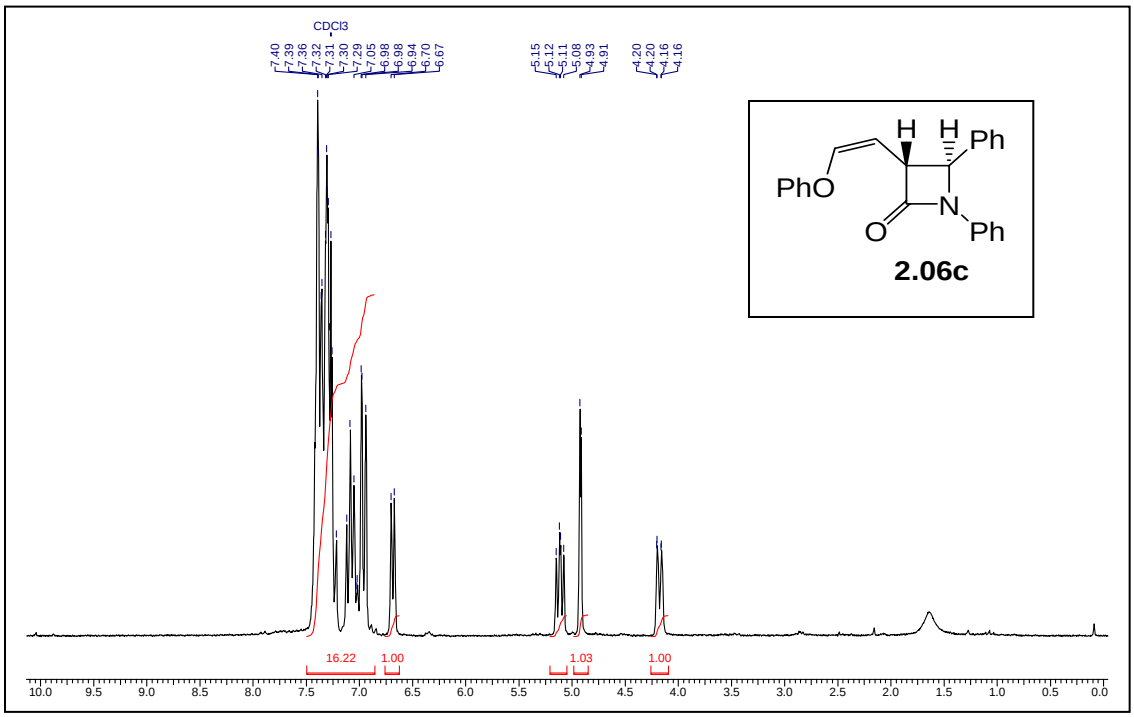
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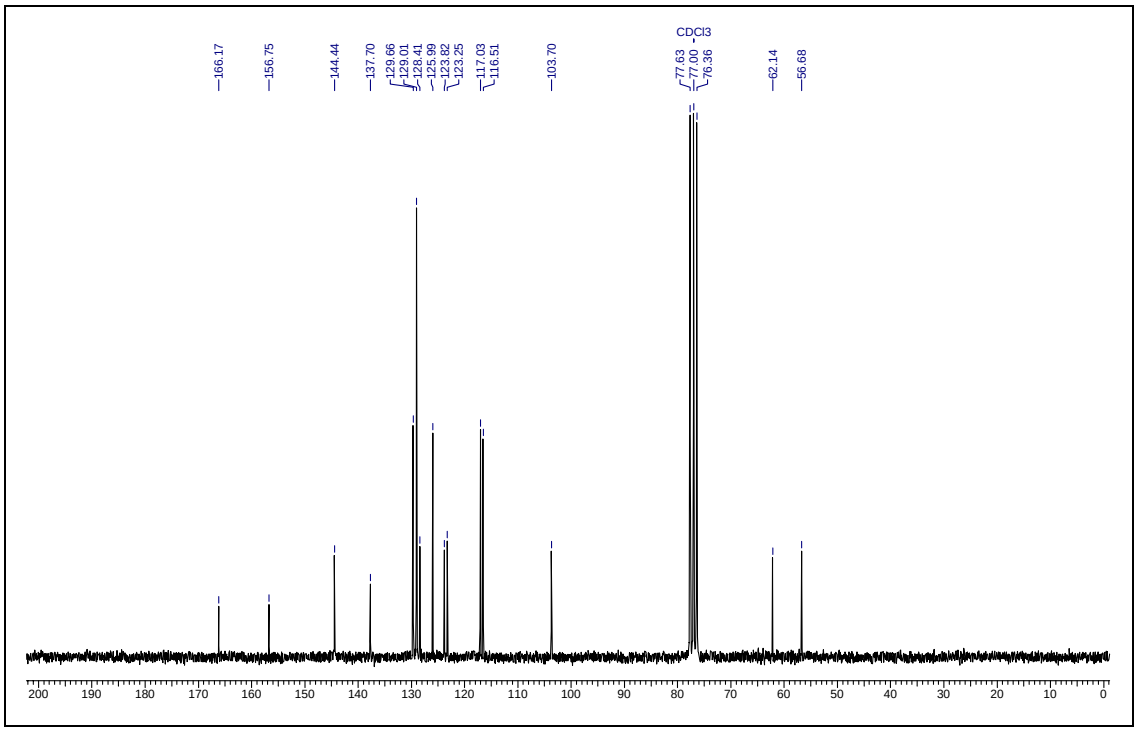
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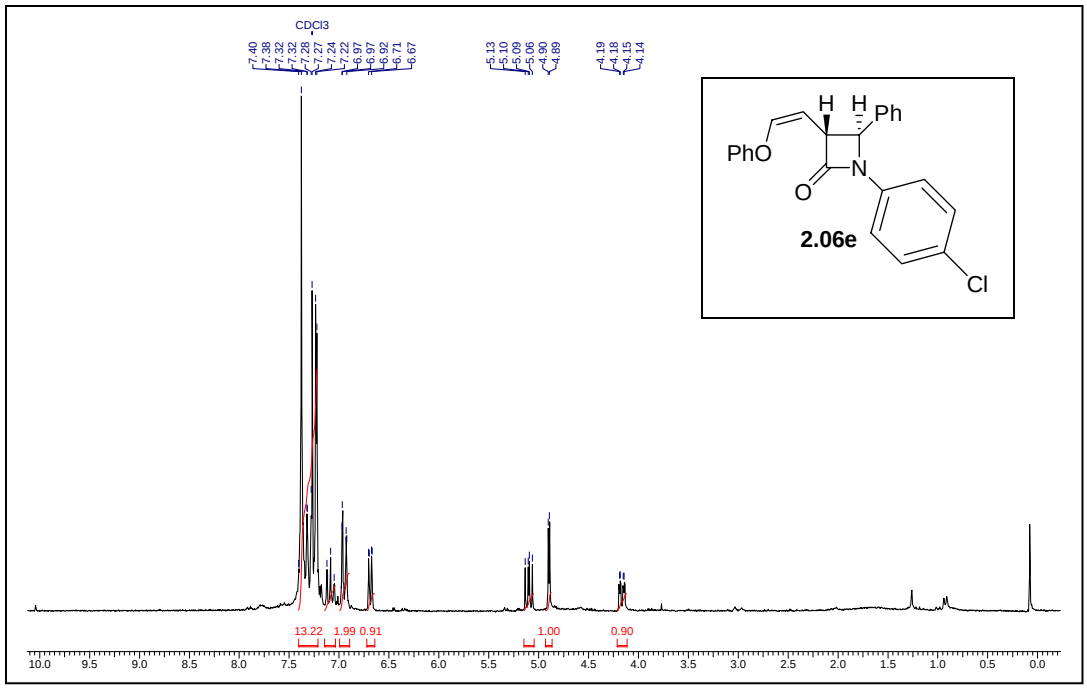
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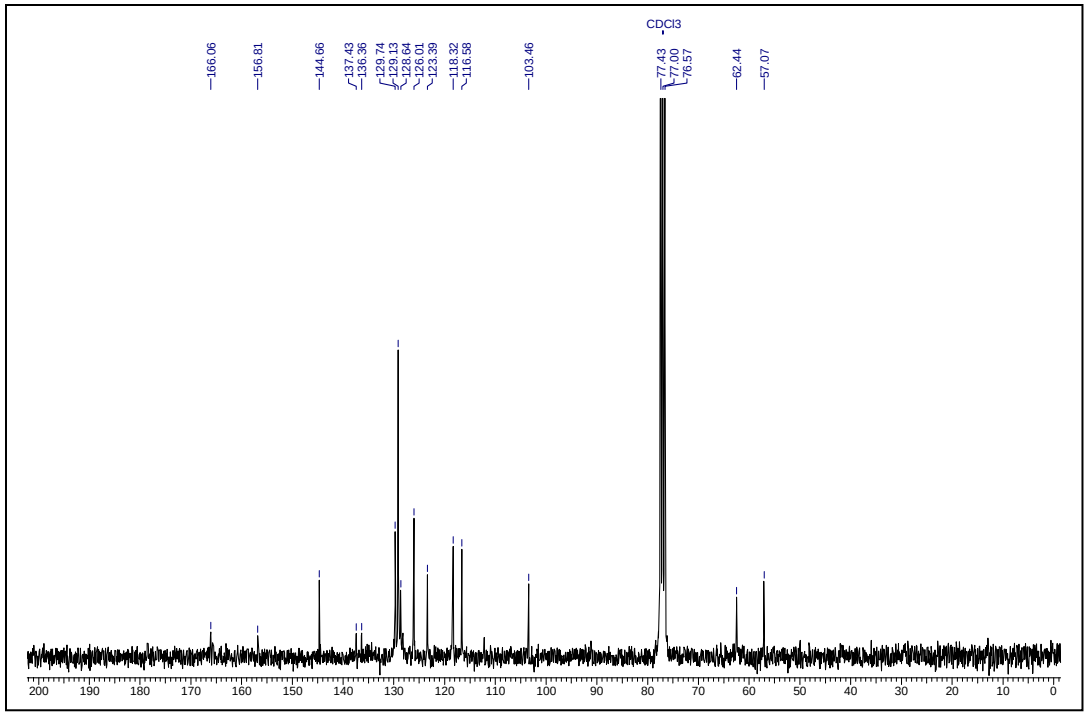
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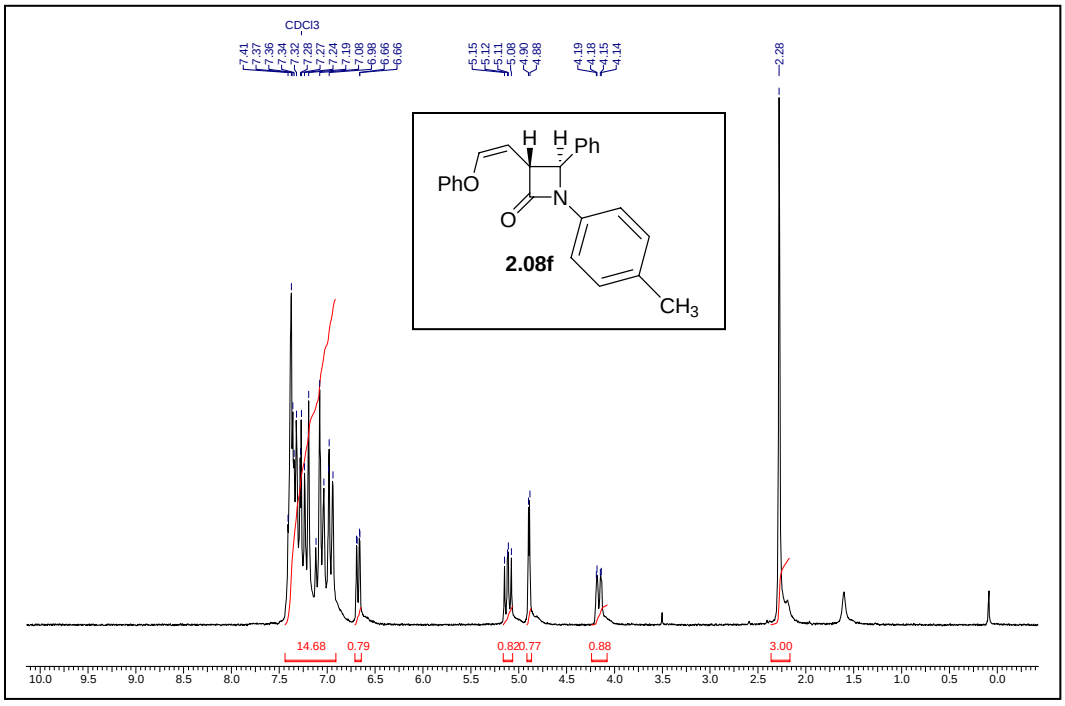
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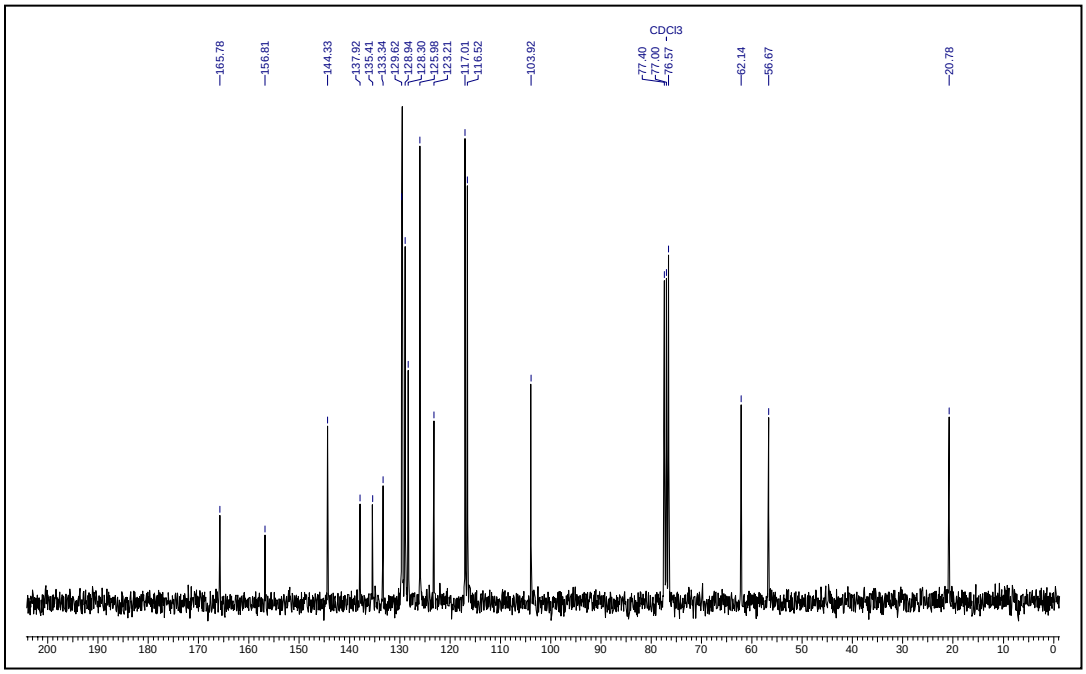
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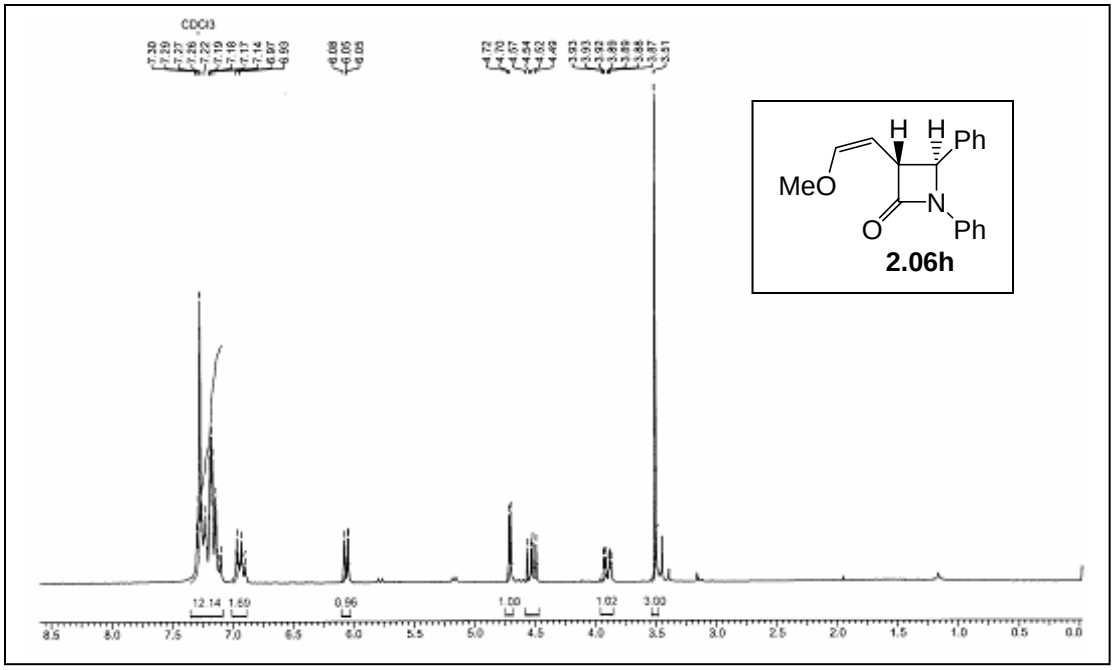
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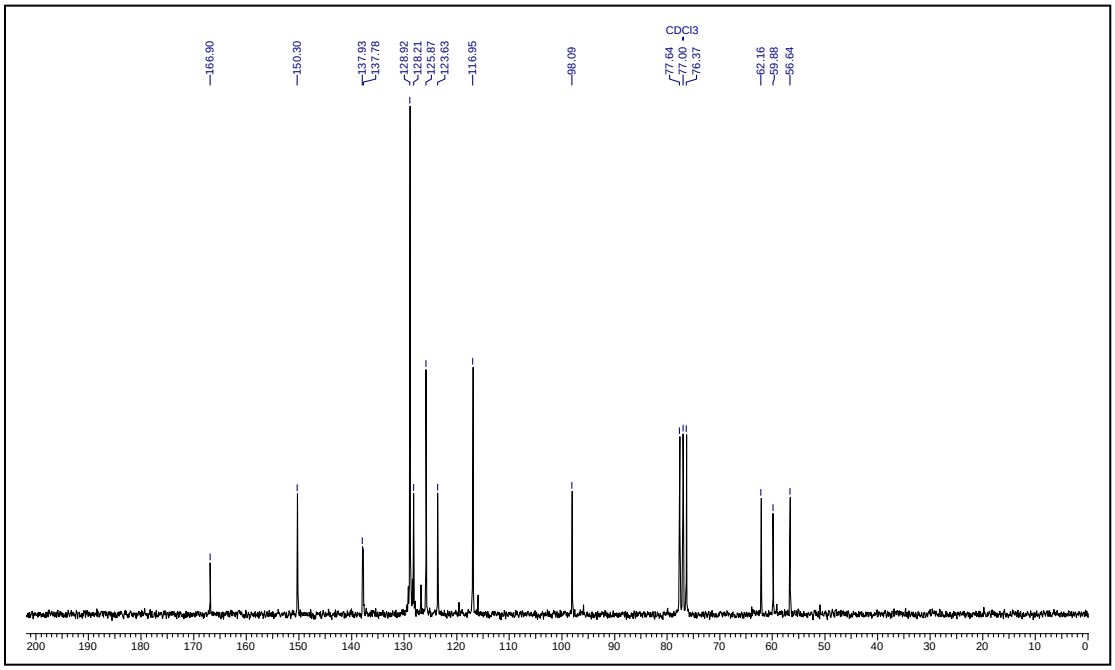
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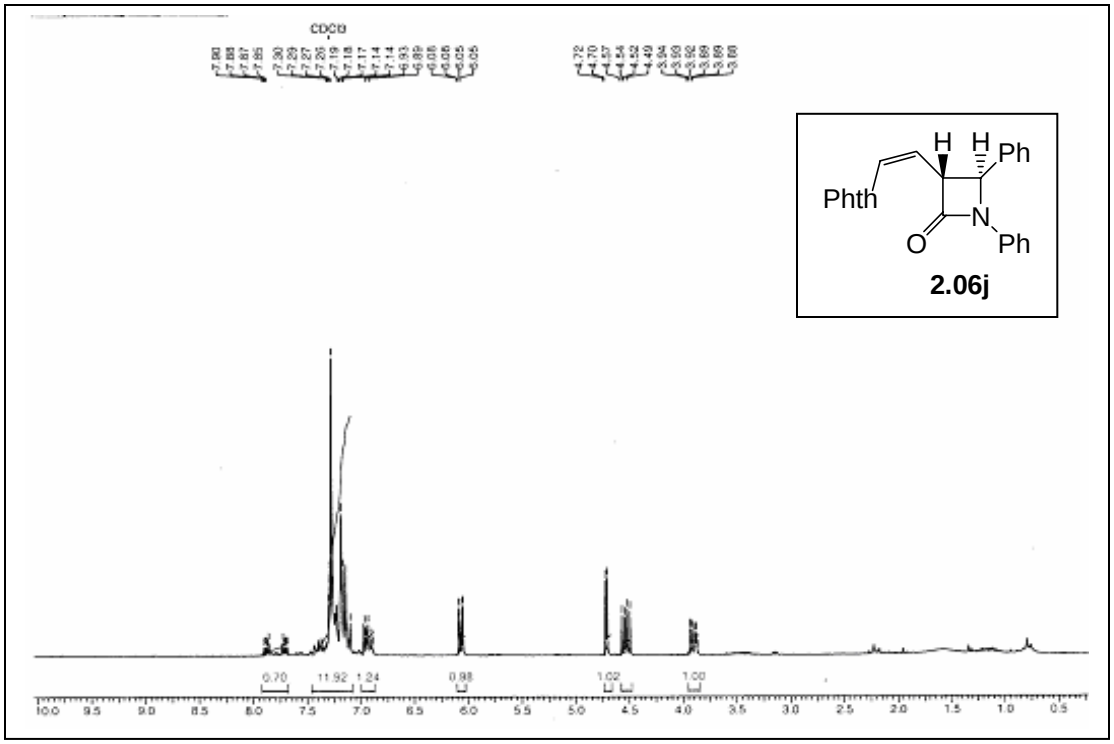
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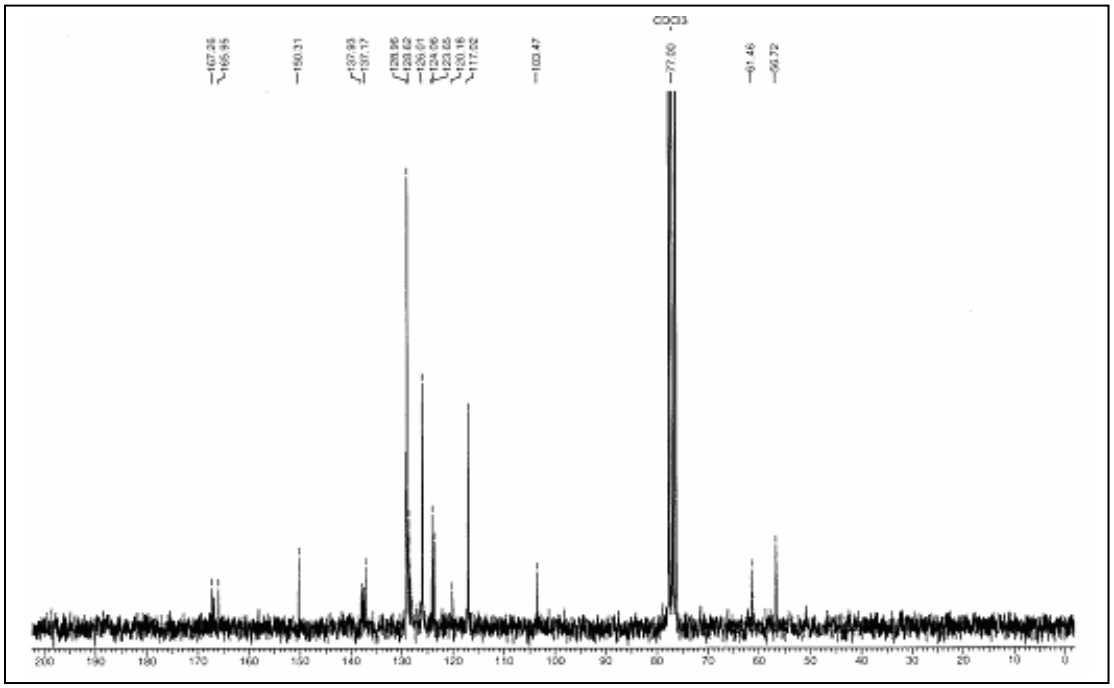
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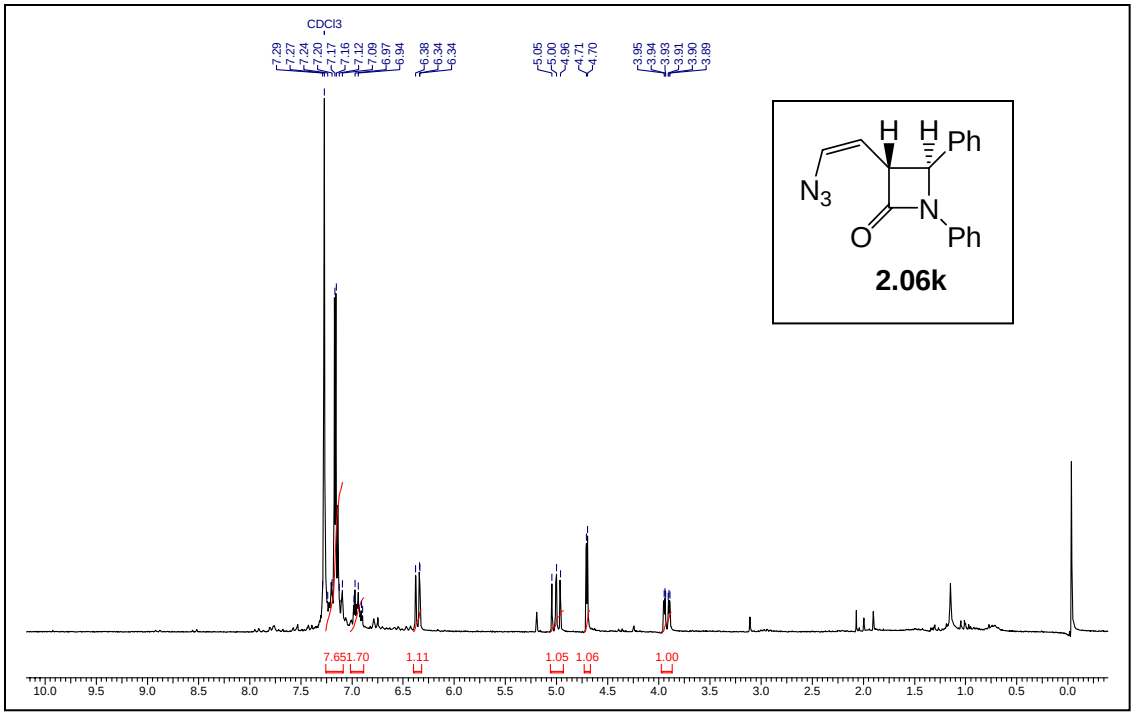
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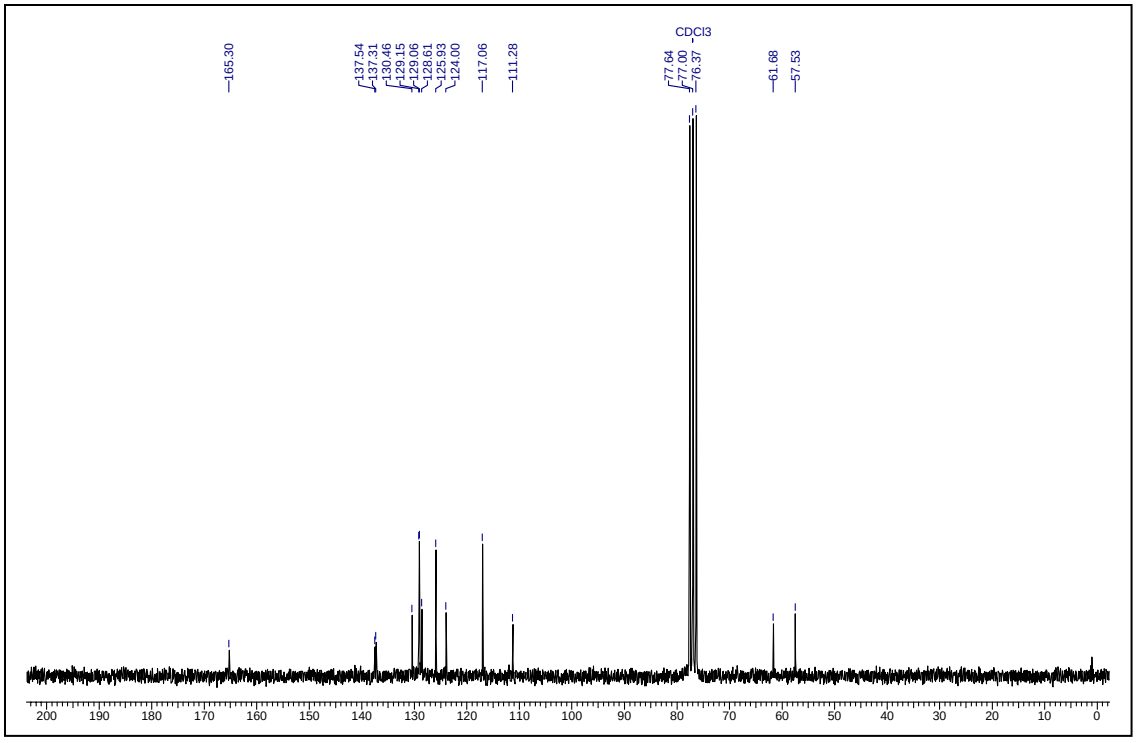
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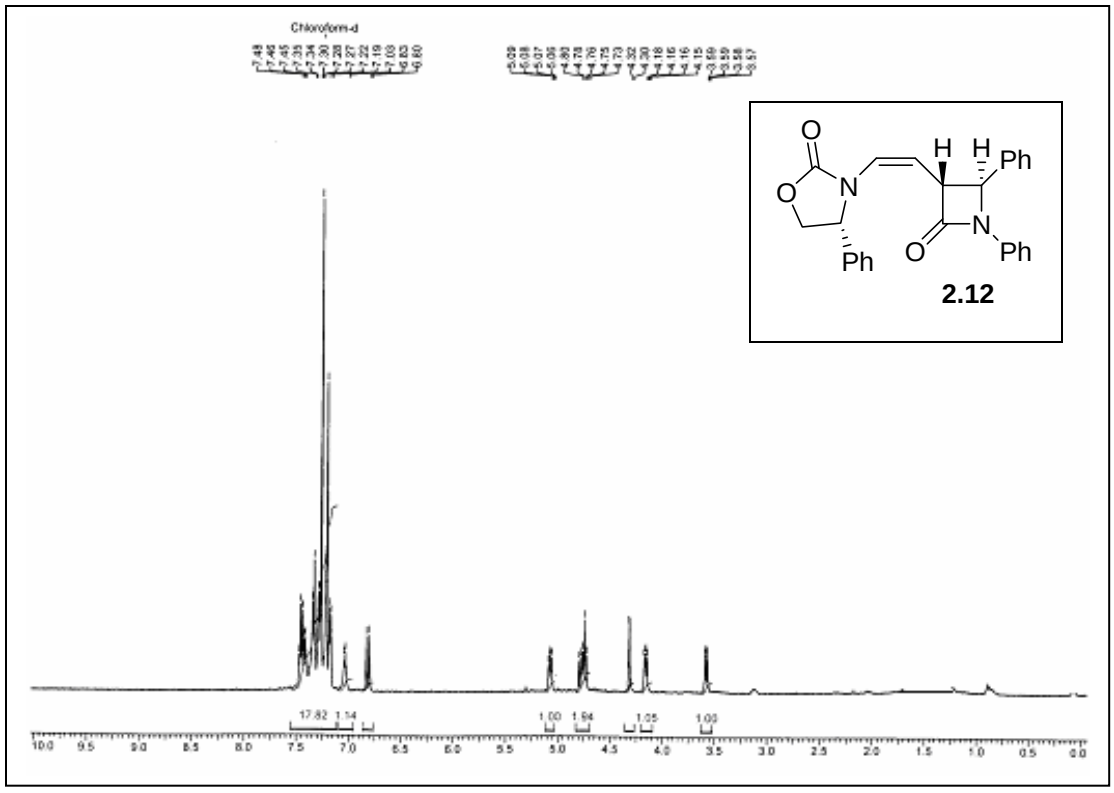
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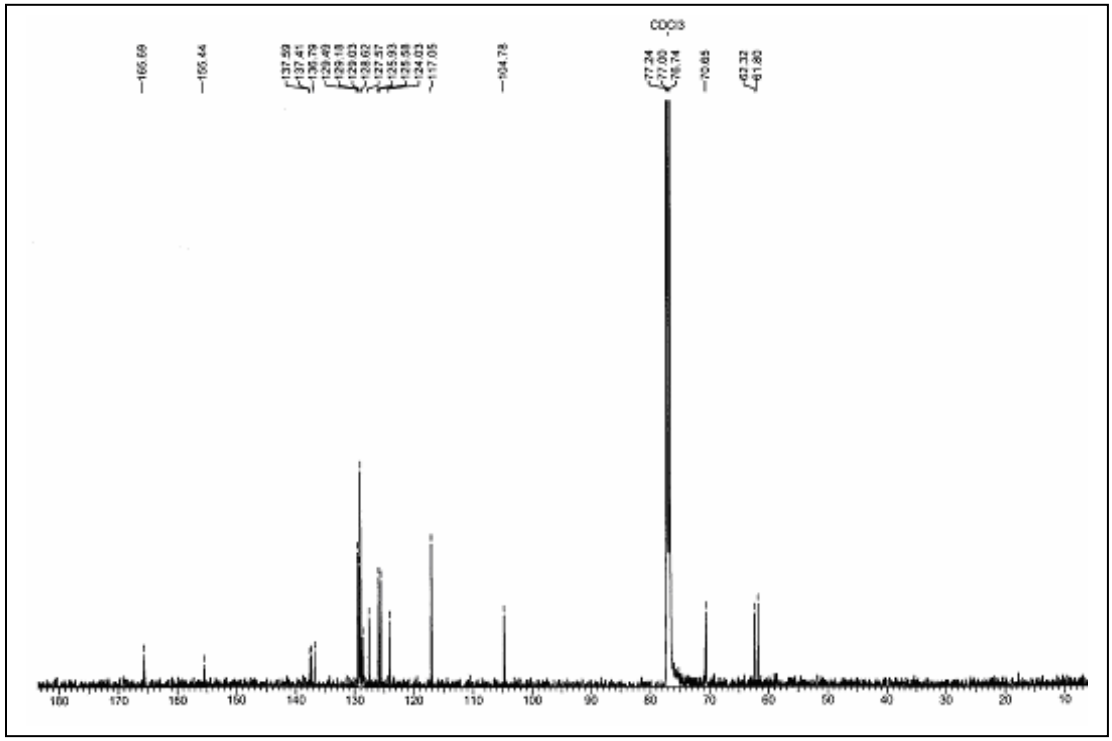

CDCl3

Chapter-III

Section A

Asymmetric synthesis of azetidin-2-ones using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral imines

Part of this work has been published in *Tetrahedron*, **2007**, *63*, 3380-3388

3.1: Introduction

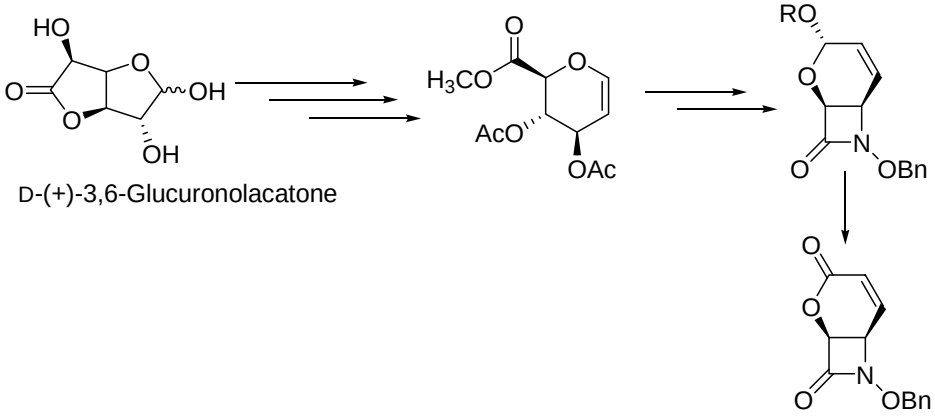
Carbohydrates, a cheap and naturally occurring *chiral pool*, have attracted considerable attention for their applications as chiral starting materials in the asymmetric syntheses of chiral drugs as well as biologically useful organic molecules.[1] The carbohydrate derived chiral auxiliaries have been used for the synthesis of unnatural amino acids *via* opening of β-lactam ring.[2] Carbohydrates have been used as chiral auxiliary in various forms *viz* aldehydes, amine and ketene in ketene-imine cycloaddition reaction (Staudinger reaction) leading to the formation of β-lactams. Several methods have been reported on the synthesis of β-lactams from carbohydrates (for detail discussion see Chapter 1). Some of the methods are described here briefly.

The cycloaddition reaction of fluoroacetyl chloride with the imine derived from *p*-anisidine and D-glyceraldehyde acetonide, to give optically pure α-halo β-lactam in 68% yield as a single diastereomer [3] (Scheme 1.81).

Scheme 1.81

Miller et. al [4] have developed a methodology for the conversion of glucuronic acid glycosides to novel bicyclic β-lactam. The key feature of this strategy included a diastereoselective Ferrier reaction of glucuronic acid glucal and selective β-lactam ring formation (Scheme 1.82).

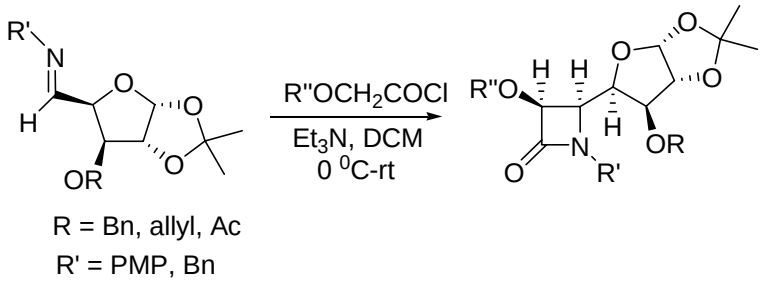
Scheme 1.82



D-(+)-3,6-Glucuronolacatone

Arun et al.[5] have employed a D-glucose derived chiral aldehyde for the diastereospecific synthesis of *cis*-β-lactams in good yield using asymmetric Staudinger reaction (Scheme 1.83).

Scheme 1.83

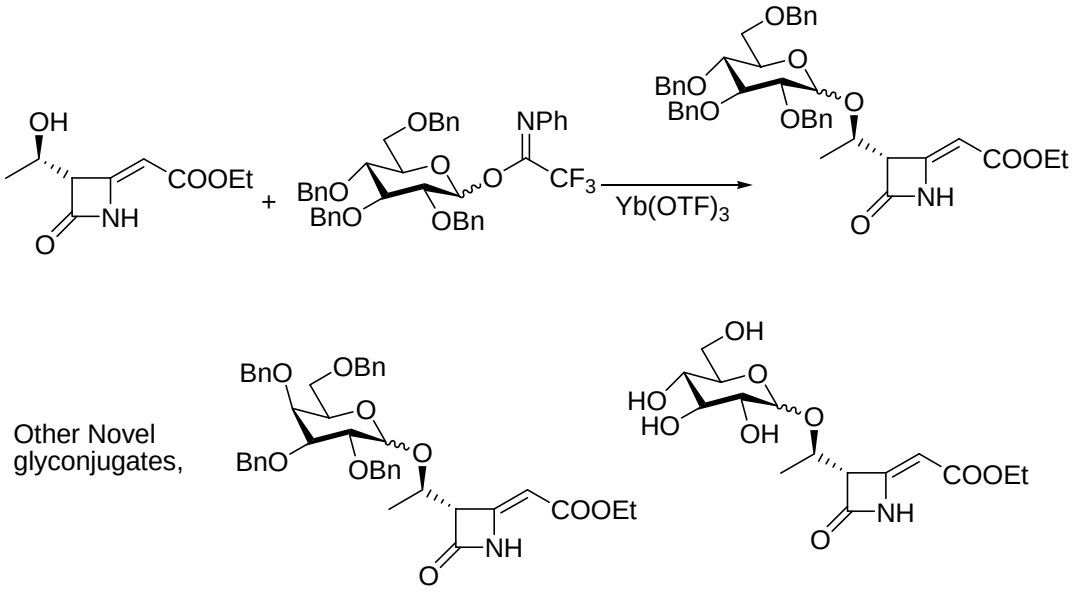


R = Bn, allyl, Ac

R' = PMP, Bn

A new class of glycoconjugated β-lactams [6] was accessed by direct glycosidation of a suitable 4-alkylenede-azetidin-2-one acceptor with several perbenzylated (*N*-phenyl) trifluoroacetimidates donors activated by catalytic $Yb(OTf)_3$ (Scheme 1.84). These β-lactams are providing a novel tethering approach in the active field of glycoconjugates.

Scheme 1.84



Staudinger reaction (ketene-imine cycloaddition reaction) is the most attractive and widely used method in β-lactam ring construction. Over the past few years, asymmetric versions of this reaction has been extensively developed using a combination of either chiral ketenes and achiral imines or achiral ketenes and chiral imines, generally providing good diastereoselectivity.[7]

In the diastereoselective synthesis of β-lactams chiral starting materials such as aldehydes, acids/acid halides and amines have been widely used. High levels of stereoselections were achieved when the β-carbon of the chiral aldehyde is attached to a heteroatom.[8] In recent years several researchers have studied different approaches to optically pure β-lactams of predictable absolute stereochemistry.[9,10] It has been shown that the reaction of an acid chloride (or equivalent) with a Schiff base derived from an optically active aldehyde and an achiral amine, in the presence of triethylamine leads to a very high level of diastereoselectivity. In some cases a single, optically pure, *cis* β-lactam is obtained.[11 d, e, f]

3.2: Present work

We have been studying the Staudinger reaction for the diastereoselective construction of the β-lactam ring for several years.[11] In this chapter, we wish to report our work on the application of isosorbide derived optically pure (3a*R*,4*S*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde, a bicyclic aldehyde, (**3.05**) for the synthesis of variously substituted chiral *cis*-β-lactams *via* the Staudinger reaction. The cycloaddition reaction was found to be highly diastereoselective, in some cases giving a single diastereomer of *cis*-azetidin-2-one in very good yields.

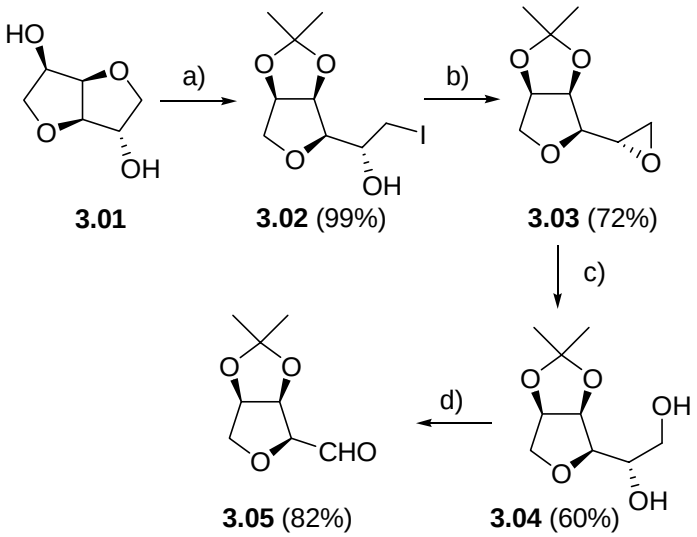
Isosorbide is commercially available in large quantities as a by-product from the starch industry and it is obtained by dehydration of D-sorbitol.[12] Apart from its nitro derivatives being used in medicine as vasodilators,[13] benzamidines as factor Xa inhibitors,[14] and in spite of its commercial availability, it has not been fully exploited in the asymmetric organic syntheses. However, there are some sporadic instances, where it has been transformed to a chiral phase transfer catalyst,[15] chiral aminoalcohols,[16] and also used as a chiral auxiliary.[17] As a part of our ongoing research programme on the application of commercially available inexpensive chiral materials for asymmetric synthesis of β-lactams [10a,c,d,f,18] we have used isosorbide as a chiral source for the synthesis of β-lactams.

3.3: Results and discussion

Isosorbide was treated with two equivalents of iodotrimethylsilane (obtained *in situ* from chlorotrimethylsilane and sodium iodide) in acetone, stereoselectively transformed to

an iodoalcohol **3.02** by a known procedure.[19] It was further converted to epoxide **3.03** by treating with sodium hydride in THF at 0 °C.

Scheme 1.85



Reagetns and conditions: a) TMSCl, NaI, Acetone, rt, 12 h;
b) NaH,THF, rt, 5 h; c) NaOH,THF reflux, 48 h;
d) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 6 h.

The epoxide **3.03** on reaction with aqueous sodium hydroxide in refluxing THF gave diol **3.04** as a white crystalline solid. Our attempt to convert iodoalcohol **3.02** to diol **3.04** directly by the treatment with aqueous sodium hydroxide was unsuccessful. The diol **3.04** on oxidative cleavage with sodium metaperiodate gave (3a*R*,4*S*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (**3.05**), a chiral bicyclic aldehyde, in very good over all yield (Scheme 1.85). We envisaged that the Schiff's base derived from aldehydes **3.05** would give a good diastereoselectivity in the cycloaddition reaction with ketene as it has a hetero-atom on the β-carbon atom and also the rigid *cis*-fused bicyclic ring structure would provide very good facial selectivity. This is clear from the molecular structure shown in Figure 1.[20]

The aldehyde **3.05** was treated with different amine **3.06a-c** to give Schiff's bases **3.07a-c** in excellent yield (Scheme 1.86). These imines were characterized by spectral analysis. The structure **3.07a** was established by IR and ^{1}H NMR data. The IR spectrum of **3.07a** showed a band at 1689 cm^{-1} for C=N stretching.

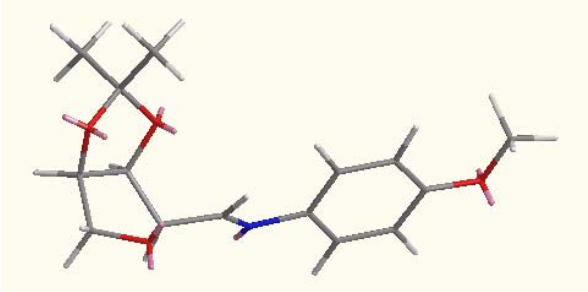


Figure 1. Molecular model of Schiff base **3.07a**

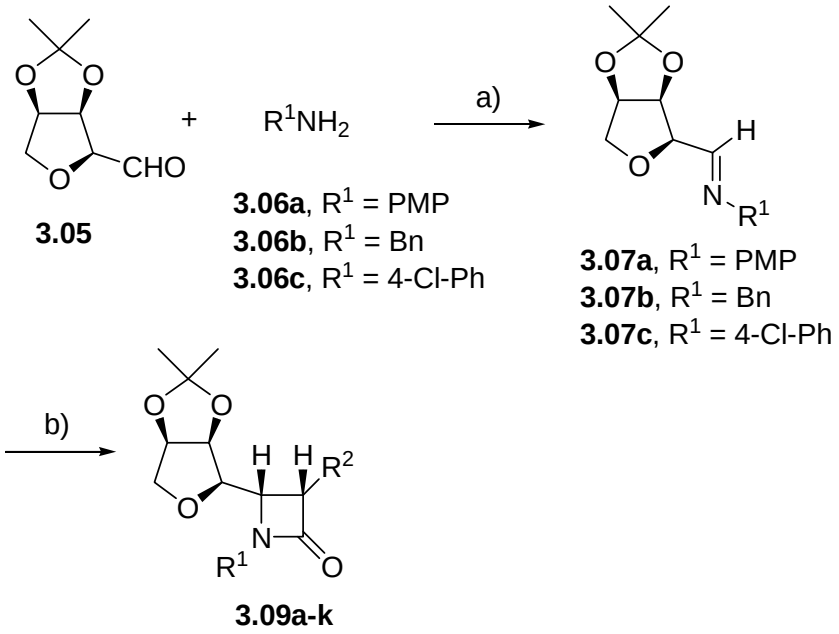
The ^{1}H NMR spectrum showed two singlets at 1.41 and 1.50 ppm corresponding to the two methyl groups. A multiplet appeared at 3.75-3.83 ppm for methylene proton along with a singlet for methoxy proton. The three methine protons showed a multiplet in the range 4.43-4.91 ppm. The aromatic protons showed two multiplet at 6.85-7.06 and 7.43-7.48 ppm respectively for the two protons each. A characteristic doublet appeared at 8.34 ppm for the imine proton (J = 1.6 Hz).

The chiral imines **3.07a-c** derived from isosorbide were then subjected to Staudinger reaction with different acid chloride in presence of triethylamine gave exclusively a single diastereomer of *cis*-β-lactam (**3.09a-k**). No trace of the other diastereomer was detected either in the ^{1}H NMR spectrum or from HPLC analysis of the crude reaction product.[21] The generality of this reaction was established by preparing large number of β-lactams in very good yields and excellent optical purities (Scheme 1.86, Table 1). All the β-lactams were purified by flash column chromatography. The *cis* stereochemistry of the β-lactam ring was ascertained from the coupling constant of the β-lactam ring protons (J = 5.4 Hz for *cis*-isomer). The structures of β-lactams **3.09a-k** were established by IR, ^{1}H NMR and ^{13}C NMR spectral data. We have chosen a representative compound **3.09a** for the spectral discussion.

The IR spectrum of **3.09a** showed a sharp peak at 1745 cm^{-1} which is characteristic of the β-lactam carbonyl group.

The ^{1}H NMR spectrum of **3.09a** showed a singlet at 1.36 and 1.56 ppm which was attributed to the methyl groups of isosorbide moiety. A doublet of doublet appeared at 3.43 ppm (J = 10.9, 3.7 Hz) and 3.70 ppm (J = 7.5, 3.7 Hz) for the methylene group (C11-H_2) attached to oxygen. The methoxy group attached to C-3 carbon appeared as a singlet at 3.68 ppm. A singlet appeared at 3.79 ppm correspond to aromatic methoxy group.

Scheme 1.86



3.05

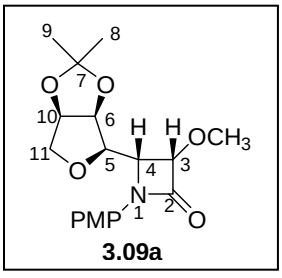
3.06a, R^1 = PMP
3.06b, R^1 = Bn
3.06c, R^1 = 4-Cl-Ph

3.07a, R^1 = PMP
3.07b, R^1 = Bn
3.07c, R^1 = 4-Cl-Ph

3.09a-k

Reagents and conditions: a) $MgSO_4$, CH_2Cl_2, rt, 15 h;
b) R^2OCH_2COCl (**3.08**), Et_3N, CH_2Cl_2, 0 ^oC to rt, 15 h

A doublet showed at 4.09 ppm (J =10.9 Hz) for the methine proton of acetonide (C6-*H*). The C4 proton of β-lactam ring appeared as doublet of doublet at 4.52 ppm (J = 8.7, 5.4 Hz) and C3 proton of β-lactam ring appeared as doublet at 4.69 ppm (J = 5.4 Hz). The coupling constant of 5.4 Hz is typical of a *cis* β-lactam. The methine proton (C10-*H*) attached with methylene proton appeared as multiplet at 4.78 ppm. A doublet of doublet appeared at 4.91 ppm (J = 6.1, 3.7) for the methine proton attached to C5 carbon atom. The ortho coupling aromatic protons appeared as doublets at 6.85 ppm (J = 9.8 Hz) and 7.64 ppm (J = 9.8 Hz).



3.09a

In the ^{13}C NMR spectrum of **3.09a**, showed two peaks at 24.7 and 26.1 ppm which corresponds to two methyl groups. The methoxy carbon attached to C3 carbon appeared at 55.4 ppm. The methoxy carbon attached to aromatic ring showed at 58.9 ppm. The C4 and C3 carbon of the β-lactam ring appeared at 59.8 and 80.8 ppm respectively. The methylene carbon appeared at 72.7 ppm. It was confirmed by DEPT experiment. The other methine carbons of isosorbide moiety appeared at 82.7, 82.8, 83.1 ppm. The quaternary carbon attached to two oxygen atom appeared at 112.2 ppm

Table 1. Synthesis of azetidin-2-ones (**3.09a-k**)

Entry No.	Comp.	R^1	R^2	HPLC[b] Purity	Yield[c] (%)
1	**3.09a**	PMP[a]	OCH_3	98	74
2	**3.09b**	PMP	OBn	99	78
3	**3.09c**	PMP	OPh	97	75
4	**3.09d**	PMP	OAc	97	75
5	**3.09e**	CH_2Ph	OCH_3	95	67
6	**3.09f**	CH_2Ph	OBn	96	70
7	**3.09g**	CH_2Ph	OPh	96	60
8	**3.09h**	CH_2Ph	OAc	96	61
9	**3.09i**	4-Cl-Ph	OCH_3	98	68
10	**3.09j**	4-Cl-Ph	OBn	98	71
11	**3.09k**	4-Cl-Ph	OPh	97	62

[a] PMP = *p*-Methoxyphenyl. [b] Purity was determined by HPLC analysis on Chromsphere Chromsep 5 C-18, 250 x 4.6 mm (5 μm) column; solvent system (v/v): MeCN: H_2O (60:40), flow rate 1.5 mL/min.[c] Isolated yields.

The aromatic carbons showed at 113.9, 119.5 and 131.3. The aromatic carbon attached to the methoxy group appeared at 156.4 ppm. The characteristics peak for β-lactam carbonyl appeared at 165.0 ppm. The mass spectrum of **3.09a** showed a molecular ion, M^+ peak m/z 349, also supporting the structure. This compound gave satisfactory elemental analysis data.

The stereochemistry of the β-lactam ring was confirmed by single crystal X-ray analysis of **3.09a**.

X-ray structure determination of 3.09a:

The absolute stereochemistry of the newly formed chiral centers (C-3 and C-4) was established as 3*S*, 4*R* from the single crystal X-ray analyses of the β-lactam **3.09a** (Figure 2).

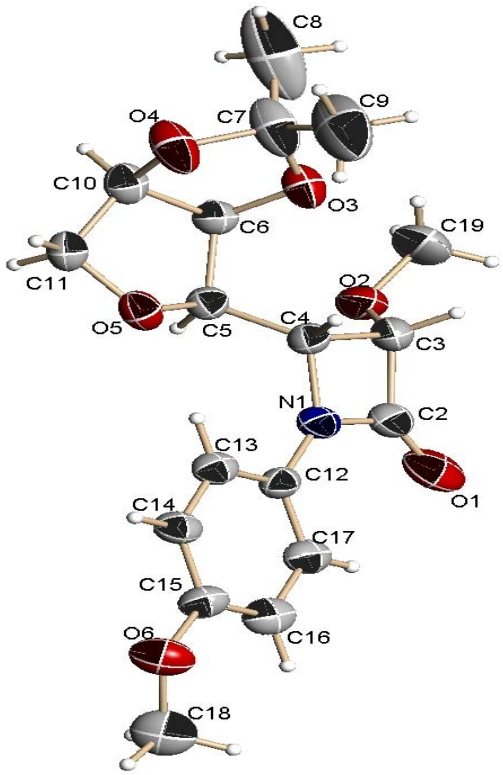


Figure 2. ORTEP diagram for compound **3.09a**

Single crystals of the compound **3.09a** were grown from ethyl acetate and petroleum ether (8:2) solution. Colourless cubes of approximate size 0.45 x 0.40 x 0.40 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, hemisphere data acquisition. Total scans = 3, total frames = 1271, Oscillation / frame -0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.23 to 25.00 deg, completeness to θ of 25.00º is 99.9 %. All the data were corrected for Lorentzian, polarisation and absorption effects. The structure was solved by direct methods using SHELX-97 (ShelxTL) [22] and refined by full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

Table 2: Crystal data and structure refinement for **3.09a**

Empirical formula	$C_{18}\ H_{23}\ N\ O_6$
Formula weight	349.37
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	*a* = 12.4688(7) Å *b* = 10.7999(6) Å *c* = 13.3993(8) Å
Volume	1804.4(2) $Å^3$
Z, Calculated density	4, 1.286 mg m^{-3}
Absorption coefficient	0.097 mm^{-1}
Crystal size	0.45 x 0.40 x 0.40 mm
Reflections collected /unique	3170
Final R indices [I>2σ(I)]	R = 0.0406, Rw = 0.0985

X-ray analysis revealed the stereochemistry of the compound **3.09a** to be 3*S*, 4*R* at C3 and C4 respectively. The same absolute stereochemistry of was 3*S*, 4*R* assigned to all other β-lactam **3.09b-k**.

Conclusion:

In conclusion, we have synthesized bicyclic chiral aldehyde from isosorbide and the imines derived from this aldehyde were used in the synthesis of azetidin-2-ones *via* [2+2] cycloaddition reaction with ketenes. The reaction was highly stereoselective and in most of the cases a single diastereomer was obtained in very good yields. Several optically pure *cis* β-lactams were prepared in excellent yield with very high diastereoselectivity.

Chapter-III

Section B

Asymmetric synthesis of azetidin-2-ones using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral acids

Part of this work has been published in *Tetrahedron*, **2007**, *63*, 3380-3388

3.4: Present work

After establishing the excellent diastereoselectivity in the cycloaddition reaction of imines derived from isosorbide and ketenes, we were also interested to know the diastereoselectivity in the cycloaddition reaction of chiral ketenes derived from isosorbide and achiral imines. It has been shown that the two hydroxyl groups present in isosorbide have different reactivities as they are sterically and electronically different. The C-5 *endo* hydroxyl group is involved in intramolecular H-bonding while the other C-2 *exo* hydroxyl group is free (Figure 3).[23] One can selectively acylate the C-2 hydroxyl groups.[24] We have exploited this reactivity difference and prepared two chiral acetic acid derivatives from isosorbide and used them as ketene precursors in the synthesis of β-lactams using Staudinger cycloaddition reaction with various imines.

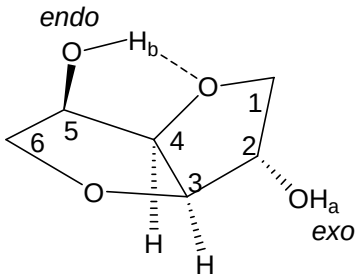


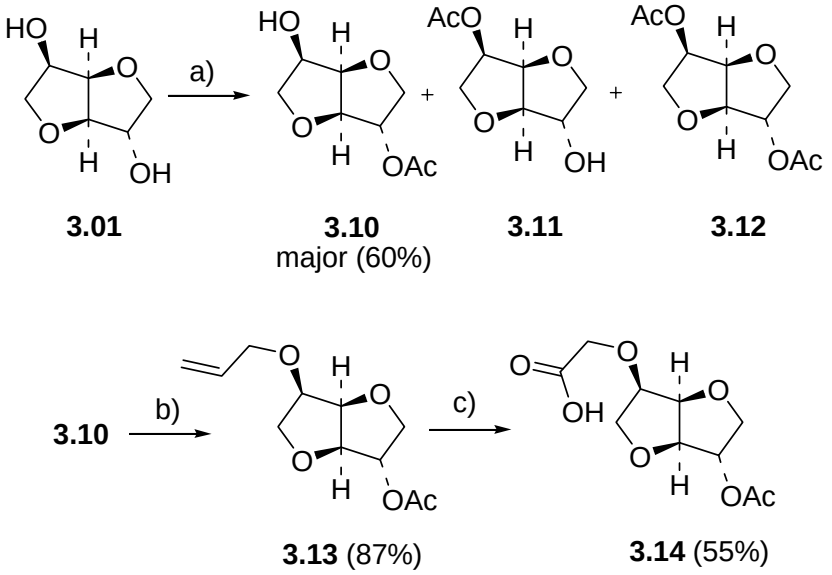
Figure 3. Structure of isosorbide **3.01**

3.5: Results and discussion

The acylation of isosorbide with acetic acid using DCC gave a mixture monoacetates **3.10**, **3.11** and diacetate **3.12** of which the pure major monoacetate **3.10** (60%) was separated by column chromatography. All our efforts to alkylate C-5 *endo*-hydroxyl with ethylbromoacetate using sodium hydride under various reaction conditions were unsuccessful. Therefore, it was reacted with allyl bromide in the presence of silver oxide and calcium sulphate to get the *O*-ally-monoactate-isosorbide **3.13** in very good yield. The *O*-ally-monoactate **3.13** was further oxidized with catalytic $RuCl_3$ and $NaIO_4$ as secondary oxidant in $CH_3CN/CCl_4/H_2O$ (2:2:3) [25] for 12 hours at 0 ˚C to furnish the desired chiral bicyclic acid **3.14** in 53% yield (Scheme 1.87). The structure of chiral bicyclic acid **3.14** was established by IR, ^1H NMR and ^{13}C NMR data.

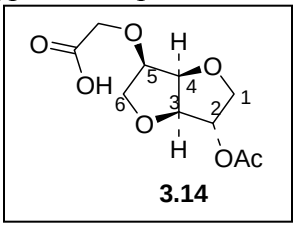
The IR spectrum of **3.14** showed a broad band at 3300 cm^{-1} which was attributed for the hydroxy group of the carboxylic acid. The sharp peak at 1733 cm^{-1} corresponds to acid carbonyl group.

Scheme 1.87



Reagents and Conditions: a) AcOH, CH_2Cl_2/ DMAP/DCC, rt, 3 h; b) Allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark rt; c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, 0 ^oC, 6 h.

The ^1H NMR spectrum of **3.14** showed a singlet at 2.08 ppm which was attributed to the methyl group. The multiplet appeared in the range 3.80-4.29 ppm corresponds to the isosorbide methylene along with methine C5-*H* (seven). A doublet appeared at 4.51 ppm (J = 4.3 Hz) for the methine proton attached to C4 carbon. The methine proton attached to C3 carbon showed a triplet at 4.75 ppm (J = 4.3 Hz). The multiplet showed in the range 5.19-5.20 ppm for methine proton attached to C2 carbon. A broad singlet appeared at 6.90 ppm for the corresponding hydroxy group of acid.



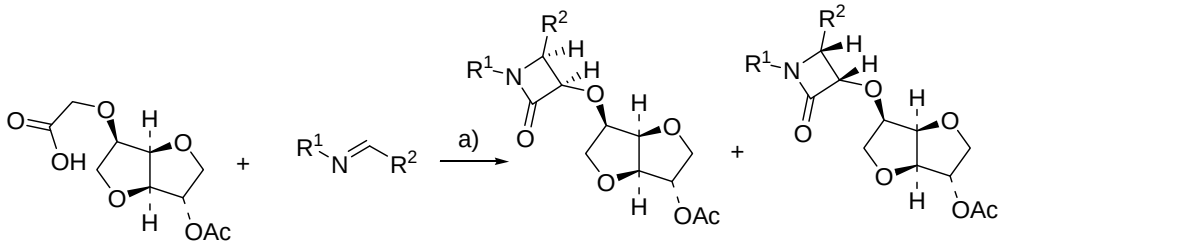
3.14

In the ^{13}C NMR spectrum of **3.14**, the acetate methyl peak appeared at 20.8 ppm. The three methylene carbons appeared at 68.1, 70.9 and 73.8 ppm. It was confirmed from DEPT experiment. The four methine carbons showed at 78.1, 80.5, 81.2 and 86.0 ppm. The acetate carbonyl peak observed at 170.0 ppm and the acid carbonyl peak appeared at 172.5

ppm. The mass spectrum of **3.14** showed a peak at m/z 247 (M^+) also supports the structure. The acid **3.14** also gave satisfactory elemental analysis.

The Staudinger reaction of this *endo*-chiral bicyclic acid **3.14** with imine **3.15a** in presence of Et_3N, triphosgene as an acid activator [26] in dichloromethane at 0 ^{0}C to room temperature for 15 h gave a diastereomeric mixture of β-lactams **3.16a** and **3.17a** (~80:20, from ^{1}H NMR of the crude product) (Scheme 1.88). All our efforts to purify the major diastereomer by flash column were unsuccessful. However, the major diastereomer **3.16a** was obtained in pure form as a white crystalline solid by crystallization from methanol.

Scheme 1.88



3.14

3.15a R^1 = Ph, R^2 = Ph
3.15b R^1 = 4-Cl-Ph, R^2 = Ph

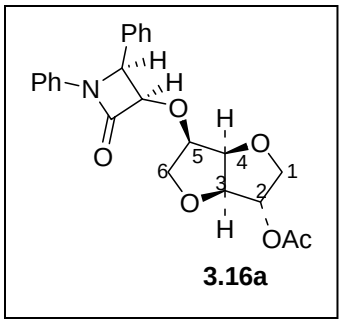
3.16a R^1 = Ph, R^2 = Ph (65%)
3.16b R^1 = 4-Cl-Ph, R^2 = Ph (68%)

3.17a R^1 = Ph, R^2 = Ph
3.17b R^1 = 4-Cl-Ph, R^2 = Ph

Reagents and conditions: a) triphosgene, Et_3N, DCM, 0 ^{o}C to rt, 15 h

The IR spectrum of **3.16a** showed a sharp peak at 1743 cm^{-1} for β-lactam carbonyl and a peak at 1735 cm^{-1} for the acetate carbonyl.

The ^{1}H NMR spectrum of **3.16a** showed a singlet at 2.06 ppm which was attributed to the acetate methyl group. The multiplet appeared at 3.13-3.28 ppm which was attributed to the methylene and methine protons of isosorbide (three protons). A doublet of doublet appeared at 3.74 ppm (J = 10.5, 5.4 Hz) for a methine proton attached to C3 carbon. A broad doublet appeared at 3.95 ppm (J = 2.8Hz) for isosorbide ring methylene protons (two protons). One of the β-lactam proton appeared as doublet at 4.33 ppm (J = 5.4Hz). The *cis* stereochemistry of the β-lactam ring was ascertained from the coupling constant of the ring protons (J = 5.4 Hz for *cis*-isomer). A triplet was seen at 5.07 ppm (J = 2.4Hz) corresponds to the methine proton attached to the C2 carbon. A doublet of doublet appeared at 5.21 ppm (J = 8.2, 5.4 Hz) which was corresponds to methine proton attached to C3 carbon and other β-lactam



3.16a

proton (two protons). All the aromatic protons appeared as multiplet in the range 7.03-7.43 ppm.

The ^{13}C NMR spectrum of **3.16a** showed the acetate methyl peak appeared at 20.9 ppm. The one of the carbons of β-lactam ring appeared at 61.8 ppm. The two methylene carbons appeared at 70.6 and 73.7 ppm. It was confirmed from DEPT experiment. The other carbon of β-lactam ring appeared at 86.2 ppm. The methine carbons of isosorbide ring appeared at 78.3, 78.8, 81.0 and 83.1 ppm. The aromatic carbons were seen at 117.5, 124.5, 128.1, 128.6, 129.1, 133.4 and 137.1 ppm. The characteristics β-lactam carbonyl peak appeared at 163.3 ppm. The acetate carbonyl peak observed at 170.0 ppm. The mass spectrum of **3.16a** showed a molecular ion peak at m/z 410 (M^+) also supports the structure. The chiral β-lactam **3.16a** also gave satisfactory elemental analysis.

The stereochemistry of the β-lactam ring was confirmed by single crystal X-ray analysis of **3.16a**.

X-ray structure determination of 3.16a:

The absolute stereochemistry of the newly formed chiral centers (C-3 and C-4) was established as 3*R*, 4*S* from the single crystal X-ray analyses of the β-lactam **3.16a** (Figure 4).

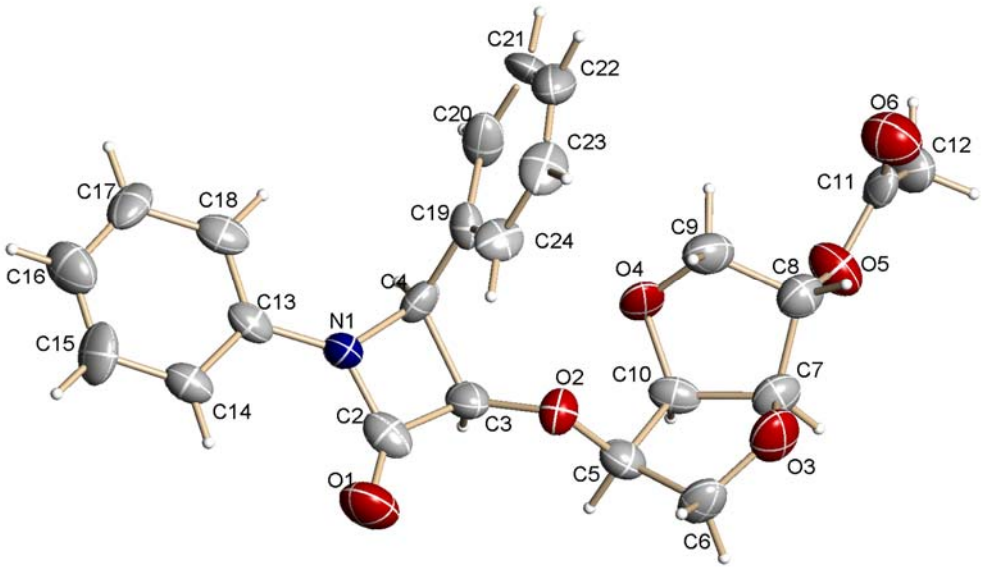


Figure 4. ORTEP diagram for compound **3.16a**

Single crystals of the compound **3.16a** were grown by recrystallization through methanol. Data were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 23.49°. The structure was solved by direct methods using SHELXTL.[22] Hydrogen atoms were geometrically fixed. The refinements were carried out using SHELXL-97.

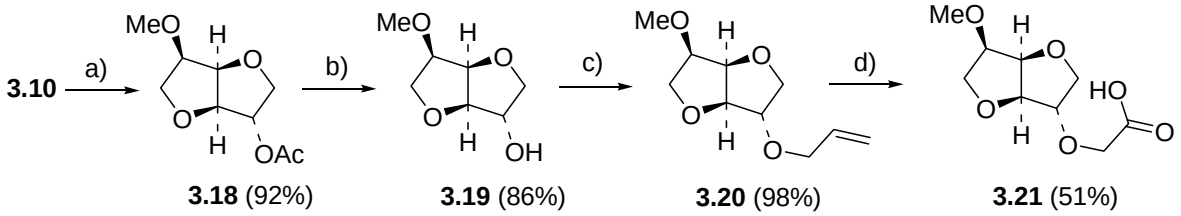
Table 3: Crystal data and structure refinement for **3.16a**

Empirical formula	C_{23} H_{23} N O_6
Formula weight	409.42
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	*a* = 6.623(2) Å
	b = 9.627(3) Å
	c = 32.182(10) Å
Volume	2052.0(12) $Å^3$
Z, Calculated density	4, 1.325 mg m^{-3}
Absorption coefficient	0.096 mm^{-1}
Crystal size	0.33 x 0.02 x 0.02 mm
F(000)	864
Reflections collected /unique	3039
Final R indices [I>2σ(I)]	R = 0.0898, Rw = 0.1746

As there was moderate selectivity in the cycloaddition reaction of ketenes derived from *endo*-acid **3.14**, we also wanted to examine the selectivity with acid **3.21** possessing an *exo*-acetic acid side chain on C-2 oxygen of the isosorbide. This *exo*-acid **3.21** can be easily prepared by a synthetic manipulation as shown in Scheme 1.89. The monoacetate **3.10** was methylated using methyl iodide and Ag_2O in the presence of calcium sulfate to get methoxyacetate **3.18** in 92% yield. This methoxyacetate **3.18** was further hydrolyzed with ethanolic potassium hydroxide to give methoxyalcohol **3.19**, which was alkylated with allyl bromide under similar reaction conditions used in the synthesis of **3.13** to get an allyl ether

3.20 in excellent yield. The allyl ether **3.20** was oxidized with catalytic $RuCl_3$ and $NaIO_4$ as secondary oxidant in $CH_3CN/CCl_4/H_2O$ but we got very poor yield of the bicyclic acid **3.21**. Therefore, it was oxidized with $KMnO_4$ in acetone in the presence of K_2CO_3 to get chiral bicyclic *exo*-acid **3.21** in 51% yield.

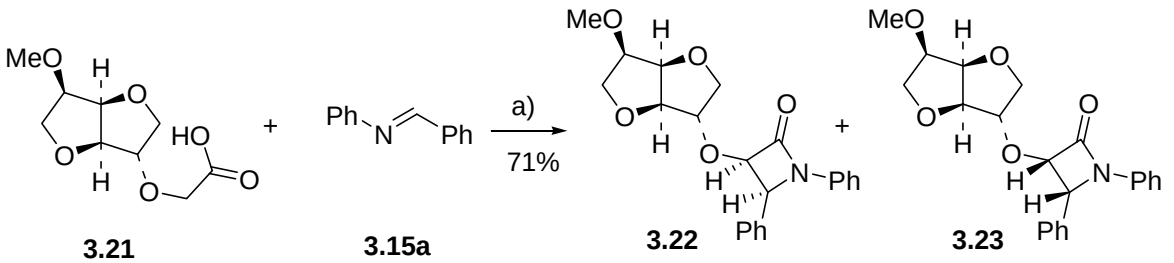
Scheme 1.89



Reagents and conditions: a) CH_3I, Ag_2O, $CaSO_4$, 2 days, dark rt, b) KOH, EtOH, 30 min, 50 ^{0}C, c) Allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark rt, d) $KMnO_4$, K_2CO_3, Acetone, rt, 3 h.

The asymmetric Staudinger reaction of chiral bicyclic acid **3.21** with achiral imine **3.15a** afforded an inseparable diastereomeric mixture of two *cis*-β-lactams **3.22** and **3.23** (Scheme 1.90). In this case there was no diastereoselectivity in the β-lactam formation (~50:50 from ^{1}H NMR of the crude product).

Scheme 1.90



Reagents and conditions: a) triphosgene, Et_3N, DCM, 0 ^{o}C to rt, 15 h

All our attempts to separate these isomers either by flash column chromatography or recrystallization were unsuccessful. A low diastereoselectivity in the β-lactam formation in case of *exo*-ketene was expected, as there is no facial differentiation in the transition state during the ketene-imine cycloaddition reaction. However, in case of *endo*-ketene generated from acid **3.14**, the rigid bicyclic framework of the isosorbide has considerable effect on the diastereoselectivity in the cycloaddition reaction with imine.

Conclusion:

In conclusion, we have synthesized two chiral bicyclic acids from isosorbide and these acids were used in the synthesis of azetidin-2-ones *via* [2+2] cycloaddition reaction with achiral imines. The *endo*-chiral ketene derived from isosorbide also showed diastereoselectivity in the Staudinger cycloaddition reaction. However, no selectivity was observed when *exo*-chiral ketene was used in the cycloaddition reaction.

3.6: Experimental

3.6.1. (*S*)-1-((3a*R*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethane-1,2-diol (3.04): To the solution of epoxide **3.03** (0.5 g, 2.66 mmol) in a mixture of THF (10 mL) and water (5mL) was added aqueous NaOH (1M, 3.5 mL) and refluxed for 48 h. The THF was removed then under reduced pressure and the aqueous layer acidified dropwise with dilute HCl (pH = 2) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give diol **3.04** as a white solid (0.330 g, 60%).

MP	**:**	89-90 °C
IR ($CHCl_3$)	**:**	3433, 1382, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.32 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 2.45 (2H, bs, O*H*), 3.47-3.54 (2H, m, C*H*$_2$OH), 3.79 (2H, t, *J* = 3.6 Hz, CHC*H*$_2$O), 4.06-4.13 (2H, m, OC*H*C*H*OH), 4.72 (1H, dd, *J* = 6.2, 3.6 Hz, OC*H*CH), 4.81(1H, dd, *J* = 6.2, 3.6 Hz, OC*H*CH$_2$O)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 24.4, 25.8, 63.5, 70.7, 72.6, 80.6, 81.3, 82.2, 112.4
MS (m/z)	**:**	204 (M^+)
Analysis ($C_9H_{16}O_5$)	**:**	Calculated: C, 52.93; H, 7.89 Observed: C, 52.84; H, 7.82
Optical rotation		$[\alpha]^{26}_D$ -40.0 (*c* 1.0, $CHCl_3$)

3.6.2. (3a*R*,4*S*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxole-4-carbaldeyhde (3.05): To a vigorously stirred suspension of chromatographic grade silica (3.3 g) in dichloromethane (15 mL) in a 100 mL flask was added aqueous solution (0.65 M) of $NaIO_4$ (3.5 mL) dropwise with stirring. Diol **3.04** (0.330 g, 1.61 mmol) in dichloromethane (15 mL) was then added drop-wise and the reaction was stirred at room temperature. The reaction was stirred until the disappearance of the starting material (5 h, by TLC). The

reaction mixture was filtered and the filtrate was washed with water (10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to afford pure bicyclic aldehyde **3.05** as oil (0.228 g, 82%).

IR ($CHCl_3$)	**:**	1737, 1350, 1215 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.31 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 3.63 (1H, dd, *J* = 10.7, 3.6 Hz, CH$_a$*H*$_b$OH), 3.97 (1H, d, *J* = 4.8 Hz, C*H*$_a$H$_b$OH), 4.23 (1H, d, *J* = 10.7 Hz, OC*H*CH$_2$O), 4.86 (1H, dd, *J* = 5.9, 3.6 Hz, OC*H*CH), 5.03 (1H, dd, *J* = 5.9, 4.8 Hz, C*H*CHO), 9.67 (1H, s, C*H*O)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 24.5, 25.8, 73.3, 80.7, 81.8, 85.9, 113.2, 198.4
MS (m/z)	**:**	172 (M^+)
Analysis ($C_8H_{12}O_4$)	**:**	Calculated: C, 55.80; H, 7.02 Observed: C, 55.73; H, 6.96
Optical rotation		$[\alpha]^{26}_D$ -97.1 (*c* 0.2, $CHCl_3$)

3.6.3a.(*E*)-*N*-(((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene)-4-methoxybenzenamine (3.07a): To a solution of aldehdye **3.05** (0.210 g, 1.22 mmol) in dichloromethane (20 mL) and anhydrous $MgSO_4$ (0.307 g, 2.44 mmol) was added *p*-anisidine (0.165 g, 1.34 mmol) in dichloromethane (10 mL) at room temperature and the mixture stirred for 15 h. Then the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give imine **3.07a** (0.320 g, 94%) as brown oil.

IR ($CHCl_3$)	**:**	1689, 1600, 1500, 1244 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.41 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 3.75-3.83 (5H, m, CHC*H*$_2$O and OC*H*$_3$), 4.43-4.91 (3H, m, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 6.85-7.06 (2H, m, Ar-*H*), 7.43-7.48 (2H, m, Ar-*H*), 8.34 (1H, d, *J* = 1.6 Hz,

OCHCHC*H*=N)

3.6.3b.(*E*)-*N*-(((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene) (phenyl methanamine) (3.07b):

Yield 95 %; pale yellow oil.

IR ($CHCl_3$) : 1683, 1558, 1456, 1217 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.28 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.51 (1H, dd, *J* = 10.8, 3.2 Hz, CHCH_aH$_b$O), 3.82 (2H, s, CH_2Ph); 3.96-4.11 (1H, m, CHCH$_a$$H_b$O), 4.55-4.85 (3H, m, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 7.15-7.30 (5H, m, Ar-*H*), 7.89 (1H, d, *J* = 1.6 Hz, OCHCHC*H*=N)

3.6.3c.(*E*)-4-chloro-*N*-(((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene) benzenamine (3.07c):

Yield 96 %; yellow oil.

IR ($CHCl_3$) : 1681, 1600, 1495, 1269 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.45 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.31-4.95 (5H, m, CHCH_2O, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 6.53-6.68 (2H, m, Ar-*H*), 7.09-7.33 (2H, m, Ar-*H*), 8.35 (1H, d, *J* = 1.6 Hz, OCHCHC*H*=N)

The imines **3.07a-c** were used without purification for the next step.

3.6.4a. Typical procedure for the synthesis of (3*S*, 4*R*)-4-((3a*S*, 4*R*, 6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-3-methoxy-1- (4-methoxyphenyl) azetidin-2-one (3.09a): A solution of the methoxyacetyl chloride (0.188 g, 1.73 mmol) in dichloromethane (10 mL) was added to a cooled solution of imine **3.07a** (0.320 g, 1.15 mmol) and triethylamine (0.350 g, 3.46 mmol) in anhydrous dichloromethane (15 mL) at 0 °C. It was then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was then diluted with dichloromethane (10 mL) and washed successively with water (2 x 10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product on purification by

flash column chromatography using 20% ethyl acetate/petroleum ether as an eluent gave a single diastereomer, *cis*-β-lactam **3.09a** as white crystalline solid (0.300 g, 74%). The R_f value (20% Ethyl acetate/Petroleum ether) is 0.52.

MP	**:**	155-156 °C
IR ($CHCl_3$)	**:**	1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.36 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$), 3.43 (1H, dd, *J* = 10.9, 3.7 Hz, C*H*$_a$H$_b$OCH), 3.68 (3H, s, OC*H*$_3$), 3.70 (1H, dd, *J* = 7.5, 3.7 Hz, CH$_a$*H*$_b$OCH), 3.79 (3H, s, PhOC*H*$_3$), 4.09 (1H, d, *J* = 10.9 Hz, OCHC*H*), 4.52 (1H, dd, *J* = 8.7, 5.4 Hz, C$_4$*H*), 4.69 (1H, d, *J* = 5.4 Hz, C$_3$*H*), 4.78 (1H, m, OC*H*CH$_2$), 4.91 (1H, dd, *J* = 6.1, 3.7 Hz, OC*H*CH), 6.85 (2H, d, *J* = 9.8 Hz, Ar-*H*), 7.64 (2H, d, *J* = 9.8 Hz, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 24.7, 26.1, 55.4, 58.9, 59.8, 72.7, 80.8, 82.7, 83.1, 112.2, 113.9, 119.5, 131.3, 156.4, 165
MS (m/z)	**:**	349 (M^+)
Analysis ($C_{18}H_{23}NO_6$)	**:**	Calculated: C, 61.86; H, 6.64; N, 4.01 Observed: C, 61.70; H, 6.57; N, 4.00
Optical rotation		$[\alpha]^{26}_D$ -138.8 (*c*, 0.8, $CHCl_3$)

Following the similar procedure other *cis*-β-lactam **3.09b-k** were synthesized.

3.6.4b.(3*S*,4*R*)-3-(benzyloxy)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(-4-methoxyphenyl) azetidin-2-one (3.09b): The benzyloxyacetyl chloride (0.417 g, 2.26 mmol) on treatment with imine **3.07a** (0.418 g, 1.50 mmol) in presence of triethylamine (0.452 g, 4.52 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (20% ethyl acetate/petroleum ether) to give colourless oil, **3.09b** (0.480 g, 78%). R_f (20% ethyl acetate/petroleum ether) 0.47.

IR ($CHCl_3$)	**:**	1751 cm^{-1}
^{1}H NMR	**:**	δ_H 1.39 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 3.41 (1H, dd, *J* = 10,

($CDCl_3$)		3.3 Hz, CH_aH$_b$OCH), 3.71-3.77 (1H, m, CH$_a$$H_b$OCH), 3.79
(200 MHz)		(3H, s, PhOCH_3), 4.12 (1H, d, J = 11.5 Hz, OCH_aH$_b$Ph), 4.55 (1H, d, J = 5.4 Hz, C$_4$$H$), 4.75 (1H, dd, J = 5.4, 4.4 Hz, C$_3$$H$), 4.85 (1H, d, J = 11.5 Hz, OCH$_a$$H_b$Ph), 4.92-5.04 (3H, m, OCHCH$_2$, OCHCH, OCHCH), 6.86 (2H, d, J = 8.8 Hz, Ar-H), 7.35-7.41 (5H, m, Ar-H), 7.67 (2H, d, J = 8.8 Hz, Ar-H)
^{13}C NMR	**:**	δ_C 24.6, 26.0, 55.3, 59.0, 72.5, 73.6, 80.7, 83.0, 112.0, 113.8,
($CDCl_3$)		119.4, 127.7, 127.9, 128.4, 131.3, 137.2, 156.3, 165
(50 MHz)		
MS (m/z)	**:**	425 (M^+)
Analysis	**:**	Calculated: C, 67.74; H, 6.40; N, 3.29
($C_{24}H_{27}NO_6$)		Observed: C, 67.53; H, 6.28; N, 3.12
Optical rotation		$[\alpha]^{26}_D$ -118.1 (*c*, 1, $CHCl_3$)

3.6.4c. (3*S*,4*R*)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3.09c): The phenoxyacetyl chloride (0.399 g, 2.34 mmol) on treatment with imine **3.07a** (0.433 g, 1.56 mmol) in presence of triethylamine (0.473 g, 4.68 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (15% ethyl acetate/petroleum ether) to give white solid, **3.09c** (0.481 g, 75%). R_f (15% Ethyl acetate/Petroleum ether) 0.66.

MP	**:**	177-178 °C
IR ($CHCl_3$)	**:**	1747 cm^{-1}
^{1}H NMR	**:**	δ_H 1.29 (3H, s, CH_3), 1.56 (3H, s, CH_3), 3.49 (1H, dd, J = 10,
($CDCl_3$)		3.5, Hz, CH_aH$_b$OCH), 3.81 (3H, s, PhOCH$_3$), 3.91 (1H, dd, J =
(200 MHz)		8.7, 3.5 Hz, CH$_a$$H_b$OCH), 4.12 (1H, d, J = 10.8 Hz, OCHCH), 4.71-4.82 (2H, m, OCHCH$_2$, OCHCH), 4.95 (1H, dd, J = 5.4, 3.6 Hz, C$_4$$H$), 4.46 (1H, d, J = 5.4 Hz, C$_3$$H$), 6.88 (2H, d, J = 8.6 Hz, Ar-H), 7.35-7.41 (5H, m, Ar-H), 7.72 (2H, d, J = 8.6 Hz, Ar-H)

^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 24.3, 26.0, 55.3, 58.7, 72.8, 80.0, 80.7, 82.8, 112.0, 113.8, 116.2, 119.5, 122.5, 129.4, 131.1, 156.4, 157.8, 163.4
MS (m/z)	**:**	411 (M^+)
Analysis ($C_{23}H_{25}NO_6$)	**:**	Calculated: C, 67.13; H, 6.13; N, 3.41 Observed: C, 67.09; H, 6.08; N, 3.28
Optical rotation		$[\alpha]^{26}_D$ -224.3 (c, 1.2, $CHCl_3$)

3.6.4d. (2*R*,3*S*)-2-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (9d): The acetoxyacetyl chloride (0.214 g, 1.57 mmol) on treatment with imine **3.07a** (0.290 g, 1.05 mmol) in presence of triethylamine (0.317 g, 3.14 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (20% ethyl acetate/petroleum ether) to give thick oil, **3.09d** (0.295 g, 75%). R_f (20% ethyl acetate/petroleum ether) 0.38.

IR (Neat)	**:**	1750 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.31 (3H, s, C*H*$_3$), 1.52 (3H, s, C*H*$_3$), 2.19 (3H, s, C*H*$_3$COO), 3.5 (1H, dd, *J* = 11, 3 Hz, C*H*$_a$H$_b$OCH), 3.44-3.79 (1H, m, CH$_a$*H*$_b$OCH and 3H, s, PhOC*H*$_3$), 4.31 (1H, d, *J* = 10.8 Hz, OCHC*H*), 4.59-4.63 (1H, m, OC*H*CH$_2$), 4.72-4.89 (2H, m, OC*H*CH and C$_4$*H*), 6.24 (1H, d, *J* = 5.4 Hz, C$_3$*H*), 6.85 (2H, d, *J* = 8.8 Hz, Ar-*H*), 7.65 (2H, d, *J* = 8.8 Hz, Ar-*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 20.6, 24.4, 25.9, 55.3, 58.9, 72.3, 72.7, 80.6, 82.8, 112.5, 113.9, 119.5, 130.9, 156.6, 162.3, 168.3
MS (m/z)	**:**	377 (M^+)
Analysis ($C_{19}H_{23}NO_7$)	**:**	Calculated: C, 60.47; H, 6.14; N, 3.71 Observed: C, 60.38; H, 6.08; N, 3.65
Optical rotation		$[\alpha]^{26}_D$ -134.1 (c, 0.9, $CHCl_3$)

3.6.4e. (3*S*,4*R*)-1-benzyl-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro [3,4-*d*][1,3]dioxol-4-yl)-3-methoxyazetidin-2-one (3.09e): The methoxyacetyl chloride (0.215 g, 1.98 mmol) on treatment with imine **3.07b** (0.346 g, 1.32 mmol) in presence of triethylamine (0.406 g, 3.97 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (10% ethyl acetate/petroleum ether) to give thick oil, **3.09e** (0.295 g, 67%). R_f (10% ethyl acetate/petroleum ether) 0.33.

IR (Neat)	**:**	1751 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.30 (3H s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 3.42 (1H, dd, *J* = 10.8, 3.4 Hz, C*H*$_a$H$_b$OCH), 3.53-3.58 (1H, m, CH$_a$*H*$_b$OCH), 3.59 (3H, s, OC*H*$_3$), 3.91 (1H, dd, *J* = 8.8, 3.4 Hz, OCHC*H*), 4.04-4.09 (1H, m, OC*H*CH$_2$), 4.25 (1H, d, *J* = 14 Hz, NC*H*$_a$H$_b$Ph), 4.51 (1H, d, *J* = 4.5 Hz, C$_3$*H*), 4.70 (1H, d, *J* = 14 Hz, NCH$_a$*H*$_b$Ph), 4.74-4.76 (2H m, OC*H*CH and C$_4$*H*), 5.25-5.31 (5H, m, Ar-*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 24.8, 25.9, 45.1, 56.6, 59.4, 72.8, 80.5, 81.0, 83.0, 83.3, 111.3, 127.4, 128.5, 128.8, 167.2
MS (m/z)	**:**	333 (M^+)
Analysis	**:**	Calculated: C, 64.84; H, 6.95; N, 4.20
($C_{18}H_{23}NO_5$)		Observed: C, 64.72; H, 6.88; N, 4.13
Optical rotation		$[\alpha]^{26}_D$ -65.0 (*c*, 1.0, $CHCl_3$)

3.6.4f.(3*S*,4*R*)-1-benzyl-3-(benzyloxy)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)azetidin-2-one (3.09f): The benzyloxyacetyl chloride (0.233 g, 1.26 mmol) on treatment with imine **3.07b** (0.220 g, 0.842 mmol) in presence of triethylamine (0.255 g, 2.52 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (15% ethyl acetate/petroleum ether) to give thick oil, **3.09f** (0.241 g, 70%). R_f (15% ethyl acetate/petroleum ether) 0.32.

IR (Neat)	**:**	1757 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.31 (3H, s, CH_3), 1.40 (3H, s, CH_3), 3.43 (1H, dd, *J* = 11.7, 3.3 Hz, CH_aH$_b$OCH), 3.65 (1H, dd, *J* = 8.3, 3.3 Hz, CH$_a$$H_b$OCH), 3.95 (1H, dd, *J* = 8.3, 5.1 Hz, OCHC*H*), 4.09 (1H, d, *J* = 10.6 Hz, NCH_aH$_b$Ph), 4.25 (1H, d, *J* = 14.6 Hz, OCH_aH$_b$Ph), 4.71-4.77 (5H, m, C$_3$*H*, C$_4$*H*, OC*H*CH$_2$, OC*H*CH, NCH$_a$$H_b$Ph), 4.92 (1H, d, *J* = 11.6 Hz, OCH$_a$$H_b$Ph), 7.26-7.37 (10H, m, Ar-*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 24.7, 25.9, 45.1, 56.8, 72.7, 73.1, 80.5, 80.9, 81.3, 83.0, 112.1, 127.4, 127.6, 127.8, 128.2, 128.5, 128.7, 136.0, 137.7, 167.3
MS (m/z)	**:**	409 (M^+)
Analysis	**:**	Calculated: C, 70.38; H, 6.65; N, 3.42
($C_{24}H_{27}NO_5$)		Observed: C, 70.29; H, 6.54; N, 3.33
Optical rotation		$[\alpha]^{26}_D$ -58.0 (*c*, 1.0, $CHCl_3$);

3.6.4g. (3*S*, 4*R*)-1-benzyl-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro [3,4-*d*][1,3]dioxol-4-yl)-3-phenoxyazetidin-2-one (3.09g): The phenoxyacetyl chloride (0.480 g, 2.81 mmol) on treatment with imine **3.07b** (0.490 g, 1.87 mmol) in presence of triethylamine (0.568 g, 5.63 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (5% acetone/petroleum ether) to give thick oil, **3.09f** (0.444 g, 60%). R_f (5% Acetone/Petroleum ether) 0.30.

IR (Neat)	**:**	1758 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.23 (3H, s, CH_3), 1.40 (3H, s, CH_3), 3.48 (1H, dd, *J* = 10.8, 3.4 Hz, CH_aH$_b$OCH), 3.78 (1H, dd, *J* = 8.8, 3.4 Hz, CH$_a$$H_b$OCH), 4.10-4.19 (2H, m, OCHC*H* and OC*H*CH$_2$), 4.34 (1H, d, *J* = 14.5 Hz, NCH_aH$_b$Ph), 4.56-4.58 (1H, m, NCH$_a$$H_b$Ph), 4.71-4.82 (2H, m, C$_4$*H* and OC*H*CH), 5.26 (1H, d, *J* = 5.5 Hz, C$_3$*H*), 6.90-7.39 (10H, m, Ar-*H*)

^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 24.6, 25.9, 30.8, 45.5, 56.5, 73.0, 80.5, 81.0, 82.7, 112.2, 114.6, 116.0, 122.0, 122.2, 127.6, 128.5, 128.8, 137.7, 165.3
MS (m/z)	**:**	395 (M^+)
Analysis ($C_{23}H_{25}NO_5$)	**:**	Calculated: C, 69.84; H, 6.38; N, 3.54 Observed: C, 69.73; H, 6.29; N, 3.44
Optical rotation		$[\alpha]^{26}_D$ -70.0 (*c*, 1.0, $CHCl_3$)

3.6.4h.(2*R*,3*S*)-1-benzyl-2-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-4-oxoazetidin-3-yl acetate (3.09h): The acetoxyacetyl chloride (0.353 g, 2.58 mmol) on treatment with imine **3.07b** (0.450 g, 1.72 mmol) in presence of triethylamine (0.522 g, 5.17 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (15% ethyl acetate/petroleum ether) to give thick oil, **3.09h** (0.379 g, 61%). R_f (15% Ethyl acetate/Petroleum ether) 0.33.

IR (Neat)	**:**	1747 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 1.27 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 2.14 (3H, s, C*H*$_3$COO), 3.48 (1H, dd, *J* = 10.7, 3.5 Hz, C*H*$_a$H$_b$OCH), 3.69 (1H, dd, *J* = 8.8, 3.5 Hz, CH$_a$*H*$_b$OCH), 4.10 (1H, dd, *J* = 8.8, 5.2 Hz, OCHC*H*), 4.25 (1H, d, *J* = 14.6 Hz, NC*H*$_a$H$_b$Ph), 4.40 (1H, d, *J* = 14.6 Hz, NCH$_a$*H*$_b$Ph), 4.61-4.78 (3H, m, C$_4$*H*, OC*H*CH and OC*H*CH$_2$), 5.95 (1H, d, *J* = 5.1 Hz, C$_3$*H*), 7.27-7.37 (5H, m, Ar-*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 20.5, 24.5, 25.8, 45.4, 56.1, 72.7, 73.9, 80.3, 81.0, 82.6, 112.6, 127.6, 128.5, 128.7, 164.5, 168.6
MS (m/z)	**:**	361 (M^+)
Analysis ($C_{19}H_{23}NO_6$)	**:**	Calculated: C, 63.15; H, 6.41; N, 3.88 Observed: C, 63.07; H, 6.26; N, 3.78

Optical rotation $[\alpha]^{26}_{D}$ -37.7 (*c*, 1.1, $CHCl_3$)

3.6.4i.(3*S*,4*R*)-1-(4-chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-3-methoxyazetidin-2-one (3.09i): The methoxyacetyl chloride (0.214 g, 1.98 mmol) on treatment with imine **3.07c** (0.371 g, 1.32 mmol) in presence of triethylamine (0.400 g, 3.96 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (10% ethyl acetate/petroleum ether) to give thick oil, **3.09i** (0.316 g, 68%). R_f (10% ethyl acetate/petroleum ether) 0.44.

IR ($CHCl_3$)	**:**	1749 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.28 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$), 3.35 (1H, dd, *J* = 10.9, 3.4 Hz, C*H*$_a$H$_b$OCH), 3.60 (3H, s, OC*H*$_3$), 3.63-3.68 (1H, m, CH$_a$*H*$_b$OCH), 4.12 (1H, d, *J* = 10.9 Hz, OCHC*H*), 4.45 (1H, dd, *J* = 8.7, 5.4, Hz, C$_4$*H*), 4.62 (1H, d, *J* = 5.4 Hz, C$_3$*H*), 4.69-4.74 (1H, m, OC*H*CH), 4.80-4.89 (1H, m, OC*H*CH$_2$), 7.18 (2H, d, *J* = 8.6 Hz, Ar-*H*), 7.59 (2H, d, *J* = 8.6 Hz, Ar-*H*)
^{13}C NMR ($CDCl_3$) (50 MHz)	**:**	δ_C 24.6, 26.1, 59.0, 59.9, 72.7, 80.7, 80.8, 82.8, 83.0, 112.2, 119.4, 128.7, 129.3, 136.3, 165.5
MS (m/z)	**:**	353 (M^+)
Analysis	**:**	Calculated: C, 57.77; H, 5.71; N, 3.97; Cl, 9.90
($C_{17}H_{20}NO_5Cl$)		Observed: C, 57.68; H, 5.61; N, 3.87; Cl, 9.79
Optical rotation		$[\alpha]^{26}_{D}$ -128.0 (*c*, 0.5, $CHCl_3$)

3.6.4j.(3*S*,4*R*)-3-(benzyloxy)-1-(4-chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro [3,4-*d*][1,3]dioxol-4-yl)azetidin-2-one (3.09j): The benzyloxyacetyl chloride (0.110 g, 0.60 mmol) on treatment with imine **3.07c** (0.112 g, 0.40 mmol) in presence of triethylamine (0.120 g, 1.20 mmol) at 0 °C gave the crude product which was

separated by flash column chromatography (10% ethyl acetate/petroleum ether) to give thick oil, **3.09j** (0.121 g, 71%). R_f (10% ethyl acetate/petroleum ether) 0.28.

IR ($CHCl_3$)	**:**	1755 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.30 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.33 (1H, dd, J = 11, 3.4 Hz, CH_aH$_b$OCH), 3.62-3.69 (2H, m, CH$_a$$H_b$OCH, OCHC$H$), 4.01 (1H, d, J = 9.6 Hz, OCH_aH$_b$Ph), 4.47-4.69 (1H, m, OCH$_a$$H_b$Ph), 4.67-4.72 (1H, m, OCHCH), 4.78-4.94 (3H, m, C_3H, C_4H and OCHCH$_2$), 7.16-7.58 (7H, m, Ar-H), 7.60 (2H, d, J = 8.6 Hz, Ar-H)
^{13}C NMR ($CDCl_3$) (100 MHz)	**:**	δ_C 24.6, 26.1, 59.2, 72.6, 73.8, 80.7, 80.8, 83.0, 112.1, 119.4, 127.8, 128.0, 128.1, 128.5, 128.7, 129.3, 136.3, 137.0, 165.6
MS (m/z)	**:**	429 (M^+)
Analysis ($C_{23}H_{24}NO_5Cl$)	**:**	Calculated: C, 64.32; H, 5.64; N, 3.26; Cl, 8.15 Observed: C, 64.21; H, 5.73; N, 3.19; Cl, 8.09
Optical rotation		$[\alpha]^{26}_D$ -117.1 (c, 0.7, $CHCl_3$)

3.6.4k.(3*S*,4*R*)-1-(4-chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxol-4-yl)-3-phenoxyazetidin-2-one (3.09k): The phenoxyacetyl chloride (0.263 g, 1.54 mmol) on treatment with imine **3.07c** (0.290 g, 1.54 mmol) in presence of triethylamine (0.312 g, 3.09 mmol) at 0 °C gave the crude product which was separated by flash column chromatography (10% ethyl acetate/petroleum ether) to give thick oil, **3.09k** (0.265 g, 62%). R_f (10% ethyl acetate/petroleum ether) 0.34.

IR ($CHCl_3$)	**:**	1764 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.23 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.43 (1H, dd, J = 10.0, 3.6 Hz, CH_aH$_b$OCH), 3.84 (1H, dd, J = 10.0, 3.6 Hz, CH$_a$$H_b$OCH), 4.08 (1H, d, J = 11.0 Hz, , OCHCH), 4.69-4.76 (2H, m, OCHCH and OCHCH$_2$), 4.90 (1H, dd, J = 5.8, 3.6

		Hz, C_4H), 5.41 (1H, d, J = 5.8 Hz, C_3H), 6.77-7.31 (7H, m, Ar-H), 7.66 (2H, d, J = 8.9 Hz, Ar-H)
^{13}C NMR (CDCl$_3$) (100 MHz)	**:**	δ_C 24.4, 26.0, 58.9, 72.9, 80.2, 80.7, 80.8, 112.3, 114.6, 115.2, 119.6, 121.8, 122.7, 128.8, 129.6, 136.2, 169.5
MS (m/z)	**:**	415 (M^+)
Analysis ($C_{22}H_{22}NO_5Cl$)	**:**	Calculated: C, 63.54; H, 5.33; N, 3.37; Cl, 8.52 Observed: C, 63.48; H, 5.22; N, 3.29; Cl, 8.45
Optical rotation		$[\alpha]^{26}_D$ -117.9 (*c*, 0.6, $CHCl_3$)

3.6.5.2-((3*R*,3a*R*,6*S*,6a*R*)-6-acetoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)aceticacid (3.14): To a solution of the 2-*O*-acetyl-5-*O*-allyl-1,4:3,6-dianhydro-D-gluctiol **3.13** (1.0 g, 4.38 mmol) in the mixture of solvent CH_3CN: CCl_4: H_2O (2:2:3, 30 mL), powdered $NaIO_4$ (2.8 g, 13.2 mmol) was added followed by catalytic amount of hydrated $RuCl_3$ (5 mg) at 0 ˚C. The reaction mixture was stirred for 6 h at this temperature. After completion of reaction (TLC), the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was washed with saturated $NaHCO_3$ (10 mL) and the alkaline extract was neutralized with dilute HCl (10%) and again extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with water (10 mL), brine(10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get pure *endo*-bicyclic acid **3.14** (0.57 g, 53%) as pale yellow oil.

IR (CHCl$_3$)	**:**	3300, 1731, 1371, 1238 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 2.08 (3H, s, COOCH_3), 3.80-4.29 (7H, m, OCHCH_2, OCH_2CH, OCH_2COOH, OCHCH), 4.51 (1H, d, J = 4.3 Hz, OCHCH), 4.75 (1H, t, J = 4.3 Hz, HCOCH$_2$COOH), 5.19-5.20 (1H, m, HCOCH$_2$COOMe), 6.91 (1H, bs, OH)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 20.8, 68.1, 70.9, 73.8, 78.1, 80.5, 81.2, 86.0, 170.0, 172.5

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

Analysis : Calculated: C, 48.71; H, 5.64

($C_{10}H_{14}O_7$) Observed: C, 48.78; H, 5.73

Optical rotation $[\alpha]^{26}_D$ +89.7 (*c*, 0.75, $CHCl_3$)

3.6.6.(3*S*,3a*R*,6*R*,6a*R*)-6-((3*R*,4*S*)-2-Oxo-1,4-diphenylazetidin-3-yloxy)-hexahydrofuro[3,2-*b*]furan-3-yl acetate (3.16a): To a stirred solution of the *endo*-bicyclic acid **3.14** (0.142 g, 0.57 mmol), imine **3.15a** (0.104 g, 0.57 mmol) and dry triethylamine (0.174 g, 1.73 mmol) in anhydrous dichloromethane (10 mL), a solution of triphosgene (0.085 g, 0.29 mmol) in dichloromethane was added dropswise at 0 ºC. The reaction mixture was allowed to come to room temperature and stirred at this temperature for 15 h. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (3 x 10 mL), saturated bicarbonate solution (3 x 10 mL) and brine (15 mL), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude product as brown oil, which was purified by flash column chromatography (30 % ethyl acetate/petroleum ether) to get diastereomeric mixture of *cis*-β-lactams **3.16a** and **3.17a** (80:20). A major diastereomer of white solid **3.16a** (0.153 g, 65%) was obtained in pure form by recrystallization of diastereomeric mixture from methanol. R_f (30% ethyl acetate/petroleum ether) 0.34.

MP : 72-73 °C

IR ($CHCl_3$) : 1743, 1735, 1238 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 2.06 (3H, s, COOC*H*$_3$), 3.13-3.28 (3H, m, OCHC*H*$_2$ and OC*H*CH), 3.74 (1H, dd, *J* = 10.5, 5.4 Hz, OC*H*CHAc), 3.95 (2H, broad d, *J* = 2.8 Hz, OC*H*$_2$CH), 4.33 (1H, d, *J* = 5.2 Hz, C$_4$*H*), 5.07 (1H, t, *J* = 2.4 Hz, *H*COCHC=O), 5.21(2H, dd, *J* = 8.2, 5.2 Hz, C$_3$*H* and *H*COCH$_2$COOMe), 7.03-7.43 (10H, m, Ar-*H*)

^{13}C NMR : δ_C 20.9, 61.8, 70.6, 73.7, 77.2, 78.3, 78.8, 81.0, 83.1, 86.2,

($CDCl_3$)		117.5, 124.5, 128.1, 128.6, 129.1, 133.4, 137.1, 163.3, 170.0
(125 MHz)		
MS (m/z)	**:**	410 (M^+)
Analysis	**:**	Calculated: C, 67.38; H, 5.55; N, 3.35
($C_{23}H_{23}NO_6$)		Observed: C, 67.47; H, 5.66; N, 3.42
Optical rotation		$[\alpha]^{26}_D$ +66.0 (*c*, 0.20, $CHCl_3$)

3.6.6. (3*S*,3a*R*,6*R*,6a*R*)-6-((3*R*,4*S*)-1-(4-chlorophenyl)-2-oxo-4-phenylazetidin-3-yloxy)-hexahydrofuro[3,2-*b*]furan-3-yl acetate (3.16b): Following the similar procedure for compound **3.16a**, the *endo*-bicyclic acid **3.14** (0.140 g, 0.57 mmol), imine **3.15b** (0.122 g, 0.57 mmol) and dry triethylamine (0.172 g, 1.70 mmol) in anhydrous dichloromethane (10 mL), a solution of triphosgene (0.085 g, 0.28 mmol) in dichloromethane was added dropswise at 0 ºC. A single diastereomer was obtained by flash column chromatography (30 % ethyl acetate/petroleum ether) to get thick oil **3.16b** (0.170 g, 68%). R_f (30% ethyl acetate/petroleum ether) 0.44.

IR ($CHCl_3$)	**:**	1747, 1737, 1494, 1244 cm^{-1}
^{1}H NMR	**:**	δ_H 2.15 (3H, s, COOC*H*$_3$), 3.74-4.15 (4H, m, OCHC*H*$_2$ and OC*H*$_2$CH), 4.55-4.66 (2H, m, OC*H*CH and OC*H*CHCAc), 4.68 (1H, d, *J* = 4.8 Hz, C_4H), 4.90 (1H, t, *J* = 3.8 Hz, *H*COCHC=O), 5.18-5.26 (2H, m, C_3H and *H*COCH$_2$COOMe), 7.33-7.48 (9H, m, Ar-*H*)
($CDCl_3$)		
(200 MHz)		
^{13}C NMR	**:**	δ_C 20.9, 64.0, 70.2, 73.9, 77.2, 78.0, 78.3, 85.9, 86.0, 90.2, 118.8, 126.1, 129.1, 129.4, 129.6, 135.4, 135.6, 163.7, 170.0
($CDCl_3$)		
(100 MHz)		
MS (m/z)	**:**	444 (M^+)
Analysis	**:**	Calculated: C, 62.24; H, 4.99; N, 3.15; Cl, 7.99
($C_{23}H_{22}NO_6Cl$)		Observed: C, 62.16; H, 4.87; N, 3.08; Cl, 7.91
Optical rotation		$[\alpha]^{26}_D$ +73 (*c*, 0.2, $CHCl_3$)

3.6.7. (3*S*, 3a*R*, 6*R*, 6a*R*)-3-(allyloxy)-6-methoxy-hexahydrofuro[3,2-*b*]furan (3.20): To a solution of 2-*O*-methyl-5-*O*-hydroxy-1,4:3,6-dianhydro-D-gluctiol **3.19** (3.7 g, 23.12 mmol) in freshly distilled allyl bromide (40 mL) were added Ag_2O (7.07 g, 30.52 mmol) and $CaSO_4$ (15 g). The resulting suspension was stirred for 2 days in the dark at room temperature, then diluted with ether (100 mL), filtered through Celite, and concentrated under reduced pressure to give the crude product as a brown oil. It was purified by column chromatography (20% ethyl acetate/petroleum ether) to get 2-*O*-methyl-5-*O*-allyl-1,4:3,6-dianhydro-D-gluctiol **3.20** (4.54 g, 98%) as pale yellow oil. R_f (40% ethyl acetate/petroleum ether) 0.64.

IR (Neat)	**:**	1735, 1647, 1463, 1220 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 3.46 (3H, s, OC*H*$_3$), 3.52-3.63 (1H, m, OC*H*CH), 3.87-4.05 (7H, m, OCHC*H*$_2$,OC*H*$_2$CH, OC*H*CHO-olefin and OC*H*$_2$CH=C), 4.52 (1H, dd, *J* = 4.2, 1.0 Hz, *H*COMe), 4.67 (1H, t, *J* = 4.2 Hz, *H*CO-oleifin), 5.15-5.33 (2H, m, HC=C*H*$_2$), 5.79-5.98 (1H, m, *H*C=CH$_2$)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 57.9, 69.4, 70.2, 73.4, 79.6, 81.5, 83.4, 86.0, 117.1, 133.9
MS (m/z)	**:**	201 (M^+)
Analysis ($C_{10}H_{16}O_4$)	**:**	Calculated: C, 59.98; H, 8.05 Observed: C, 59.87; H, 7.95
Optical rotation		$[\alpha]^{26}_D$ +91 (*c*, 0.37, $CHCl_3$)

3.6.8.2-((3*S*,3a*R*,6*R*,6a*R*)-6-methoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)aceticacid (3.21): 2-*O*-methyl-5-*O*-allyl-1,4:3,6-dianhydro-D-gluctiol **3.20** (0.5 g, 2.50 mmol) was dissolved in anhydrous acetone (10 mL) and potassium carbonate (0.025 g) added. This mixture was cooled to 0 ºC and then powdered potassium permanganate (1.0 g, 6.32 mmol) was added portionwise with stirring in about 1-2 h at 0-5 ºC. The reaction mixture was stirred at room temperature for 3 h and filtered through Buchner funnel. The maganese dioxide residue was washed with acetone and then extracted with hot water (3 X 10 mL).

The aqueous alkaline extract was cooled and acidified with 10 % Conc. HCl, saturated with NaCl and extracted with dichloromethane (3 X 20 mL). The dichloromethane extract was washed with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get pure *exo*-bicyclic acid **3.21** (0.280 g, 51%) as colourless oil.

IR (Neat)	**:**	3469, 1741, 1647, 1463, 1217 cm^{-1}
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	δ_H 3.45 (3H, s, OC*H*$_3$), 3.52-3.63 (1H, m, OC*H*CH), 3.89-4.17 (7H, m, OCHC*H*$_2$,OC*H*$_2$CH, OC*H*CHOCH$_2$COOH and OC*H*$_2$COOH), 4.58 (1H, d, *J* = 4.3 Hz, *H*COMe), 4.71 (1H, t, *J* = 4.3 Hz, *H*CCH$_2$COOH), 6.62 (1H, bs, O*H*)
^{13}C NMR (CDCl$_3$) (50 MHz)	**:**	δ_C 58.2, 69.8, 73.1, 75.7, 79.9, 81.6, 84.9, 85.8, 177.2
MS (m/z)	**:**	219 (M^+)
Analysis ($C_9H_{14}O_6$)	**:**	Calculated: C, 49.54; H, 6.46 Observed: C, 49.48; H, 6.40
Optical rotation		$[\alpha]^{26}_D$ +35.9 (*c*, 0.27, $CHCl_3$)

3.6.9. Diastereomeric mixture of β-lactams 3.22 and 3.23: To a stirred solution of the *exo*-bicyclic acid **3.21** (0.145 g, 0.66 mmol), imine **3.15a** (0.120 g, 0.66 mmol) and dry triethylamine (0.201 g, 1.99 mmol) in anhydrous dichloromethane (10 mL), a solution of triphosgene (0.098 g, 0.33 mmol) in dichloromethane was added dropswise at 0 ºC. The reaction mixture was allowed to come to room temperature and stirred at this temperature for 15 h. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (3 x 10 mL), saturated bicarbonate solution (3 x 10 mL) and brine (15 mL), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude product as yellow solid. It was purified by flash column chromatography (30 % ethyl acetate/petroleum ether) to get diastereomeric mixture of β-lactams **3.22** and **3.23** (0.180 g, 71%). After recrystallization through Methanol, it was obtained as white solid which was

an inseparable diastereomeric mixture of β-lactams (50:50). R_f (30% ethyl acetate/petroleum ether) 0.60.

MP	**:**	175-176 °C
IR ($CHCl_3$)	**:**	1757, 1500, 1338 cm^{-1}
^{1}H NMR ($CDCl_3$) (400 MHz)	**:**	δ_H 3.27 (1H, dd, *J* = 10.3, 2.0 Hz, OC*H*$_a$CH), 3.37 (3H, s, OC*H*$_3$), 3.41 (3H, s, OC*H*$_3$), 3.42-3.54 (3H, m, OCHC*H*$_2$, OCH$_a$*H*$_b$CH), 3.68-3.72 (1H, m, OC*H*$_a$H$_b$CH), 3.77-4.02 (9H, m, OCHC*H*$_2$, OC*H*$_2$CH, OC*H*$_b$CH, OCHC*H*$_a$, OCHC*H*$_b$, *H*$_a$COCHC=O and C$_4$*H*$_a$), 4.52 (1H, t, *J* = 4.2 Hz, *H*$_b$COCHC=O), 4.59 (1H, d, *J* = 4.2 Hz, C$_4$*H*$_b$), 5.05 (2H, dd, *J* = 13.3, 4.7 Hz, C$_3$*H*$_a$ and *H*$_a$COMe), 5.25 (2H, dd, *J* = 7.5, 4.7 Hz, C$_3$*H*$_b$ and *H*$_b$COMe), 7.24-7.42 (20H, m, Ar-*H*)
^{13}C NMR ($CDCl_3$) (100 MHz)	**:**	δ_C 58.0, 58.1, 62.0, 62.4, 69.6, 69.7, 73.0, 73.4, 77.2, 79.5, 79.9, 81.6, 81.7, 82.7, 83.3, 84.6, 85.6, 85.9, 86.0, 117.6, 124.6, 128.0, 128.3, 128.6, 128.8, 128.9, 129.1, 133.1, 133.5, 136.9, 163.6, 163.8.

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20. This molecular structure is drawn by using software programme Chem 3D Pro.
21. The purity of all new β-lactams was determined by HPLC: HP-1050 Ti series pump; Detector: JASCO 970 (at 254 nm) connected to Integrator: HP-3396 Series-II; Column: Chromsphere Chromsep 5 C-18, 250 x 4.6 mm (5 μm); Solvent system (v/v): MeCN:H_2O (60:40), flow rate 1.5 mL/min.
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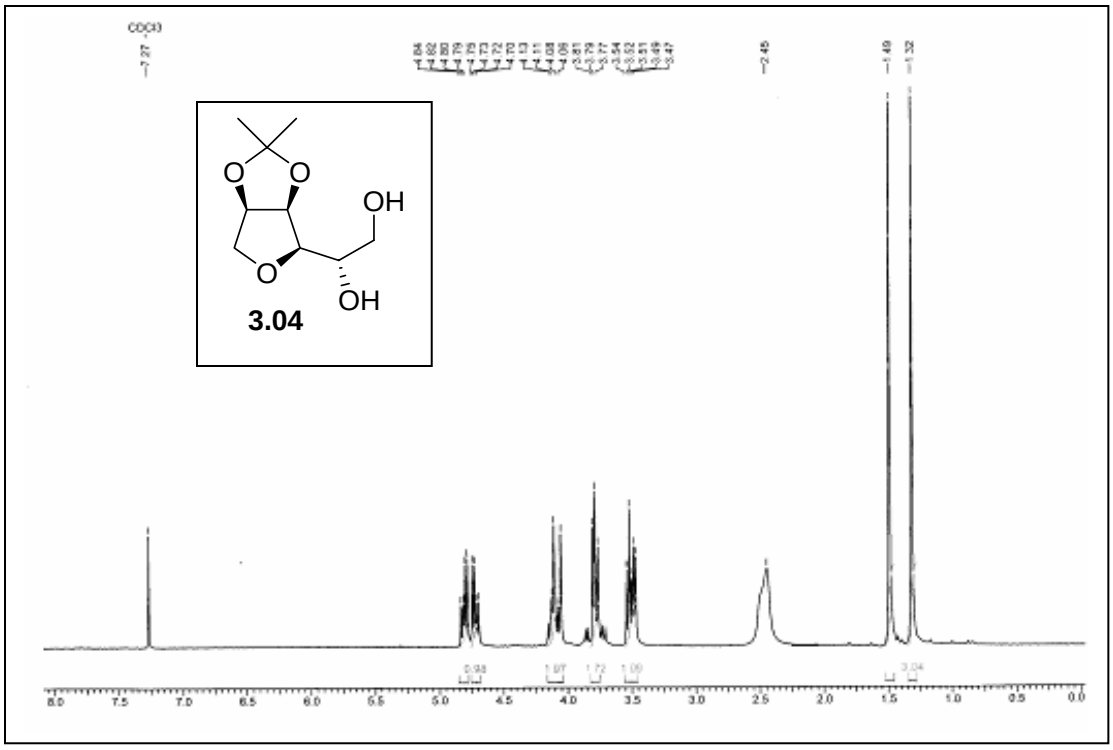
Chapter III

Spectra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7.11
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3.54
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3.51
3.49
3.47
2.45
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OH
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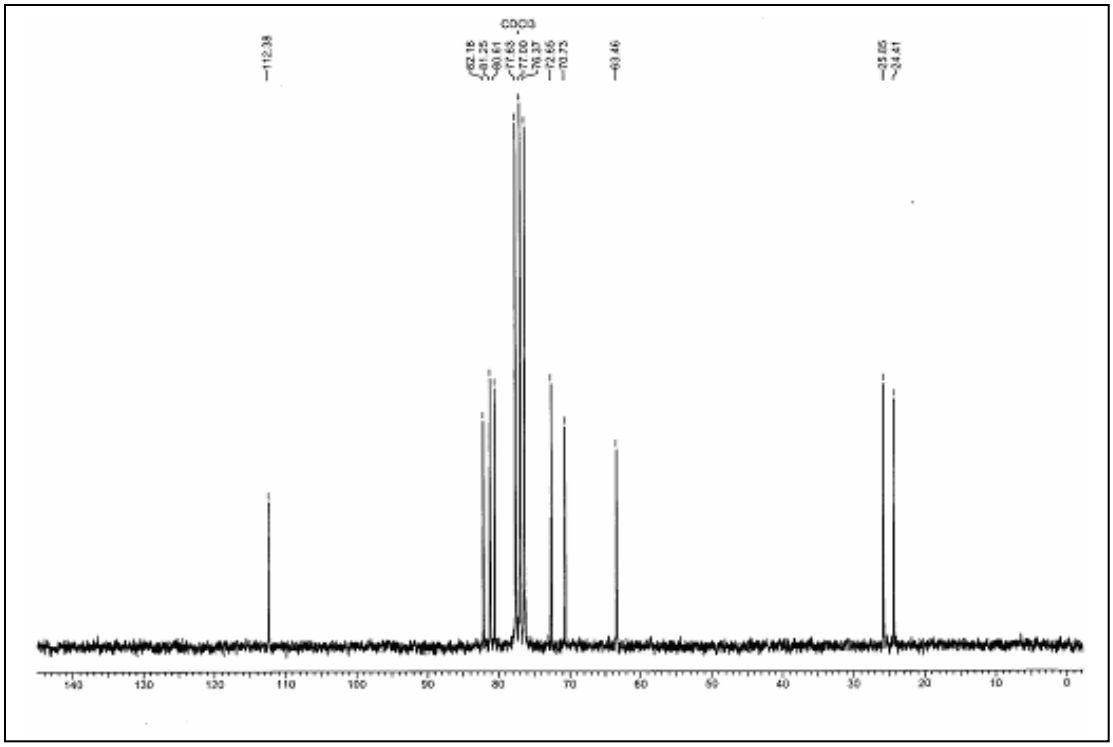
3.04

3.04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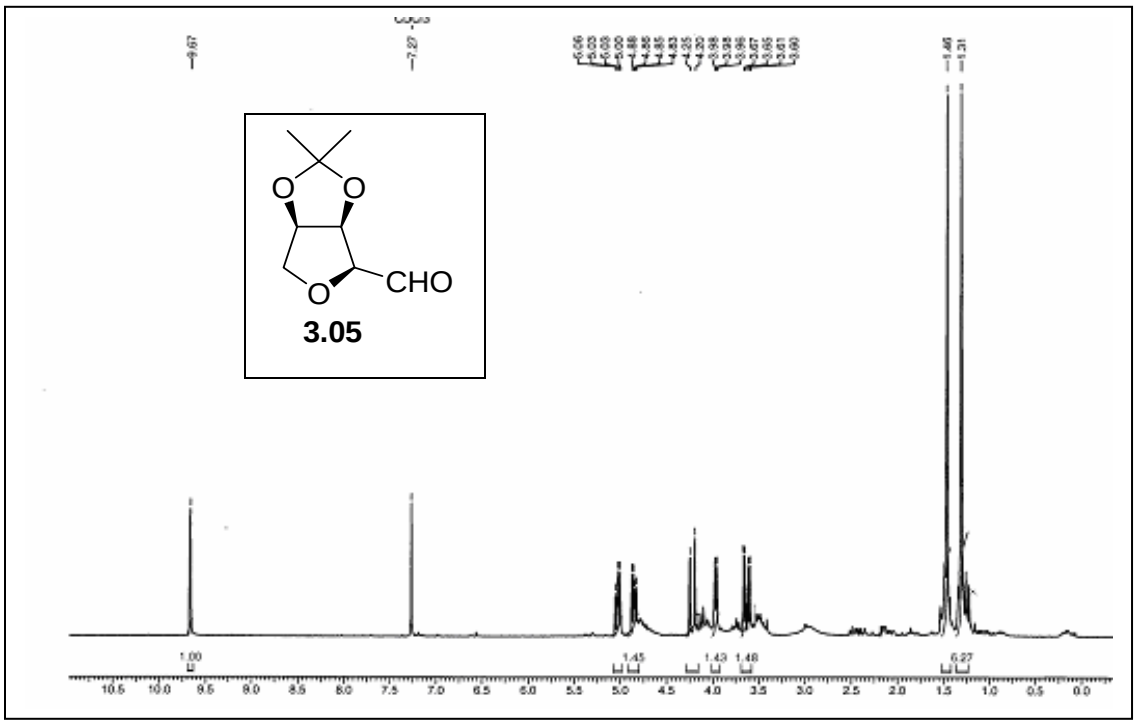
24.41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4.85
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3.96
3.67
3.65
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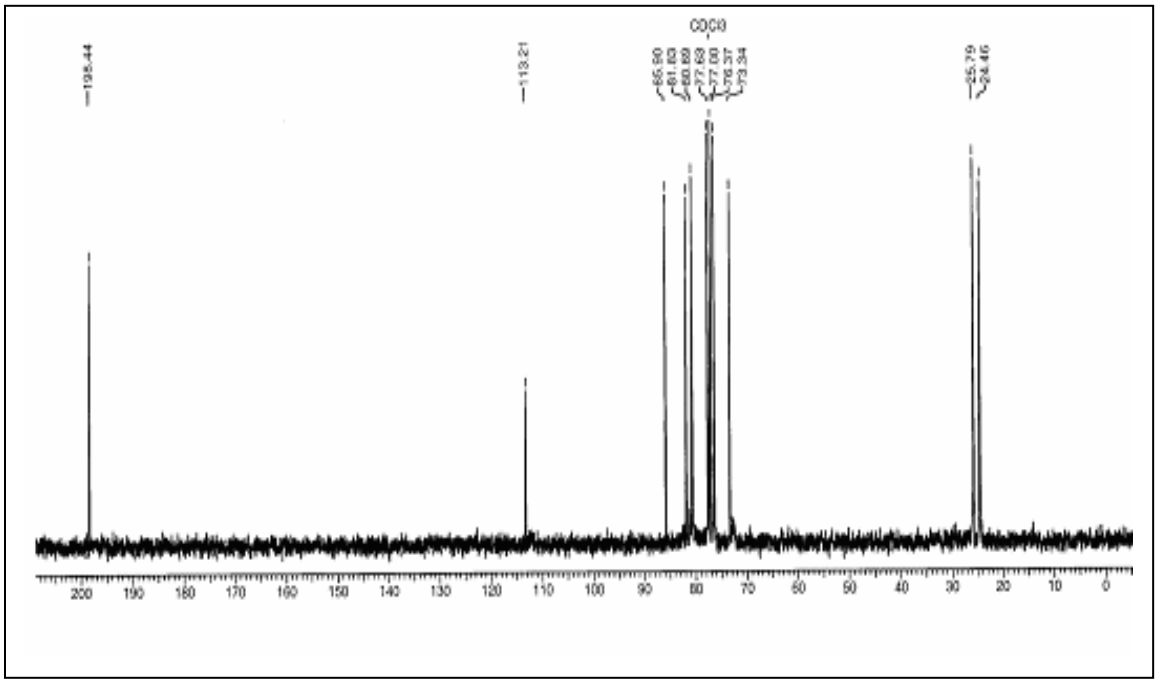
6.27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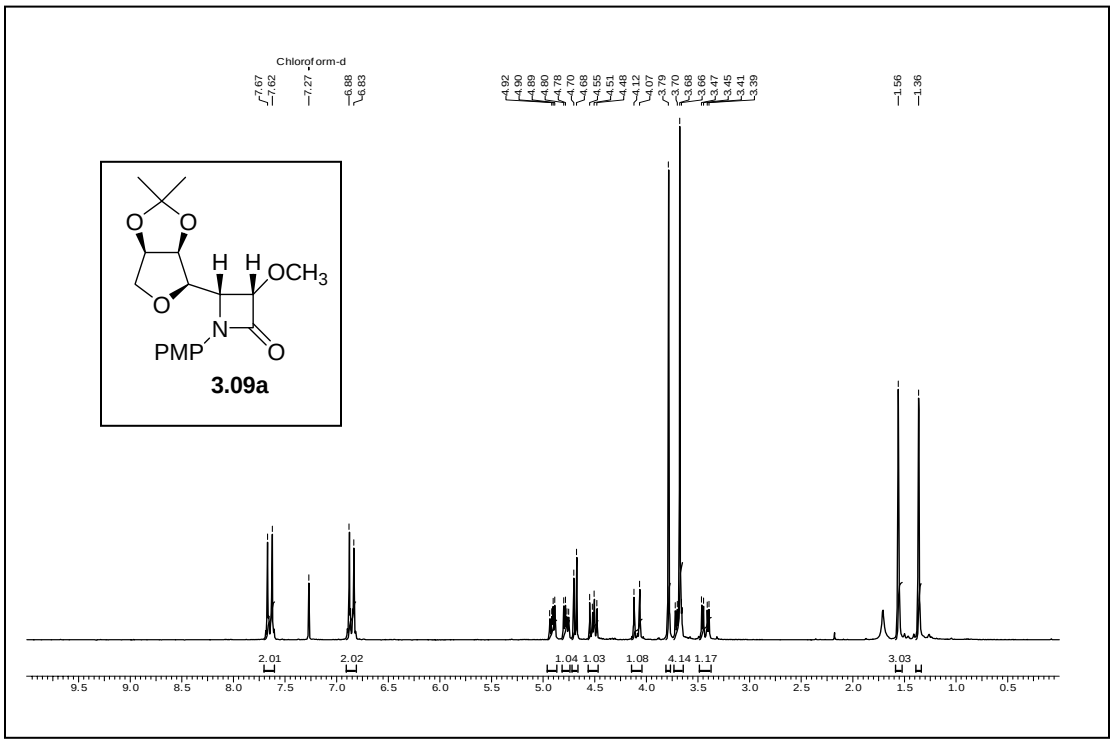
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4.70
4.69
4.55
4.51
4.48
4.12
4.07
3.79
3.70
3.68
3.66
3.47
3.45
3.41
3.39
1.56
1.36
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O
O
H
H
OCH3
N
PMP
O
3.09a
2.01
2.02
1.04
1.03
1.08
4.14
1.17
3.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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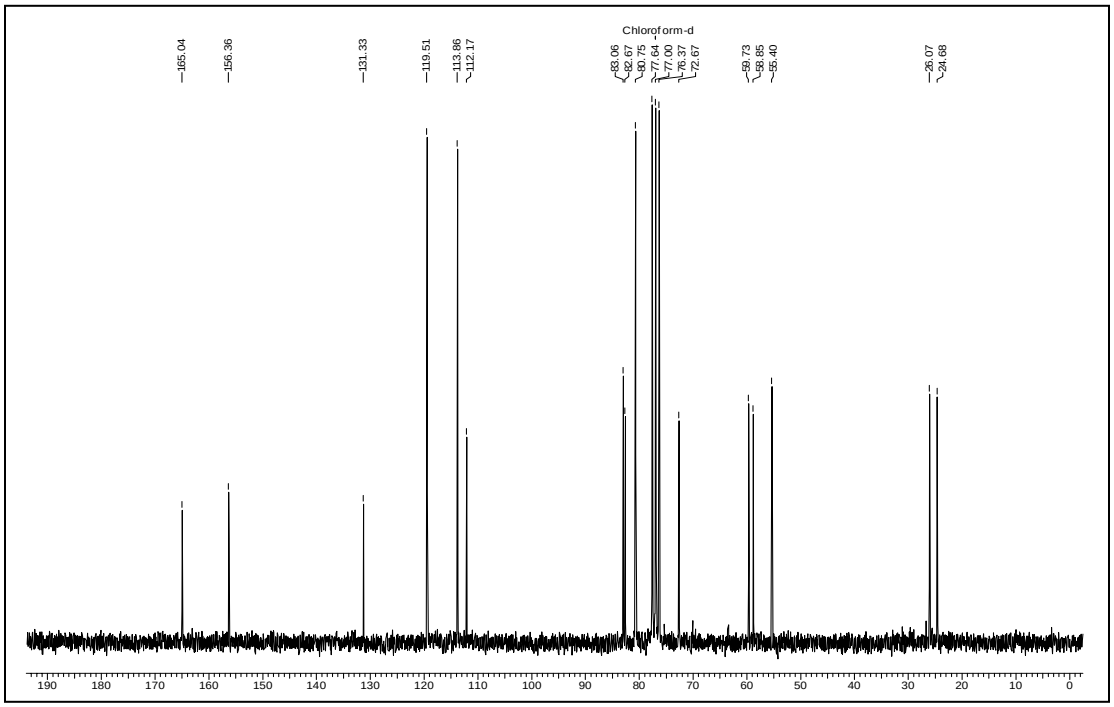
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76.77
72.67
59.73
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55.40
26.07
24.68
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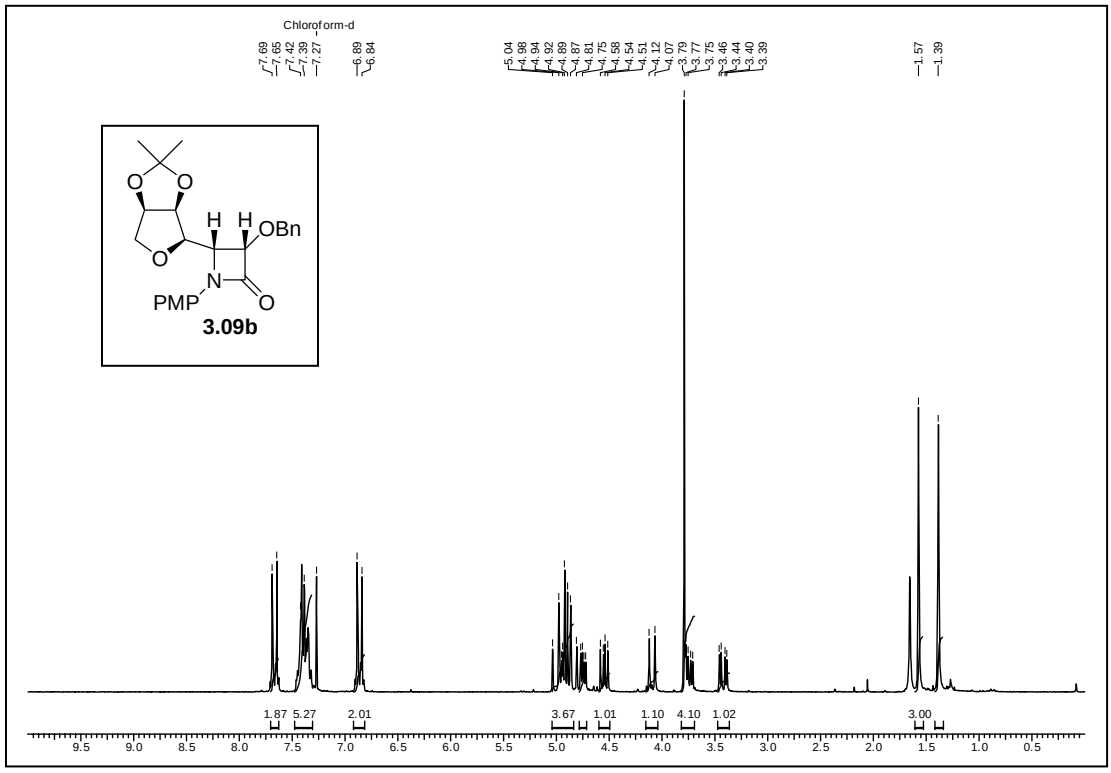
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4.89
4.87
4.81
4.75
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4.54
4.51
4.12
4.07
3.79
3.77
3.75
3.46
3.44
3.40
3.39
1.57
1.39
O
O
O
H
H
OBn
N
PMP
O
3.09b
1.87
5.27
2.01
3.67
1.01
1.10
4.10
1.02
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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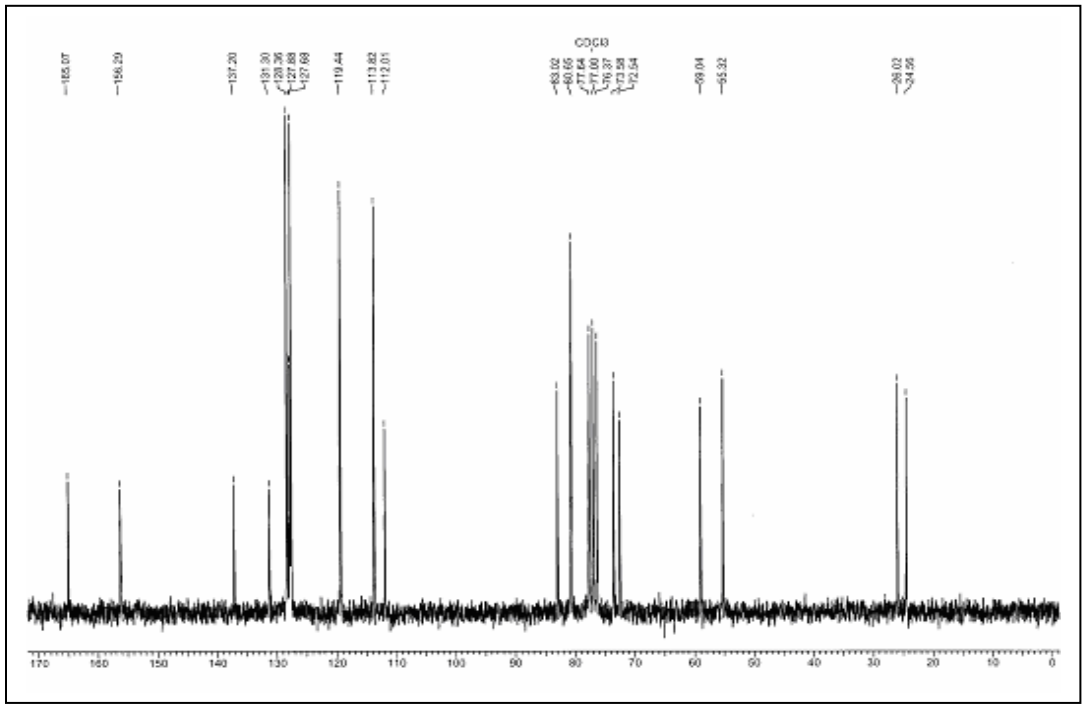
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83.02
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77.64
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76.37
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72.54
69.04
55.32
28.02
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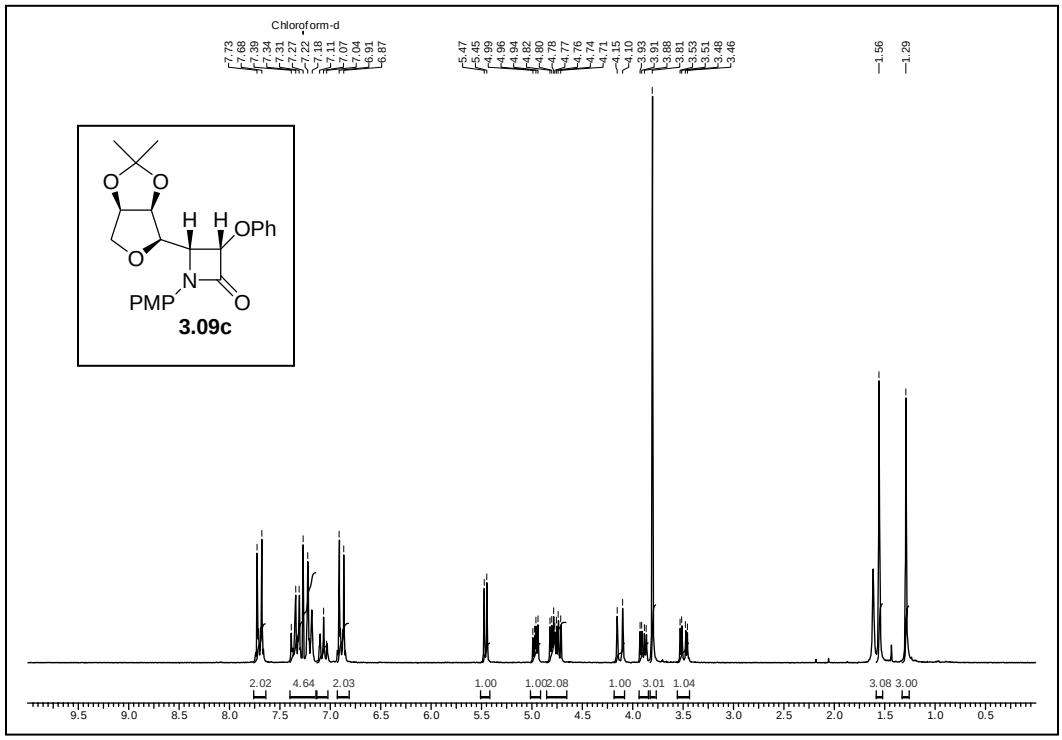
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7.11
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7.04
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6.87
5.47
5.45
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4.82
4.80
4.78
4.77
4.76
4.74
4.71
4.15
4.10
3.93
3.91
3.88
3.81
3.53
3.51
3.48
3.46
1.56
1.29
O
O
O
H
H
OPh
N
PMP
O
3.09c
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4.64
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1.00
2.08
1.00
3.01
1.04
3.08
3.00
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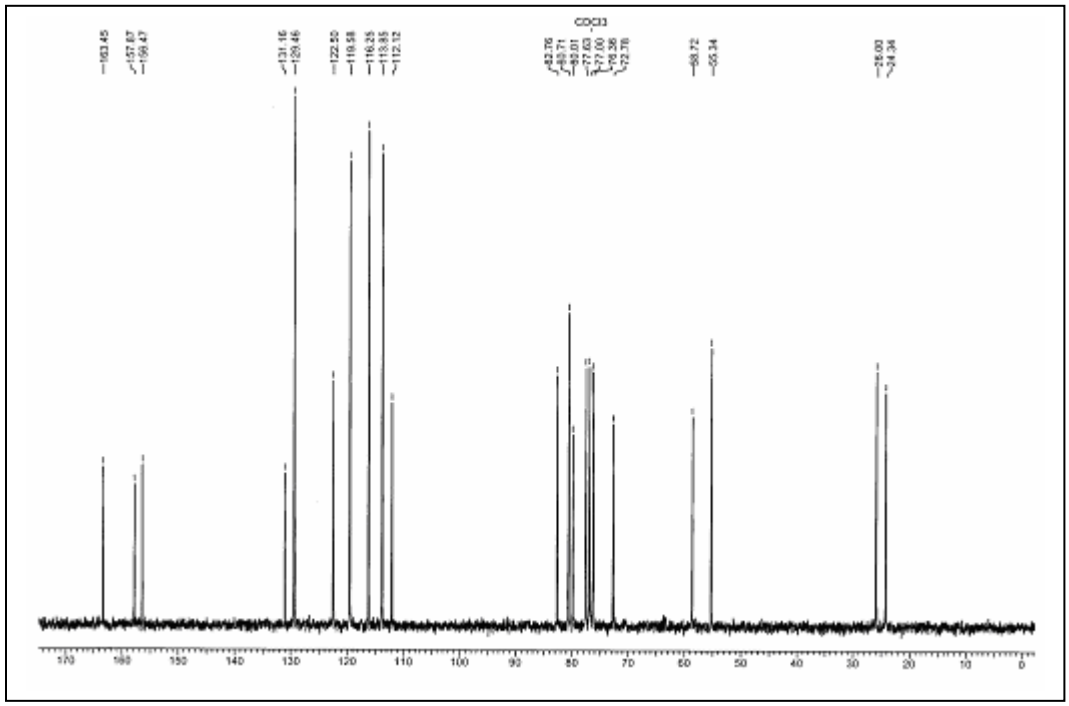
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55.34
25.00
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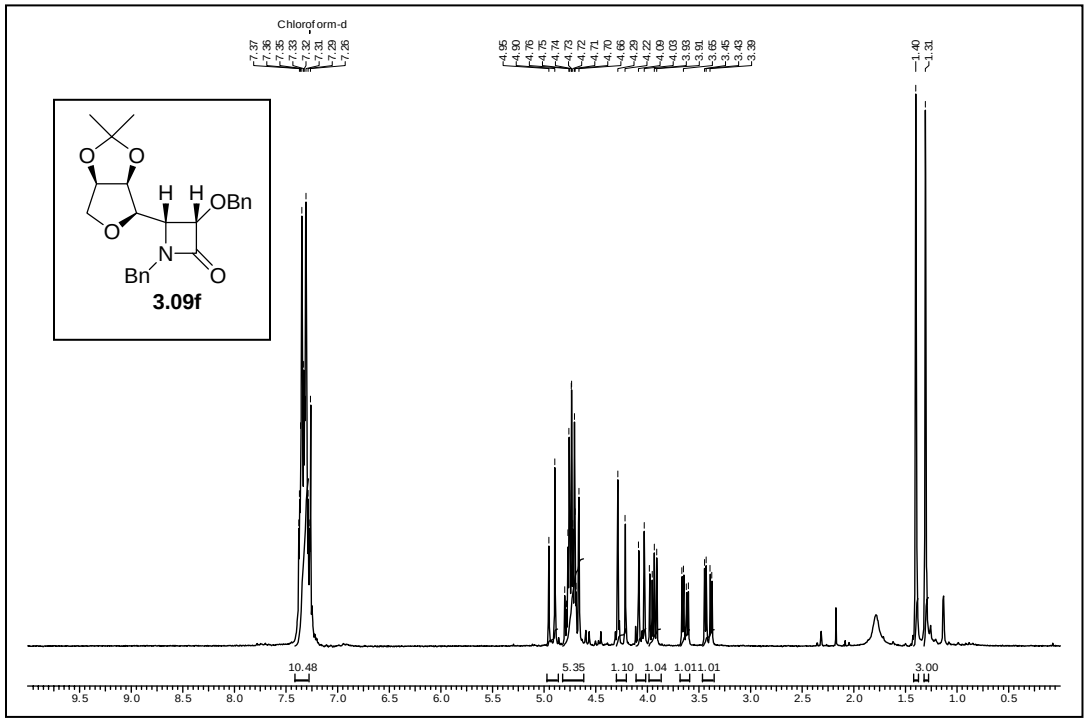
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4.75
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4.73
4.72
4.71
4.70
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4.29
4.22
4.09
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H
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O
N
Bn
O
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10.48
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1.01
1.01
3.00
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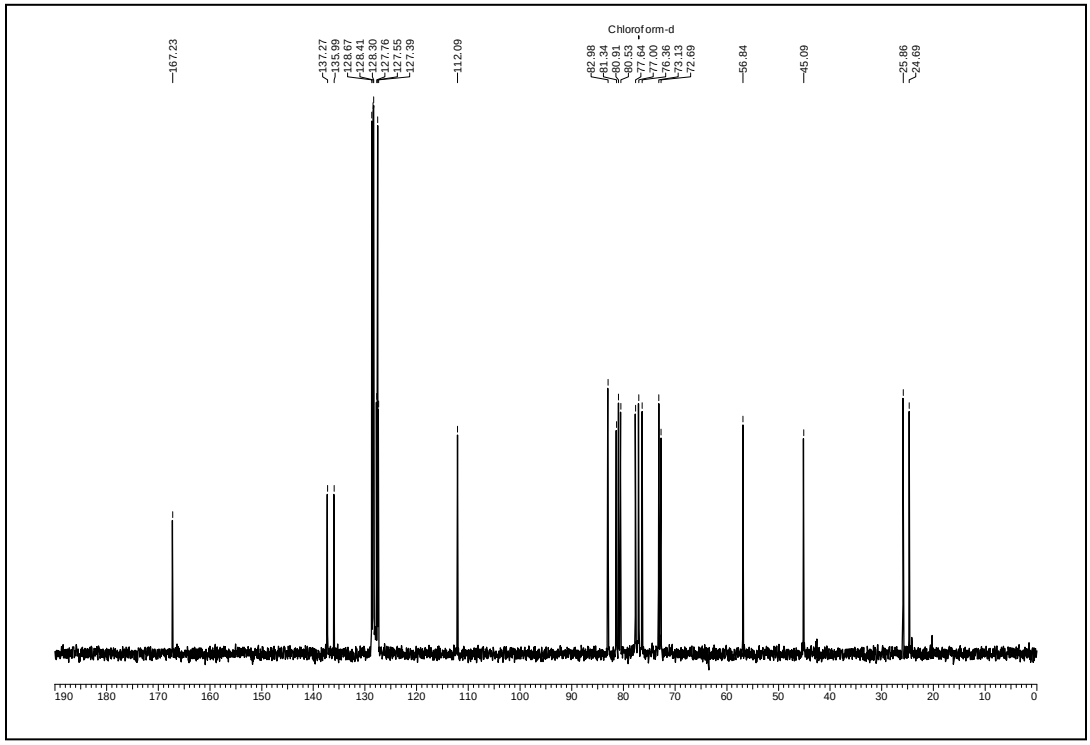
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77.64
77.00
76.36
73.13
72.69
56.84
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24.69
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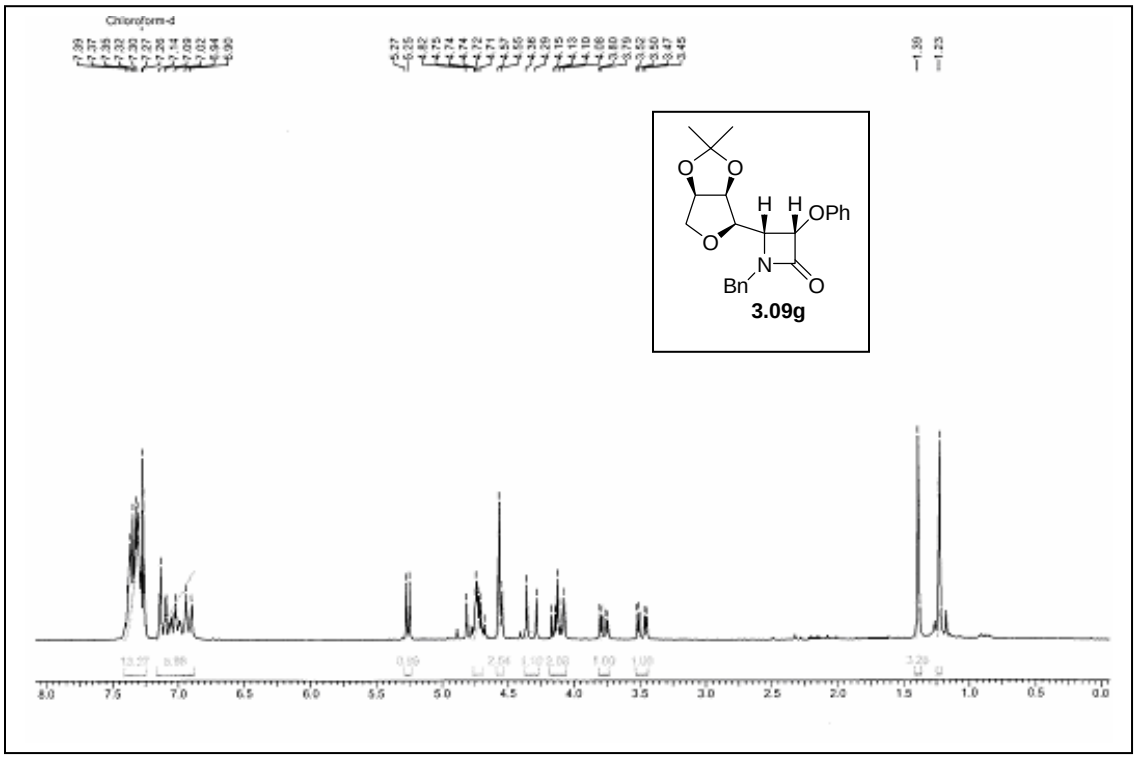
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O
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Bn
O
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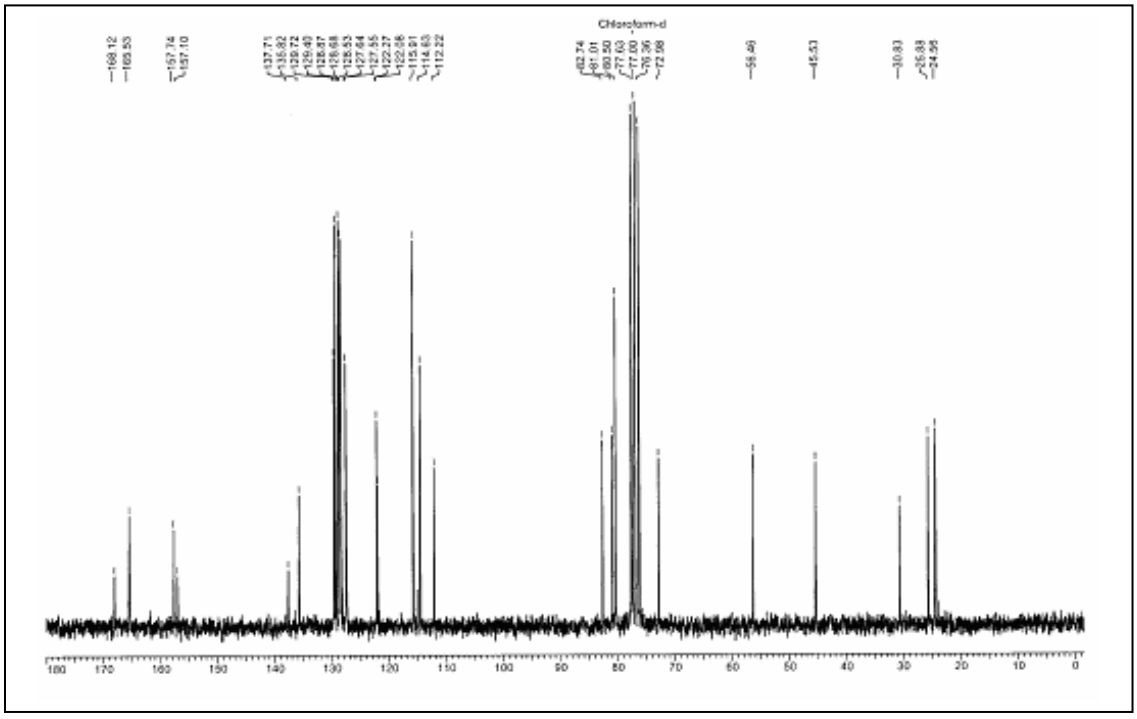
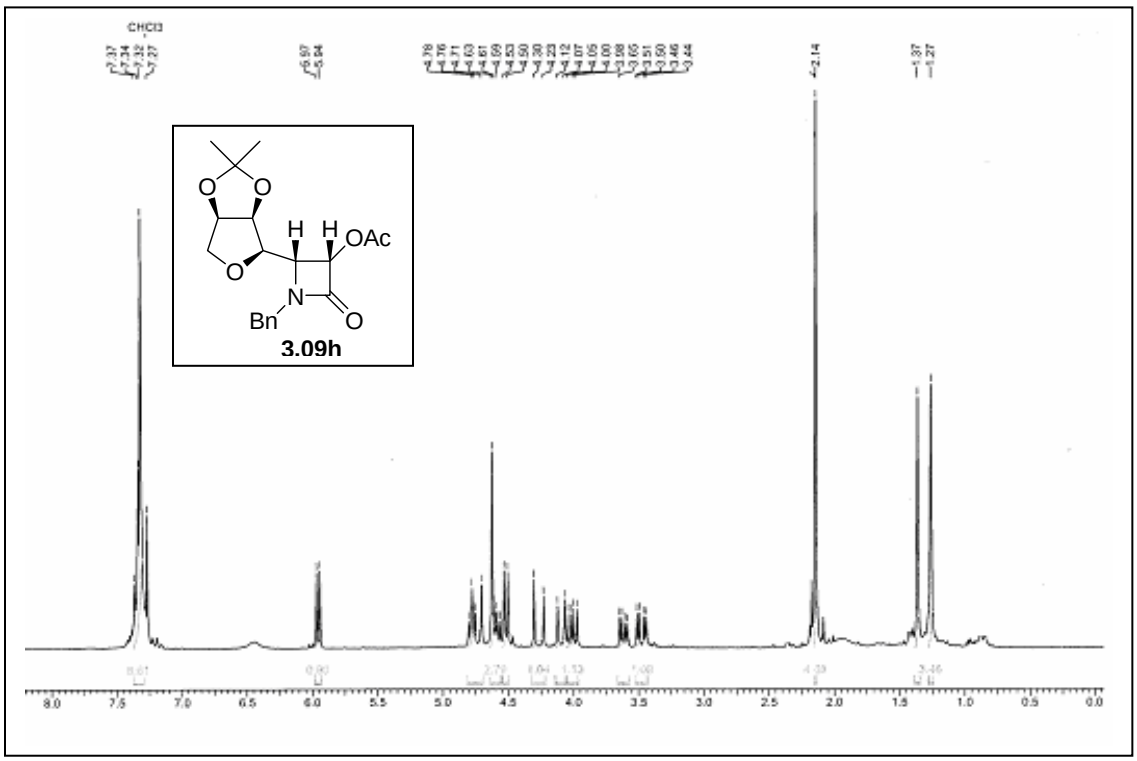

Chloroform-d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4.53
4.50
4.30
4.23
4.12
4.07
4.05
4.00
3.98
3.65
3.51
3.50
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1.37
1.27
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H
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Bn
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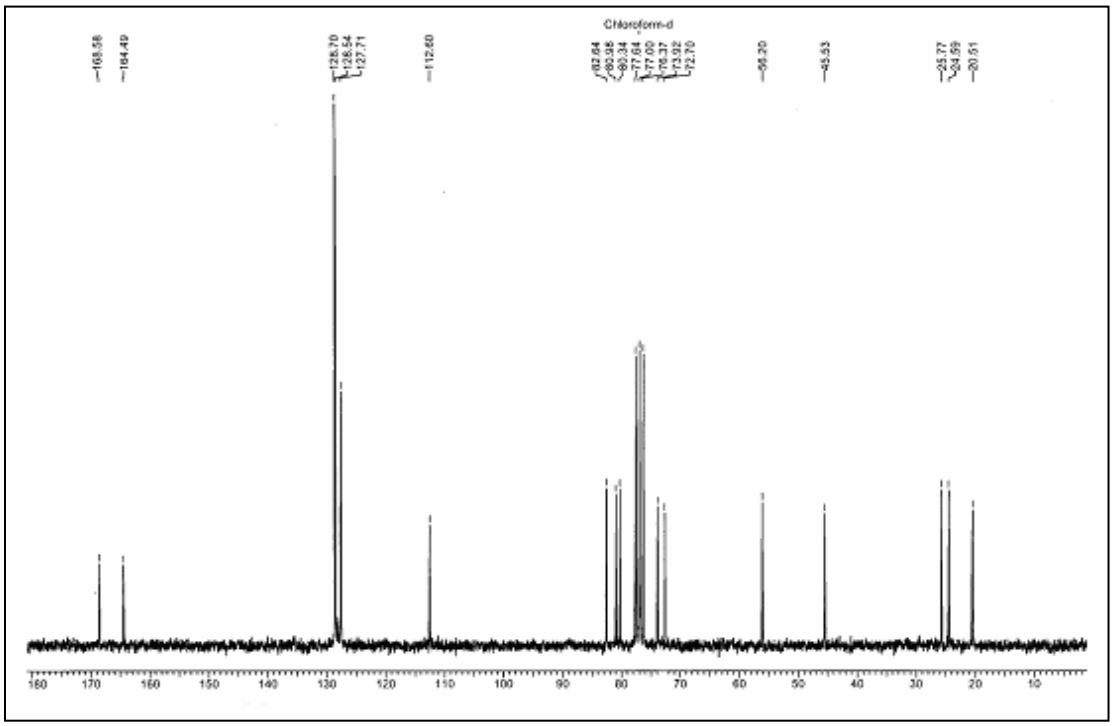
3.09h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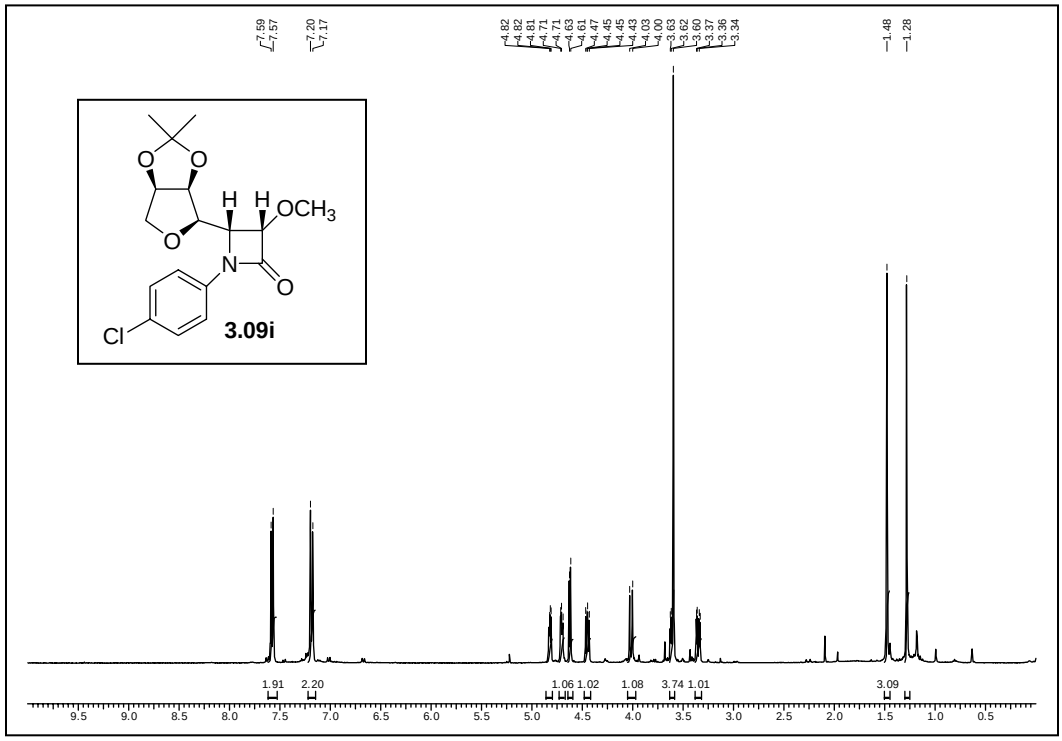
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4.61
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4.45
4.43
4.03
4.00
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3.36
3.34
1.48
1.28
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O
O
H
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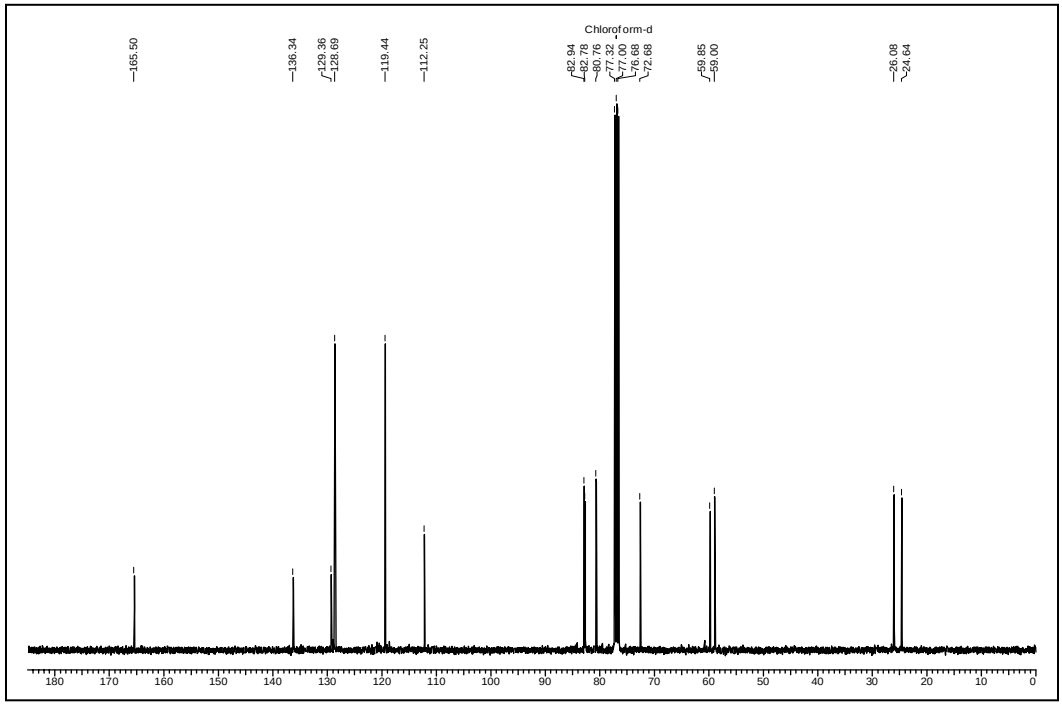
3.09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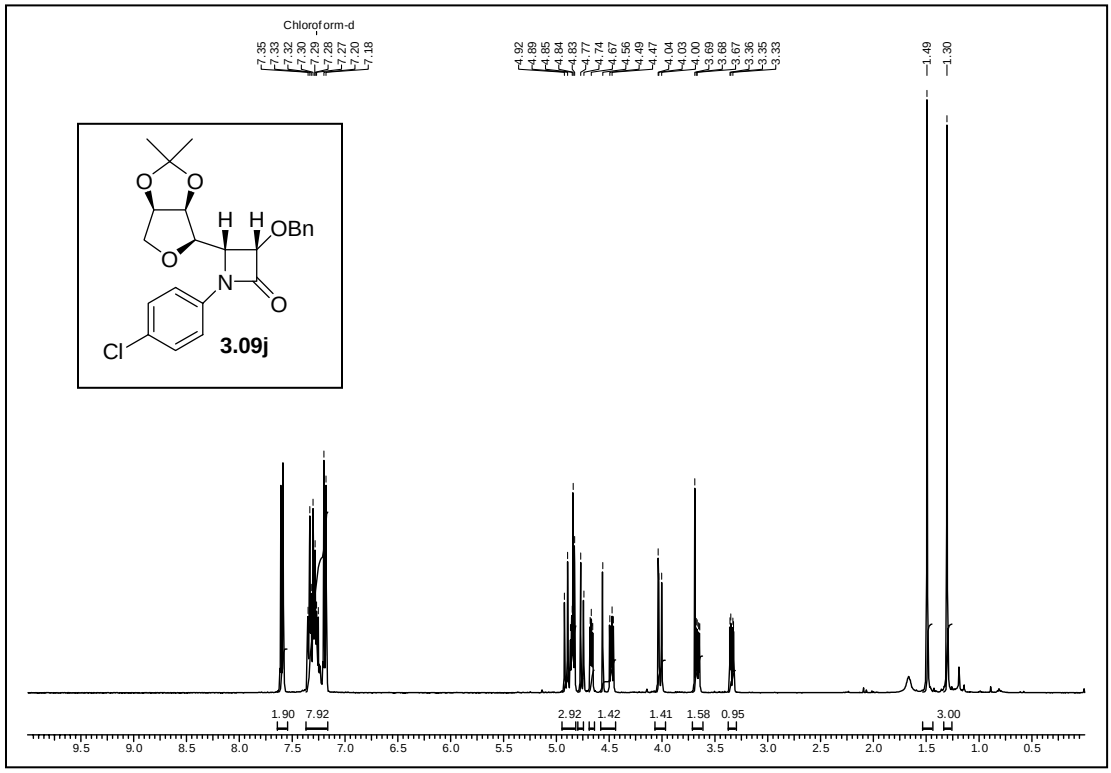
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4.83
4.77
4.74
4.67
4.56
4.49
4.47
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4.03
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3.68
3.67
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1.30
O
O
O
H
H
OBn
N
O
Cl
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8.0
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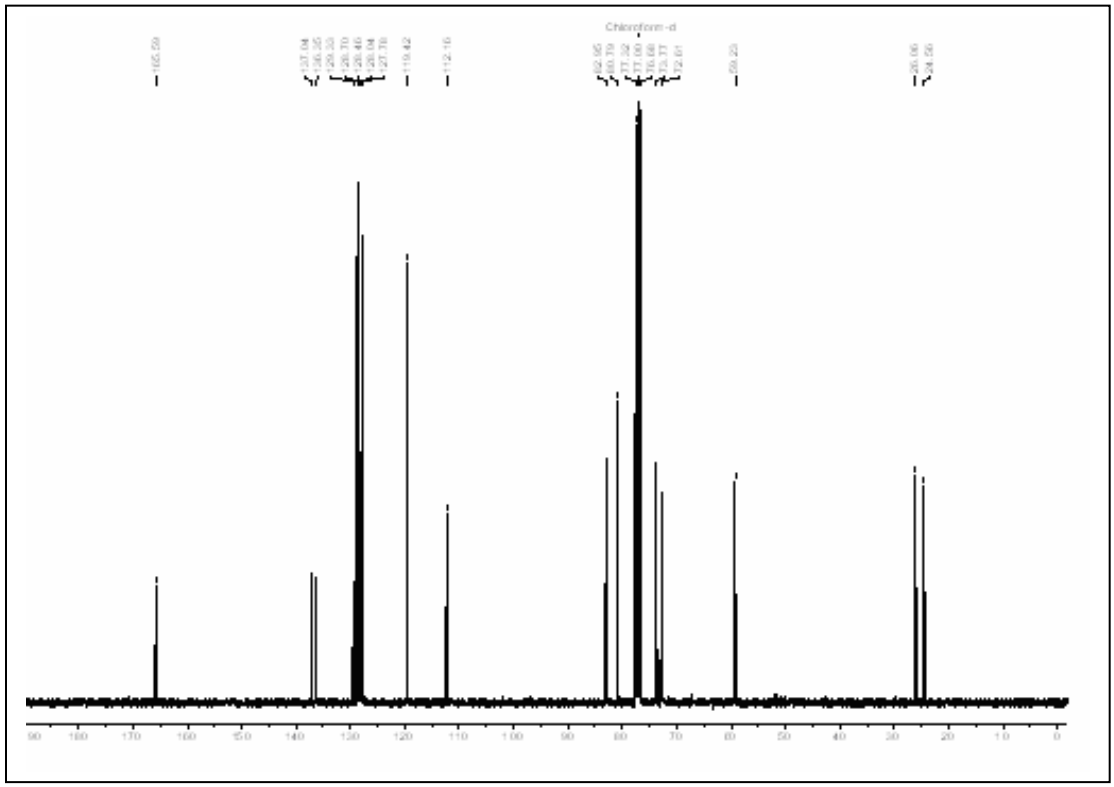
Chloroform-d
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80.79
77.32
77.00
76.68
73.37
72.67
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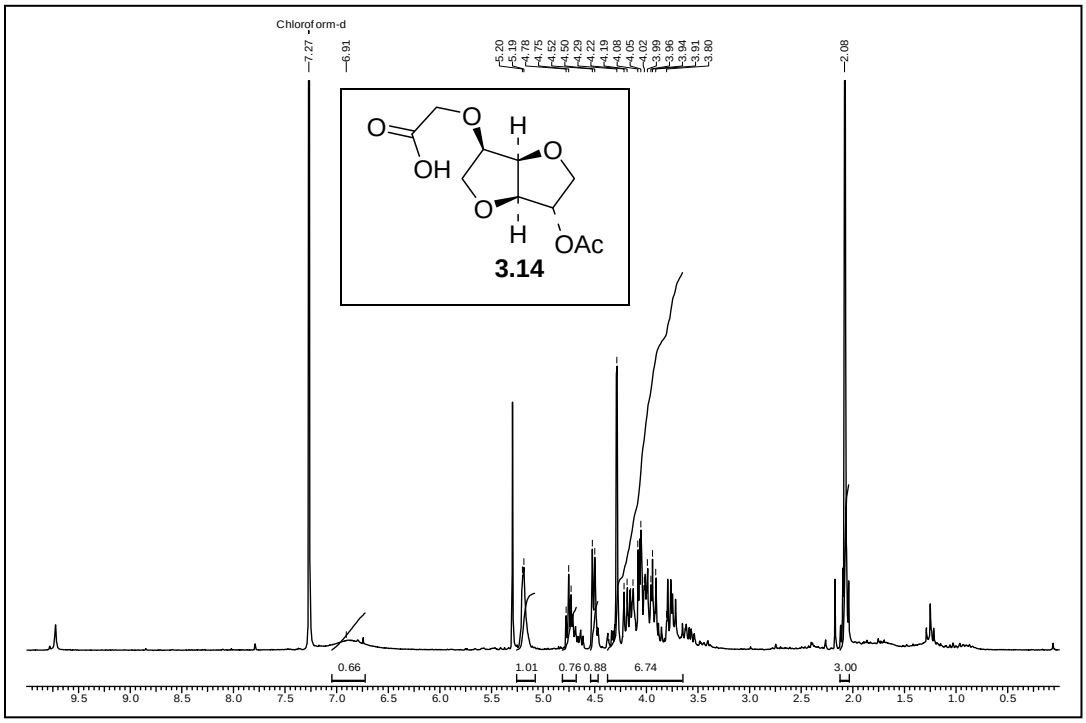
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4.08
4.05
4.02
3.99
3.96
3.94
3.91
3.80
2.08
O
O
H
OH
O
O
H
OAc
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0.88
6.74
3.00
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7.5
7.0
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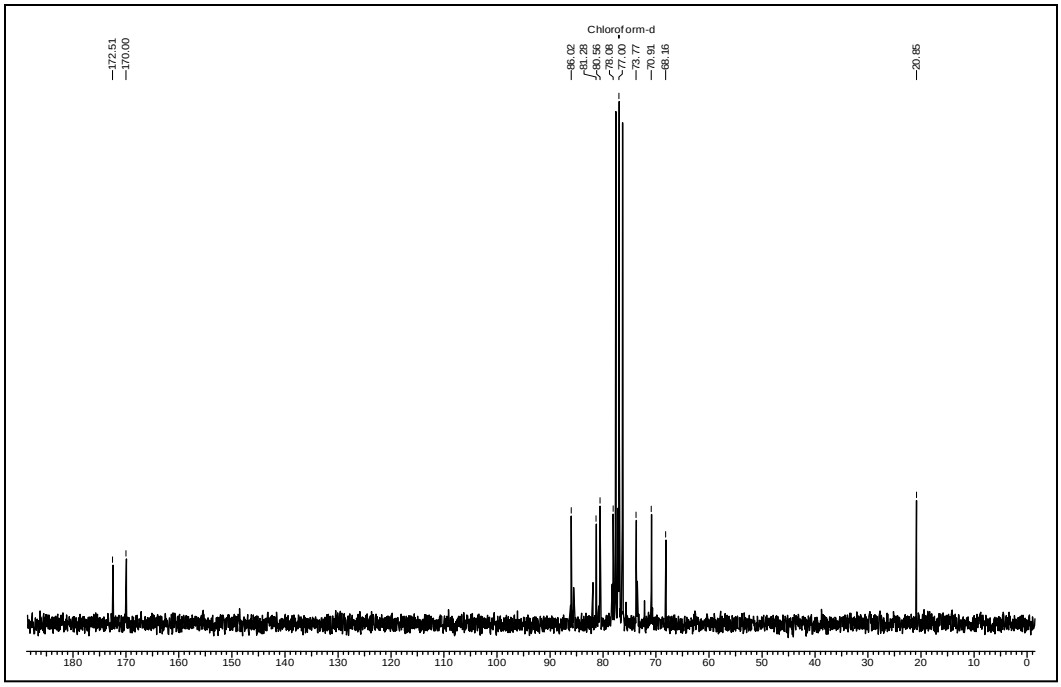
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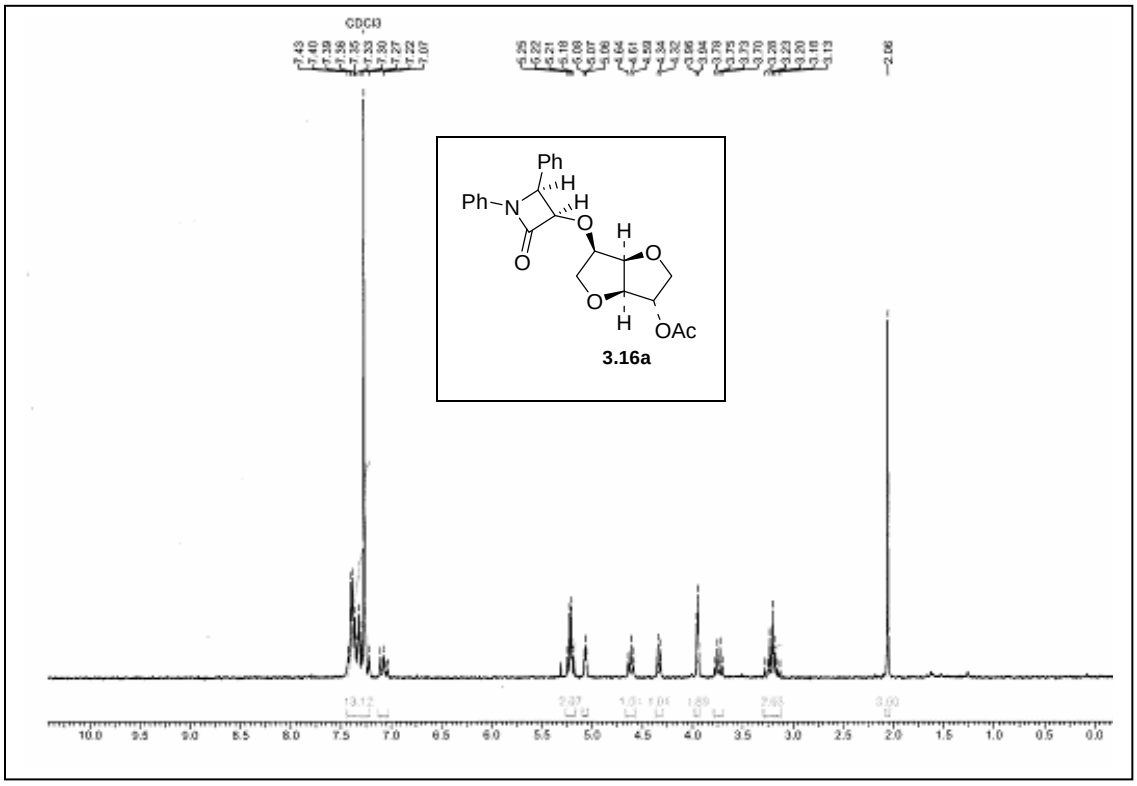
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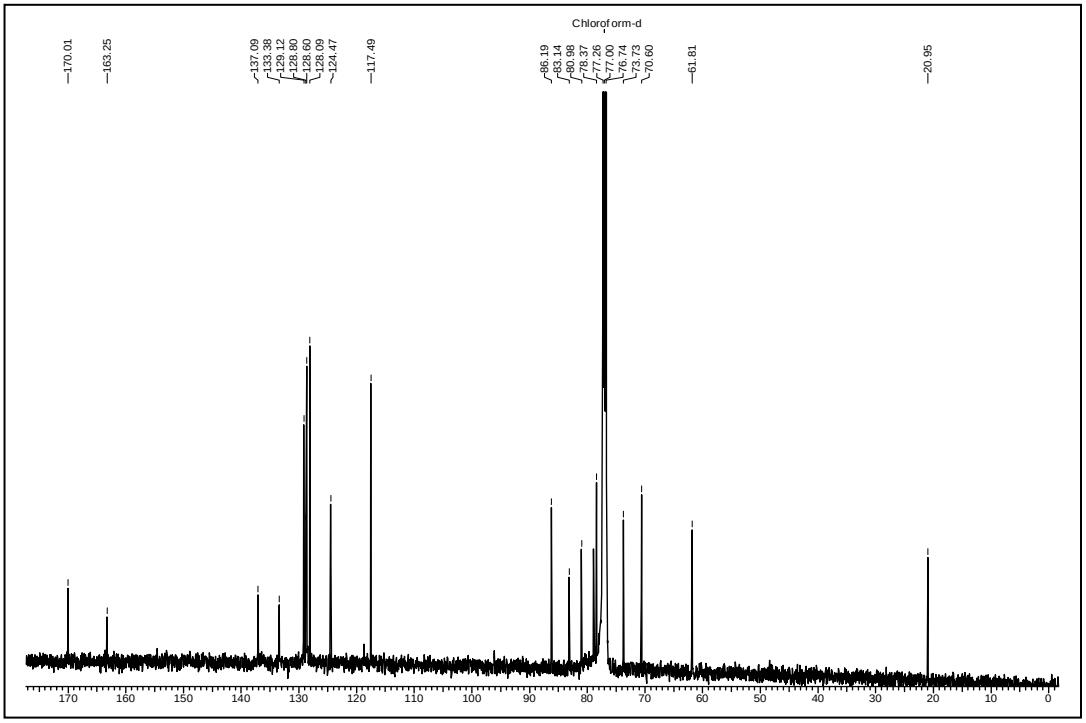
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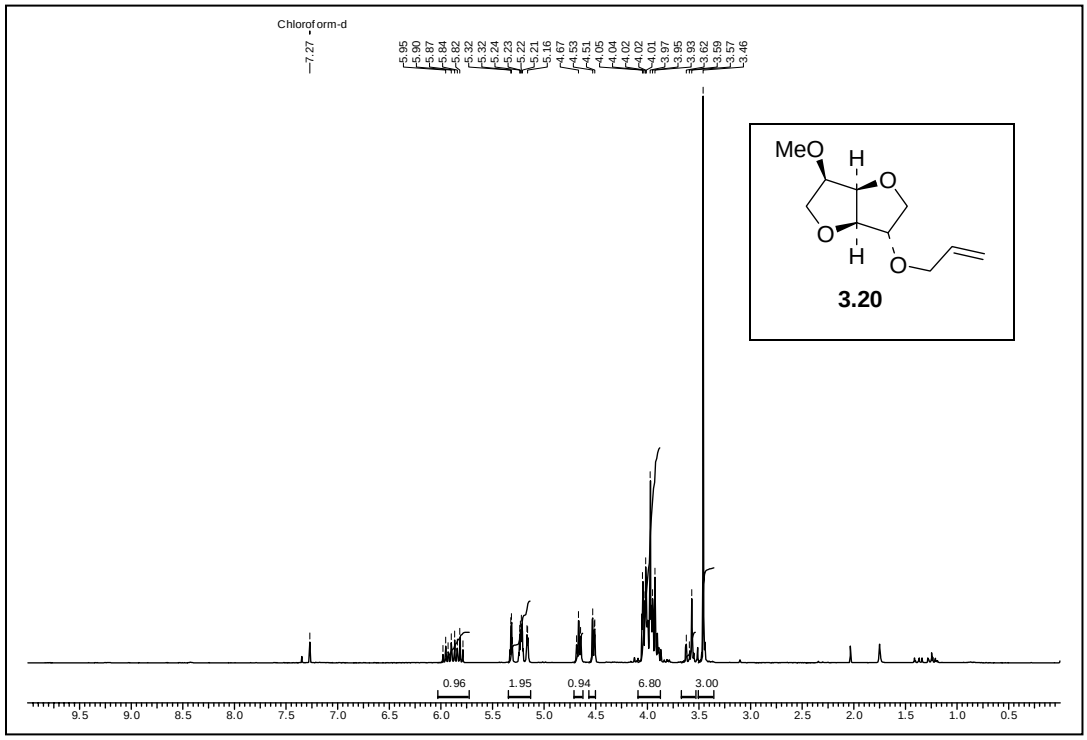
Chloroform-d
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5.21
5.16
4.67
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4.51
4.05
4.04
4.02
4.02
4.01
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H
O
O
H
O
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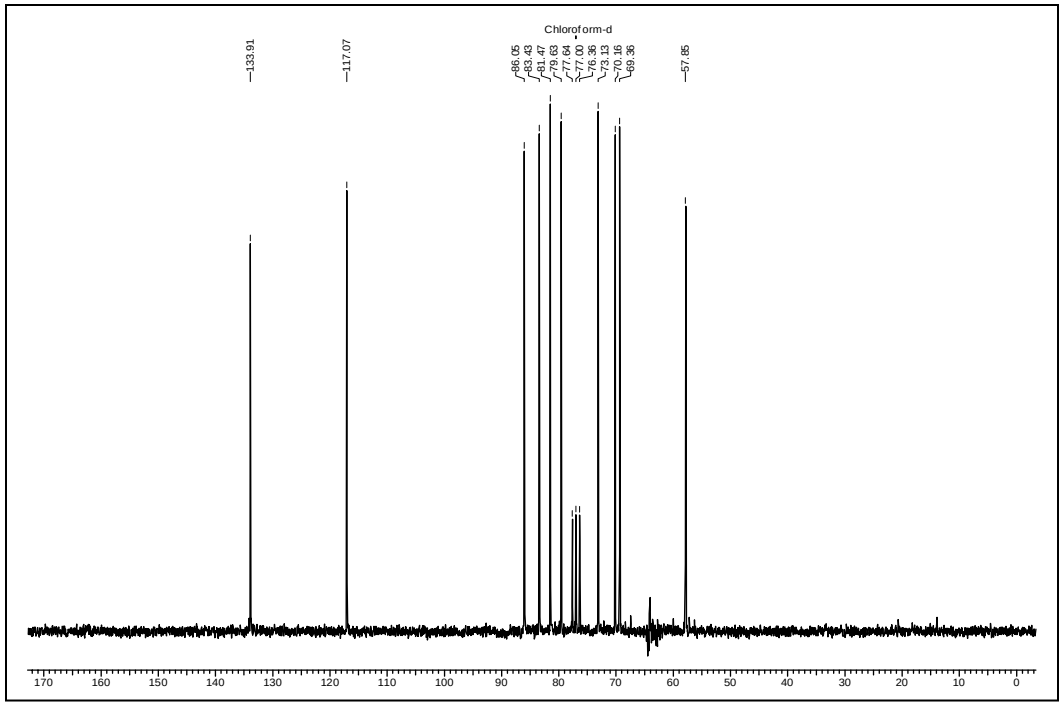
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90
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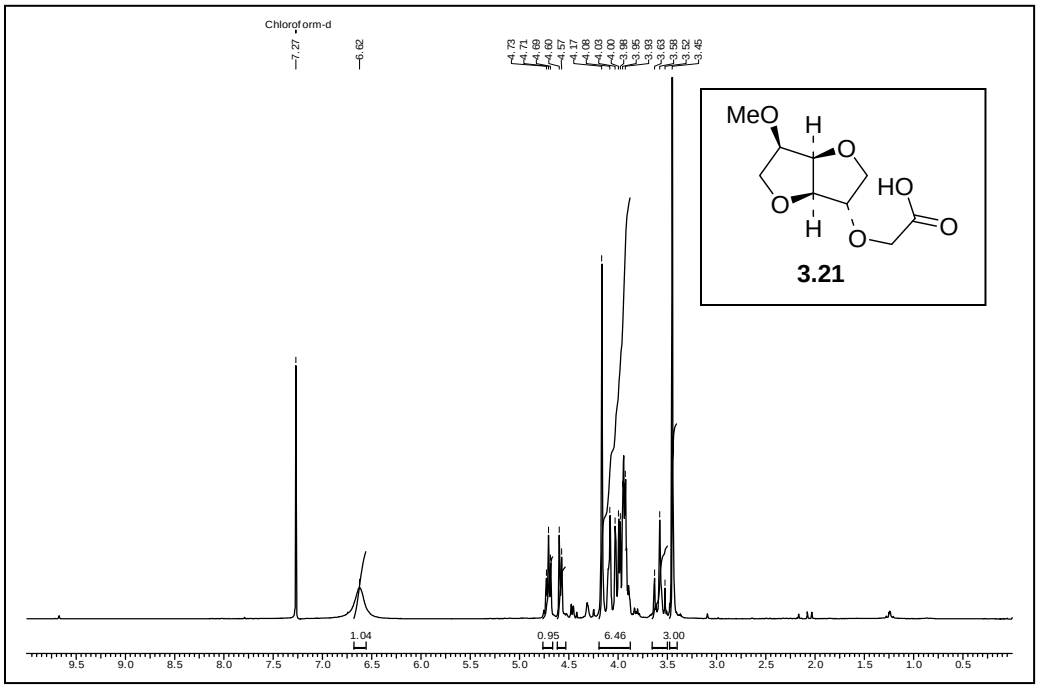
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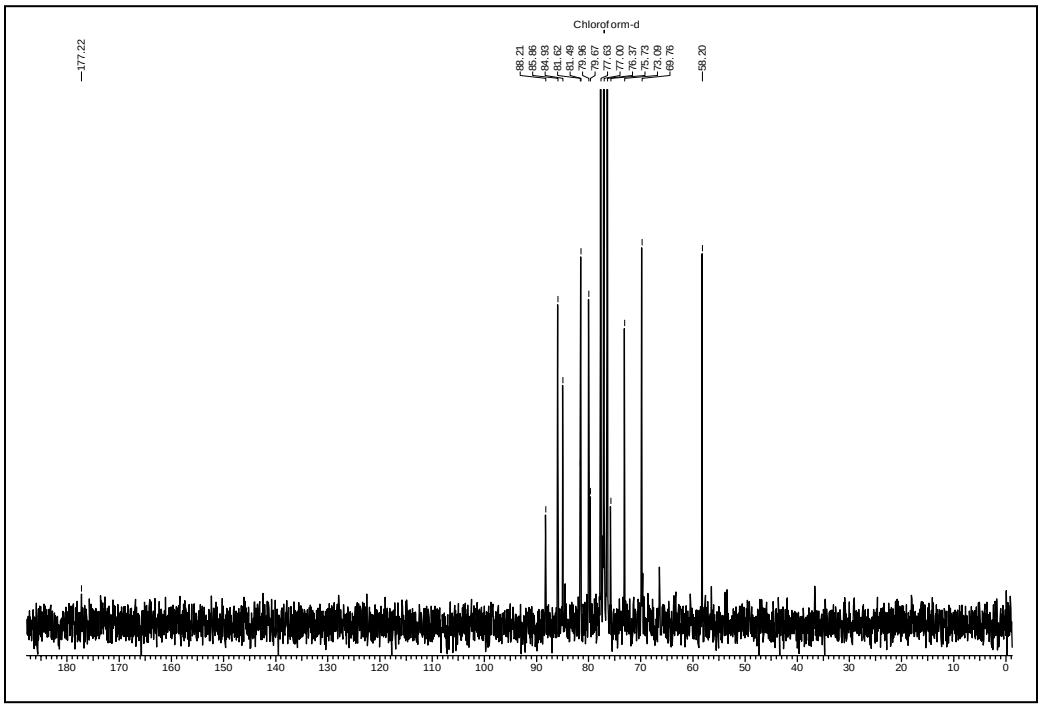
6.62
4.73
4.71
4.69
4.60
4.57
4.17
4.08
4.03
4.00
3.98
3.95
3.93
3.63
3.58
3.52
3.45
MeO
H
O
HO
O
H
O
O
3.21
1.04
0.95
6.46
3.00


Chloroform-d
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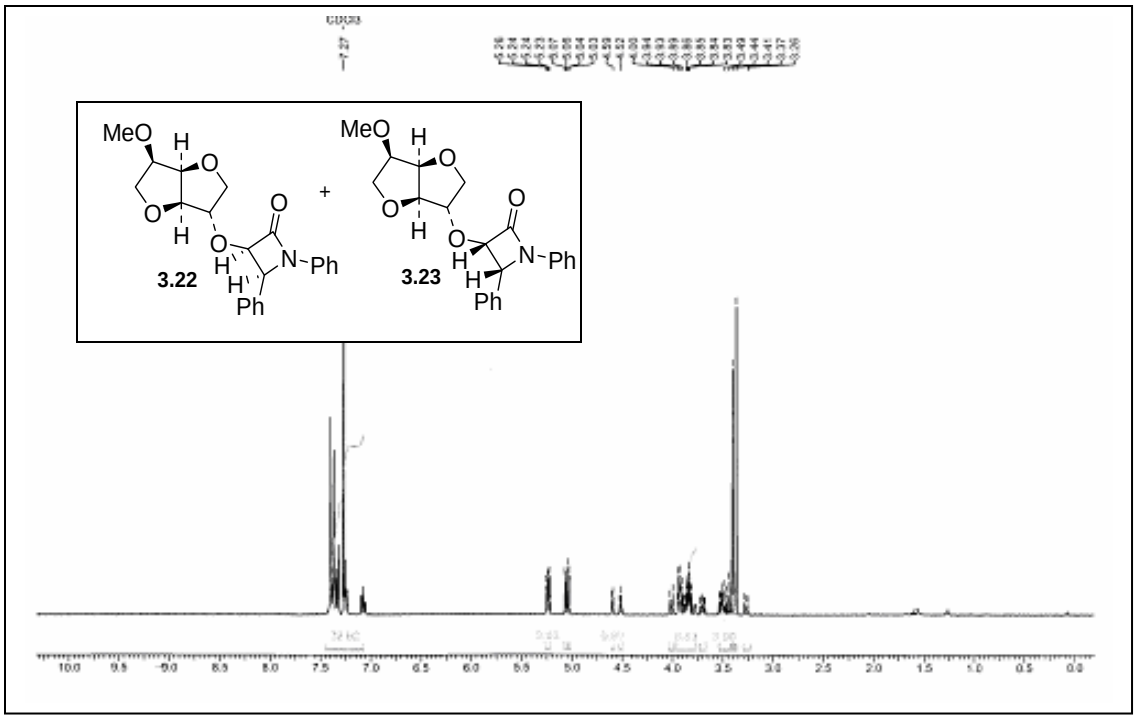
88.21
85.86
84.93
81.62
81.46
79.96
79.67
77.63
77.00
76.37
75.73
73.09
69.76
58.20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H
O
O
H
O
H
H
Ph
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N
Ph
3.22
+
MeO
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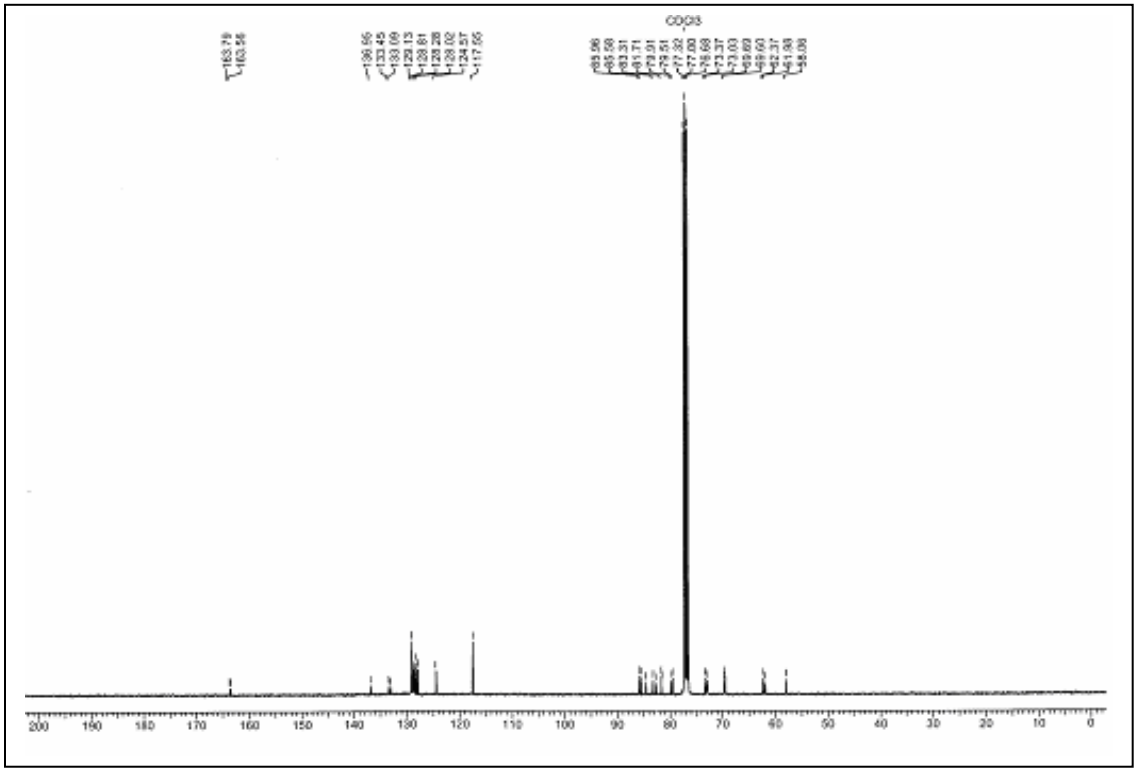
H
Ph
O
N
Ph
3.23


CDCl3

Chapter IV

Study directed towards synthesis of 3-hydroxy-4-carboethoxy azetidin-2-ones from L(+) diethyl tartrate

4.1: Introduction

The synthesis of the β-lactam ring *via* formation of the C_4-N_1 bond is the synthetic route selected by nature for the biosynthesis of azetidinone-containing antibiotics (Figure 1).[1] For the organic chemist, retrosynthetic analysis involving cleavage of the C_4–N_1 azetidinone bond has generated a significant number of synthetic approaches to the preparation of this important heterocycle.[2] Here, we have highlighted many of these methodologies which are developed over the past decade for this conversion.

New methods for the preparation of the β-lactam ring through formation of C_4–N_1 bond have been dominated by strategies involving the intramolecular displacement of a leaving group attached to C-4 with an appropriately activated nitrogen. In the simplest sense, this has been realized as S_N2-type displacements of primary halogens by an amide nitrogen under basic conditions. These straightforward cyclizations have been performed with a variety of bases under various conditions.[3,4]

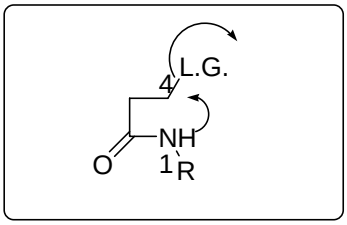


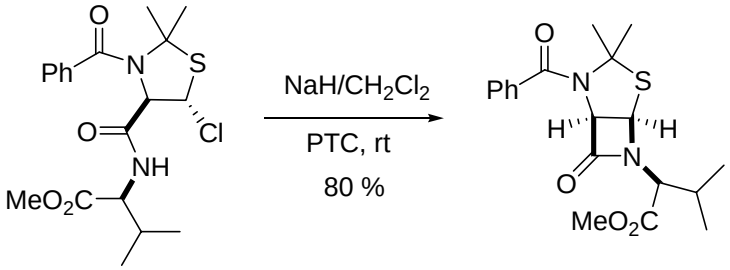
Figure 1 C_4-N_1 bond formation

4.2: Background for present work

There are several syntheses known in the literature for β-lactam ring *via* formation of the C_4-N_1 bond. A few of them are explained here in briefly.

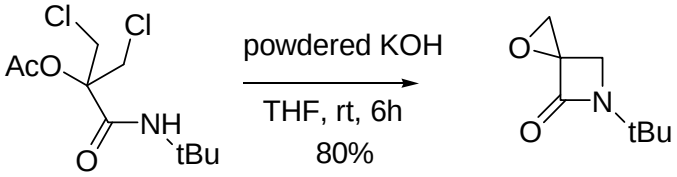
In 1975, Baldwin et al.[5] reported the synthesis of a single diastereomeric penicillin-derived compound *via* intramolecular cyclization with sodium hydride as a base, in 81% yield (Scheme 1.91).

Scheme 1.91



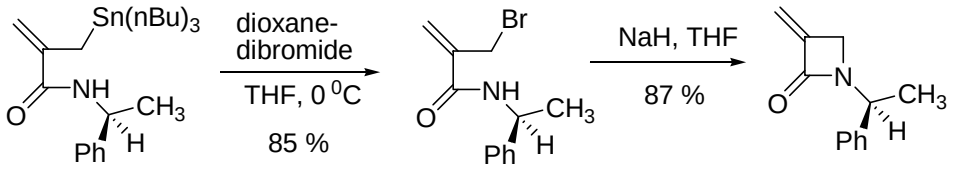
Sebti and Foucaud reported the intramolecular cyclization of dichlorosusbtitued amide to the epoxy β-lactam, in 80 % yield under heterogeneous conditions using powdered potassium hydroxide in THF (Scheme 1.92).[6]

Scheme 1.92



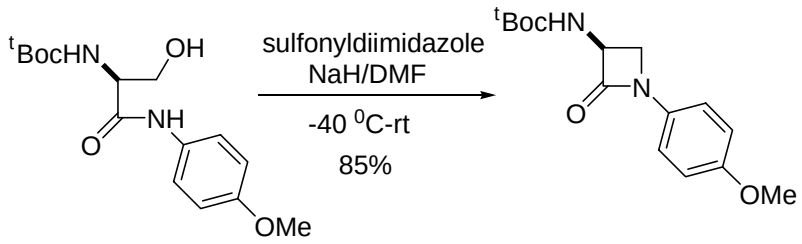
In 1986, Tanaka et al. used chiral pool at N_1 position of the chiral amide in the intramolecular cyclization reaction to get the chiral β-lactam in 87% yield (Scheme 1.93).[7]

Scheme 1.93



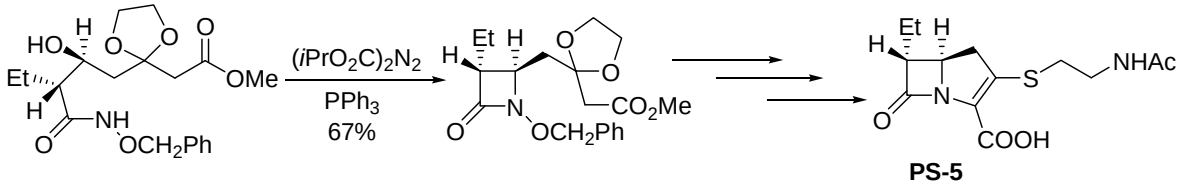
Hanessian at al.[8] utilized the reaction of hydroxy groups of *N*-substituted serine amides with imidazoylsulfonate functionality, which undergoes facile intramolecular ring closure with the amide nitrogen, providing β-lactam in 85% yield (Scheme 1.94).

Scheme 1.94



Miller et. al have made a significant contribution for the synthesis of β-lactam *via* formation of C_4–N_1 bond.[9] The key feature of this approach involves the intramolecular cyclization of chiral β-hydroxy hydroxamates derived from readily available chiral β-hydroxy acids under Mitsunobu reaction condition.[10] The chiral β-hydroxy hydroxamate was cyclized to the PS-5 precursor with 93% enantiomeric excess and 67% yield (Scheme 1.95).[11]

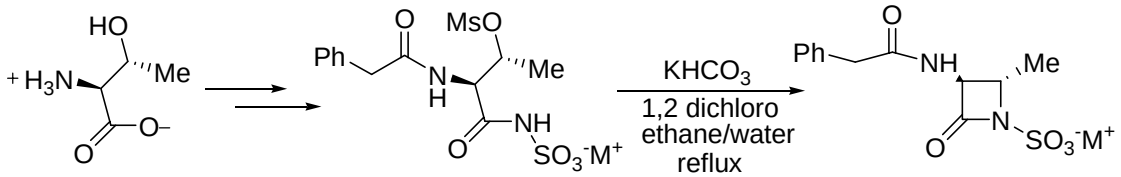
Scheme 1.95



PS-5

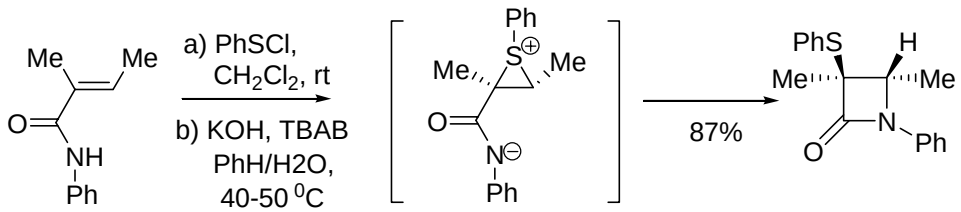
Floyd et. al have reported a novel synthesis of chiral azetidi-2-one. L-Threonine was transformed into the acyclic acyl sulfamate, which in turn was readily cyclized to the azetidin-2-one in 92% yield. The key feature of this approach was activation of the amide nitrogen. This is especially a useful process, as many of the important monobactams (e.g. azetreonam) are functionalized on the azetidin-2-one nitrogen with sulfonic acid moiety (Scheme 1.96).[12]

Scheme 1.96



Kamenti and co-workers developed a new methodology for the formation of azetidin-2-one rings *via* construction of C_4-N_1 bond are named as "sulfeno-cycloamination". In this process, an intermediate episulfonium ion forms which then undergoes facile intramolecular cyclization to get azetidin-2-one in 87% yield.

Scheme 1.97



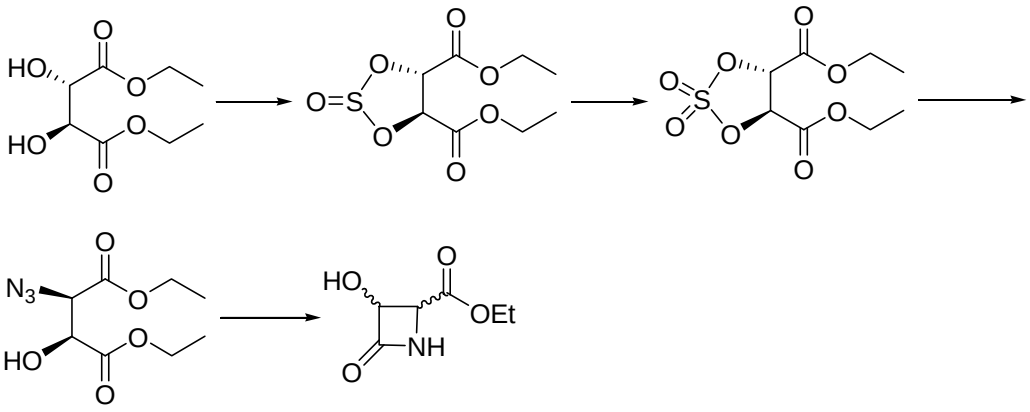
The resulting β-lactam bears a sulfide functionality which is readily removed or used to facilitate the introduction of another useful functionality onto the ring. The sulfeno-cycloamination process has been applied to the synthesis of intermediates useful for the preparation of monobactams and carbapenems (Scheme 1.97).[13,14]

4.3: Present work

We were interested in the asymmetric synthesis of 3-hydroxy-4-carboethoxy β-lactams *via* intramolecular cyclization of the C_4-N_1 bond formation starting from optically pure L(+)-diethyl tartrate. L(+)-tartaric acid is a convenient and highly functionalized four carbon component for asymmetric synthesis. Recently, it has received considerable attention as a chiralty transfer agent, especially in asymmetric epoxidation,[15]direct incorporation of tartaric acid's framework into synthetic targets is also of interest.[16]

3-Hydroxy-4-substituted β-lactam is an important synthon in Organic synthesis. It has been shown that a suitably substituted 3-hydroxy-β-lactam can serve as a synthetic equivalent for the phenylisoserine side chain of taxol,[17,18] a unique complex diterpene, is considered to be the most exciting drug in the anticancer chemotherapy in particular, for the treatment of lung, breast and ovarian cancer.[19] A direct coupling of 7-(triethylsilyl)baccatin III with a protected 3-hydroxy-β-lactam has also been used for the synthesis of taxol.[20] There are various strategies employed for the synthesis of 3-hydroxy-β-lactam in the literature. This chapter describes our attempts towards the development of a methodology to get enantiometrically pure 3-hydroxy-β-lactam *via* C_4-N_1 bond formation. Therefore, we planned the synthetic strategy as depicted in the Scheme 1.98.

Scheme 1.98

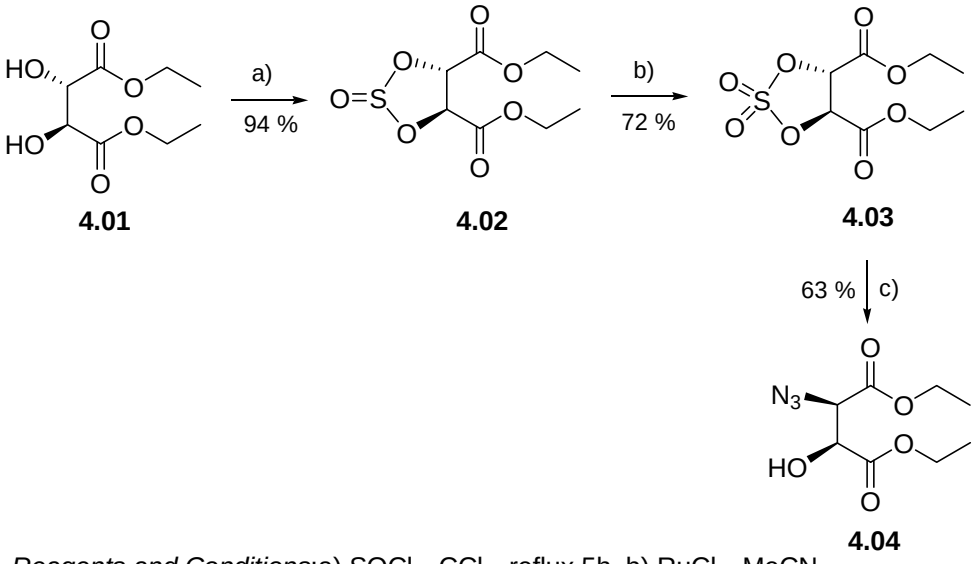


4.4: Result and Discussion

The L(+)-diethyl tartrate (**4.01**) was reacted with thionyl chloride in refluxing carbon tetrachloride as a solvent for 5h to get cyclic sulphite **4.02,** which was further

oxidized with $NaIO_4$ and $RuCl_3$ in acetonitrile and carbon tetrachloride mixture (1:1) to give the cyclic sulfate **4.03** in 72% yield by a reported procedure.[21] The nucleophilic ring opening of cyclic sulfate **4.03** was carried out with the aq. lithium azide in THF-H_2O mixture (1:1) at room temperature to give the optically pure azido-alcohol **4.04**, which is a precursor for the intramolecular cyclization reaction of β-lactam ring formation [22] (Scheme 1.99). The IR spectrum of azido-alcohol **4.04** showed a charactertics peak at 2119 cm^{-1} for azide group.

Scheme 1.99

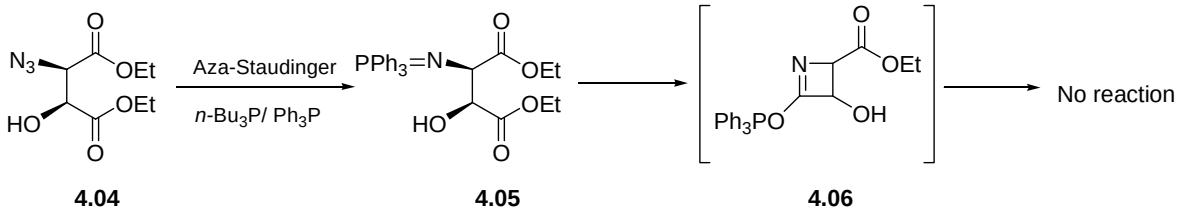


4.01 **4.02** **4.03** **4.04**

Reagents and Conditions:a) $SOCl_2$, CCl_4, reflux 5h, b) $RuCl_3$, MeCN, $NaIO_4$, CCl_4/H_2O, 50-60 min, c) aq. LiN_3, THF, 6 h

The azido-alcohol **4.04** was reacted with *n*-Bu_3P/Ph_3P in THF at room temperature for 12 h (Aza-Staudinger reaction). We thought that it would form Aza-Wittig salt **4.05** and further cyclized into the intermediate **4.06** to give 3-hydroxy-4-carboethoxy-β-lactam. But, we did not get the desired 3-hydroxy-4-carboethoxy-β-lactam. Then we refluxed the reaction mixture for 5 h and got the polymeric reaction mixture (Scheme 2.00). We tried different reagents and reaction conditions to cyclized the azido-alcohol **4.04** to the 3-hydroxy-4-carboethoxy-β-lactam but our all efforts to get the cyclized product was not successful.

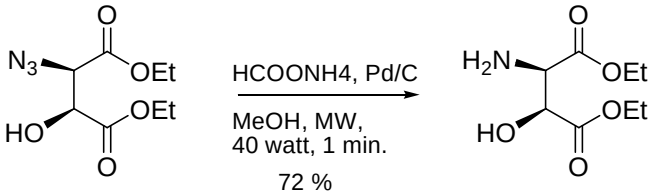
Scheme 2.00



4.04 **4.05** **4.06**

Then we planned to synthesize amino-alcohol **4.07** from azido-alcohol **4.04.** The azido-alcohol **4.04** was reduced with $HCOONH_4$, Pd/C and ethyleneglycol as solvent in Microwave oven for 1 minute we did get the amino-alcohol **4.07** along with polymeric impurities. When methanol was used as solvent for this reaction, we got the desired optically pure amino-alcohol **4.07** in 72% yield (Scheme 2.01).

Scheme 2.01



4.04 **4.07**

The structure of the amino-alcohol **4.07** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

The IR spectrum of **4.07** showed a sharp peak at 1741 cm^{-1} which is characteristic of the ester carbonyl group. The broad peak showed at 3375 and 3461 cm^{-1} indicated the presence of amino and hydroxy functionalities.

The ^{1}H NMR spectrum of **4.07** showed a multiplet at 1.20-1.30 ppm which was attributed to the two methyl groups. A broad singlet was seen at 2.54 ppm for amino and hydroxy protons. A doublet appeared at 3.89 ppm (J = 3.1 Hz) for the methine proton near to amino group. A multiplet appeared at 4.15-4.23 ppm for two methylene groups. A doublet appeared at 4.48 ppm (J = 3.1 Hz) for the methine proton near to hydroxy group.

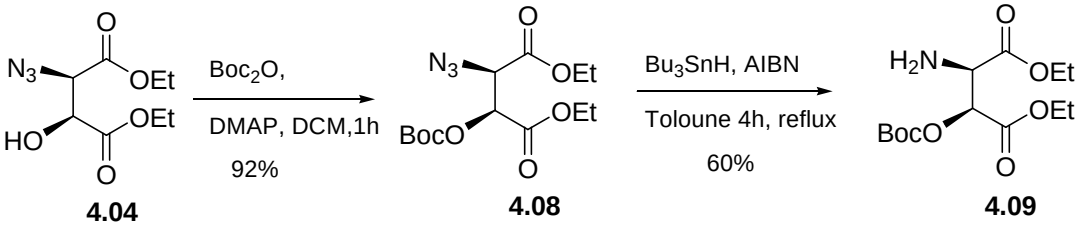
In the ^{13}C NMR spectrum of **4.07**, the two methyl peak appeared at 13.9 ppm. The methine carbon attached to the amino group showed at 57.4 ppm. The two methylene carbons appeared at 61.4 and 61.7 ppm. It was confirmed from DEPT experiment. The

methine carbon attached to the hydroxy group appeared at 72.6 ppm. The two carbonyl carbons appeared at 171.6 and 171.8 ppm. The mass spectrum of **4.07** showed a peak at m/z 205 (M^+) also supports the structure. The amino-alcohol **4.07** also gave satisfactory elemental analysis.

The amino-alcohol **4.07** was treated with Grignard reagent, *t*-BuMgCl in THF at different reaction conditions did not give the desired cyclized product 3-hydroxy-4-carboethoxy-β-lactam and the starting material was recovered back. We have also tried to cyclize the amino-alcohol **4.07** in acid catalyzed reaction as well as base catalyzed reaction at different reaction conditions but all our attempts were unsuccessful.

Then we planned to protect hydroxyl group of azido-alcohol **4.04** with Boc-anhydride to get azido-boc tartrate **4.08** in 92% yield. The azido-boc tartrate **4.08** was reduced with 10% Pd/C, Raney Ni and transfer hydrogenation conditions but we couldn't get the pure amino-boc tartrate **4.09.** Finally, the azido-boc tartrate **4.08** was converted to the amino-boc tartrate **4.09** with tributyltinhydride and AIBN in toluene at reflux for 4h in 60% yield (Scheme 2.02).

Scheme 2.02



4.04 **4.08** **4.09**

The structure of the amino-boc tartrate **4.09** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

The IR spectrum of **4.09** showed peaks at 1726 and 1737 cm^{-1} which are attributed to the ester and anhydride carbonyl group respectively. The broad peak showed at 3442 cm^{-1} indicated the presence of amino group.

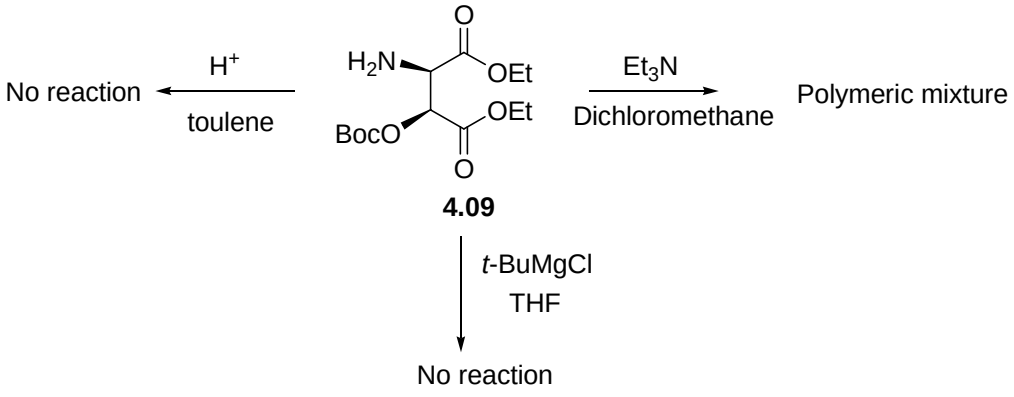
The ^{1}H NMR spectrum of **4.09** showed a multiplet at 1.19-1.40 ppm which was attributed to the two methyl groups of ester. A singlet appeared at 1.43 ppm for three methyl groups of boc-protection. A multiplet appeared at 4.14-4.48 ppm for two methylene groups. A broad singlet resonated at 4.48 ppm for amino group. A doublet appeared at 4.80

ppm (J = 3.5 Hz) for the methine proton attached to amino group. A doublet appeared at 5.50 ppm (J = 3.5 Hz) for the methine proton attached to boc protection.

In the ^{13}C NMR spectrum of **4.09**, the two methyl peaks appeared at 13.9 and 14.0 ppm. The three methyl carbons of boc-group appeared at 28.2 ppm. The tetra-substituted carbon of boc-group appeared at 56.9 ppm. The two methylene carbons appeared at 61.9 and 62.2 ppm. It was confirmed from DEPT experiment. The methine carbon attached to the amino group showed at 72.1 ppm. The methine carbon attached to the boc-group appeared at 80.5 ppm. The boc-carbonyl appeared at 155.6 ppm. The two carbonyl carbons of an ester appeared at 168.6 and 171.6 ppm. The mass spectrum of **4.09** showed a peak at m/z 305 (M^+) also supports the structure. The amino-boc tartrate, **4.09** also gave satisfactory elemental analysis.

The amino-boc tartate **4.09** was treated with Grignard reagent, *t*-BuMgCl in THF at different reaction conditions. We also tried cyclization in acid catalyzed and base catalyzed reaction in different reaction conditions. But, all our efforts to cyclized the amino-boc tartrate **4.07** into the desired product 3-hydroxy-4-carboethoxy-β-lactam were unsuccessful. We recovered the starting material and in some cases polymeric mixture (Scheme 2.03).

Scheme 2.03



4.5: Conclusion

We have synthesized optically pure azido-alcohol, amino-alcohol and their derivatives which are synthetically very useful precursors. We have also studied different intramolecular cyclization reactions and synthesis of 3-hydroxy-4-carboethoxy substituted azetidin-2-ones is still in progress.

4.6: Experimental

4.6.1. Synthesis of cyclic sulphite 4.02: In 100 mL, two- necked round-bottom flask equipped with a reflux condenser, $CaCl_2$ guard tube and a rubber septum was placed L (+) diethyl tartrate (5 g, 24.2 mmol) in dry CCl_4 (25 mL). Thionyl chloride (2.5 mL, 36.3 mmol) was added via syringe slowly in 15 minutes. The resulting mixture was refluxed for 5 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure on rotary evaporator, which was further purified by flash column chromatography to give pure cyclic sulphite **4.02** as colourless oil (5.71g, 94 %).

IR ($CHCl_3$)	**:**	1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.28 (m, 6H, C*H*$_3$), 4.20-4.32 (m, 4H, C*H*$_2$), 5.22 (d, *J* = 4.3 Hz, 1H, N-C*H*), 5.66 (d, *J* = 4.3 Hz, 1H, O-C*H*)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 13.5, 62. 6, 79.0, 79.6, 166.0
MS (m/z)	**:**	252 (M^+)
Analysis ($C_8H_{12}O_7S$)	**:**	Calculated: C, 38.09; H 4.79; S 12.71 Observed: C, 37.89; H 4.61; S 12.55
Optical rotation	**:**	$[\alpha]^{25}_D$ -170.6 (*c*, 2.0, $CHCl_3$)

4.6.2. Synthesis of cyclic sulfate 4.03: To an ice-cooled, solution of cyclic sulfite (5g, 19.8 mmol) in a mixture of MeCN (7.5 mL) / CCl_4 (7.5 mL) was added $NaIO_4$ (6.24 g, 50.32 mmol) followed by $RuCl_3$ (catalytic) and H_2O (11 mL). The resulting mixture was stirred for 50-60 min at room temperature (TLC). The mixture was then diluted with Et_2O (30mL). The organic layer was washed with water, saturated $NaHCO_3$, brine and dried over $NaSO_4$. The solvent was evaporated under reduced pressure to give pure cyclic sulfate **4.03** as white crystalline solid (3.82 g, 72 %).

MP	**:**	75-76 °C
IR ($CHCl_3$)	**:**	1743 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.38 (t, *J* = 6.0 Hz, 6H, C*H*$_3$), 4.40 (q, 4H, C*H*$_2$), 5.46 (s, 2H, C*H*)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 13.7, 63.8, 77.1, 164.3
MS (m/z)	**:**	268 (M^+)
Analysis ($C_8H_{12}O_8S$)	**:**	Calculated: C, 35.82; H, 4.51; S,11.93 Observed: C, 35.69; H, 4.63; S, 11.74
Optical rotation	**:**	$[\alpha]^{25}_D$ -72.8 (*c*, 0.3, $CHCl_3$)

4.6.3. Synthesis of azido-alcohol 4.04: The cyclic sulfate **4.03** (0.5g, 1.86 mmol) was dissolved in THF (10 mL) and then nucleophile LiN_3 (0.2 ml, 20% aq. solution) was added at 0 ^{0}C. Then added H_2O (10 mL). The resulting suspension was stirred at room temperature until no cyclic sulfate **4.03** remained (TLC). The solution was concentrated and the residue was stirred with 20% aq. H_2SO_4 for 10-12 h at room temperature. Then the organic phase was discarded and the aqueous phase was adjusted to pH = 10 with 20 % aq. NaOH and extracted with diethyl ether (3 x 10 mL). The combined organic layer washed with brine (20 ml) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get the crude product which on further purification by flash column chromatography gave azido-alcohol **4.05** (0.270 g, 63 %) as colourless oil.

IR ($CHCl_3$)	**:**	2119, 1745 cm^{-1}
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	δ_H 1.27-1.35 (m, 6H, C*H*$_3$), 3.0 (br, s, O*H*), 4.26-4.33 (m, 5H, N-C*H* and C*H*$_2$), 4.63 (d, *J* = 2.8 Hz, 1H, O-C*H*)
^{13}C NMR ($CDCl_3$)	**:**	δ_C 13.7, 62.1, 62.4, 64.3, 71.9, 166.9, 170.6

(75 MHz)

MS (m/z) : 231 (M^+)

Analysis : Calculated: C, 41.55; H, 5.66; N, 18.17

($C_8H_{13}N_3O_5$) Observed: C, 41.37; H, 5.47; N, 18.00

Optical rotation : $[\alpha]^{26}_D$ -5.85 (*c*, 0.15, $CHCl_3$)

4.6.4. Synthesis of amino-alcohol 4.05: The azido-alcohol **4.04** (0.100 g, 0.43 mmol) was dissolved in MeOH (4 mL) and added ammonium formate (0.136 g, 2.17 mmol) and 10% Pd/C (catalytic). The reaction mixture was kept in Microwave oven for 1 minute. Then TLC indicated the disappearance of the starting material. The reaction mixture was washed with MeOH (5 mL) and added water (5 mL). Then reaction mixture was filtered through sintered funnel. The filtrate was extracted with dichloromethane (3 x 10 mL). The combined organic layer washed with brine (10 mL) and dried over Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get pure amino-alcohol **4.05** (0.061 g, 63 %) as pale yellow oil.

IR ($CHCl_3$) : 3461, 3375, 1741 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.20-1.30 (m, 6H, C*H*$_3$), 2.54 (br, s, O*H* and N*H*$_2$), 3.89 (d, *J* = 3.1 Hz, 1H, N-C*H*), 4.15-4.23 (m, 4H, C*H*$_2$), 4.48 (d, *J* = 3.1 Hz, 1H, O-C*H*)

^{13}C NMR ($CDCl_3$) (75 MHz) : δ_C 13.9, 57.4, 61.4, 61.7, 72.6, 171.6, 171.8

MS (m/z) : 205 (M^+)

Analysis : Calculated: C, 46.82; H, 7.37; N, 6.83

($C_8H_{15}NO_5$) Observed: C, 46.71; H, 7.30; N, 6.90

Optical rotation : $[\alpha]^{26}_D$ +25.5 (c, 0.4, $CHCl_3$)

4.6.5. Synthesis of azido-boc tartrate 4.06: The azido-alcohol **4.04** (0.500 g, 2.16 mmol) was dissolved in dry dichloromethane (10 mL) and added DMAP (catalytic). The reaction mixture was kept at 0 ^{0}C and added boc-anhydride (0.93 g, 4.32 mmol) slowly via syringe. After 1 h, TLC indicated the disappearance of the starting material. The reaction mixture was washed with water (5 mL) and the reaction mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layer washed with brine (10 mL) and dried over Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude product which on flash column chromatography (10% ethyl acetate/ pet ether) to get the pure azido-boc tartrate **4.06** (0.658 g, 92 %) as colourless oil.

IR ($CHCl_3$) : 2121, 1753 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ_H 1.23-1.37 (m, 6H, C*H*$_3$), 1.47, 1.50 (s, 9H, boc-C*H*$_3$), 4.21-4.37 (m, 4H, C*H*$_2$), 4.46 (d, *J* = 3.2 Hz, 1H, N_3-C*H*), 5.43 (d, *J* = 3.2 Hz, 1H, O-C*H*)

^{13}C NMR ($CDCl_3$) (75 MHz) : δ_C 13.8, 27.5, 61.9, 62.1, 62.6, 73.9, 83.8, 152.0, 166.9

MS (m/z) : 331 (M^+)

Analysis ($C_8H_{13}N_3O_5$) : Calculated: C, 47.13; H, 6.39; N, 12.68

Observed: C, 47.06; H, 6.21; N, 12.52

Optical rotation : $[\alpha]^{26}_D$ -31.5 (*c*, 0.3, $CHCl_3$)

4.6.6. Synthesis of amino-boc tartrate 4.07: The azido-boc tartrate **4.06** (0.200 g, 0.60 mmol) was dissolved in dry toluene (15 mL) and added tributyltinhydride (0.360 g, 1.20 mmol) and AIBN (catalytic). The reaction mixture was refluxed for 3-4 h. Then, the reaction mixture was pouring on the neutral alumina and purified by flash column chromatography (20% ethyl acetate/ pet ether) to get the pure amino-boc tartrate **4.07** (0.110 g, 60 %) as pale yellow oil.

IR ($CHCl_3$) : 3442, 1737, 1726cm^{-1}

^{1}H NMR : δ_H 1.19-1.37 (m, 6H, C*H*$_3$), 1.43 (s, 9H, boc-C*H*$_3$), 4.48 (bs,

($CDCl_3$) (200 MHz)		NH_2), 4.14-4.48 (m, 4H, CH_2), 4.80 (d, J = 3.5 Hz, 1H, N-CH), 5.50 (J = 3.5 Hz), (d, J = 3.5 Hz, 1H, O-CH)
^{13}C NMR ($CDCl_3$) (75 MHz)	**:**	δ_C 13.9, 14.0, 28.2, 56.9, 61.9, 62.2, 72.1, 80.5, 155.6, 168.6, 171.6
MS (m/z)	**:**	305 (M^+)
Analysis ($C_{13}H_{23}NO_7$)	**:**	Calculated: C, 51.14; H, 7.59; N, 4.59 Observed: C, 51.07; H, 7.43; N, 4.48
Optical rotation	**:**	$[\alpha]^{26}_D$ +20.0 (c, 0.2, $CHCl_3$)

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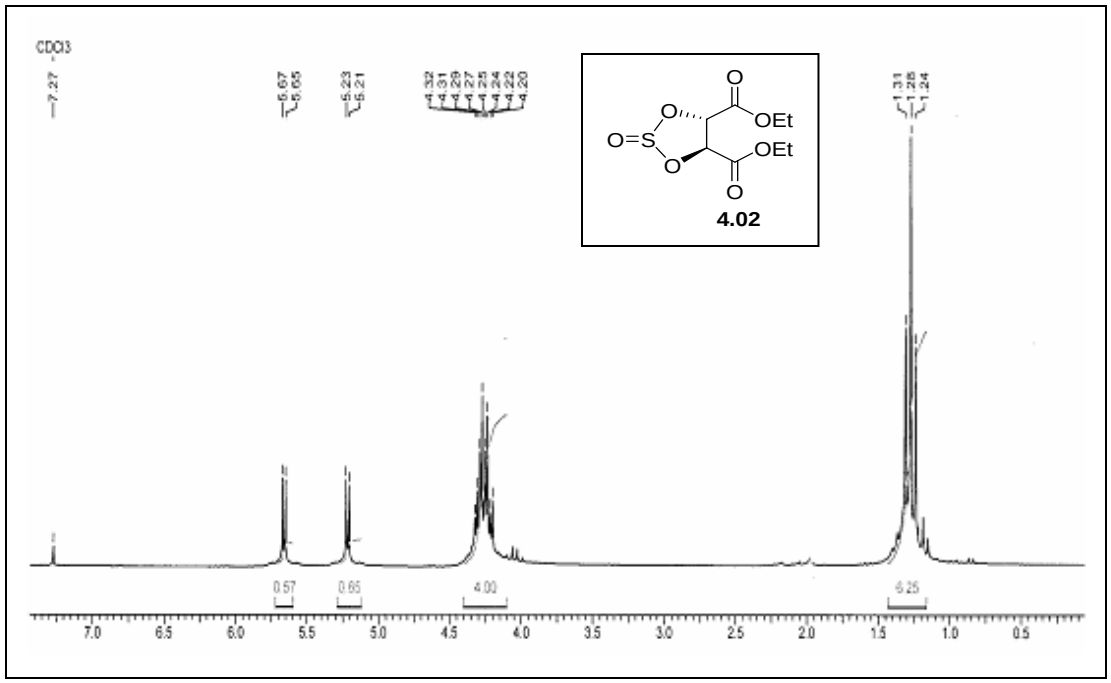
Chapter IV

Spectra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4.20
1.31
1.28
1.24
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0.65
4.00
6.25
7.0
6.5
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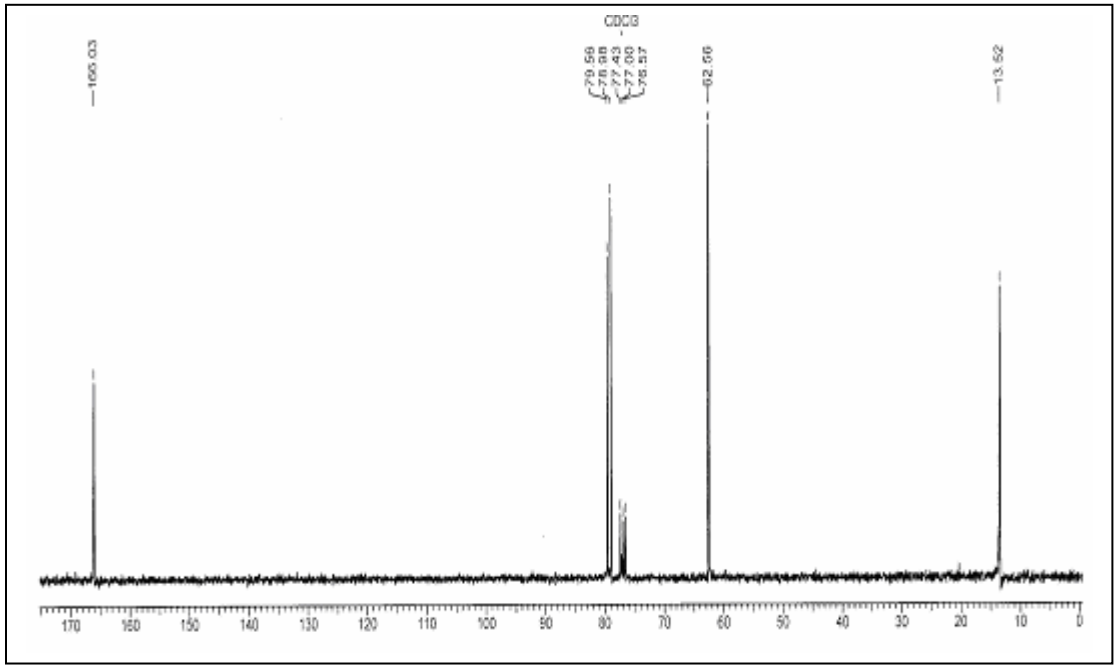
0.5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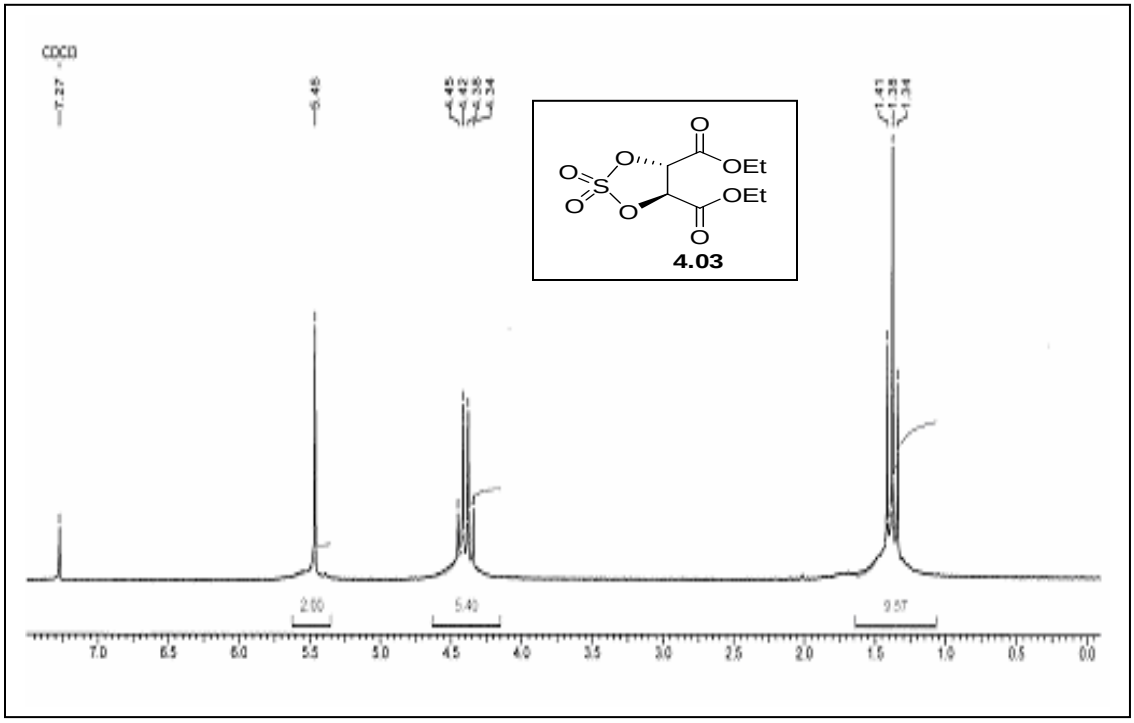
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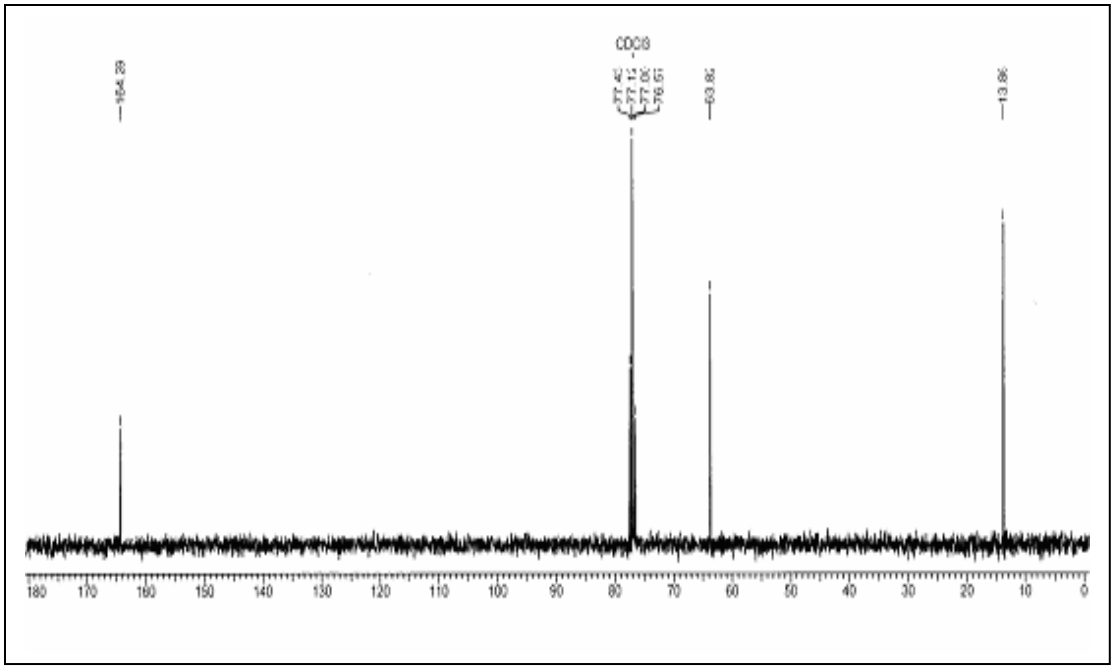
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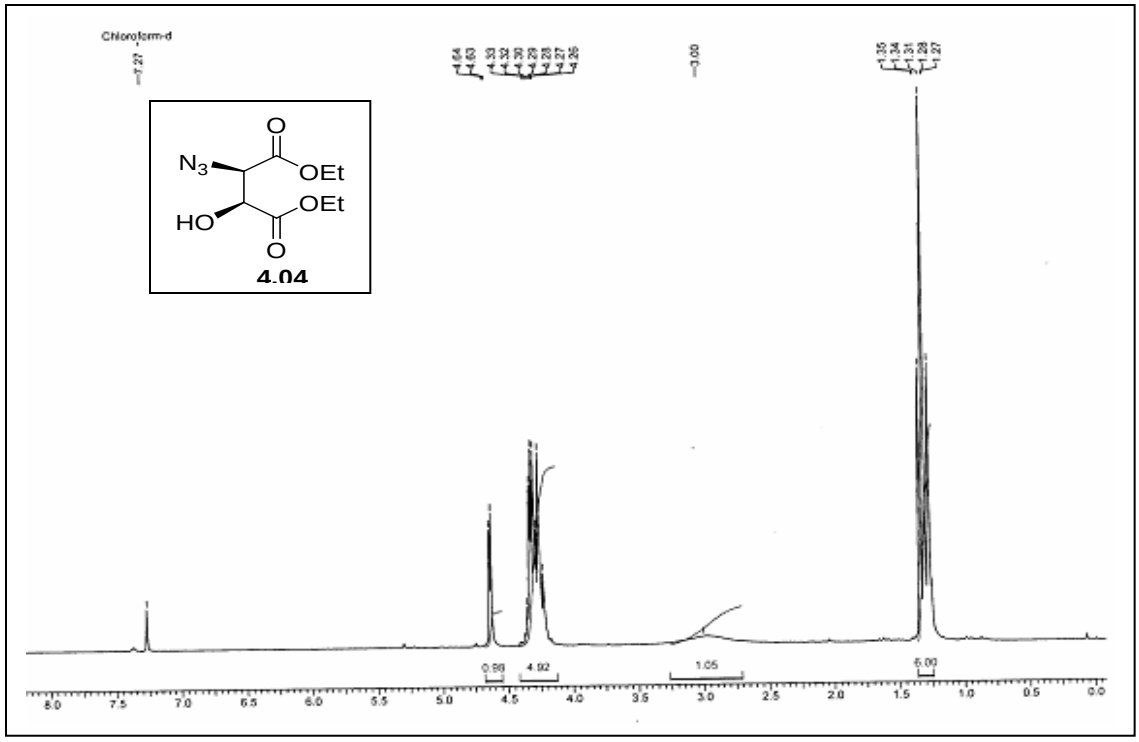
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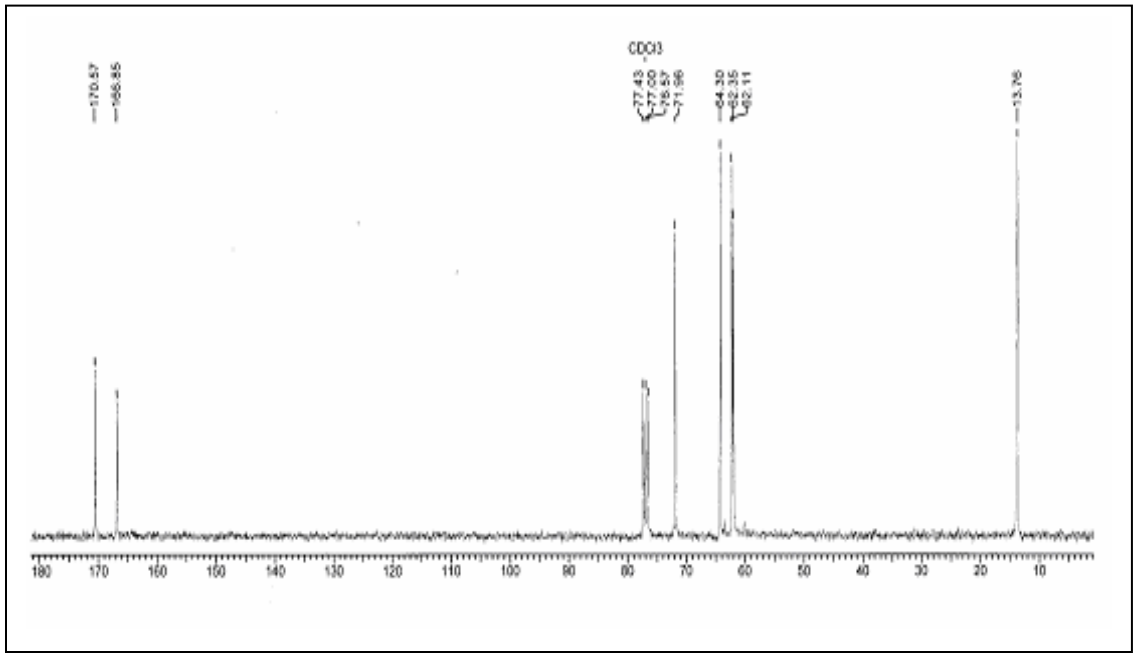
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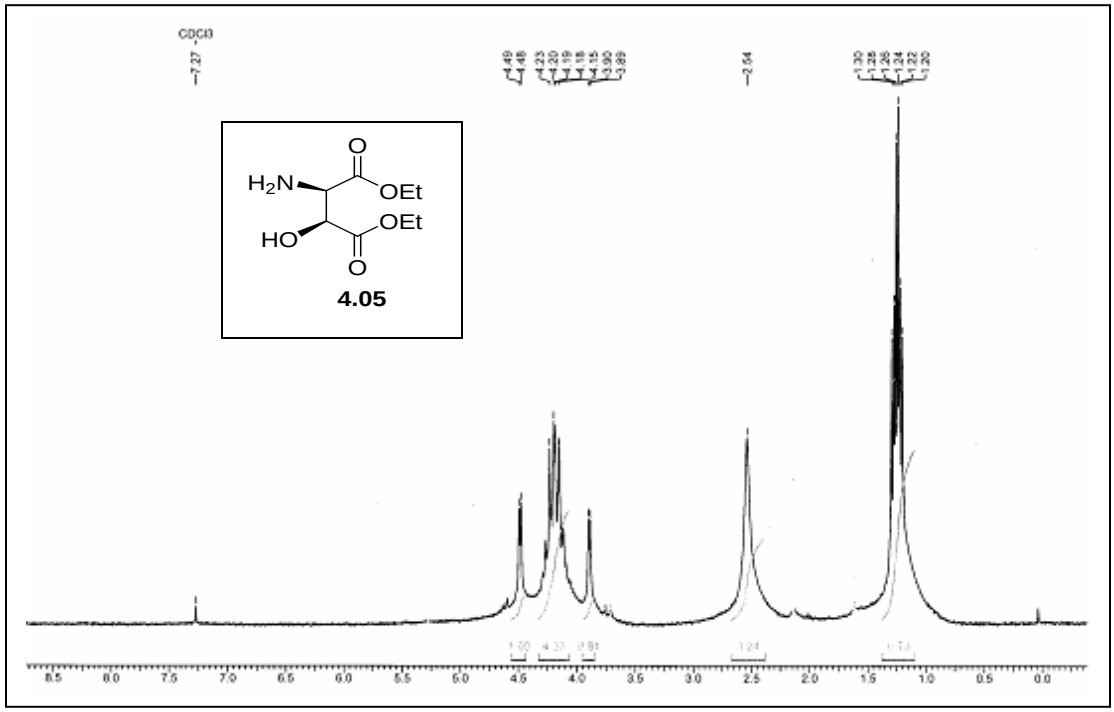
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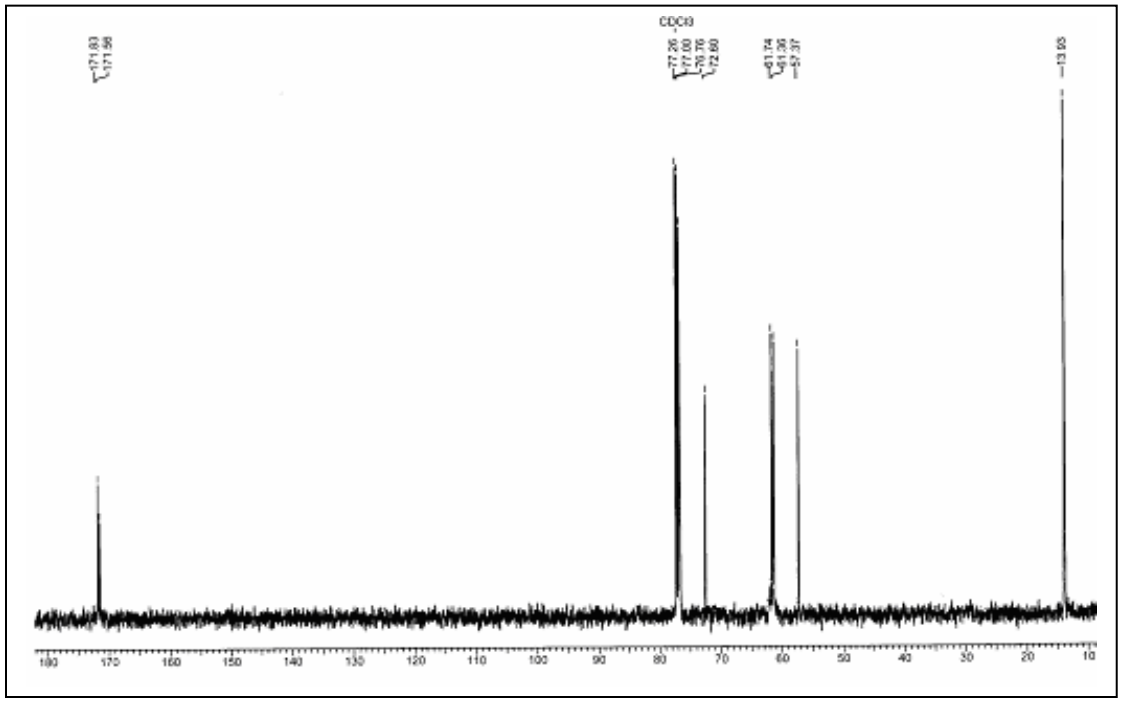
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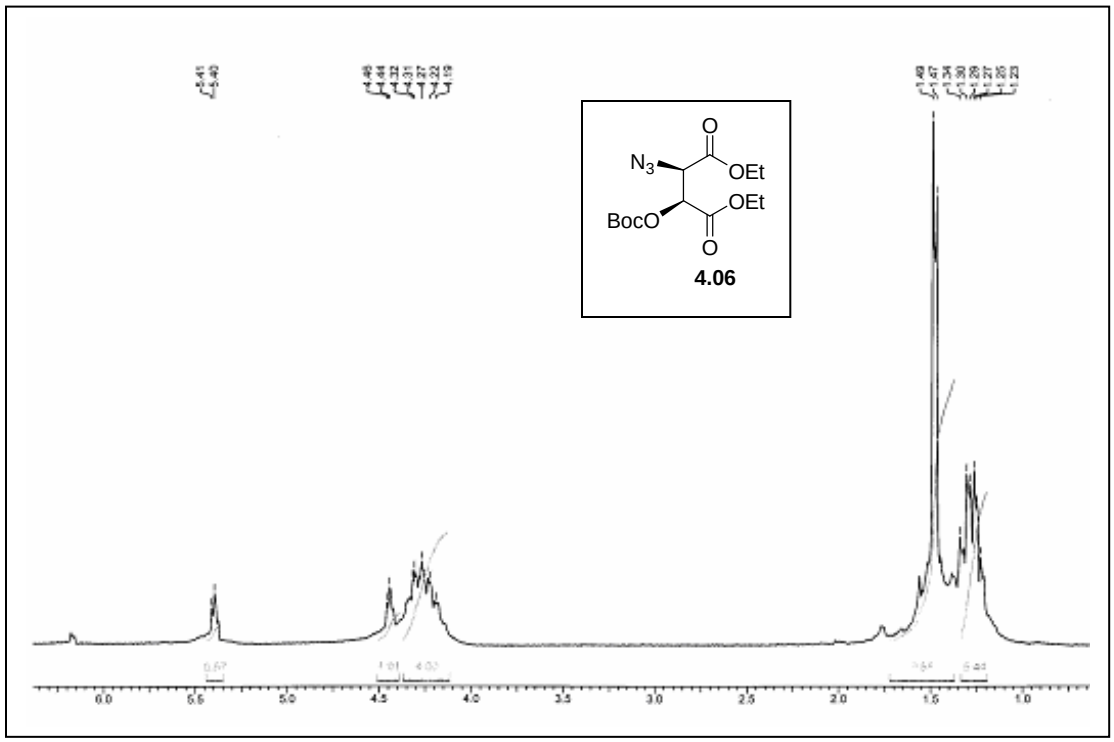
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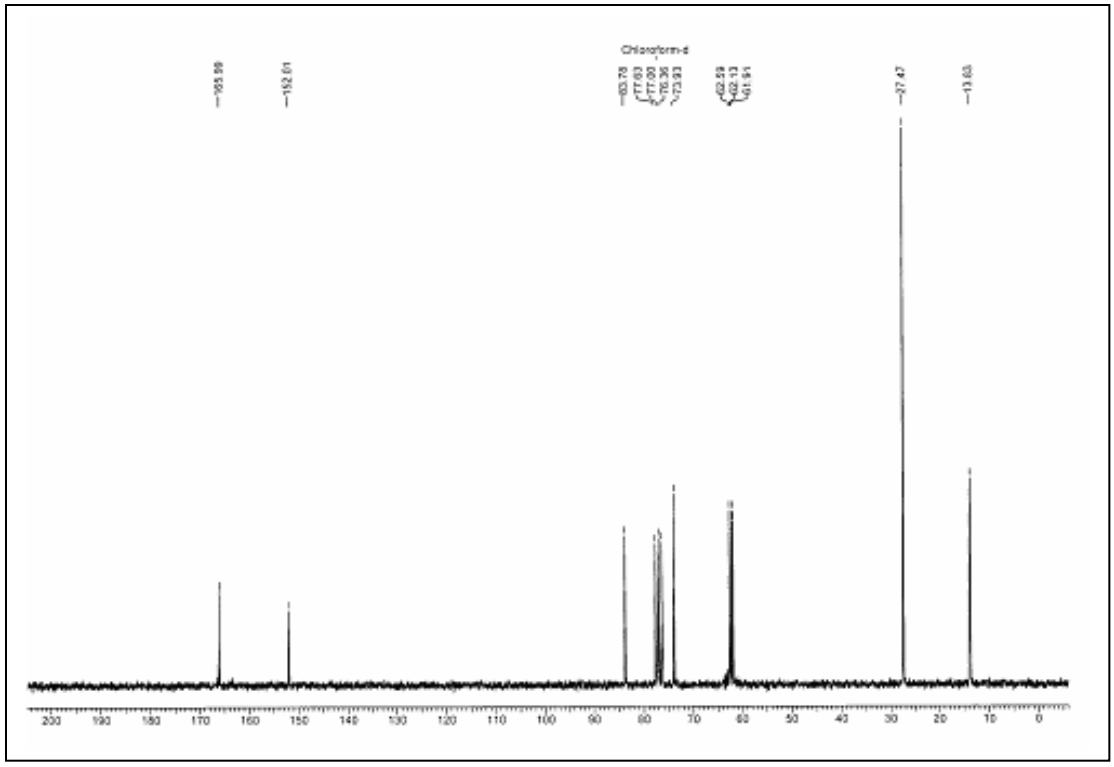
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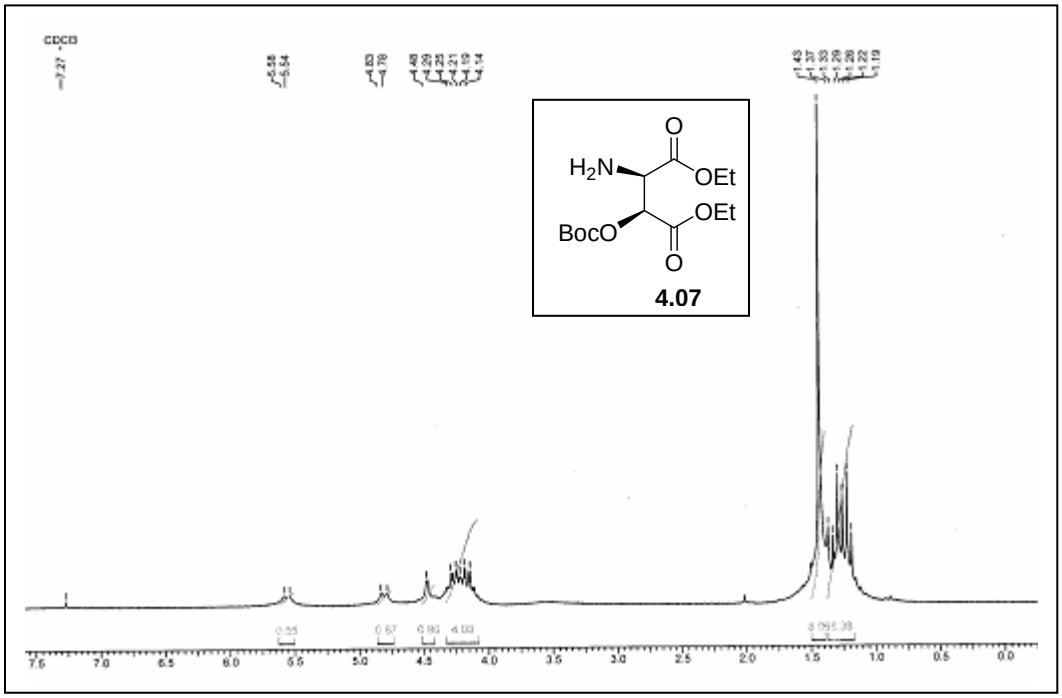
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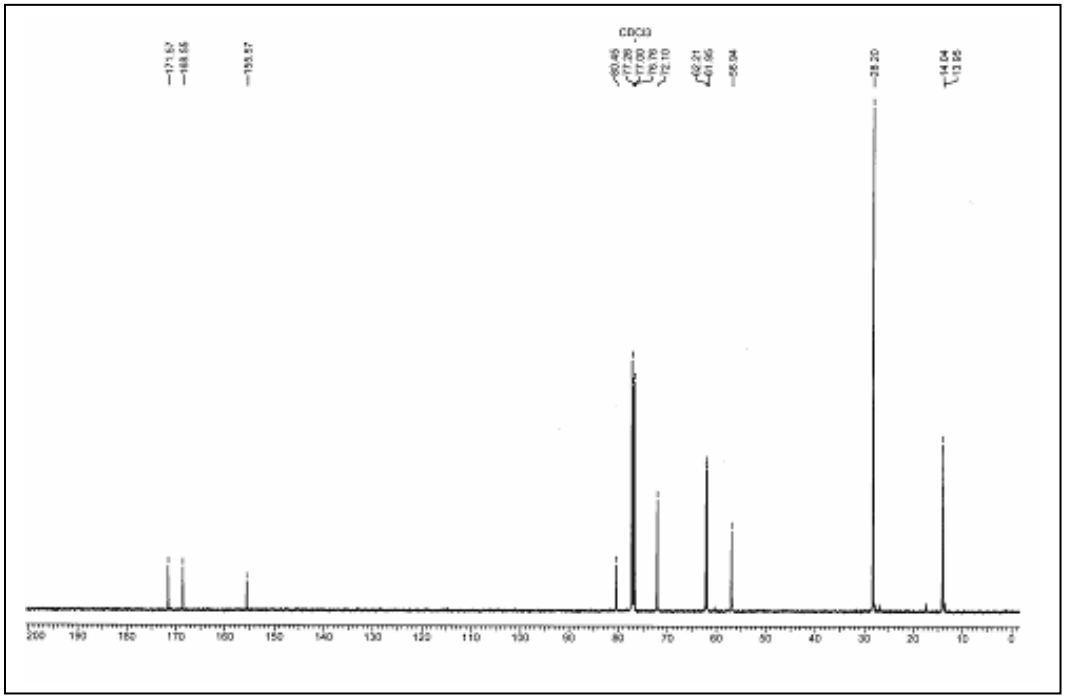
CDCl3

List of Publications

1. Synthesis of *cis* bis-β-lactams via Staudinger cycloaddition reaction using C_2-symmetric1, 2 diamines.

   Aarif L. Shaikh, Vedavati G. Puranik and A. R. A. S. Deshmukh, *Tetrahedron* **2005**, *61*, 2441-2451.

2. γ-Heteroatom directed stereocontrolled Staudinger cycloaddition reaction of vinylketenes and imines.

   Aarif L. Shaikh, Vedavati G. Puranik and A. R. A. S. Deshmukh, *Tetrahedron Letters* **2006**, *47*, 5993-5996.

3. Benzannulated cyclooctanol derivatives by samarium diiodide induced intramolecular carbonyl-alkene coupling-scope, limitations, and strereoselectivity.

   Hans-Ulrich Reissig, Faiz Ahmed Khan, Regina Czerwonka, Chimmanamada U. Dinesh, **Aarif L. Shaikh** and Reinhold Zimmer.

   European Journal of Organic Chemistry **2006**, 4419-4428.

4. Asymmetric synthesis of azetidin-2-ones by [2+2] cycloaddition using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral pools.
   A. L. Shaikh, A. S. Kale, Md. Abrar Shaikh, Vedavati G. Puranik, and A. R. A. S. Deshmukh, *Tetrahedron* **2007**, *63*, 3380-3388.

5. Highly Stereoselective Synthesis of *trans*-3-vinylazetidin-2-ones.

   Aarif L. Shaikh, Vedavati G. Puranik and A. R. A. S. Deshmukh (manuscript under process)

Erratum