DIASTEREOSELECTIVE STAUDINGER REACTION

FOR THE SYNTHESIS OF AZETIDIN-2-0NES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

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DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE – 411 008.

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Diastereoselective Staudinger reaction for the synthesis of azetidin-2-ones"*** submitted by ***Mr. K. Karupaiyan*** was carried out by him under my supervision at National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date:

National Chemical Laboratory

Pune – 411 008.

(Dr. B. M. Bhawal)

Research Guide

Acknowledgement

It is indeed a great pleasure to take this opportunity to express a deep sense of gratitude to my research guide Dr. B. M. Bhawal for his constant encouragement and teaching through out the course of my thesis work.

I thank all my labmates for their support and cooperation during the course of this work. I would like to thank my seniors Dr. M. Jayaraman and Dr. V. Srirajan for their useful suggestions.

I would like to thank Dr. K. N. Ganesh, Head, Div. of Organic Chemistry (Synthesis) for providing me necessary facilities.

I am thankful to the director, National Chemical Laboratory, Pune, for permitting to me to submit this work in the form of a thesis.

Help from Spectroscopic, microanalysis and HPLC groups is gratefully acknowledged. In particular I thank Mr. A. Samuel, Mr. Sathe and Dr. Rajamohanan for helping to me get NMR spectra in time. I also thank Mrs. Dr. V. G. Puranik for her help in X-ray data collection.

I thank all my friends inside and outside the NCL for their valuable help and moral support. Thanks are also due to staff members and students of the division for constant cooperation.

I am indebted to my to parents, sisters, and their family and relatives for their constant encouragement and moral support during the course this work.

Finally I would like to thank CSIR, New Delhi for providing me fellowship.

K. Karupaiyan.

DEDICATED

TO MY PARENTS AND SISTERS

Contents

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on Celsius scale.

2. IR spectra were recorded as nujol mull or chloroform, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattson, UK, Model-RS-1 FT-IR using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).

3. ^{1}H NMR spectra were recorded using trimethylsilane as internal reference on Bruker AC-200, Bruker MSL-300 and Bruker DRX-500. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz*., s = singlet, d = doublet, t = triplet, dd = doublet of doublet, bs = broad singlet, m = multiplet have been used to describe spectral data. $CDCl_3$ was used as 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 50.3, 75.2 and 125.3 respectively.

5. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.

6. Elemental analysis (C, H, N & S) was obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.

7. Optical rotation was measured on a JASCO-181 digital polarimeter using sodium line (5893 A°). Concentration is expressed in gm/ml.

8. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck). Purification of products was carried out by column chromatography using silica gel obtained from SD fine chemicals (60-120 mesh, 25049 grade; 100-200 mesh, 25121 grade) and Merck (230-400 mesh, 9385 grade).

9. Pet. ether refers to the petroleum faction boiling between 60-80 °C.

10. ^{1}H NMR and ^{13}C NMR spectra of the compounds are attached at the end of the corresponding chapter.

ABBREVIATIONS

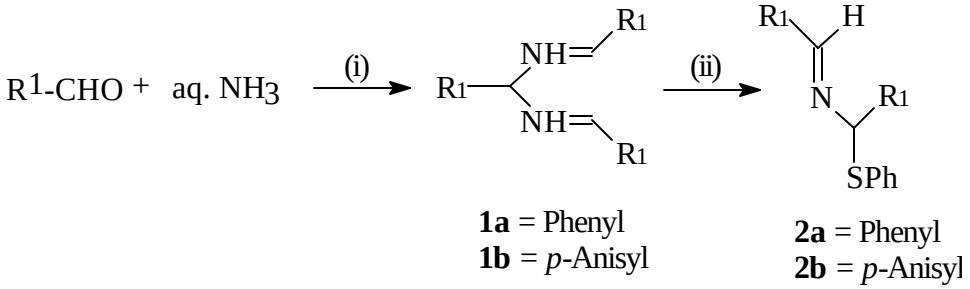
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Fu	Furfuryl
Ph	Phenyl
Me	Methyl
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
TMS	Trimethylsilyl
TBDMS	*tert*-butyldimethylsilyl
p	Para
de	Diastereomeric excess
RT	Room temperature
M.P.	Melting point
LDA	Lithium diisopropylamide
CAN	Ceric ammoniumnitrate
Re Ni	Raney Nickel
LAH	Lithium aluminiumhydride
PTSA	*p*-Toluenesulfonic acid
PCC	Pyridinium chlorochromate
PPA	Polyphosphoric acid
MeCN	Acetonitrile
DCM	Dichloromethane
$CHCl_3$	Chloroform
EtOEt	Ethyl ether
THF	Tetrahyrofuran
PhH	Benzene
MeOH	MeOH
EtOH	EtOH
EtOAc	Ethylacetate

SYNOPSIS OF THE THESIS

Chapter-I: Synthesis of N1-Unsubstituted b-lactam via a facile deprotection of N1-[(a-thiophenyl) benzyl] group.

The choice of the protective group is based on the ease of selective removal at appropriate time. This chapter describes the use of novel N-protective group in β-lactam chemistry and its deprotection under mild reaction conditions.

The aromatic aldehydes on treatment with aq. NH_3 gave corresponding hydrazamides 1a and 1b in very good yields. These hydrazamides (1) on reaction with thiophenol gave the imines (2a,b) in excellent yields.

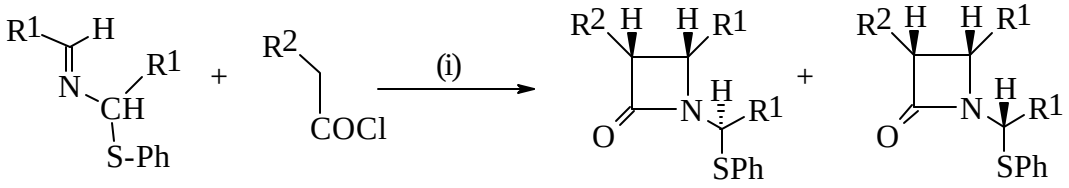


1a = Phenyl
1b = *p*-Anisyl

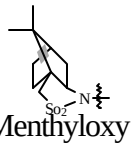
2a = Phenyl
2b = *p*-Anisyl

Reagents and reaction conditions (i): RT, r.t./3h, (ii): PhSH/dioxane, ref. 10h.

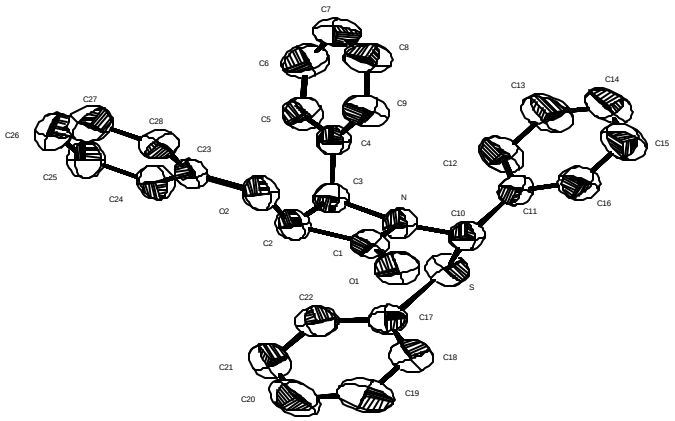
The imines (2) on cycloaddition (Staudinger) reaction with ketene precursor 3 in the presence of triethylamine at 0 °C gave diastereomeric mixture of only cis-β-lactams (4 a-g and 5 a-g) in good yields with moderate diastereoselectivity (determined by ^{1}H-NMR and HPLC analysis of crude reaction mixture). The maximum diastereomeric excess (de = 92%) was obtained in the case of 4f with chiral acid derived from Oppolzer's sultam. The relative configuration of the major isomer 4a was found to be (1′S, 3S, 4R) from its X-ray analysis.



2 **3** **(±)-4a-g** **(±)-5a-g**

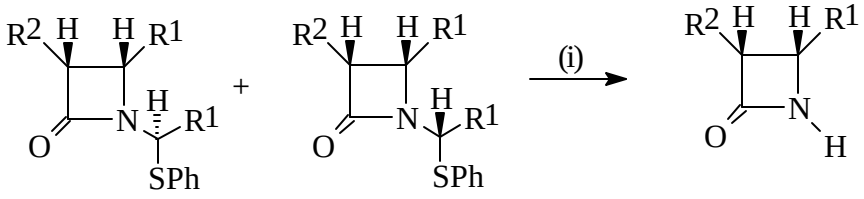
4 &5	R1	R2	4 &5	R1	R2
a	Ph	PhO	e	p-Anisyl	BnO
b	Ph	BnO	f	Ph	
c	Ph	AcO	g	Ph	Menthyloxy
d	p-Anisyl	PhO			

Reagents and reaction conditions (i): Et_3N/DCM, 0 °C, r.t. 13h.

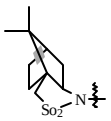


The ORTEP diagram of the β-lactam 4a

The Oxidative cleavage of N1-[(α-thiophenyl)benzyl] group using $K_2S_2O_8$, afforded the N1-unsubtituted β-lactams (6 a-e). The absolute stereochemistry of 6d was proved to be 3R, 4S by converting the mixture 4f and 5f into earlier known compounds.



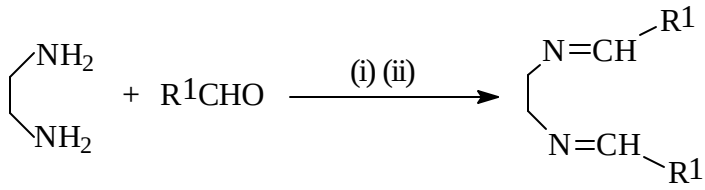
(±)-4a,b,d,f,g **(±)-5a,b,d,f,g** **(±)-6a-e**

6	R^1	R2	6	R^1	R2
a	Ph	PhO	d	Ph	
b	Ph	BnO			
c	p-Anisyl	PhO	e	Ph	Menthyloxy

Reagents and reaction conditions (i): $K2S2O_8$, $MeCN/H_2O$, ref. 4h.

Chapter-II: Stereoselective synthesis of cis-bis-b-lactams Linked with an ethylene bridge

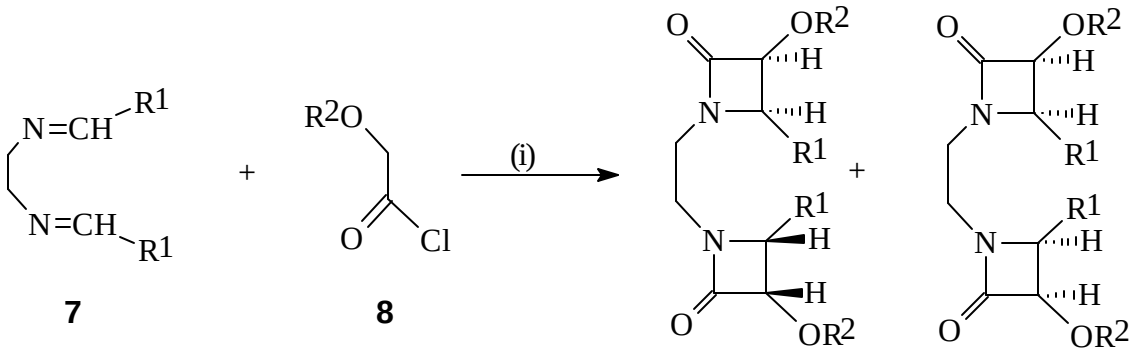
The synthesis of cis-bis-β-lactams has been achieved in one step from the bis-imines (7a-c) derived from ethylene diamine. These bis-imines have been prepared by condensing the corresponding aldehydes with ethylene diamine.



7a R^1 = p-Anisyl
7b R^1 = Ph
7c R^1 = -CH=CHPh

Reagents and reaction conditions (i): An.hyd $MgSO_4$/DCM, overnight (7a &7b), (ii): EtOH/ ref. 3h (7c) .

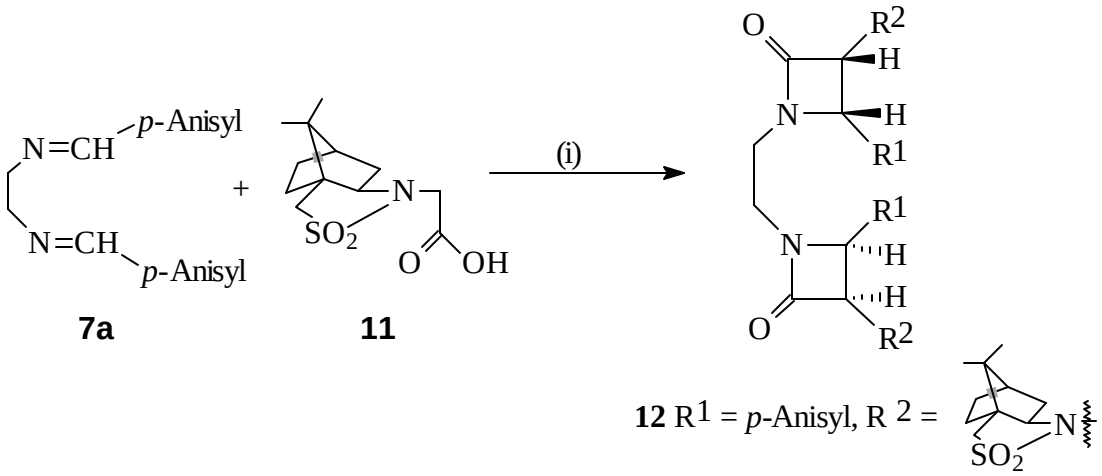
These bis-imines (7) on [2+2] cycloaddition (Staudinger reaction) with acid chlorides (8) in the presence of triethylamine at 0 °C gave a mixture of bis-β-lactams (9 a-g and 10 a-g) in very good yields with moderate diastereoselectivity (^{1}H-NMR). The bis-imine (7a) derived from *p*-anisaldehyde with the chiral acid 11 derived from Oppolzer's sultam in the presence of phenyl dichlorophosphate and triethylamine gave single diastereomer 12 (^{1}H NMR and HPLC analysis).



7 **8** **(±)-9a-g** **(±)-10a-g**

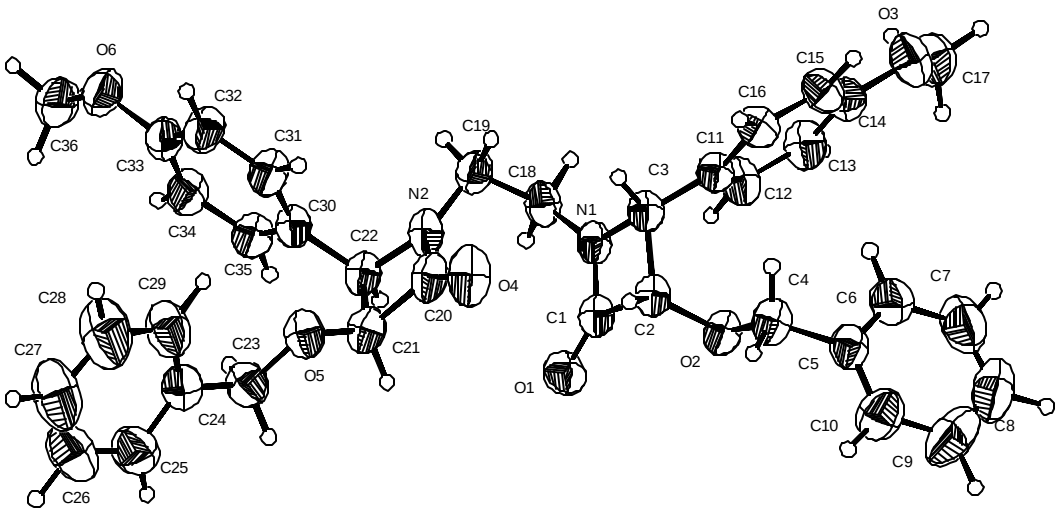
9 & 10	R1	R2	9 & 10	R1	R2
a	p-Anisyl	Ph	e	Ph	Bn
b	p-Anisyl	Bn	f	Styryl	Bn
c	p-Anisyl	Ac	g	Styryl	Ph
d	Ph	Ph			

Reagents and reaction conditions (i): Et_3N/DCM, 0 °C, r.t. 13h.

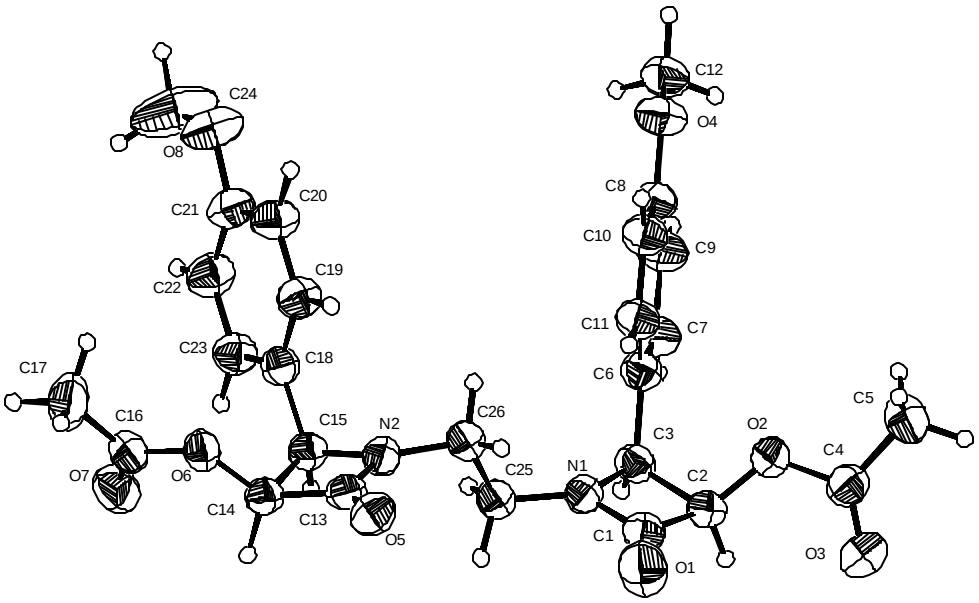


Reagents and reaction conditions (i): $Ph(PO)Cl_2$, Et_3N/DCM, 0 °C, r.t. 13h.

The relative stereochemistry of (±) bis-β-lactams 9b and 10c were assigned as 3S, 4R, 3′S, 4′R or 3R, 4S, 3′R, 4′S and 3S, 4R, 3′R, 4′S or 3R, 4S, 3′S, 4′R respectively from single crystal X-ray analysis. The absolute stereochemistry of bis-β-lactam 12 was ascertained as 3R, 4S, 3′R, 4′S based on analogy with our earlier results.



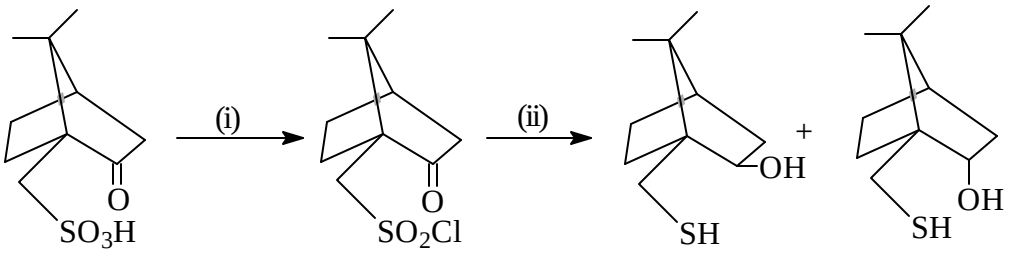
The ORTEP diagram of the β-lactam 9b



The ORTEP diagram of the β-lactam 10c

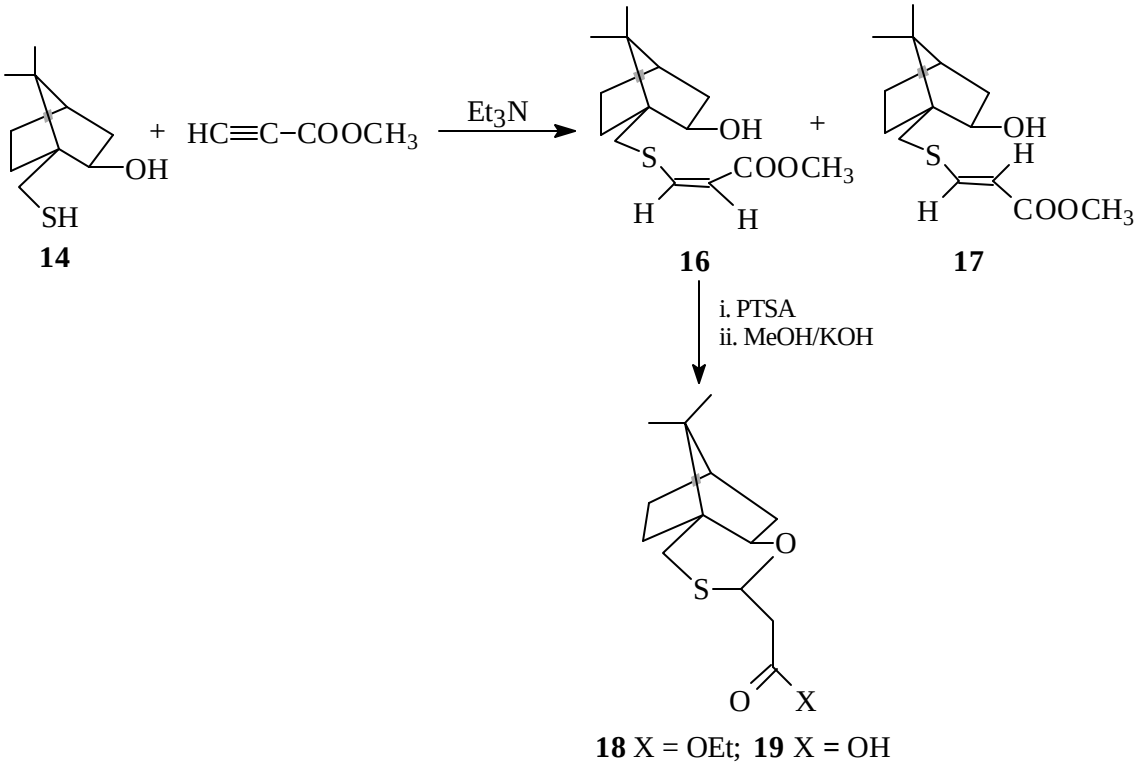
Chapter-III: Synthesis of chiral acid from camphor-10-sulfonic acid and its attempted application for the synthesis of b-lactam

Camphor-10-sulfonic acid on treatment with thionyl chloride gave sulphonyl chloride **13**, which on reduction with $LiAlH_4$ gave the isomeric thio alcohols **14** and **15** in good yield. The isomers were separated by column chromatography. The exo isomer **14** on 1,4 addition (Michael addition) with methyl propiolate in the presence of triethylamine at 0 °C gave a mixture of adducts **16** (Z-isomer) and **17** (E-isomer) in very good yield. The Z-isomer (**16**) was separated out as a crystalline solid, which on treatment with PTSA underwent cyclization to give ester **18**. The ester **18** on alkaline hydrolysis with methanolic KOH at room temperature offered corresponding acid **19** in very good yield.



13 **14** **15**

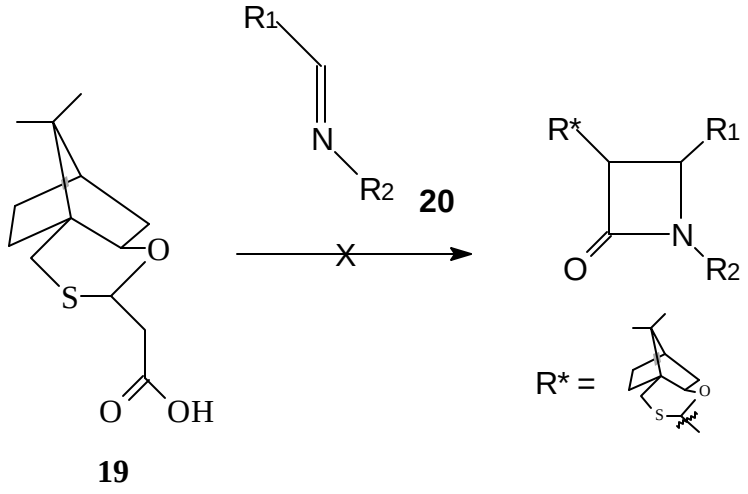
Reagents and reaction conditions (i): $SOCl_2$ ref. 5h. (ii): $LiAlH_4$/EtOEt -78 °C-ref. overnight.



14 **16** **17**

18 X = OEt; **19** X = OH

The treatment of acid **19** with different imines (**20**) in the presence of phenyl dichlorophosphate, an acid activator, and triethylamine failed to under go cycloaddition reaction leading to corresponding β-lactams.

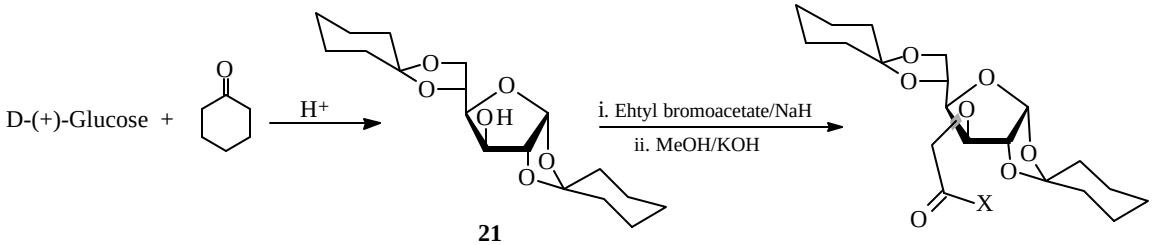


19

Reagents and reaction conditions (i): $Ph(PO)Cl_2$, Et_3N/DCM, 0 °C, r.t. 13h.

Chapter-IV: The use of chiral acid derived from D-glucose for diastereoselective synthesis of b-lactam.

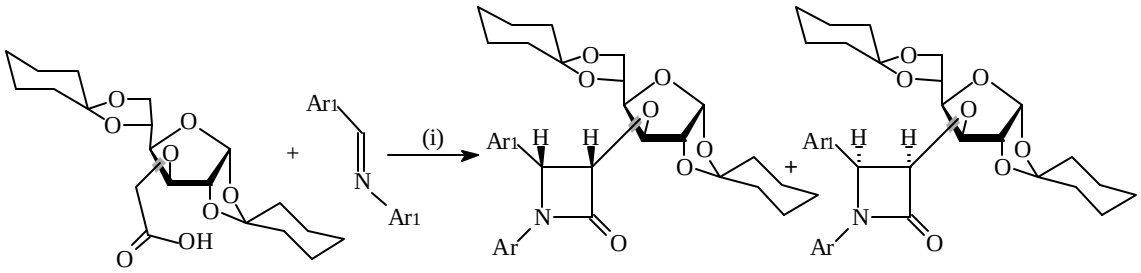
This chapter describes the use of chiral ketene derived from D-glucose for diastereoselective synthesis of β-lactams. D-Glucose on reaction with cyclohexanone in the presence of acid gave 1,2:5, 6-di-O-cyclohexylidine glucofuranoside (**21**) in moderate yield. The akylation of alcohol **21** with ethyl bromoacetate in the presence of NaH gave ester **22** in very good yield. The ester on hydrolysis with methanolic KOH afforded acid **23** in 95% yield.



21

22 X = OEt; **23** X = OH

The acid **23** on reaction with imines **24** in the presence of an acid activator (phenyl dichloro phosphate or triphosgene) and triethylamine at 0 °C gave almost 1:1 diastereomeric mixture of *cis*-β-lactams (**25a-e** and **26a-e**) in moderate yields. This mixture could not be separated either by column chromatography or by fractional crystallization. The cycloaddition reaction when carried out at lower temperatures (-15 and –40°C) did not improve the diastereoselectivity.



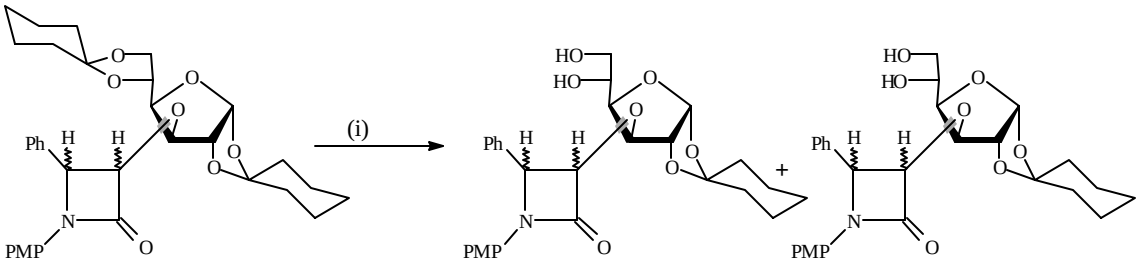
23 **24** **25** **26**

25 & 26	Ar1	Ar
a	Ph	PMP
b	PMP	PMP
c	PMP	Ph
d	Styryl	PMP
e	Fu	PMP

Reagents and reaction conditions (i): $Ph(PO)Cl_2$/ $CO(OCCl_3)_2$, Et_3N/DCM, 0 °C, r.t. 13h.

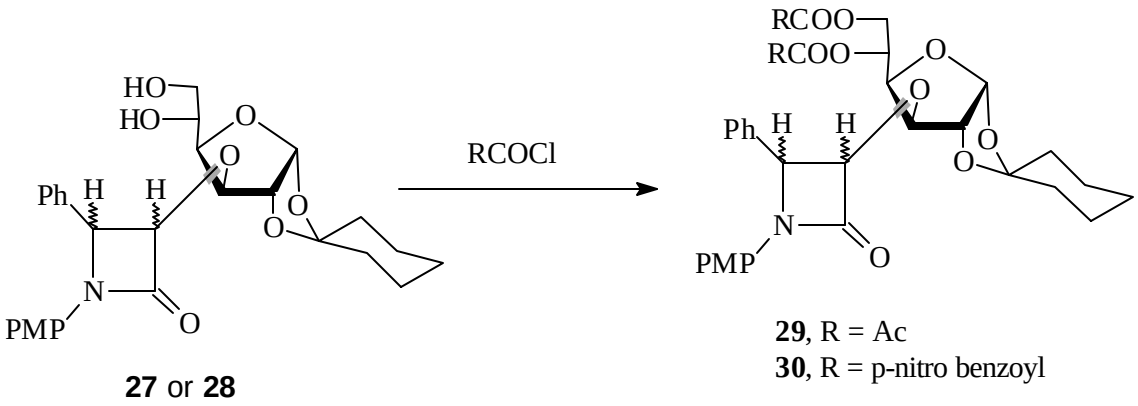
The monoketal deprotection of diastereomeric mixture of β-lactams (**25a** and **26a**) was effected by the treatment of 75% aq. AcOH at 80°C which gave selectively a mixture of

5, 6-O-deprotected diols **27** and **28** in 98% yield. These diols (**27** and **28**) were separated by flash column chromatography. Both diastereomers were found to be cis β-lactams as revealed from the coupling constant of β-lactam ring protons (^{1}H NMR spectral analysis). The absolute stereochemistry could not be determined by X-ray crystal analysis, even though the pure dilols were isolated as solids, as various crystallization attempts were unsuccessful to get X-ray quality crystals.



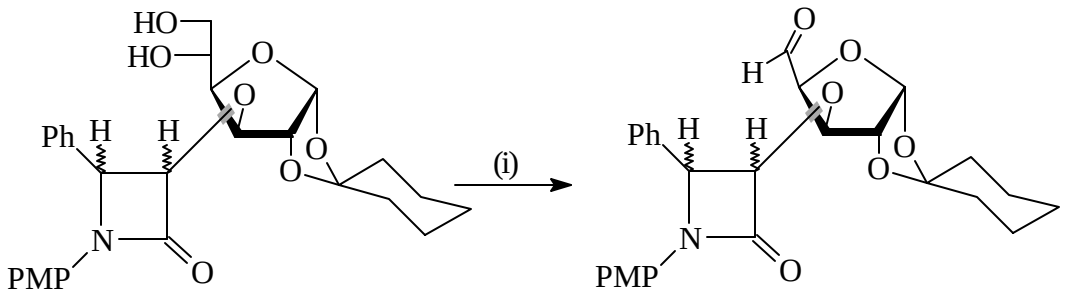
Reagents and reaction conditions (i): 75% aq. AcOH/ 80 °C, r.t. 3h.

One of these diols (**27** & **28**) was acylated to give acyl derivatives **29** and **30**. These derivatives could not give X-ray quality crystals for absolute stereochemistry determination.



Reagents and reaction conditions (i): Et_3N/DCM, 0 °C, r.t. 4h.

Both the diols (**27** & **28**) were separately oxidized with $NaIO_4$ to give respective aldehydes **31** and **32** in 98% yields.

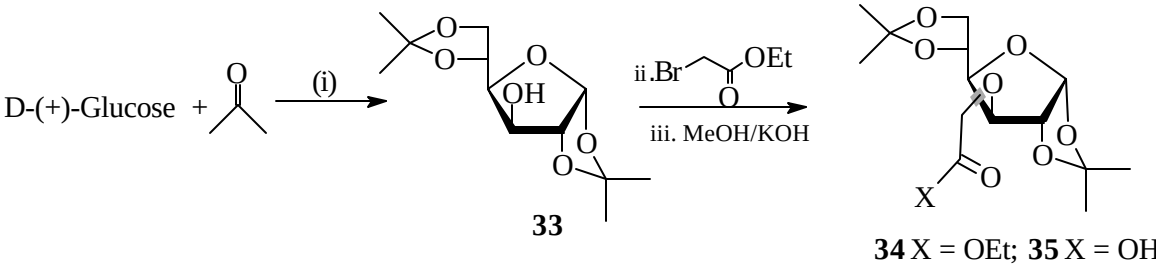


27 or **28** **31** or **32**

Reagents and reaction conditions (i): $NaIO_4$/ MeOH:H_2O, RT. r. t. 4h.

The chiral acid **23** derived from 1,2; 5,6-di-O-cyclohexylidine did not give diastereoselectivity in β-lactam formation. Other chiral acid (**35**) derived from 1,2; 5,6-di-O-isopropylidine glucose was used for the synthesis of β-lactam in order to check its effect on diastereoselectivity.

D-glucose with acetone in presence of $ZnCl_2/H^+$ gave the alcohol 1,2; 5,6-di-O-isopropylidine glucose (**33**) in moderate yield. This alcohol on alkylation with ethyl bromo acetate in presence of NaH gave the ester **34** in good yield, which on hydrolysis with methanolic KOH gave required acid **35** in excellent yield.

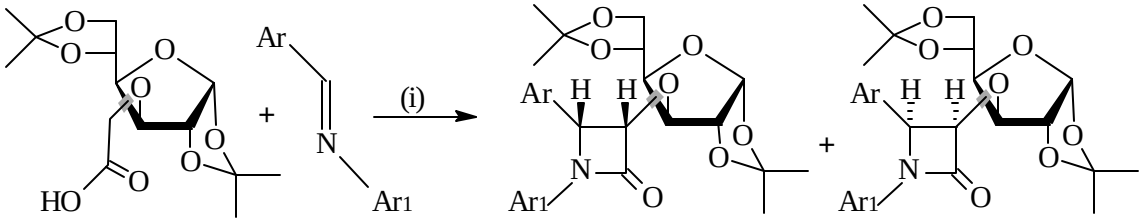


33

34 X = OEt; **35** X = OH

Reagents and reaction conditions (i): $ZnCl_2$/ H_3PO_4, 24h. r.t, (ii): NaH/ THF ref. 15h.

The cycloaddition reaction of acid **35** with imines **36** under similar reaction conditions also gave only 1:1 mixture of diastereomers **37** and **38**.



35 **36** **37** **38**

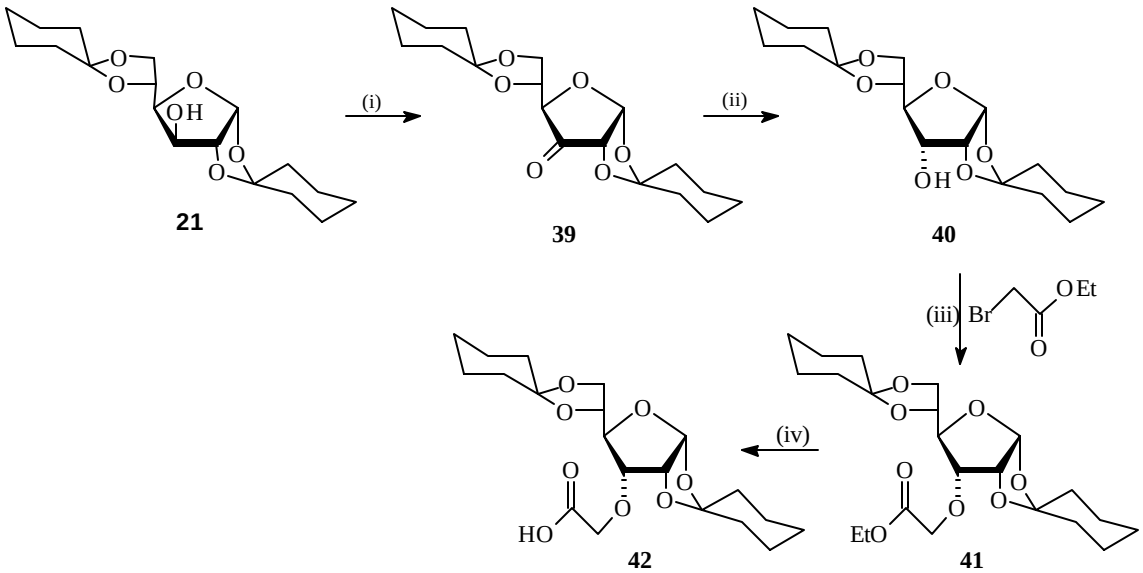
37 & 38	**Ar**	**Ar1**
a	Ph	PMP
b	PMP	PMP

Reagents and reaction conditions (i): $CO(OCCl_3)_2$, Et_3N/DCM, 0 °C, r.t. 13h.

The stereochemistry of these compounds could not be assigned as these compounds also did not provide X-ray quality crystals.

Since the acids **23** and **35** did not give good diastereoselectivity in β-lactam ring formation the C-3 center of the acid **23** was inverted by stepwise synthesis to give a chiral acid **42**.

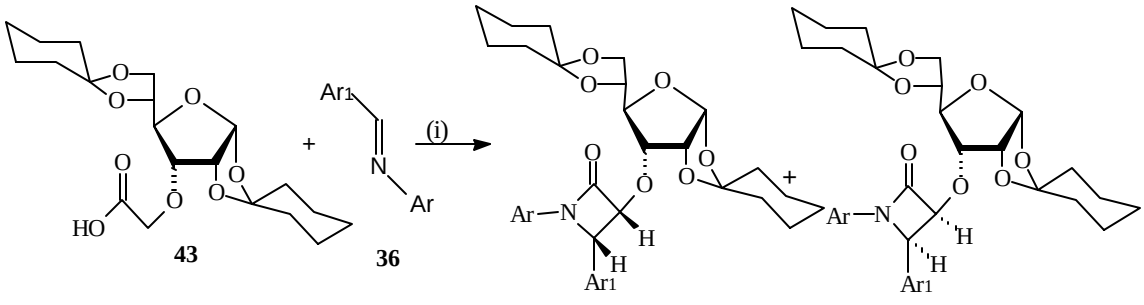
The alcohol **21** was oxidized with PCC to give ketone **39** in very good yield, which was reduced with $NaBH_4$ to give alcohol **40** in very good yield, with inverted C-3 center. This alcohol **40** on alkylation with ethyl bromoacetate in presence of NaH gave ester **41** in good yield. This ester was hydrolyzed with methanolic KOH to give the acid **42** in excellent yield.



21 **39** **40** **41** **42**

Reagents and reaction conditions (i): PCC/ DCM, 15h. (ii): $NaBH_4$/ MeOH:H_2O (iii): NaH/THF, ref. 15h (iv): MeOH/KOH, r. t. overnight.

The chiral acid **43** was subjected to annulation with imine **36** under the similar reaction conditions to give diastereomeric mixture of β-lactams **44** and **45** in good yield with a slight improvement in diastereoselectivity (59:41) was observed by using imine **36a**. The diastereomeric ratio was determined by ^{1}H-NMR and HPLC analysis. The cis stereochemistry was assigned to β-lactam protons based on ^{1}H-NMR coupling constant values. Both the isomers were separated by flash column chromatography. The absolute stereochemistry of these compounds also could not be determined as none of them gave X-ray quality crystals.



44 & 45	Ar^{1}	Ar
a	Ph	PMP
b	PMP	PMP

Reagents and reaction conditions (i): $CO(OCCl_3)_2$, Et_3N/DCM, 0 °C, r.t. 13h.

Note: The compound numbers incorporated in the synopsis are different from those in the thesis.

Chapter I

Synthesis of N1-Unsubstituted b-lactam via a facile deprotection of N1-[(a-thiophenyl) benzyl] group

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Part of this work has been published in

Tetrahedron Letters, **1997**, *38*, 4281
and
Tetrahedron, **1998**, *54*, 4375

1.1 Introduction

The discovery of penicillin in 1929[1] has revolutionized medicine.[2] Many of the potentially lethal bacterial infections lost their specter as life threatening diseases-a situation that could change again soon.[3] The penicillins were the first antibiotics, and for a long time the term “penicillin” was used by the general public as synonym for “antibiotic”.

Further milestones were set with the structure of penicillin[4] and the first total synthesis of a naturally occurring penicillin.[5] The laboratory synthesis of penicillin and its derivatives turned out to be quite challenge because of its bicyclic nature, which makes the β-lactam ring partially labile.[6] It is not surprising then that the question “ how does nature do it?” attracted the attention of the scientific community, consequently several β-lactam antibiotics have been discovered. The second drug of this class of β-lactam antibiotics was cephalosporin.[7] The discovery of 7 α-methoxy cephalosporin from streptomyces in 1971, stimulated researchers to discover novel β-lactam antibiotics. The immense efforts made by the chemist led to the successful discovery of carbapenem,[8] monocyclic norcardicin,[9] monobactams[10] and clavulinic acid.[11] These β-lactam antibiotics have been classified according to their structural frame work.

- Penicillin
- Cephalosporin
- Cephamycin
- Oxacephems
- Penems
- Oxapenems like Clavulinic acid
- Carbapenems likeThienamycin
- Nocardicin
- Monobactam

The chronology of these antibiotics is illustrated in fig. 1.

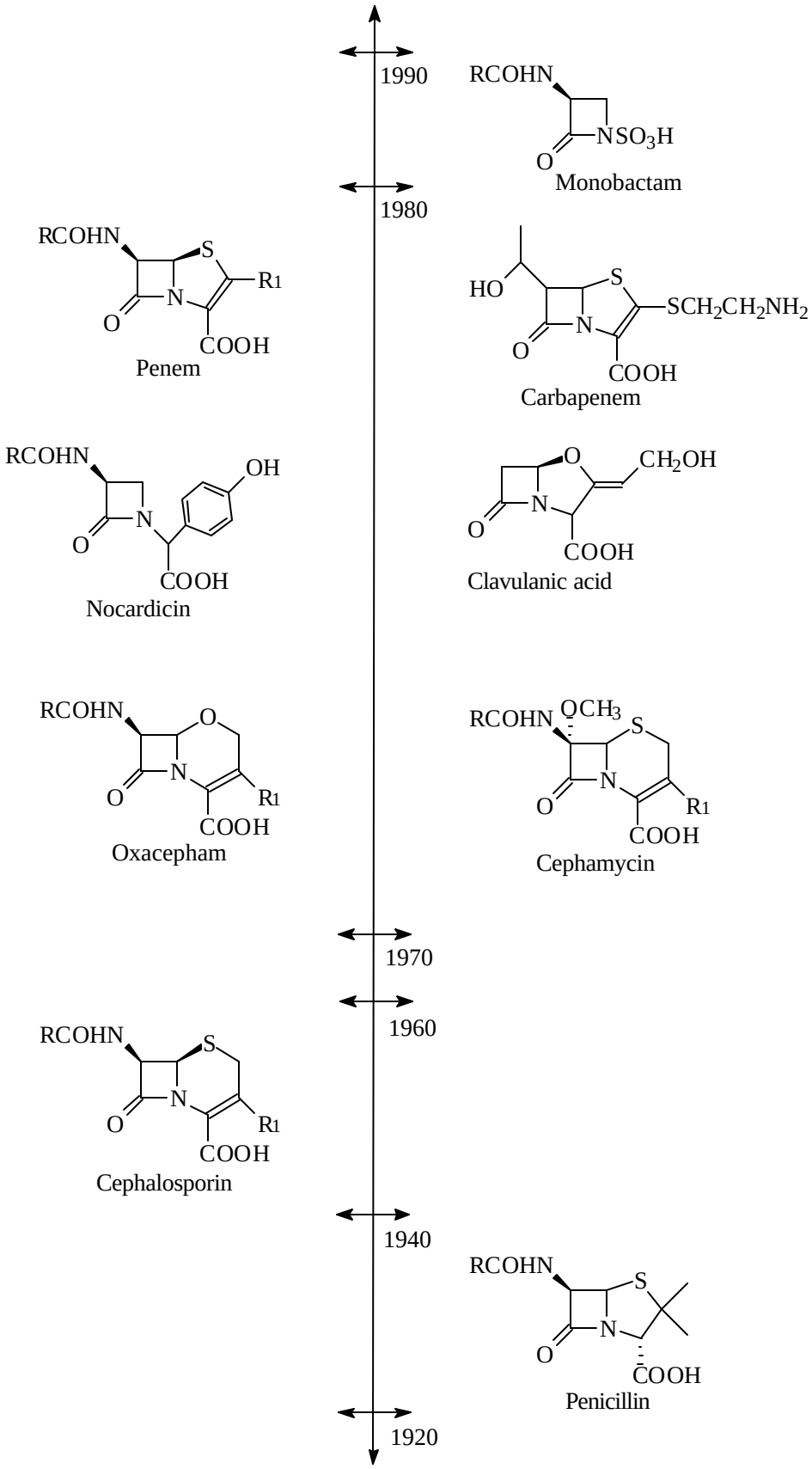

1990
RCOHN
NSO3H
O
Monobactam
1980
RCOHN
S
R1
N
O
COOH
Penem
HO
S
SCH2CH2NH2
N
O
COOH
Carbapenem
RCOHN
OH
N
O
COOH
Nocardicin
O
CH2OH
N
O
COOH
Clavulanic acid
RCOHN
O
N
O
R1
COOH
Oxacepham
RCOHN
OCH3
S
N
O
R1
COOH
Cephamycin
1970
1960
RCOHN
S
N
O
R1
COOH
Cephalosporin
1940
RCOHN
S
N
O
COOH
Penicillin
1920

Fig. 1

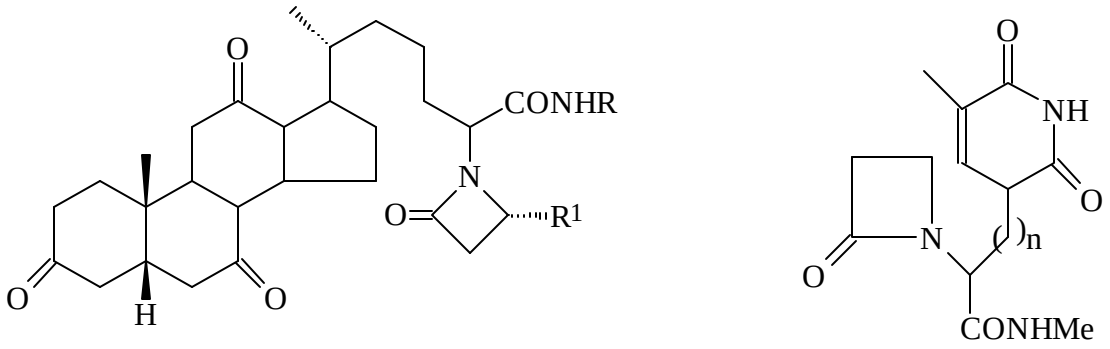
The structural diversity of these β-lactams requires an extensive and sophisticated study on the structure activity relationship.[12]

The properly substituted β-lactams can be used for the construction of bicyclic β-lactam antibiotics.[13] Recently, β-lactams have also been used as starting materials for several naturally occurring and biologically active non β-lactam molecules.[14] Therefore, many efforts have been made for the stereoselective construction of β-lactam ring with appropriate substituents at proper positions.[15] An extensive report by Ojima[16] on the use of β-lactam as a synthons for natural products has appeared in early nineties.

In 1995, a new class of compounds was reported in the β-lactam family in which the antibiotic property of β-lactams and antiviral property of nucleosides were incorporated together to afford dual properties of the drug.[17] Kehagia et al[18] reported a new class of β-lactams in which steroidal and

β-lactam units were coupled together *via* Ugi reaction in one step process (Scheme 1.01).

Scheme 1.01



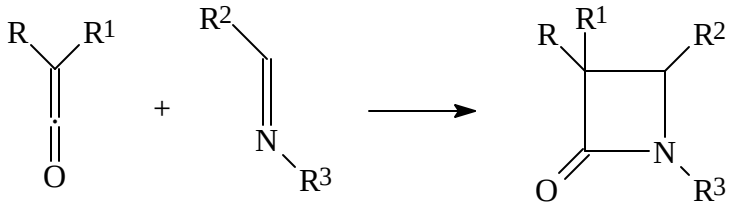
1. 1. 1 Methods for constructing b -lactam ring

Staudinger Reaction:

The first synthesis of β-lactam was achieved by Staudinger[19] in 1707 by the [2+2] cycloaddition of ketene and imine. This reaction is called as Staudinger or ketene-imine cycloaddition reaction. An excellent review on the Staudinger reaction has appeared in

1993.[20] In the modified Staudinger reaction, acid chlorides or activated carboxylic acids were used in the presence of base, as a ketene precursor (Scheme 1.02).

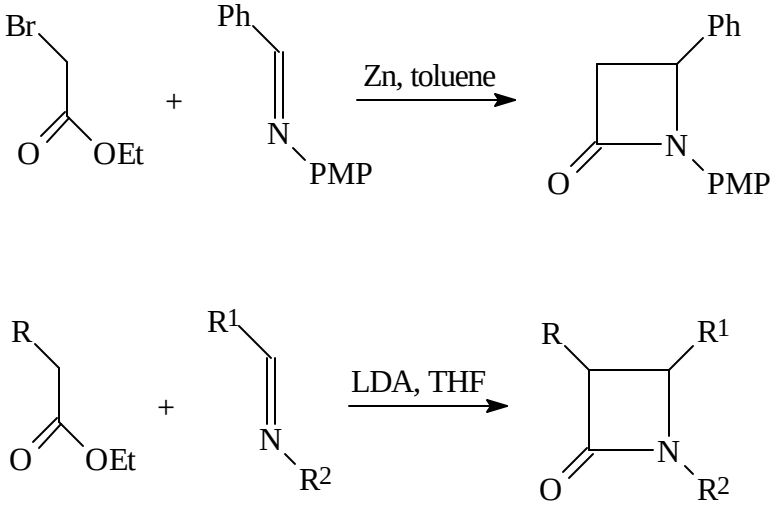
Scheme 1.02



Enolate-Imine cycloaddition

Gilman and Specter[21] have reported the first example of this type of reaction by the reaction of zinc enolate (Reformatsky reagent) with imines to give β-lactams (Scheme 1.03). Other metal enolates have also been used in enolate-imine cycloaddition reaction to achieve diastereoselective synthesis of β-lactams[22] (Scheme 1.03).

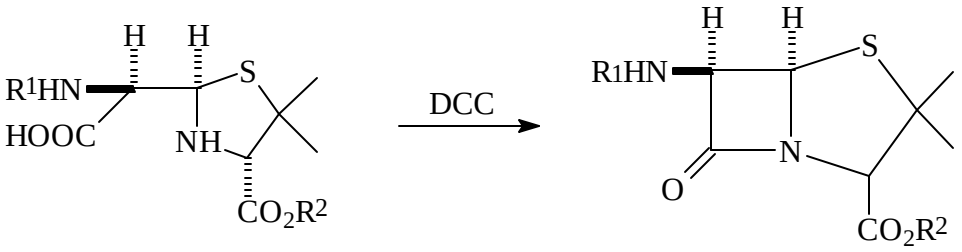
Scheme 1.03



Formation of N-C_2 bond:

Sheehan and Henery-Logan[5] have used this methodology for the synthesis of penicillin by cyclization of β-amino acid using dicyclohexylcarbodiimide (DCC) as a condensing agent (Scheme 1.04).

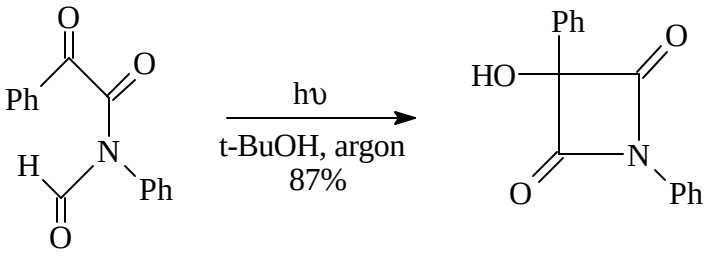
Scheme 1.04



Formation of C_2-C_3 bond:

In contrast to N_1-C_2 amide bond formation, azetidinone synthesis *via* C_2-C_3 bond formation is not that common due to the inherent difficulty in forming a carbon-carbon bond versus an amide bond. Among the various methods available for C_2-C_3 bond formation, the photochemical approach which leads to the formation of 4-keto-β-lactams[23] is the most favorable one (Scheme 1.05). Conversion of these products to the 4-deoxygenated β-lactam remains a synthetic challenge

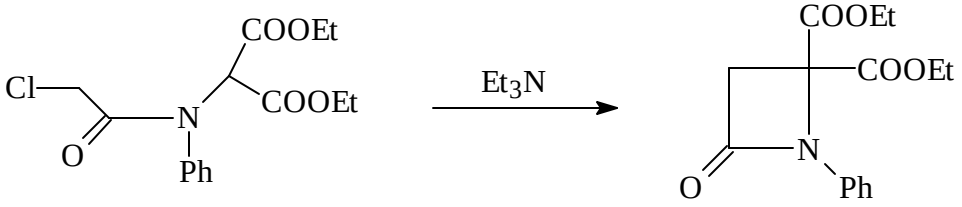
Scheme 1.05



Formation of C_3-C_4 bond:

Sheehan and Bose[24] have reported an elegant synthesis for 3-unsubstituted β-lactams *via* C_3-C_4 bond formation. The cyclization of α-haloacylaminomalonates in presence of a base gave very high yield of β-lactams (Scheme 1.06).

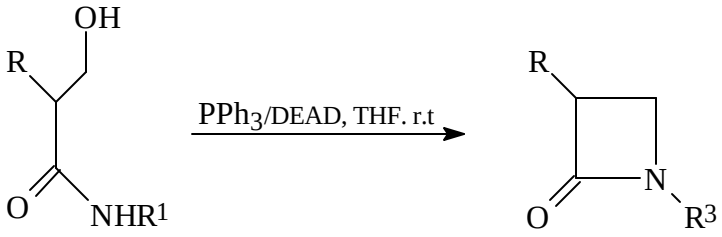
Scheme 1.06



Formation of N-C_4 bond:

Miller has developed very efficient methodology for construction of β-lactam ring, which involves S_N2 displacement of a good leaving group attached at β-carbon by intramolecular nucleophilic attack of amide nitrogen. He has reported synthesis of various β-lactams by the cyclization of β-hydroxy amide derivatives under Mitsunobu reaction conditions[25] (Scheme 1.07).

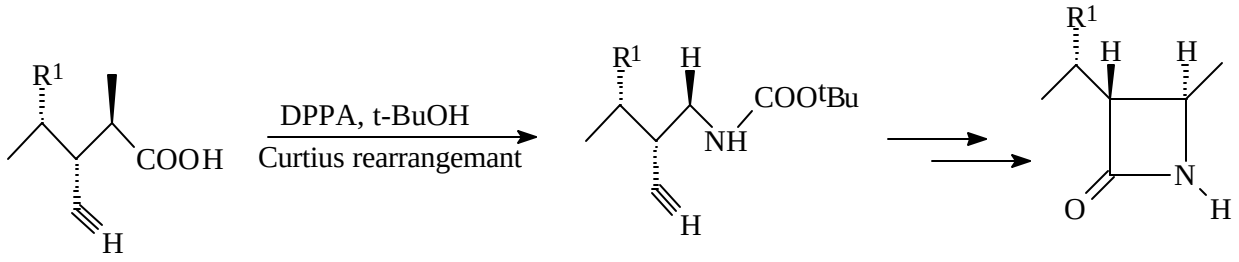
Scheme 1.07



Miscellaneous Methods:

Jacobi et al [26] have used acetylenic carboxylic acid as a synthon for the preparation of β-lactam via Curtius rearrangement in a four-step process (Scheme 1.08).

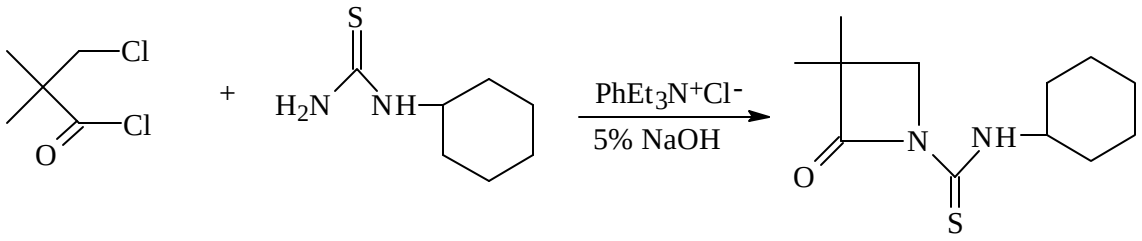
Scheme 1.08



DPPA = diphenylphosphorazidate

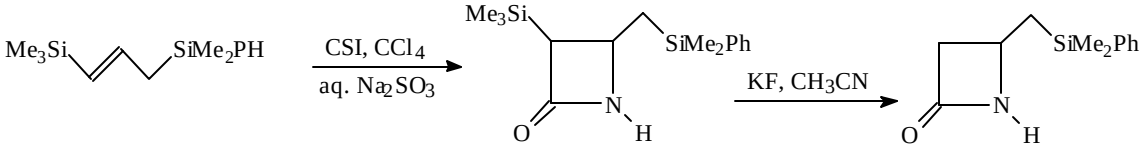
The condensation of a bis-electrophile with N-alkyl thio urea to form β-lactam[27] has been reported to proceed via simultaneous or step-wise formation of two bonds at the N1 center (Scheme 1.09).

Scheme 1.09



The addition of chlorosulfonyl isocyanate (CSI) to olefin is well documented for the preparation of β-lactams.[28] Colvin et al[29] have used CSI addition on allyl and allenyl silanes, which afforded a highly functionalised β-lactam (scheme 1.10). The substituents at C3 position can also be cleaved to generate a useful β-lactam intermediate.

Scheme1.10

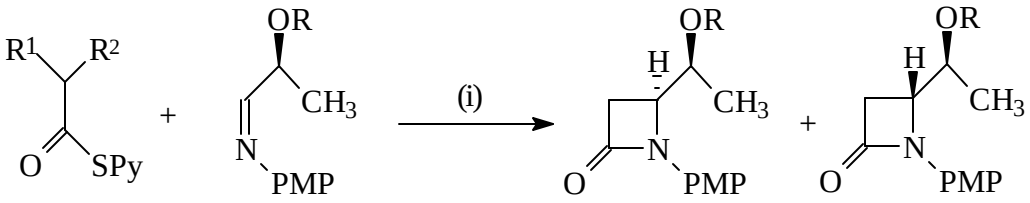


1. 1. 2 Asymmetric synthesis of b-lactams

Asymmetric synthesis of β-lactams is of current interest and several reports have appeared during the last decade. The Staudinger reaction is the most widely used method for the asymmetric synthesis of β-lactams due to its simplicity and predictability of stereochemical out come of the reaction. The approaches followed to induce asymmetry in ketene-imine cycloaddition are based on the use of chiral auxiliary attached either to ketene precursor or imine (derived from chiral aldehyde or amine). The use of chiral acids for asymmetric synthesis of β-lactams will be discussed in Chapter III. Following is a brief review on use of chiral aldehydes and chiral amines for asymmetric synthesis of β-lactams.

The reaction[30] of imines derived from lactaldehyde with titanium enolate of thio esters gave optically active β-lactams in 42-71% yield with 98% diastereomeric excess (de) (Scheme 1.11).

Scheme 1.11

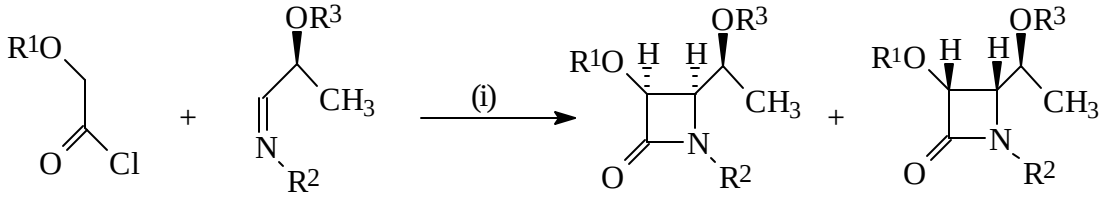


R = TBS, Bn
$R^1 = R^2 = H$

Reagents and reaction conditions (i): $TiCl_4$, Et_3N/DCM, −78 °C-RT, Overnight.

A high level of diastereoselectivity (de 95%) was observed in β-lactam ring construction *via* cycloaddition[31] reaction of ketenes with imines derived from lactaldehyde with sterically demanding O-protecting groups (Scheme 1.12).

Scheme 1.12

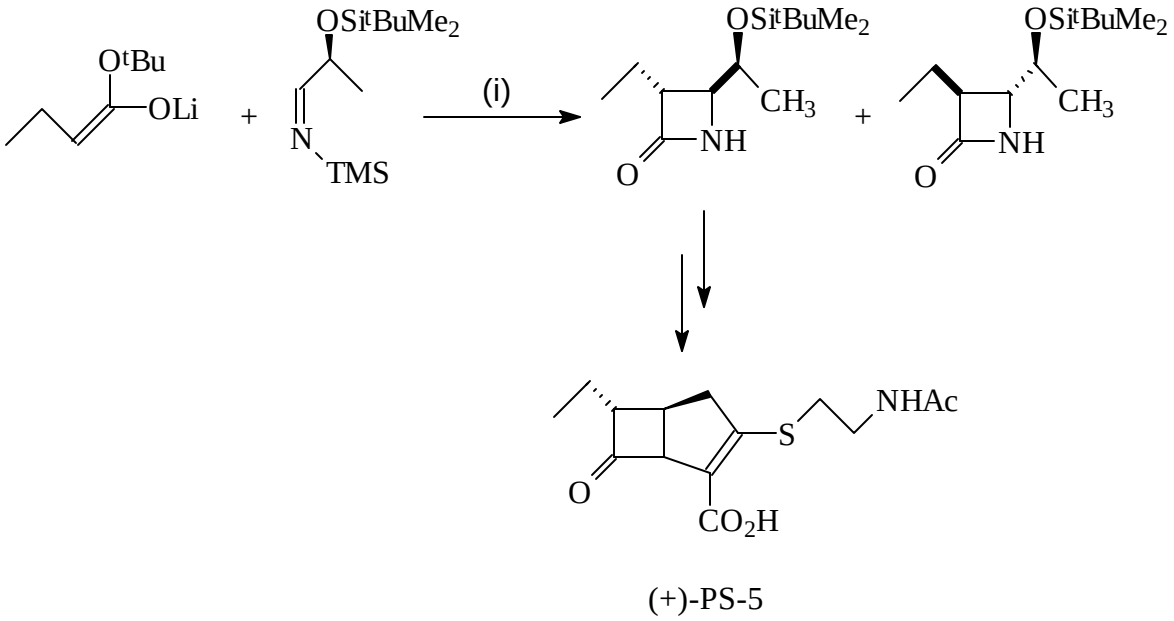


R^1 = Ac, Me, Bn
R^2 = PMP, Bn
R^3 = t-BuPh_2Si, TBDMS

Reagents and reaction conditions (i): Et_3N/DCM, −78 °C-RT, 20-24 h.

The silyl imines derived from lactaldehyde have been treated with ester enolates to give optically active β-lactams in good yields with maximum diastereoselectivity of 96:4. The major isomer was used for the synthesis of PS-5 antibiotics[32] (Scheme 1.13).

Scheme 1.13

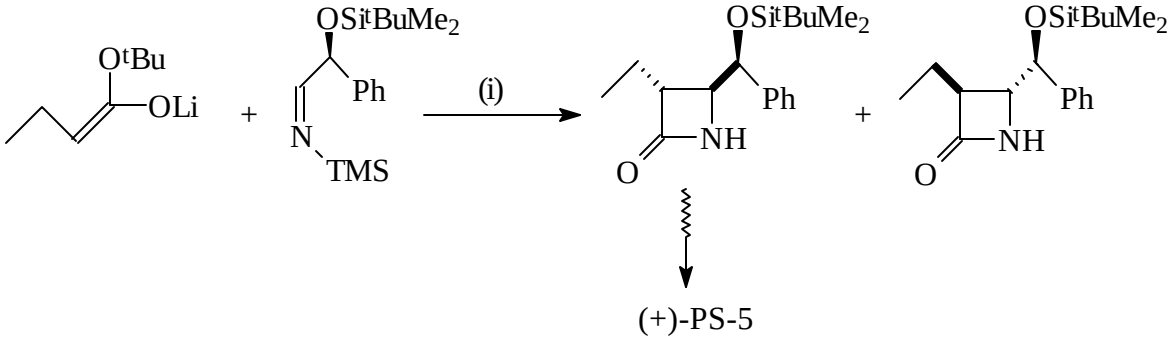


(+)-PS-5

Reagents and reaction conditions (i): Et_3N/THF, −78 °C to RT, 8 h.

Similar synthesis of PS-5 has also been reported by P. Andreoli et al[33] starting from imine derived mandelaldehyde (Scheme 1.14).

Scheme 1.14

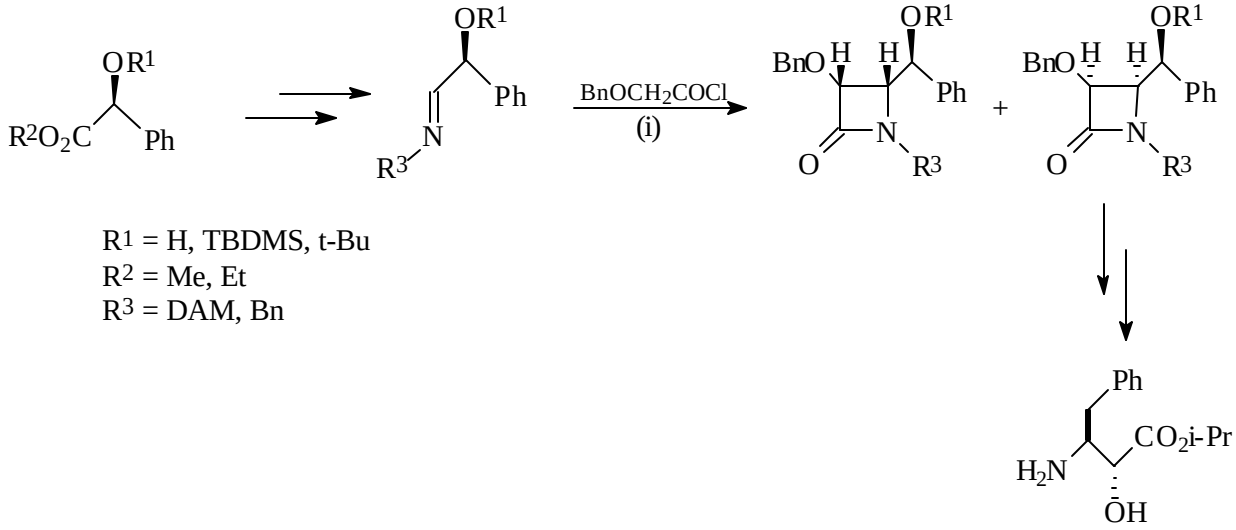


(+)-PS-5

Reagents and reaction conditions (i): Et_3N/THF, −78 °C-RT, Overnight.

The imines derived from mandelaldehyde have been made to undergo Staudinger reaction[34] with different acid chlorides to give β-lactams in 69-100% yields with maximum selectivity of 18:1. The major isomer (α) was converted into α-hydroxy-β-amino ester (Scheme 1.15).

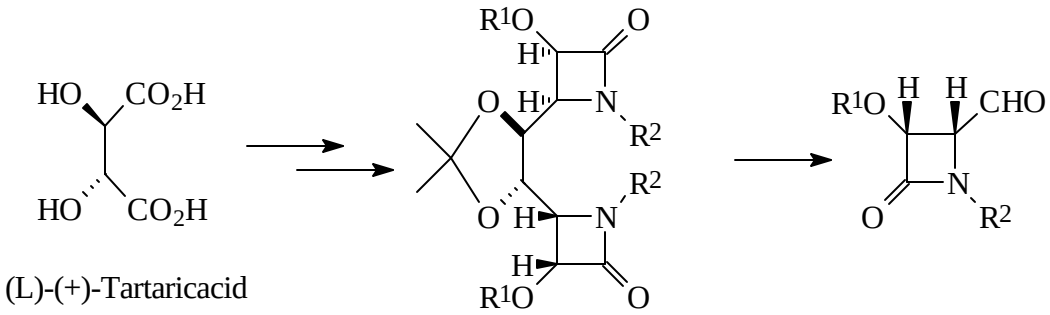
Scheme 1.15



Reagents and reaction conditions (i): Et_3N/THF, RT, Overnight.

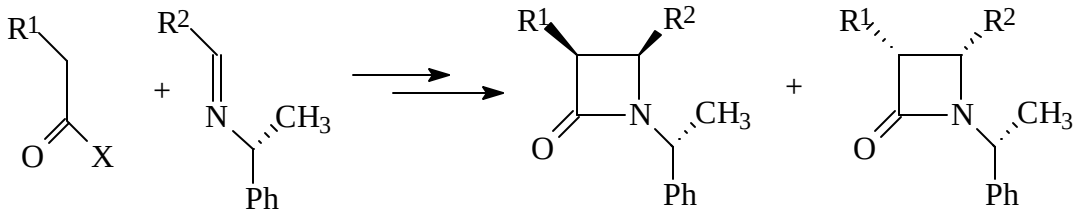
M. Jayaraman et al[35] have reported an elegant synthesis of 4-formyl-β-lactams, an intermediate for PS-5 using bis-imines derived from (L)-(+)-tartaric acid *via* C_2 symmetric bis-β-lactams (Scheme 1.16).

Scheme 1.16



The readily available optically pure α-methylbenzylamine has been used as a chiral amine in β-lactam ring formation[36] (Scheme 1.17). Maximum of 90:10 diastestereoselectivity could be obtained in this case.

Scheme 1.17

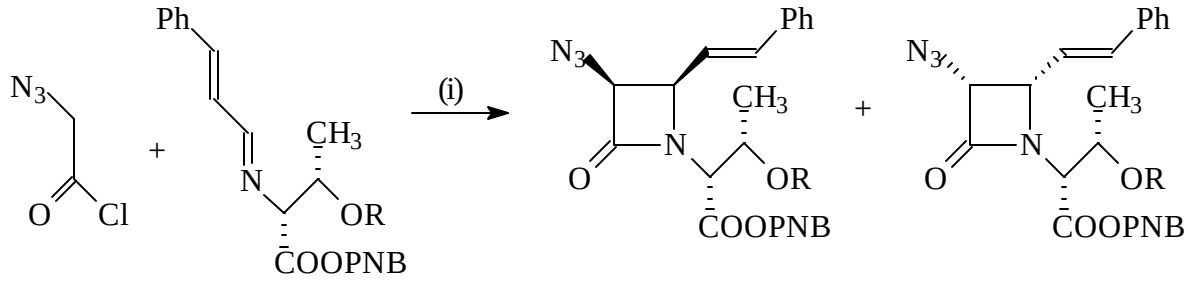


R^1 = $CH_3COCH{:}CH(CH_3)NH$
R^2 = Styryl

R^1 = BnOCO
R^2 = Styryl

D-Threonine as a chiral amine component of imines has been used in the ketene imine reaction[37] (Scheme 1.18). A high diastereoselectivity of 9:1 was obtained.

Scheme 1.18

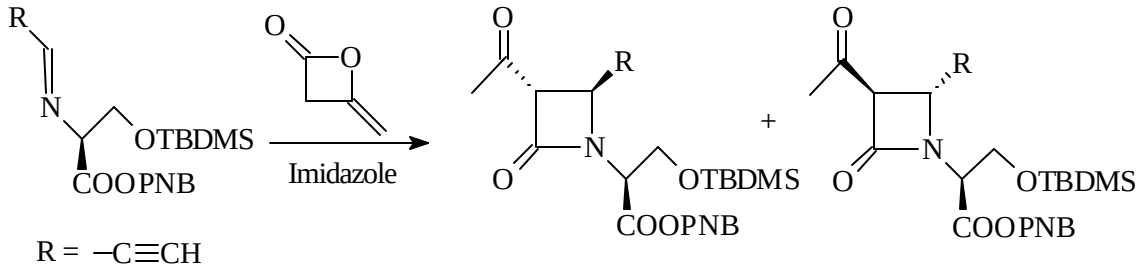


R = TBDMS

Reagents and reaction conditions (i): Et_3N/DCM, –10 °C.

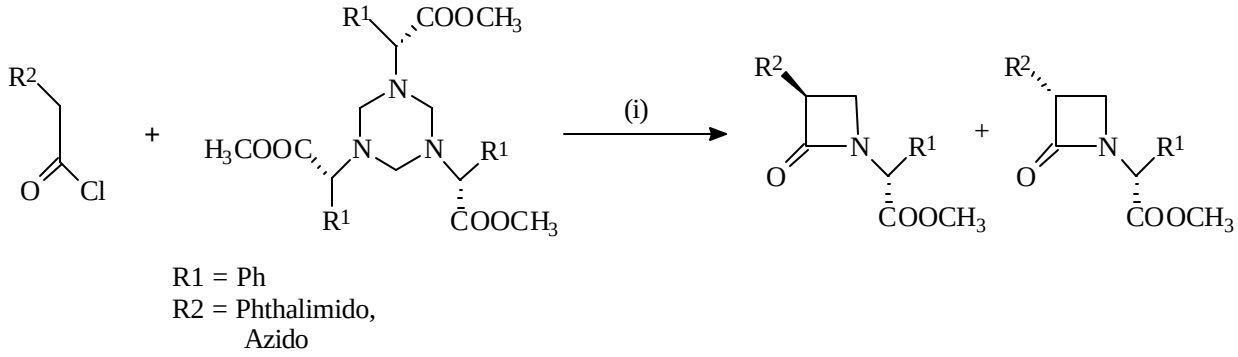
The propargylidine schiff's base derived from L-serine on cycloaddition reaction with diketene provided a mixture of cis and trans β-lactams in the ratio of 1:2.2 (Scheme1.19). Just and Liak have reported racemization during the β-lactam ring formation[38] when schiff's base derived from L-serine and cinnamylidene was reacted with azidoacetyl chloride in the presence of triethylamine.

Scheme1.19



The reaction of phthalimido acetyl chloride with chiral triazine, an imine equivalent, in the presence of $BF_3.Et_2O$ gave β-lactam with high diastereoselectivity of 10:1[39] (Scheme 1.20).

Scheme 1.20



Reagents and reaction conditions (i): Py/DCM, $BF_3.Et_2O$, –78 °C, 3 h.

1. 1. 3 Mechanism of ketene-imine cycloaddition reaction

Although the ketene-mine cycloaddition reaction (Staudinger reaction) has been studied extensively, the mechanism of this reaction is still uncertain. Several papers have appeared on the mechanism of this reaction. Based on these results a two-step zwitterionic mechanism has been preferred over a concerted [2+2] cycloaddition reaction.

The ketenes can be generated either by thermally, photochemically or from activated acid or acid chlorides in presence of a base. The *in situ* formation of the ketene in the reaction of 3-hydroxybutyric acid chloride with an imine in the presence of a base, has been studied

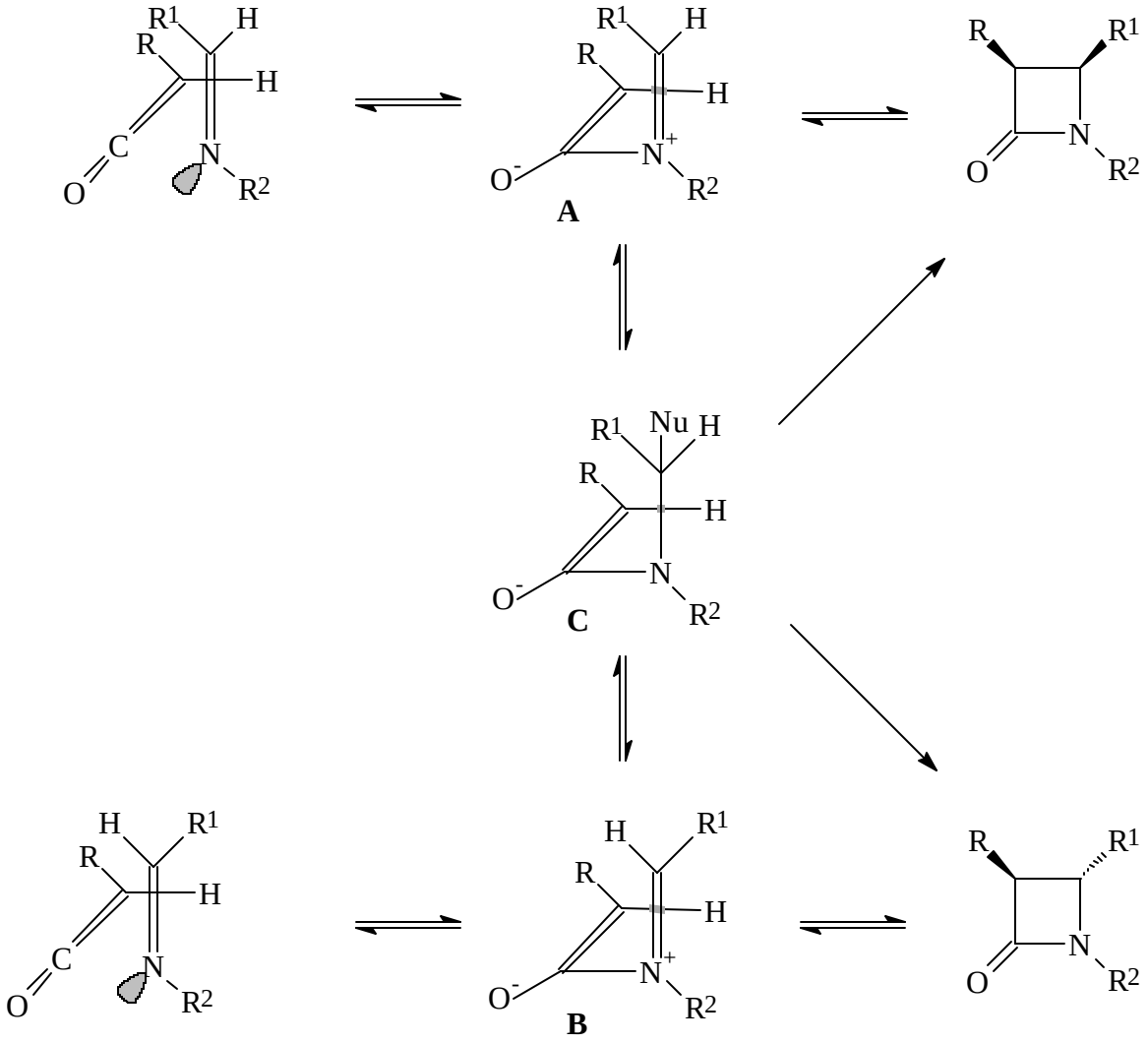
by monitoring the course of reaction with FT-IR.[40] A strong band corresponding to a ketene was observed at 2120 in FT-IR. This indicates that the *in situ* generated ketene reacts with imine to form a zwitterionic intermediate (scheme 1.21), which cyclises to β-lactam. The possibility of acylation of imine with acid chloride under the reaction conditions has been ruled out as the acid chloride when reacts with imine in the absence of base leads to the formation of amide instead of β-lactam.

It has been postulated that the LUMO of ketene carbonyl group lies coplanar with the other substituents of ketene. The imine can from the least hindered side of ketene orthogonally either from the top face or from the bottom face of the ketene and produce a zwirreionic intermediate in which the ketene and the imine lie perpendicular to each other.[41] The conroratory ring closure of the dipolar specie **A** will then generate the thermodynamically less stable *cis* β-lactam. This mechanism explains the formation of *cis* β-lactams from the reaction between the many acyclic imines (*anti*) and ketenes. This mechanism also explains the well-known preference for the *trans* β-lactams with cyclic imines (*syn*). An orthogonal approach between ketene and imine (*syn*) will produce the zwitterionic intermediate **C**, which on conrotatory ring closure will generate trans isomer (Scheme 1.21).

This hypothesis was also supported by the semi empirical molecular orbital calculation for the intermediate between the reaction of methyl ketene and N-methyl imine.[42]

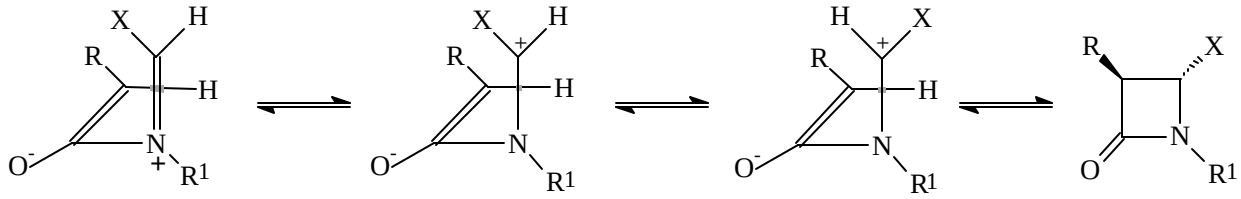
This mechanism also successfully explains the formation of a mixture of cis and trans isomer in ketene-imine reaction. A nucleophile can add to the iminium ion intermediate **A** or **B** to form an intermediate **C**. The loss of nucleophile from intermediate **C** after N-C bond rotation can result in the formation of dipolar specie **B** and subsequent trans β-lactam. The intermediate **C** can also revert back to **A** and form cis β-lactam. Thus ratio of cis and trans isomers depends upon the formation and stability of intermediate **A** and **B**. It was also observed that the initially formed cis product could undergo base catalyzed isomerisation to produce the more stable trans product[43] (Scheme 1.21).

Scheme 1.21

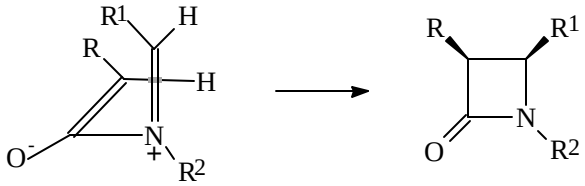


The formation of *trans* isomer by using imidates, thioimidates and sometimes C-arylimines and potentially C-alkylimines can be explained by the ability of these groups to stabilize the positive charge of the zwitterionic intermediate by inductive or mesomeric effect. This allows the isomerisation of *trans*-iminium ion to the sterically less crowded *cis*-iminium ion, which on ring closure will generate *trans* β-lactam (Scheme 1.22). On the conroratory, imine possessing electron-withdrawing substituents on imine carbon, like α-carbonyl group or α-halomethyl group, prevents the C-N bond rotation of the zwitterionic intermediate **A** and produces the *cis* isomer.

Scheme 1.22



X = OR, SR, aryl, alkyl



R^1 = COPh, $COOCH_3$, CH_2Cl, CH_2F

A detailed account of semi empirical calculation reported by Cossio et al[44] also supports the ketene-imine cycloaddition mechanism.

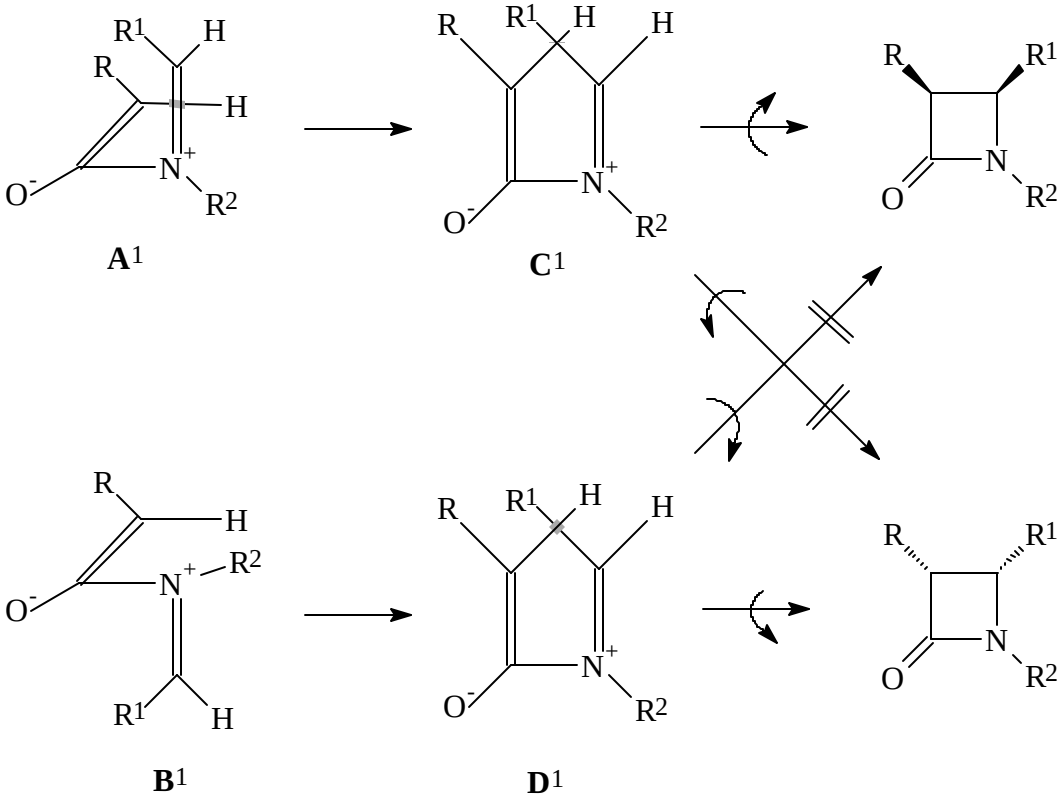
1. 1. 4 Asymmetric induction

The ketene can be approached by the imine either from top face or from bottom face to produce two possible zwitterionic intermediates **A**^{1} and **B**^{1} respectively (Scheme 1.23). Before the conrotatory ring closure can take place, the intermediates **A**^{1} and **B**^{1} have to undergo the 90° rotation around C-N bond to produce two more intermediates **C**^{1} and **D**^{1} respectively. The conrotatory ring closure of these intermediates **C**^{1} and **D**^{1}, will produce enantiomeric *cis* β-lactams. The intermediates **C**^{1} and **D**^{1} can also be formed from **A**^{1} and **B**^{1} by rotating 270° around C-N bond. According to the principle of least motion, the transformation of **A**^{1} to **C**^{1} and **B**^{1} to **D**^{1} is favored, as this transformation needs only 90° rotation.

It has been pointed out by Hegedus et al that the conrotatory ring closure of intermediate C^1 can only occur clockwise[45] as the counterclockwise ring closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is important for chiral induction, because a counterclockwise rotation would generate

the enantiomeric β-lactam. The opposite is true for intermediate **D**[1], which can undergo only counterclockwise conrotatory ring closure.

Scheme 1.23

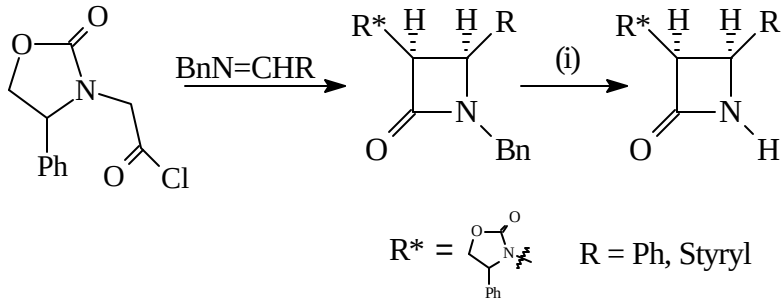


1.2 Background for present work

The β-lactam with easily deprotectable N-substituents is important building block for the synthesis of mono cyclic as well as bicyclic β-lactams.[46] The synthesis of β-lactam ring from acyclic precursors is normally proceeds with the protective group on the β-lactam nitrogen, so that the only important consideration is their selective removal at appropriate time. Among the various gruops,[47] the most popular and easily removable groups under mild reaction conditions are discussed in brief below:

The imine prepared from benzylamine was made to undergo cycloaddition reaction[48] with chiral acid chloride derived from oxazolidine in presence of triethylamine to give β-lactams with N-benzyl protecting group. This benzyl group was removed by the reduction with Li/liq. NH_3 (Scheme 1.24) to give NH-β-lactams.

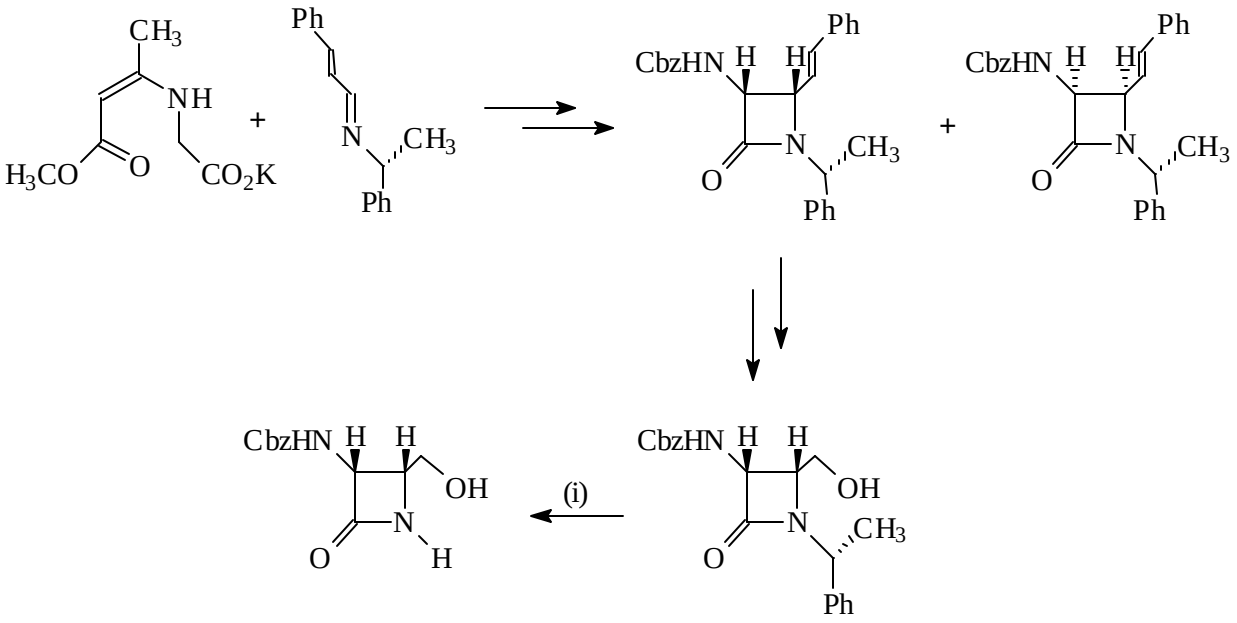
Scheme 1.24



Reagents and Conditions (i): Li/NH_3, THF / t-BuOH, −78 °C, 3 h.

The imine derived from cinnamaldehyde and α-methylbenzyl amine on reaction with Dane salt gave diastereomeric mixture of two β-lactams in 3:1 ratio. The N-α-methylbenzyl group of major diastereomer was deprotected[49] with Na/liq. NH_3 to get NH-β-lactam in 95% yield. The deprotection of N-α-methylbenzyl group has also been effected by oxidation with $K_2S_2O_8$ to get NH-β-lactam in 28% yield (Scheme 1.25).

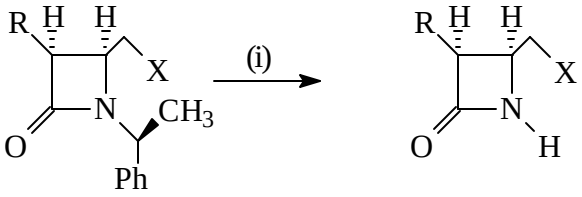
Scheme 1.25



Reagents and Conditions (i): Na/liq. NH_3 or $K_2S_2O_8$/MeCN: H2O, ref.

Aszodi et. al.[50] has reported improved yield (51.5%) of NH-β-lactam by oxidative deprotection of α-methylbenzyl group using $K_2S_2O_8$/AcOH to give (Scheme 1.26).

Scheme 1.26

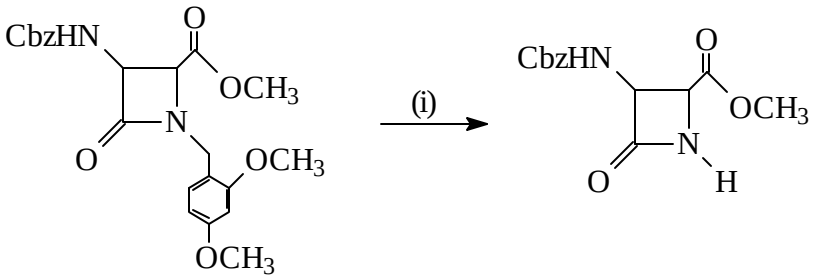


R = Phthalimido; X = F, Cl

Reagents and Conditions (i): $K_2S_2O_8$/AcOH.

S. Kishimoto et al.[51] have reported removal of N-2,4-dimethoxybenzyl group by oxidative cleavage using $K_2S_2O_8$;K_2SPO_4/MeCN:H_2O system at 95 °C to get NH-β-lactam in 79% yield (Scheme 1.27).

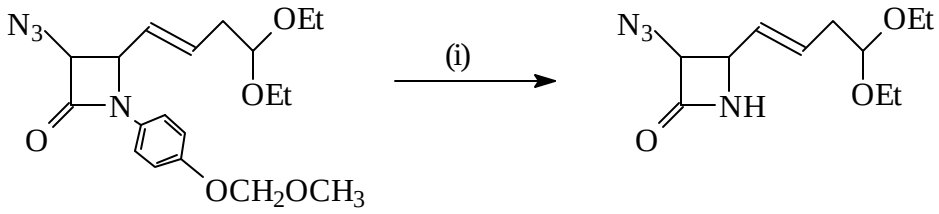
Scheme 1.27



Reagents and Conditions (i): $K_2S_2O_8$, K_2HPO_4/MeCN: H_2O, 95 °C, 2 h.

The elegant oxidative dearylation of *p*-methoxymethyloxyphenyl (*p*-MOM–Ph) group has been effected by Kronenthal et al[52] under mild reaction conditions using ceric (IV) ammonium nitrate (CAN) for the synthesis of NH-β-lactam (Scheme 1.28).

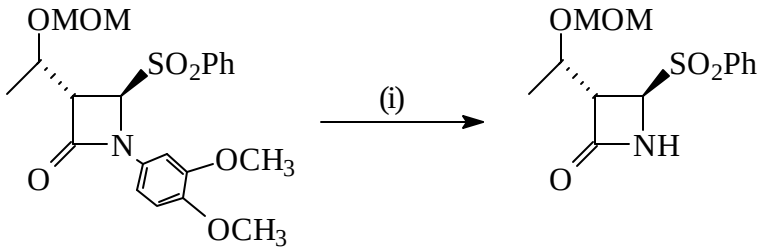
Scheme 1.28



Reagents and Conditions (i): a) HCl/MeOH, $CH(OCH)_3$; b) CAN.

The N-*p*-methoxyphenyl group has also been removed by ozonolysis to give NH-β-lactam in 57% yield by H.Yanagisawa. et al[53] (Scheme 1.29).

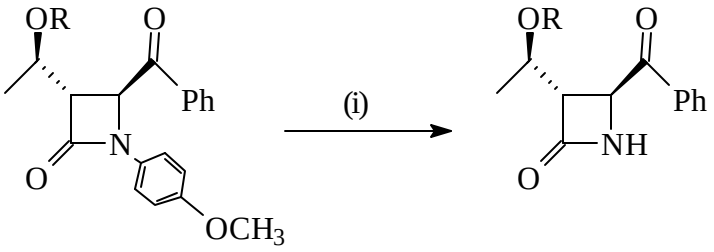
Scheme 1.29



Reagents and Conditions (i): O_3/EtOEt, Ice-Salt; $Na_2S_2O_8$, 50 °C.

The oxidative removal[54] of N-*p*-methoxyphenyl group has also been achieved using ceric (IV) ammonium nitrate (CAN)/$AgNO_3$ to furnish NH-β-lactam in good yield (Scheme 1.30).

Scheme 1.30

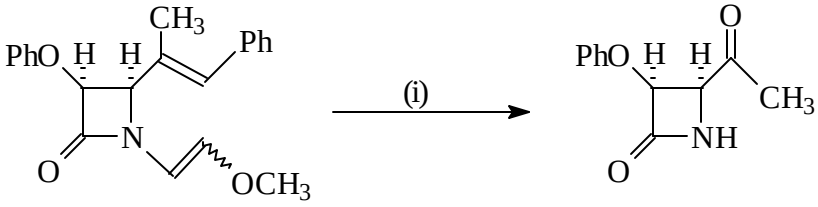


R = $SiMe_3$

Reagents and Conditions (i): $(NH_4)_2S_2O_8/AgNO_3$, MeCN: H_2O, 60 °C.

The imine prepared from allyl amine has been made to undergo cycloaddition reaction with an acid chloride to give β-lactam with N-allyl group. The N-allyl group was deblocked[55] to get NH-β-lactam in 50% yield by oxidative cleavage with $KMnO_4$ (Scheme 1.31). In this reaction the side chain at 4 position also got oxidized to corresponding ketone.

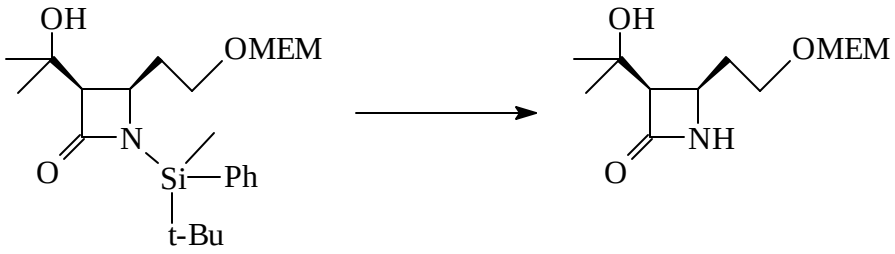
Scheme 1.31



Reagents and Conditions (i): $KMnO_4$/Acetone, 25 °C, 16h.

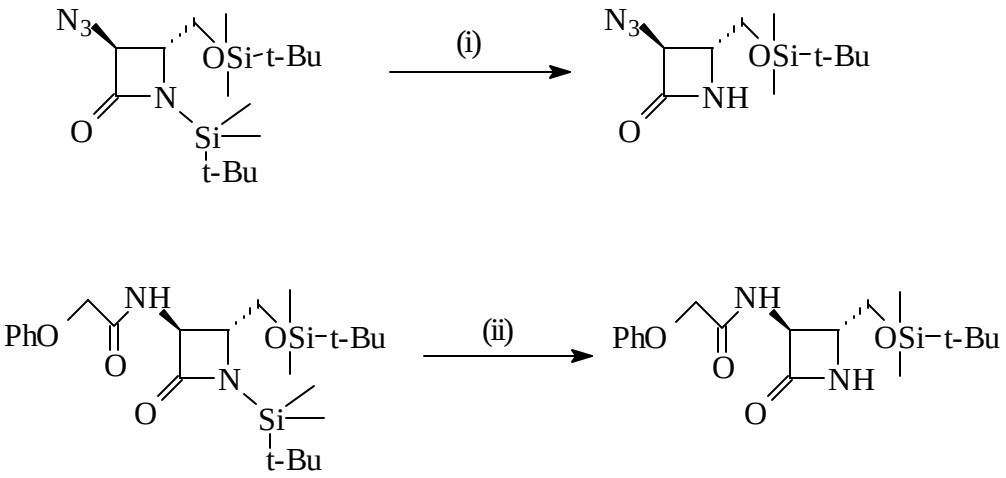
The fluoride anion induced deprotection of silyl group to get NH-β-lactam in 100% yield was reported by M. Shibasaki et al.[56] (Scheme 1.32).

Scheme 1.32



Similarly, Shibya et al[57] have also reported synthesis of NH-β-lactam in 98% yield by selective deprotection of N-silyl group using KF/MeOH in presence of O-silyl group (Scheme 1.33).

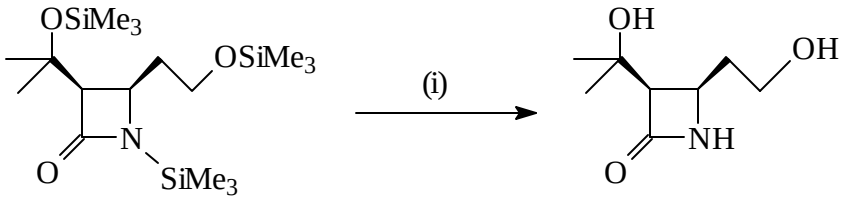
Scheme 1.33



Reagents and Conditions (i): KF/MeOH, 0 °C, 10 min.; (ii): KF/MeOH, 0 °C, 15 min.

The N-silyl group has also been removed by treatment of 1% AcOH to get NH-β-lactam in 58% yield by T. Iimon et al.[58] (Scheme 1.34). However, O-silyl group also got deprotected under this reaction condition.

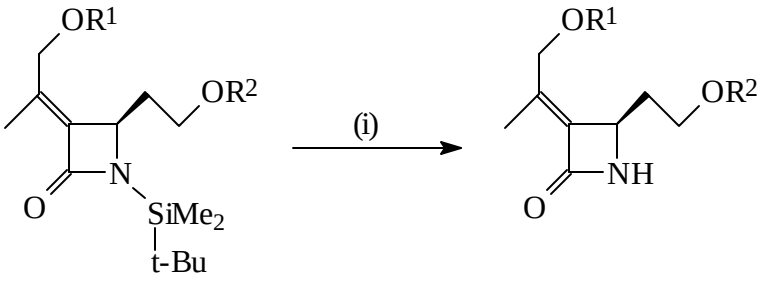
Scheme 1.34



Reagents and Conditions (i): 1% AcOH/MeOH, 25 °C, 24 h.

K.Okano et al[59] have shown that the N-silyl group of β-lactam can be cleaved with HCl/MeOH to get NH-β-lactam (Scheme 1.35).

Scheme 1.35

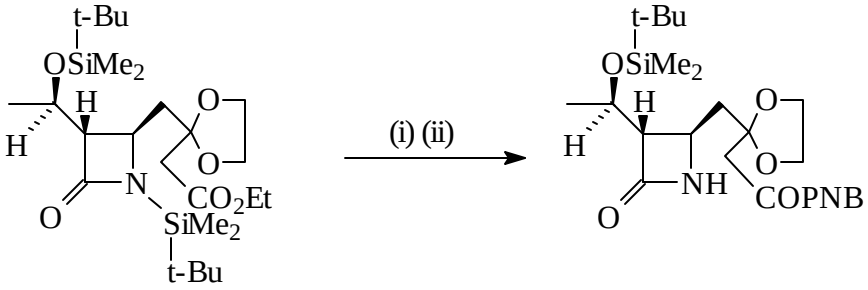


$R^1 = CO_2PNB$; $R^2 = SiMe_2tBu$

Reagents and Conditions (i): HCl/MeOH.

Kametani et al[60] have reported synthesis NH-β-lactam in 56.9% yield by selective removal of N-silyl group using 0.25 N NaOH in presence of O-silyl and ketal protection (Scheme 1.36).

Scheme 1.36



Reagents and Conditions (i): 0.25N NaOH/THF: H_2O, 25 °C, 2 h.; (ii): *p*-O_2NBnBr, 25 °C, 2 h.

1.3 Present Work

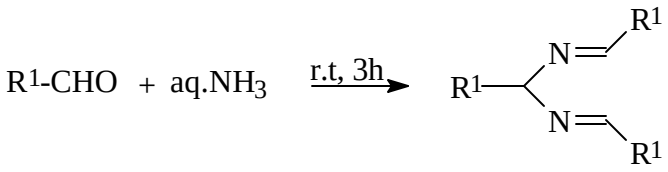
This chapter describes the use of (α-thiophenyl)benzyl group as a N-protective group for β-lactams using imines derived from (α-thiophenyl)benzyl amine *via* Staudinger reaction. This chapter also describes the synthesis of NH-β-lactams by easy removal of N-(α-thiophenyl)benzyl group under mild oxidative conditions using $K_2S_2O_8$.

1.4 Results and discussion

1.4.1 Preparation of Hydrazamides 1.01 and 1.02

The starting hydrazamides (**1.01** & **1.02**) have been prepared in excellent yields (Scheme 1.37) from aromatic aldehydes and ammonia by using reported procedure.[61]

Scheme 1.37

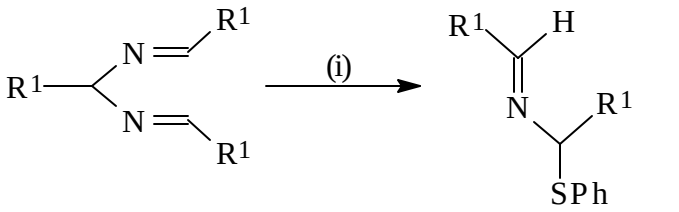


1.01 R^1 = Ph
1.02 R^1 = PMP

1.4.2 Preparation of imines 1.03 and 1.04

The imines **1.03** and **1.04** have been prepared in 92% and 89% yields respectively by reacting hydrazamides **1.01** and **1.02** with thiophenol as per the reported procedure.[62]

Scheme 1.38



1.03 R^1 = Ph
1.04 R^1 = PMP

Reagents and conditions (i): PhSH/dioxane, reflux, 10 h.

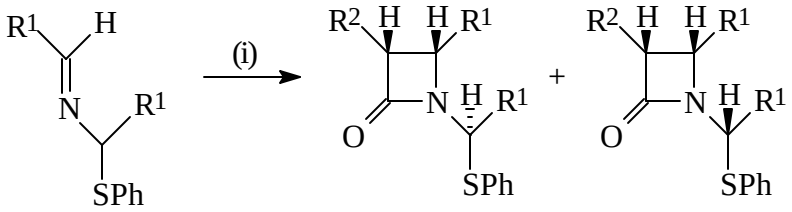
These imines were characterized by spectral analysis. The IR spectrum of **1.03** showed a band at 1628 for C=N stretching. The ^{1}H NMR spectrum of **1.03** showed a singlet at δ 5.93 corresponding to methyne proton of N-α-methyl benzyl group. Several multiplets appeared between δ 7.30-7.61 for fifteen aromatic protons. A singlet appeared at δ 8.00 was assigned to methyne proton of imine CH.

The IR spectrum of **1.04** showed a band at 1605 cm^{-1} for C=N stretching. The ^{1}H NMR spectrum of **1.04** showed two singlets at δ 3.80 and 3.86 corresponding two methoxy groups of *p*-anisyl. A signal at δ 5.90 was assigned to methyne proton of N-α-methyl benzyl group. Several multiplets appeared between δ 6.95-7.70 for thirteen aromatic protons. A singlet appeared at δ 7.95 was assigned to methyne proton of imine CH.

1.4.3 Preparation of b-lactams 1.05a-e and 1.06a-e

The treatment of imine with acid chloride in the presence of triethylamine at 0 °C gave a diastereomeric mixture of *cis*-β-lactams **1.05a-e** and **1.06a-e** in good yields (Scheme-1.39). The diastereomeric ratio of these isomers was determined from their ^{1}H NMR spectral data and HPLC analysis. The fractional crystallization of diastereomeric mixture gave β-lactams **1.05a-e** as a crystalline solid. The mother liquor on concentration offered other β-lactams **1.06a-e** in pure form as thick oils.

Scheme 1.39



1.05a-e **1.06a-e**

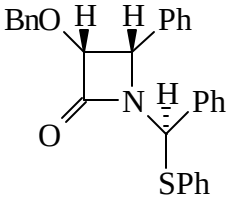
Reagent and conditions (i): R^2CH_2COCl/Et_3N, 0 °C.

Table 1. Synthesis of β-lactams **1.05** &**1.06**

Compd	$\mathbf{R^1}$	$\mathbf{R^2}$	Compound **1.05** & **1.0 6**		
			Yield[a] (%)	Ratio[b] of **1.05** & **1.06**	M.p.[c] of **1.05** (^{o}C)
a	Ph	PhO	74	74:26	214-215
b	Ph	BnO	58	64:36	119-120
c	Ph	AcO	50	74:26	153-154
d	*p*-Anisyl	PhO	79	83:17	157-159
e	*p*-Anisyl	BnO	57	78:22	149-151

[a] Isolated yields of diastereomeric mixture of **1.05** & **1.06**; [b] Ratio of **1.05** & **1.06** determined from HPLC and ^{1}H NMR spectral data; [c] M.p. of pure diastereomers **1.05a-e**, which were obtained by fractional crystallization.

The compound **1.05b** was chosen as a representative of **1.05** series for spectral discussion and characterization.



1.05b

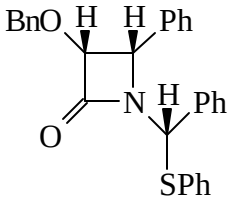
The ^{1}H NMR spectrum of **1.05b** showed two doublets at δ 4.0 and 4.15 for benzylic protons of O-benzyl group with the *J* = 10.5 Hz. The C4 and C3 β-lactam protons appeared as doublets at δ 4.50 and δ 5.05 with *J* = 4.8 Hz, which indicates the presence of *cis*-stereoisomer. A singlet appeared at δ 6.43 was assigned to methyne proton of N1-(α-thiophenyl)benzylic group. Twenty aromatic protons appeared as several multiplets between δ 6.76 and 7.65. ^{13}C NMR spectrum showed a peak at 167.0 for β-lactam carbonyl carbon and the rest of the picks are well accounting for established structure. The IR spectrum showed β-lactam carbonyl stretching at 1740 cm^{-1}. This compound gave satisfactory elemental analysis.

All other β-lactams of **1.05** series (Table 2) showed two characteristic doublets in the range of δ 4.43 –5.40 for corresponding protons at C3 and C4 of β-lactam ring with coupling constant *J* = 4.80–5.40 Hz, indicating the *cis* stereochemistry of these protons. All compounds showed satisfactory microanalysis.

Table 2: ^{1}H NMR data for β-lactam protons **1.05a-e**

Compound No	Chemical shifts for C3 and C4 protons of β-lactam		
	C4-H (δ)	C3-H (δ)	***J*** (Hz)
1.05a	5.00 (d)	5.20 (d)	5.0
1.05b	4.50 (d)	5.05 (d)	4.8
1.05c	5.22 (d)	5.40 (d)	5.3
1.05d	4.95 (d)	5.12 (d)	4.8
1.05e	4.43 (d)	4.96 (d)	5.4

The compound **1.06b** was chosen as a representative of **1.06** series for spectral discussion and characterization.



1.06b

The ^{1}H NMR spectrum of **1.06b** showed two doublets at δ 4.05 and δ 4.15 for benzylic protons of O-benzyl group with the *J* value of 10.8 Hz. The C4 and C3 β-lactam protons appeared as doublets at δ 4.35 and δ 5.65 with the *J* value of 4.8 Hz, which is characteristic of cis-isomer. A singlet at δ 6.15 was assigned to methyne proton of N1-(α-thiophenyl)benzylic group. The twenty aromatic protons appeared as several multiplets between δ 6.82 and 7.50. ^{13}C-NMR spectrum showed a signal at 165.9 for β-lactam carbonyl carbon and the rest of the lines are well accounting for established structure. The IR spectrum showed β-lactam carbonyl stretching at 1740 cm^{-1}. This compound gave satisfactory microanalysis.

All other β-lactams of **1.06** series showed two characteristic doublets in the range of δ 4.25 – 5.20 for corresponding protons at C3 and C4 of β-lactam ring with *J* = 4.80 – 5.50 Hz, indicating the *cis* stereochemistry of these protons. All compounds have showed satisfactory microanalysis.

Table 3. ^{1}H NMR data for β-lactam protons **1.06a,b,e**

Compound No	Chemical shifts for C3 and C4 protons of β-lactam		
	C4-H	C3-H	***J*** (Hz)
1.06a	5.0 (d)	5.20(d)	5.0
1.06b	4.35(d)	4.65(d)	4.8
1.06e	4.25(d)	4.63(d)	5.5

X-ray structure determination

In order to ascertain the relative configuration of the molecule, the X-ray crystal analysis was undertaken. The β-lactam **1.05a** was selected as a representative of major isomers. The X-ray crystal analysis confirmed the relative configuration of the β-lactam **1.05a** as 1′S, 3S, 4R.

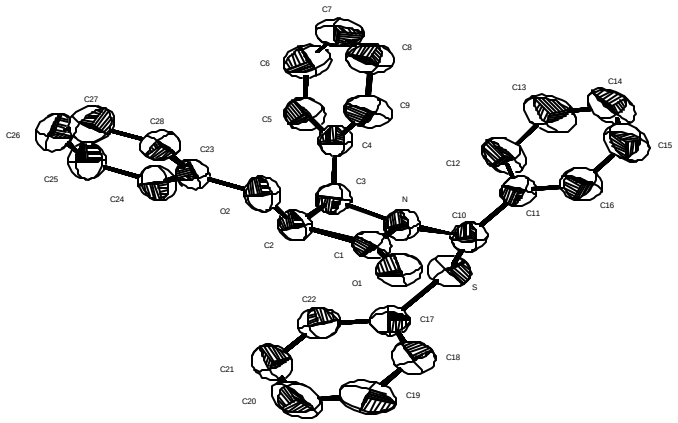


Fig. 1. ORTEP diagram of β-lactam **1.05a**

X-ray determination of 1.05a: Data was measured on pc-controlled Enraf-Nonius CAD-4 single crystal X-ray diffract meter with Mo-Kα (λ = 0.7993 A°) radiation at 293 K. Crystal belongs to mono clinic, space group $P2_1/C$ with a = 11.813 (2), b = 6.410(2), c = 30.552(4) A°; v = 2312.6 A° 3, z = 4, dcalc = 1.257 Mgm^{-3}, μ = 0.165 mm^{-1}. The structure was solved by direct methods using MULTAN-80 least squares refinement of scale factor, positional and anitropic thermal parameters for non hydrogen atom converged to R = 0.068. Hydrogen atom geometrically fixed and confirmed by difference Fouriers were held fixed during the refinement. Structure solution and refinement were carried out using NRCVAX programs.

The other isomers **1.06** were isolated as oil. The diastereomeric mixture of β-lactams **1.05** and **1.06** on oxidative N1-deprotection with potassium persulfate gave only one NH-β-lactam (see discussion in the following section), this suggests that the β-lactams **1.05** and **1.06** are diastereomeric at N1-(α-thiophenyl) benzylic position. Based on this observation the relative configuration of the minor isomers **1.06** can be assigned as 1′R, 3S, 4R.

1.4.4 N1-Deprotection

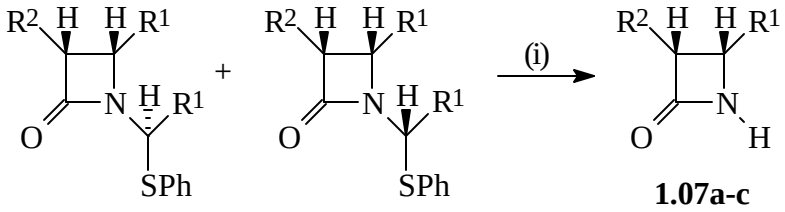
After successful utilization of imines derived from (α-thiophenyl)benzyl amine for the synthesis of β-lactams, we concentrated our efforts on the deprotection of this group under mild reaction conditions. Thus N1-(α-thiophenyl)benzylic group of β-lactams **1.05** and **1.06** was successfully removed by oxidative cleavage using potassium per sulphate to give N1-

unsubtituted β-lactams **1.07 a-c** in good yields. In all the case the oxidative cleavage of pure β-lactams **1.05** and **1.06** as well as diastereomeric mixture of these β-lactams **1.05** and **1.06** gave same NH-β-lactams **1.07**, indicating that these are diastereomeric at N1-benzylic position.

Preparation of N1-unsubtituted b-lactams 1.07a-c

To a solution of $K_2S_2O_8$ in water, a solution of β-lactam **1.05** or **1.06:1.05** was added and the reaction mixture was refluxed with stirring till the completion of reaction (TLC), then the acetonitrile was removed under reduced pressure and the residue was diluted with water and extracted with dichloromethane. After the usual work-up the reaction mixture gave crude product, which on column chromatography gave pure N1-unsubstituted β-lactams **1.07a-c**. The same reaction carried out with diastereomeric mixture of β-lactams **1.05**&**1.06** led to only one NH-β-lactam. The spectral data, microanalysis and melting of which were matching exactly with NH-β-lactam obtained from the above reaction. This clearly indicates that the β-lactams **1.05**&**1.06** are diastereomeric at N1-α-(thiophenyl)benzylic position.

Scheme 1.40

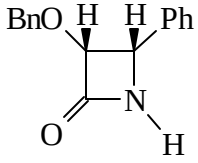


Reagent and conditions (i): $K_2S_2O_8$/MeCN: H_2O, reflux.

Table-4 Synthesis of NH-β-lactams **1.07a-c**

Compound	R^1	R^2	Compound **1.07**	
			Yield (%)	m. p. (^oC)
a	Ph	PhO	70	160
b	Ph	BnO	64	188-189
c	*p*-Anisyl	PhO	70	165-167

The compound **1.07b** was chosen as a representative of **1.07** series for spectral discussion and characterization.



1.07b

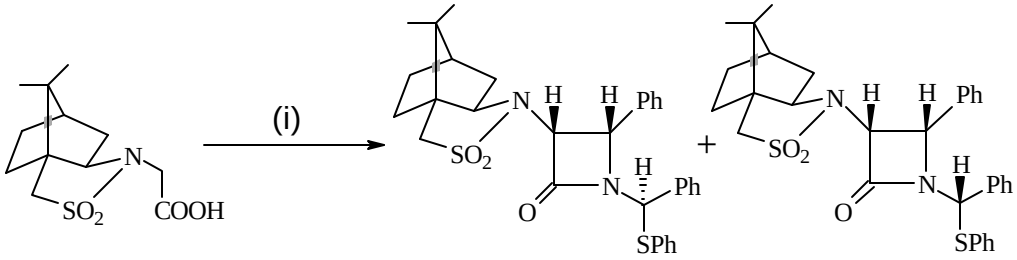
The ^{1}H NMR spectrum of **1.07b** showed a set of doublets at δ 4.25 and 4.35 for benzylic protons with the *J* = 12 Hz. The C3 β-lactam proton appeared as a doublet at δ 4.85 with *J* = 4.80 Hz and the C4 proton as broad dd at δ 4.95. The NH proton resonated between δ 6.25-6.30 as a broad singlet. Ten aromatic protons were appeared as several multiplets between δ 6.90-7.80. The IR spectrum showed β-lactam carbonyl stretching at 1750 cm^{-1} and N-H stretching at 3195 cm^{-1}. This compound gave satisfactory microanalysis.

The spectral data and microanalysis were well accounting for the other compounds **1.07a, 1.07c**.

1.4.5 Use of chiral ketene derived from Oppolzer's sultam

This methodology was extended for the asymmetric synthesis of N1-unsubstituted β-lactams. To achieve the diastereoselectivity in β-lactam ring formation *via* ketene-imine cycloaddition reaction, a sterically demanding chiral acid **1.08**, derived from camphor sultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **1.08** was obtained in overall 70% yield from camphor sultam[63] in two steps using our earlier reported procedure.[64] The cycloaddition reaction of ketene derived from the acid **1.08** with imine **1.03** in presence of triethylamine and phenyldichlorophosphate, an acid activator, offered a diastereomeric mixture of β-lactams **1.09** and **1.10** (Scheme 1.41) in the ratio of 92:8 (HPLC).

Scheme 1.41



1.08 **1.09** **1.10**

Reagent and conditions (i): PhP(O) Cl_2/Et_3N, 0 °C.

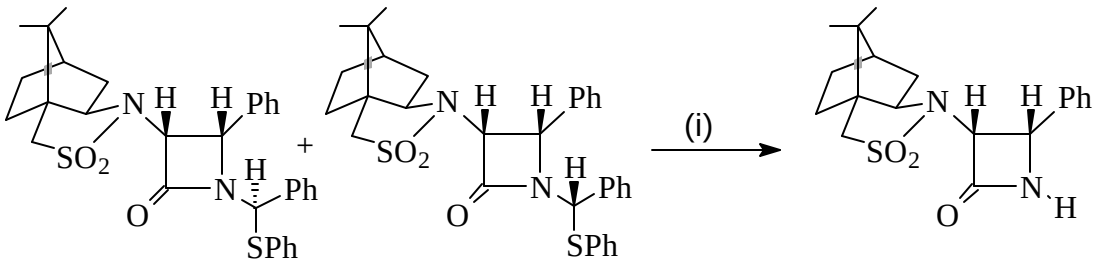
The spectral discussion and the characterization of mixture 1.09 and 1.10

^{1}H NMR spectrum showed presence of fifteen aromatic protons as several multiplets between δ 6.71 and 7.84. Two singlets appeared at δ 5.97 and 6.38 were assigned to methyne protons of N1-(α-thiophenyl)benzylic group of two diastereomers in the ration of 92:8. The C4 and C3 β-lactam protons appeared as two sets of doublet at δ 4.27, 4.78 (8%) and δ 4.67, 5.23 (92%) with 4.8 Hz coupling constant. Several multiplets appeared between δ 0.82 and 3.54 were well accounting for ten protons of sultam moiety. The two *gem*-dimethyl of sultam part have been observed as two singlets at δ 0.12 and 0.68. The IR spectrum showed β-lactam carbonyl stretching at 1755 cm^{-1}. This compound gave satisfactory microanalysis.

1.4.6 Preparation of NH-unsubstituted b-lactam 1.11 from 1.09 and 1.10

The oxidative cleavage of N1-(α-thiophenyl)benzylic group of diastereomeric mixture of β-lactams **1.09** and **1.10** with $K_2S_2O_8$ under similar reaction conditions as discussed earlier gave N1-unsubstituted β-lactam **1.11** in high yield (Scheme-1.42).

Scheme 1.42



1.09 **1.10** **1.11**

Reagent and conditions (i): $K_2S_2O_8$/MeCN: H_2O, reflux.

The spectral discussion and characterization of NH-b-lactam 1.11

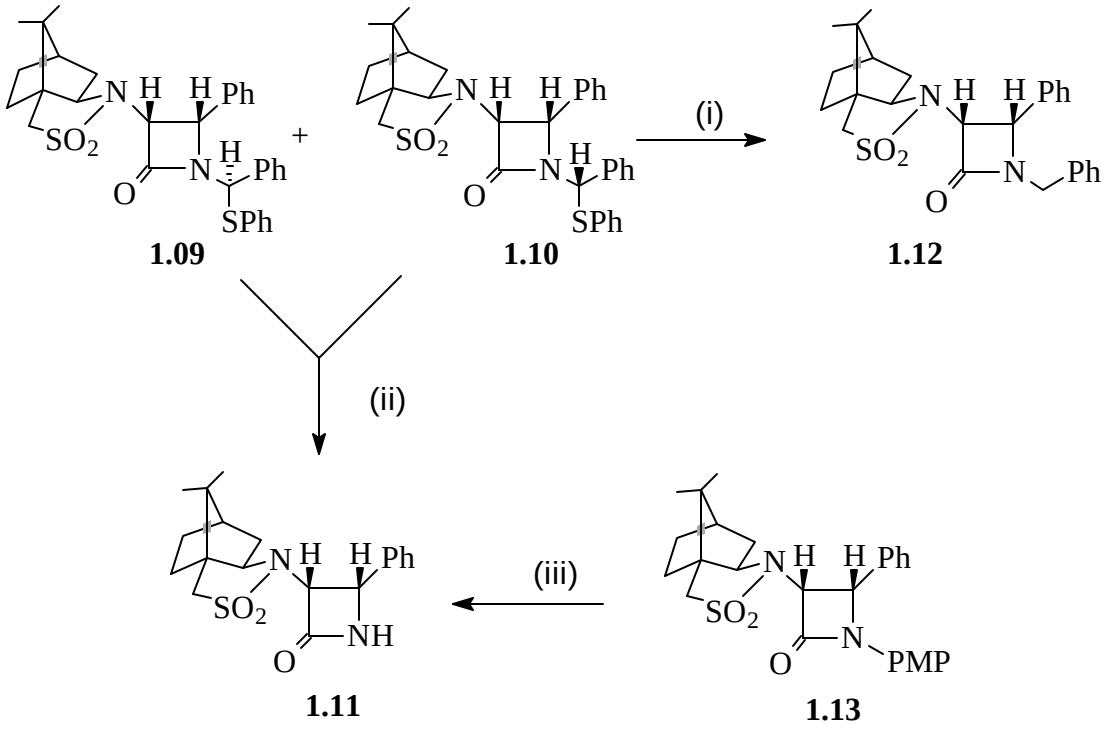
The ^{1}H NMR spectrum of β-lactam **1.11** showed two singlets at δ 0.09 and 0.71 for two *gem*-dimethyl groups of sultam moiety. The other ten protons of sultam portion appeared as several multiplets between δ 0.77 and 3.57. The C3 β-lactam proton appeared as a doublet at δ 5.00 with *J* value of 4.8 Hz and C4 β-lactam proton at δ 5.21 as a broad dd. A broad singlet appeared at δ 6.67 was assigned to N-H proton. The five aromatic protons appeared as

multiplets between δ 7.17 - 7.68. The IR spectrum showed β-lactam carbonyl stretching at 1760 cm^{-1} and N-H stretching at 3300 cm^{-1}.

Stereochemical determination of compounds 1.09, 1.10 and 1.11

The isomers (**1.09** & **1.10**) obtained were diastereomeric at N1-(α-thiophenyl) benzylic position (confirmed by deprotection of this group), which was further confirmed by converting them to N1-benzyl-*cis*-β-lactam via reductive removal of thiophenyl group. Thus, elimination of thiophenyl group of diastereomeric mixture of β-lactams **1.09** and **1.10** using Raney Ni gave N1-benzyl-*cis*-β-lactam (**1.12**) as a single diastereomer (^{1}H NMR) in high yield (Scheme 1.43). The spectral data and rotation of this β-lactam **1.12** were found to be identical with our earlier reported[64] β-lactam of known absolute configuration of 3*R*, 4*S*. Therefore, the absolute stereochemistry at 3 and 4 positions of β-lactam ring in **1.12** was assigned as 3*R*, 4*S*. As β-lactam **1.12** was obtained from a diastereomeric mixture of β-lactams **1.09** and **1.10**, these compounds also should have same 3*R*, 4*S* absolute stereochemistry at 3 and 4 positions. These assignments were further confirmed by deprotection of the N1-(α-thiophenyl)benzylic group.

Scheme 1.43



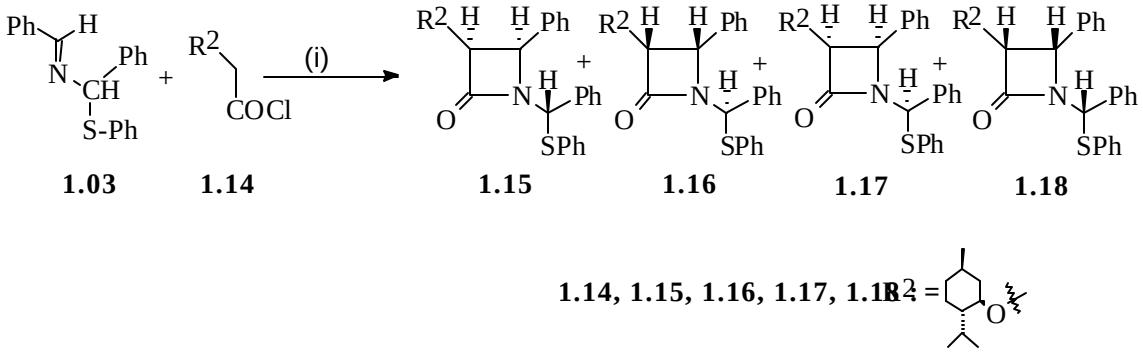
Reagent and conditions (i): Re Ni, (ii) $K_2S_2O_8$/MeCN: H_2O, reflux, 4 h. (iii) CAN/MeCN: H_2O

The oxidative removal of the N1-(α-thiophenyl)benzylic group of the diastereomeric mixture of β-lactams **1.09** and **1.10** using potassium per sulfate in acetonitrile/water under reflux conditions gave the N1-unsubstituted β-lactam (**1.11**) as a single diastereomer (^{1}H NMR) in good yield (Scheme 1.42). This N1-unsubstituted β-lactam (**1.11**) was also prepared from the N1-(*p*-methoxyphenyl)-β-lactam (**1.13**) with known 3*R*, 4*S* absolute configuration. Thus, **1.13** on treatment with ceric (IV) ammonium nitrate (CAN) in acetonitrile/water gave the NH-β-lactam **1.11** in 86.8% yield (Scheme 1.43), which showed identical spectral (NMR) and analytical (m.p. rotation) data with the NH-compound **1.11** prepared from the diastereomeric mixture of β-lactams **1.09** & **1.10**. From the above chemical transformations the absolute configuration at the 3 and 4 positions of β-lactam ring in **1.09**, **1.10** & **1.11** was unambiguously established as 3*R*, 4*S*.

1.4.7 Use of chiral ketene derived from menthyloxy acetic acid chloride

The effect of chiral ketene derived from menthyloxyacetyl chloride (**1.14**) has also been studied on diastereoselective β-lactam ring formation. The starting chiral menthyloxy acetic acid was obtained in good yield by alkylation[65] of *l*-menthol with chloroacetic acid using sodium metal in dry toluene under refluxing conditions. The menthyloxy acetic acid on treatment with thionyl chloride gave the required chiral acid chloride **1.14** in high yield. The acid chloride **1.14** on reaction with imine **1.03** in presence of triethylamine under went cycloaddition reaction to give a diastereomeric mixture of four *cis*-β-lactams (**1.15-1.18**) in good yield (Scheme 1.44).

Scheme 1.44



Reagent and conditions (i): Et_3N, 0 °C r.t.

^{1}H NMR analysis of the crude reaction product showed the presence of four *cis*-β-lactams (**1.15**, **1.16**, **1.17** & **1.18**) in the diastereomeric ratio of 35:35:18:12, the diastereomeric ratio due to N1-(α-thiophenyl)benzyl group was found to be 70:30 (**1.15** + **1.16** : **1.17** +**1.18**). However, this chiral acid chloride **1.14**, did not give appreciable asymmetric induction in β-lactam ring formation and almost equal amounts of two major (**1.15** & **1.16**) and two minor (**1.17** & **1.18**) diastereomers were formed. Crystallization of diastereomeric mixture from pet. ether: acetone (96:4) gave only one diastereomer, out of the four, in pure form as a white solid, which was found to be one of the minor diastereomers (**1.17** or **1.18**) by ^{1}H NMR spectral analysis.

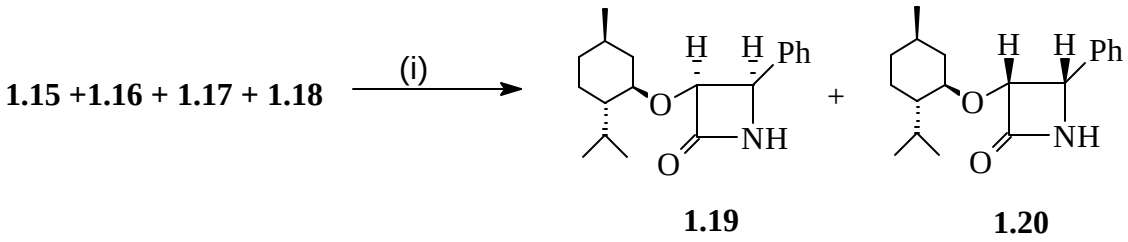
The spectral data discussion and characterization of 1.17 or 1.18

The ^{1}H NMR spectrum of single diastereomer **1,17** or **1.18** showed several multiplets between δ 6.90 and 7.60 accounting for fifteen aromatic protons. A singlet appeared at δ 6.4 was assigned to methyne proton of N1-(α-thiophenyl)benzyl group. The C4 and C3 β-lactam protons appeared as a set of doublets at δ 4.40 and 5.00 respectively with the *J* value of 5.2 Hz, which indicated the *cis* stereochemistry of these protons. The three methyl groups of menthyl moiety were seen as three separate doublets at δ 0.1, 0.48 and 0.82 with *J* = 8 Hz. The other eleven protons of menthyl part were appeared as several multiplets between δ 0.60 and 2.75. The ^{13}C NMR showed a peak at 168.96 corresponding to β-lactam carbonyl carbon and the other picks appeared were in well agreement with the structure assigned to the compound **1.17** or **1.18**. The IR spectrum showed β-lactam carbonyl stretching at 1740 cm^{-1}. This compound gave satisfactory microanalysis.

1.4.8 Preparation of N1-unsubstituted b-lactam 1.19 and 1.20 from β-lactams ***mixture1.15, 1.16, 1.17 & 1.18***

The oxidative cleavage of N1-(α-thiophenyl)benzylic group of diastereomeric mixture of β-lactams **1.15, 1.16, 1.17** & **1.18** with $K_2S_2O_8$ by usual procedure gave mixture of two N1-unsubstituted β-lactams (**1.19** and **1.20**) (Scheme 1.45). Similarly, persulfate oxidation of pure β-lactam **1.17** or **1.18** gave optically pure NH-β-lactam **1.19** or **1.20**. The absolute stereochemistry could not assigned to these compounds, as X-ray quality crystal could not be obtained.

Scheme 1.45



1.19 **1.20**

Reagents and conditions (i) $K_2S_2O_8$/MeCN: H_2O, reflux, 3 h.

The spectral data discussion and characterization of 1.19 or 1.20

The ^{1}H NMR spectrum of **1.19** or **1.20** showed a multiplet between δ 7.40 and 7.45 for five aromatic protons. A broad singlet at δ 6.30 was assigned to N-H proton. The C3 β-lactam proton appeared as doublet at δ 4.8 with *J* value 4.8 Hz, and C4 β-lactam proton appeared as dd at δ 4.88 with the *J* values of 2.2 and 4.8 Hz. The three methyl groups of menthyl moiety were appeared as three separate doublets at δ 0.26, 0.55 and 0.88 with the *J* values of 8.0 Hz. The other menthyl protons appeared as several multiplets between δ 0.76 and 2.95. The ^{13}C NMR spectrum showed a peak at 169.89 corresponding to β-lactam carbonyl carbon, the other peaks observed were in well agreement with the structure assigned either for compound **1.19** or **1.20**. The IR spectrum showed β-lactam carbonyl carbon stretching at 1759 cm^{-1} and N-H stretching at 3413 cm^{-1}. This compound gave satisfactory microanalysis.

1.5 Summary

The imines **1.03** and **1.04** on cycloaddition reaction with various acid chlorides gave β-lactams with N1-(α-thiophenyl)benzylic or N1-(α-thiophenyl)-*p*-methoxyphenyl group. The relative stereochemistry of C3 and C4 center of β-lactam **1.05** was established as 3S, 4R by single crystal X-ray analysis.

The N1-protective group was successfully removed to get N-H β-lactam by oxidative cleavage with $K_2S_2O_8$ under mild reaction conditions.

1.6 Experimental

1.6.1 Preparation of Hydrobenzamides (1.01 & 1.02)

Freshly distilled aldehyde was added to a ca. 10 fold excess of aq. NH_3 (30%). The reaction mixture was stirred for 3 h. at room temperature. The supernatant liquid was decanted off and the lumps were crushed, treated with water and filtered. The crude solid so obtained was crystallized from ethanol to give pure hydrobenzamides **1.01** and **1.02** in very high yield.

1.6.1a 1-Phenyl-N, N℄-bis (phenyl methylene) methane diamine (1.01)

Freshly distilled benzaldehyde (10.6 g, 0.1 mol) on treatment with aq. NH_3 (30%) (58.6 ml, 1.0 mol) at room temperature provided 9.1 g (92%) of c **1.01**.

M.p. : 101-102 °C [lit.[54a] m.p. 101-102 °C].

^{1}H NMR : δ 5.80 (s, 1H); 7.18 (m, 9H); 7.62 (m, 6H); 8.30 (s, 2H).

IR : 1630, 754, 693 cm^{-1}.

1.6.1b 1-*p*-Anisyl-N, N℄-bis (*p*-anisylmethylene) mehtanediamine (1.02)

Freshly distilled *p*-anisaldehyde (13.6 g, 0.1 mol) on treatment with aq. NH_3 (30%) (58.6 ml, 1.0 mol) at room temperature provided 11.5 g (89%) of hydrobenzamide **1.02**.

M.p. : 126-128 °C [lit.[54b] m.p. 128.5-130.5 °C].

^{1}H NMR : δ 3.68 (s, 3H); 3.75 (s, 6H); 5.73 (s, 1H); 6.73 (d, J = 9 Hz, 6H); 7.27 (d, J = 9 Hz, 2H); 7.62 (d, J = 9 Hz, 4H); 8.28 (s, 2H).

IR : 1610, 1030, 760 cm^{-1}.

1.6.2 General procedure for the preparation of imines 1.03 and 1.04

A solution of hydrobenzamide and thiophenol in dioxane (30 ml) was refluxed for 10 h. The dioxane was removed by distillation under reduced pressure and the residue was treated with pet. ether (10 ml) and kept in refrigerator overnight. The precipitated solid was filtered and washed with cold pet. ether (5 ml) to get required imines, which were sufficiently pure so as to be used in next step with out further purification.

1.6.2a Preparation of N- [(a -thiophenyl) benzyl] imine 1.03

The hydrobenzamide **1.01** (5.96 g, 0.02 mol) on treatment with thiophenol (3.34 g, 0.03 mol) gave 9 g (99%) of imine **1.03**.

M.p. : 79-80 °C [lit.[55] m.p. 79.5 °C].

^{1}H NMR : δ 5.93 (s, 1H); 7.30 (m, 11H); 7.48 (d, *J* = 7.5, 2H); 7.61 (d, *J* = 7.5, 2H); 8.0 (s, 1H).

IR : 1628, 749, 694 cm^{-1}.

1.6.2b Preparation of N- [(a -thiophenyl)-p-methoxybenzyl] imine 1.04

The hydroanisamide (**1.02**) (7.78 g, 0.02 mol) on treatment with thiophenol (3.1 ml, 0.03 mol) gave 11.55 g (98%) of imine **1.04**.

M.p. : 94 - 95 °C.

^{1}H NMR : δ 3.80 (s, 3H); 3.86 (s, 3H); 5.90 (s, 1H); 6.95 (d, *J* = 8.8 Hz, 4H); 7.25 (m, 3H); 7.43 (m, 2H); 7.52 (d, *J* = 8.8 Hz, 2H); 7.70 (d, *J* = 8.8 Hz, 2H); 7.95 (s, 1H).

IR : 1610, 1030, 760 cm^{-1}.

1.6.3 General procedure for the synthesis of b-lactams 1.05a-e &1.06 6a-e

A solution of the acid chloride (2 mmol) in dry CH_2Cl_2 (10 ml) was slowly added to a solution of imines (**1.03,1.04**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 ml) at 0 - ^oC. The reaction mixture was then allowed to warm-up to r.t. and stirred further for 13 h. It was then washed with water (2x15 ml), satd. $NaHCO_3$ (10 ml), brine (10 ml), and dried over anhydrous Na_2SO_4. It was filtered and filtrate on removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether: acetone, 9:1) to give diastereomeric mixture of β-lactams (**1.05a-e** & **1.06a-e**) in good yields. The major and minor diastereomers were separated by fractional crystallization from pet. ether-acetone.

1.6.3a Synthesis of 3-Phenoxy-N1-[(a -thiophenyl)benzyl]-4-phenylazetidin-2-one 1.05a and 1.06a

The phenoxy aetylchloride (320 mg, 2 mmol) on treatment with imine **1.03** (450 mg, 1.48 mmol) in the presence of triethylamine (0.55 ml, 4 mmol) at 0 ^oC provided 479 mg (74%) of diastereomeric mixture of β-lactams **1.05a** (major, solid) and **1.06a** (minor, oil). These two diastereomers were separated by fractional crystallization from pet. ether-acetone.

b-Lactam 1.05a

M.p. : 214 - 215 ^{o}C.

^{1}H NMR : δ 5.0 (d, *J* = 5 Hz, 1H); 5.2 (d, *J* = 5 Hz, 1H); 6.47 (s, 1H); 6.8 (d, *J* = 10 Hz, 2H); 6.83 (t, *J* = 10 Hz, 1H); 6.95 - 7.70 (m, 17H).

^{13}C NMR : 61.20, 62.34, 81.22, 115.64, 122.00, 127.55, 127.85, 128.08, 128.22, 128.57, 128.81, 129.08, 129.42, 132.49, 133.03, 135.07, 156.87, 165.98.

MS (m/z) : 328 (M^{+}- SPh), 199, 132 (100%), 109.

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{28}H_{23}O_2NS$.

Calculated : C, 76.86; H, 5.30; N, 3.20%.

Found : C, 76.68; H, 5.37; N, 3.27%.

b-Lactam 1.06a

M.p. : Isolated as oil.

^{1}H NMR : δ 4.45 (d, *J* = 5 Hz, 1H); 5.2 (d, *J* = 5 Hz, 1H); 6.15 (s, 1H); 6.6 (d, *J* = 10 Hz, 2H); 6.85 (t, *J* = 10 Hz, 1H); 6.95 - 7.60 (m, 17H).

^{13}C NMR : 63.23, 63.93, 80.30, 115.56, 121.95, 127.84, 128.06, 128.64, 128.75, 129.05, 129.44, 132.28, 133.04, 133.54, 135.78, 156.79, 164.91.

IR : 1740 cm^{-1}.

1.6.3b Synthesis of 3-Benzyloxy-N1-[(a -thiophenyl)benzyl]-4-phenylazetidin-2-one 1.05b and 1.06b

The benzyloxy aetylchloride (368 mg, 2 mmol) on treatment with imine **1.03** (450 mg, 1.48 mmol) in the presence of triethylamine (0.55 ml, 4 mmol) at 0 ^{o}C provided 387 mg (58%) of diastereomeric mixture of β-lactams **1.05b** (major, solid) and **1.06b** (minor, oil). These two diastereomers were separated by fractional crystallization from pet. ether-acetone.

b-Lactam 1.05b

M.p. : 119 - 120 ^{o}C.

^{1}H NMR : δ 4.0 (d, *J* = 10.5 Hz, 1H); 4.15 (d, *J* = 10.5 Hz, 1H); 4.5 (d, *J* = 4.8 Hz, 1H); 5.05 (d, *J* = 4.8 Hz, 1H); 6.43 (s, 1H); 6.76 - 6.85 (m, 2H); 7.00 - 7.65 (m, 18H).

^{13}C NMR : 61.00, 62.17, 72.24, 82.83, 127.73, 127.86, 127.99, 128.14, 128.46, 128.75, 129.32, 132.50, 133.02, 133.85, 135.25, 136.25, 167.0.

MS (m/z) : 342 (M^+- SPh), 199, 132, 109, 91 (100%).

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{29}H_{25}NO_2S$.

Calculated : C, 77.13; H, 5.58; N, 3.10%.

Found : C, 77.07; H, 5.77; N, 3.07%.

b-Lactam 1.06b

M.p. : Isolated as oil.

^{1}H NMR : δ 4.05 (d, *J* = 10.8 Hz, 1H); 4.15 (d, *J* = 10.8 Hz, 1H); 4.35 (d, *J* = 4.8 Hz, 1H); 4.65 (d, *J* = 4.8 Hz, 1H); 6.15 (s, 1H); 6.82 - 7.50 (m, 20H).

^{13}C NMR : 62.91, 63.43, 72.04, 82.67, 127.65, 127.89, 128.44, 128.60, 128.85, 131.91, 133.76, 165.92.

IR : 1740 cm^{-1}.

1.6.3c Synthesis of 3-Acetoxy-N1-[(a -thiophenyl)benzyl]-4-phenylazetidin-2-one 1.05c

The acetoxy aetylchloride (273 mg, 2 mmol) on treatment with imine **1.03** (450 mg, 1.48 mmol) in the presence of triethylamine (0.55 ml, 4 mmol) at 0 ^oC provided 299 mg (50%) of diastereomeric mixture of β-lactams **1.05c** and **1.06c**. The diastereomeric mixture on fractional crystallization from pet. ether-acetone provided **1.05c** (major) as white crystalline solid.

M.p. : 153 -154 ^oC.

^{1}H NMR : δ 1.55 (s, 3H); 5.22 (d, *J* = 5.3 Hz, 1H); 5.40 (d, *J* = 5.3 Hz, 1H); 6.44 (s, 1H); 6.85 - 7.70 (m, 15H).

^{13}C NMR : 19.57, 60.40, 62.66, 76.12, 127.54, 127.81, 128.05, 128.22, 128.42, 128.63, 128.76, 129.42, 132.59, 133.39, 134.78, 164.89, 168.76.

IR : 1750 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{24}H_{21}O_3NS$.

Calculated : C, 71.44; H, 5.25; N, 3.47%.

Found : C, 71.32; H, 5.14; N, 3.54%.

1.6.3d Synthesis of 3-Phenoxy-N1-[(a -thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one 1.05d

The phenoxy aetylchloride (320 mg, 2 mmol) on treatment with imine **1.04** (537 mg, 1.48 mmol) in the presence of triethylamine (0.55 ml, 4 mmol) at 0 ^oC provided 581 mg (79%) of diastereomeric mixture of β-lactams **1.05d** and **1.06d**. This mixture on fractional crystallization from pet. ether-acetone provided**1.05d** (major) as white crystalline solid.

M. p. : 157 - 159 ^oC.

^1H NMR : δ 3.70 (s, 3H); 3.72 (s, 3H); 4.95 (d, *J* = 4.8 Hz, 1H); 5.12 (d, *J* = 4.8 Hz, 1H); 6.4 (s, 1H); 6.50 - 7.65 (m, 18H).

^{13}C NMR : 54.97, 55.05, 60.66, 61.43, 81.05, 113.02, 113.43, 115.50, 121.78, 125.02, 127.31, 128.23, 128.95, 129.19, 129.96, 132.64, 156.82, 159.32, 159.47, 165.71.

MS (m/z) : 388 (M^+- SPh), 254, 162 (%), 109.

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{30}H_{27}O_4NS$.

Calculated : C, 72.41; H, 5.47; N, 2.81%.

Found : C, 72.44; H, 5.56; N, 2.87%.

1.6.3e Synthesis of 3-Benzyloxy-N1-(a -thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one 1.05e and 1.06e

The benzyloxy aetylchloride (368 mg, 2 mmol) on treatment with imine **1.04** (537 mg, 1.48 mmol) in the presence of triethylamine (0.55 ml, 4 mmol) at 0 ^oC provided 431 mg (57%) of diastereomeric mixture of β-lactams **1.05e** (major, solid) and **1.06e** (minor, oil). These two diastereomers were separated by fractional crystallization from pet. ether-acetone.

b-Lactam 1.05e

M.p. : 149-151 ^{o}C.

^{1}H NMR : δ 3.71 (s, 3H); 3.77 (s, 3H); 4.02 (d, *J* = 11 Hz, 1H); 4.16 (d, *J* = 11 Hz, 1H); 4.43 (d, *J* = 5.4 Hz, 1H); 4.96 (d, *J* = 5.4 Hz, 1H); 6.35 (s, 1H); 6.53 - 6.72 (m, 4H); 6.83 - 7.45 (m, 12H); 7.53 - 7.64 (m, 2H).

^{13}C NMR : 55.29, 60.59, 61.50, 72.21, 82.74, 113.37, 113.60, 125.98, 127.72, 127.80, 128.03, 128.16, 128.33, 129.17, 129.33, 130.11, 132.85, 159.61, 167.02.

IR : 1750 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{31}H_{28}O_4NS$.

Calculated : C, 72.92; H, 5.53; N, 2.74%.

Found : C, 72.24; H, 6.07; N, 2.76%.

b-Lactam 1.06e

M.p. : Isolated as oil.

^{1}H NMR : δ 3.80 (s, 3H); 3.83 (s, 3H); 4.07 (d, *J* = 10.8 Hz, 1H); 4.15 (d, *J* = 10.8 Hz, 1H); 4.25 (d, *J* = 5.5 Hz, 1H); 4.63 (d, *J* = 5.5 Hz, 1H); 6.10 (s, 1H); 6.80 – 7.45 (m, 18H).

IR : 1745 cm^{-1}.

1.6.4 General procedure for the synthesis of N1-unsubstituted b-lactams (1.07a-c)

To a solution of potassium per sulfate (0.162 g, 0.6 mmol) in water (3 ml), a solution of β-lactams **1.05** (0.2 mmol) in acetonitrile (8 ml) was added and the reaction mixture was refluxed for 4 h. After completion of the reaction (TLC), the acetonitrile was removed by distillation under reduced pressure and the residue was diluted with water (5 ml) and extracted with CH_2Cl_2 (2 x 15 ml). The organic layer was successively washed with water (15 ml) and brine (10 ml). This extract was dried over anhydrous Na_2SO_4. It was filtered and filtrate on removal of solvent provided the crude product, which was column chromatographed to get of pure unsubstituted β-lactams **1.07**.

To a solution of potassium per sulfate (0.162 g, 0.6 mmol) in water (3 ml), a solution of diastereomeric mixture of β-lactams **1.05**&**1.06** (0.2 mmol) in acetonitrile (8 ml) was added and the reaction mixture was refluxed for 4 h. After completion of the reaction (TLC),

the acetonitrile was removed by distillation under reduced pressure and the residue was diluted with water (5 ml) and extracted with CH_2Cl_2 (2 x 15 ml). The organic layer was successively washed with water (15 ml) and brine (10 ml). This extract was dried over anhydrous Na_2SO_4. It was filtered and filtrate on removal of solvent provided the crude product, which was column chromatographed to get of pure unsubstituted β-lactams**1.07**.

1.6.4a Synthesis of 3-Phenoxy-4-phenylazetidin-2-one 1.07a

The β-lactam **1.05a** or **1.05a**&**1.06a** (87.5 mg, 0.2 mmol) on treatment with potassium persulfate (162 mg, 0.6 mmol) in acetonitrile-water at reflux temperature gave crude product. This was purified by column chromatography to give 33.5 mg (70%) of NH-β-lactam **1.07a** as a white crystalline solid.

M.p. : 160 ^oC.

^1H NMR : δ 5.05 (d, *J* = 4.8 Hz, 1H, C3H); 5.5 (dd, *J* = 2.5 & 4.8 Hz, 1H, C4H); 6.6 (bs, 1H, NH); 6.8 (d, *J* = 9 Hz, 2H, Ar); 6.9 (t, J = 9 Hz, 1H, Ar); 7.10-7.40 (m, 7H, Ar).

IR : 2800-3500, 1770 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{15}H_{13}NO_2$.

Calculated : C, 75.30; H, 5.48; N, 5.85%.

Found : C, 75.51; H, 5.73; N, 5.62%.

1.6.4b Synthesis of 3-Benzyloxy-4-phenylazetidin-2-one 1.07b

The β-lactam **1.05b** or **1.05b**&**1.06b** (90.2 mg, 0.2 mmol) on treatment with potassium persulfate (162 mg, 0.6 mmol) in acetonitrile-water at reflux temperature gave crude product. This was purified by column chromatography to give 32.4 mg (64%) of NH-β-lactam **1.07b** as a white crystalline solid.

M.p. : 188-189 °C.

^1H NMR : δ 4.25 (d, *J* = 12 Hz, 1H); 4.35 (d, *J* = 12 Hz, 1H); 4.85 (d, *J* = 4.8 Hz, 1H); 4.95 (m, 1H); 6.25 - 6.30 (bs, 1H); 6.9 - 7.8 (m, 10H).

IR : 1750, 3195 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{16}H_{15}O_2N$.

Calculated : C, 75.87; H, 5.97; N, 5.53%.

Found : C, 75.48; H, 6.01; N, 5.46%.

1.6.4c Synthesis of 3-Phenoxy-4-*p*-anisylazetidin-2-one 1.07c

The β-lactam **1.05d** or **1.05d&1.06d** (99.5 mg, 0.2 mmol) on treatment with potassium persulfate (162 mg, 0.6 mmol) in acetonitrile-water at reflux temperature gave crude product. This was purified by column chromatography to give 37.6 mg (70%) of NH-β-lactam **1.07c** as a white crystalline solid.

M.p. : 165 - 167 °C.

^{1}H NMR : δ 3.80 (s, 3H); 5.03 (d, *J* = 4.5 Hz, 1H); 5.42 (dd, *J* = 2.4 & 4.5 Hz, 1H); 6.50 (s, 1H); 6.75 - 6.97 (m, 5H); 7.11 - 7.23 (m, 2H); 7.30 (d, *J* = 8.2 Hz, 2H).

IR : 1720 & 3190 cm^1.

Elemental analysis

Molecular Formula : $C_{16}H_{15}O_3N$.

Calculated : C, 71.36; H, 5.61; N, 5.20%.

Found : C, 71.78; H, 5.27; N, 5.46%.

1.6.5 Synthesis of diastereomeric mixture of {N1¢-[(α-thiophenyl) benzyl]-4¢-phenylazetidin-2¢- one-3¢-yl}-2,10-comphorsultam (1.09 & 1.10)

To a stirred mixture of acid **8** (0.4 g, 1.46 mmol), imine **3a** (0.653 g, 2.15 mmol), triethylamine (0.6 ml) and dry CH_2Cl_2 (10 ml), a solution of phenyl dichlorophosphate (0.32 ml, 2.15 mmol) in dry CH_2Cl_2 (10 ml) was added at 0 °C over a period of 20 min. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and successively washed with water (15 ml), satd. $NaHCO_3$ solution (15 ml), brine (15 ml), and dried (Na_2SO_4). It was filtered and filtrate on evaporation of solvent gave crude product, which was column chromatographed (silica gel, 60-120, pet. ether/acetone) to furnish 0.614 g (75.4%) of the diastereomeric mixture of β-lactam **1.09** & **1.10** as a white solid, m. p. 98 - 100 °C. This mixture was used for deprotection without separation.

^{1}H NMR : (Dia. mix. **1.09** & **1.10**): δ 0.12 (s, 3H); 0.68 (s, 3H); 0.82-1.03 (m, 1H); 1.1-1.47 (m, 4H); 1.50-1.85 (m, 2H); 2.82 & 3.00 (2xdd, *J* = 4.8 & 13.2 Hz, total 2H, CH_2); 3.39 & 3.54 (2xdd, *J* = 3.9 & 6.8 Hz, total 1H); 4.27 & 4.67 (2xd, *J* = 4.8 Hz, total 1H); 4.78 and 5.23 (2xd, *J* = 4.8 Hz, total 1H); 5.97 and 6.38 (2xs, total 1H); 6.71 - 6.82 (m, total 2H, Ar); 6.92 - 7.84 (m, total 13H, Ar).

IR : 1755 cm^{-1}.

$[\alpha]^{25}_D$: +96.086° (c 1, CH_2Cl_2).

(Diamix.)

Elemental analysis

Molecular Formula : $C_{32}H_{34}N_2O_3S_2$.

Calculated : C, 68.79; H, 6.13; N, 5.01.

Found : C, 68.67; H, 6.71; N, 4.50.

1.6.6 Synthesis of (2R, 3S, 6R, 3¢R, 4¢S)-[N1¢-benzyl-4¢-phenylazetidin-2¢-one-3¢-yl}-2,10-comphorsultam (1.12) from diastereomeric mixture of 1.09 & 1.10

To a solution of diastereomeric mixture of β-lactams **1.09** & **1.110** (0.1 g, 0.178 mmol) in ethanol (5 ml) was added Raney nickel (0.8 ml suspension in ethanol) and the resultant mixture was stirred for 30 min at room temperature. After completion of the reaction (TLC), it was filtered through celite pad, washed with ethanol. The filtrate on removal of solvent yielded 0.08 g (99.3%) of N1-benzyl-β-lactam (**1.12**) as a white crystalline solid, m. p. 222 - 223 °C [lit.[61] m.p. 221-222 °C].

^{1}H NMR : δ 0.20 (s, 3H); 0.75 (s, 3H); 1.30 (m, 2H); 1.7(m, 5H); 2.95 (d, *J* = 14 Hz, 1H); 3.05 (d, *J* = 14 Hz, 1H); 3.55 (t, *J* = 7 Hz, 1H); 4.05 (d, *J* = 16 Hz, 1H); 4.7 (d, *J* = 5.4 Hz, 1H); 5.0 (d, *J* = 16 Hz, 1H); 5.05 (d, *J* = 5.4 Hz, 1H); 7.10 - 7.45 (m, 10H).

IR : 1760 cm^{-1}.

$[\alpha]^{25}_D$: +62.87° (c 1.1, CH_2Cl_2); {lit.[16] $[\alpha]^{25}_D$: +62.0° (c 1, CH_2Cl_2)}.

1.6.7 Synthesis of (2R, 3S, 6R, 3¢R, 4¢S)-[4¢-phenylazetidin-2¢-one-3¢-yl]-2,10-camphorsultam (1.11) from diastereomeric mixture of 1.0 9 & 1.10

To a water solution (10 ml) of potassium per sulfate (0.850 g, 3.11 mmol), a solution of diastereomeric mixture of β-lactams **1.09** & **1.10** (0.7 g, 1.25 mmol) in acetonitrile (25 ml) was added and the reaction mixture was refluxed for 4 h. After completion of the reaction

(TLC), the reaction mixture was worked-up as described for compound **1.07**. The crude product obtained was column chromatographed to give 0.341 g (75.8%) of pure NH β-lactam **1.11** as a white solid, which was crystallized from acetone/pet. ether, m. p. 234 - 236 °C.

^{1}H NMR : δ 0.09 (s, 3H); 0.71 (S, 3H); 0.77 - 0.99 (m, 1H); 1.03 - 1.47 (m, 4H); 1.52 – 1.89 (m, 2H); 2.98 (dd, *J* = 13.66 Hz, and 33.17 Hz, 2H); 3.57 (t, *J* = 5.36 Hz, 1H); 5.00 (d, 4.8 Hz, 1H); 5.21 (bs, 1H); 6.67 (bs, 1H); 7.17 - 7.68 (m, 5H).

IR : 1760, 3300 cm^{-1}.

$[\alpha]^{25}_D$: +43.85° (c 1, CH_2Cl_2).

1.6.8 Synthesis of (2R, 3S, 6R, 3¢R, 4¢S)-[4¢-phenylazetidin-2¢-one-3¢-yl]-2,10-comphorsultam

(1.11) from (2R, 3S, 6R, 3¢R, 4¢S)-[N1¢-(p-Anisyl)-4¢-phenylazetidine-2¢-one-3¢-yl]-2,10-camphorsultam (1.13)

A solution of β-lactam **1.13** (0.074 g, 0.16 mmol) in acetonitrile/tetrahyrofuran (3:1ml) was cooled to 0°C and treated with a solution of ceric (IV) ammonium nitrate (0.482 mmol) in water (1.5 ml) over 3 min. The solution was stirred at 0 - 5 °C for 45 min. and diluted with 10 ml of water. The mixture was extracted with ethyl acetate (3x5 ml). The organic extracts were washed with satd. sodium bicarbonate (5 ml) and the aqueous solution back extracted with ethyl acetate (5 ml). The combined organic extracts were successively washed with sodium sulfite (10%, 2x10 ml), satd. sodium bicarbonate (5 ml), and brine (10 ml), It was then dried over anhydrous Na_2SO_4 and filtered through celite. The filtrate on removal of solvent furnished crude product, which was purified by column chromatography to give 0.050 g (86.8%) of NH-β-lactam **1.11** as a white solid, m. p. 233 - 234 °C. $[\alpha]^{25}_D$: + 43.6° (c 0.9, CH_2Cl_2). The spectral data for this compound was identical to the NH-β-lactam **1.11** prepared from diastereomeric mixture of **1.09** & **1.10**.

1.6.9 Synthesis of 3-Menthyloxy-N1- [(1¢-thiophenyl) benzyl]-4-phenylazetidin-2-one (1.15-1.18)

A solution of the menthyloxy acetyl chloride (**1.19**, 2 mmol) in dry CH_2Cl_2 (10 ml) was slowly added to a solution of imine (**1.03**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 ml) at 0 ^oC. The reaction mixture was then allowed to warm to room temperature and stirred further for 15 h. It was then washed with water (2x15 ml), satd. $NaHCO_3$ (10 ml),

brine (10 ml) and dried over anhydrous Na_2SO_4. The removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether: acetone, 9:1) to give 0.77 g (62.2%) of a semi solid mixture of β-lactams (**1.15-1.18**) with diastereomeric ratio of 35:35:18:12.

^{1}H NMR : (Mixture of **1.15-1.18**): δ 0.02 - 1.01 (m, total 13H); 1.02 - 1.24 (m, 2H); 1.24 – 1.58 (m, 2H); 1.85 - 2.17 (m, 1H); 2.72 - 2.83 and 3.02 - 3.22 (2xm, total 1H); 4.28, 4.31, 4.40 and 4.43 (4xd, *J* = 4.5 Hz, total 1H); 4.60, 4.67, 4.97 and 4.99 (4xd, *J* = 4.5 Hz, total 1H); 6.11, 6.16, 6.27 and 6.29 (4xs, total 1H); 6.87 - 7.88 (m, 15).

IR : 1745 cm^{-1}.

The diastereomeric mixture of β-lactams **1.15–1.18** was crystallized from pet. ether-acetone to give 60 mg of one of the minor diastereomer (**1.19** or **1.20**) in pure form.

M.p. : 158 - 160 °C.

^{1}H NMR : δ 0.1 (d, *J* = 8 Hz, 3H); 0.48 (d, *J* = 8 Hz, 3H); 0.60 - 0.75 (m, 2H); 0.82 (d, *J* = 8 Hz, 3H); 0.9 - 1.3 (m, 3H); 1.35 - 1.50 (m, 1H); 1.85 - 2.05 (m, 1H); 2.75 (m, 1H); 4.40 (d, *J* = 5.2 Hz, 1H); 5.00 (d, *J* = 5.2 Hz, 1H); 6.4 (s, 1H); 6.9 – 7.6 (m, 15H).

^{13}C NMR : 15.61, 20.61, 22.13, 22.86, 24.47, 31.17, 31.41, 34.16, 40.87, 47.53, 61.68, 61.89, 80.77, 82.19, 127.39, 127.59, 127.84, 128.05, 128.18, 128.30, 128.67, 128.88, 128.97, 129.21, 131.94, 132.70, 134.37, 135.50, 168.96.

$[a]^D_{23}$: +98.58° (c 1, $CHCl_3$).

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{32}H_{37}O_2NS$.

Calculated : C, 76.91; H, 7.46; N, 2.80%.

Found : C, 76.53; H, 7.52; N, 2.92%.

1.6.10 Synthesis of NH-b-lactams 1.19 and 1.20 form diastereomeric mixture of b-lactams 1.15 -1.18

To a water solution (3 ml) of potassium per sulfate (0.162 g, 0.6 mmol), a solution of diastereomeric mixture of β-lactams **1.15-1.18** (0.1g, 0.2mmol) in acetonitrile (8 ml) was added and the reaction mixture was refluxed for 4 h. The usual work-up as described for

compound **1.07** gave crude product, which was purified by column chromatography to give 45 mg (75%) of mixture of two NH-β-lactams (**1.19** & **1.20**).

^{1}H NMR : (Mixture of **18** & **19**): δ 0.21 - 1.08 (m, 13H); 1.12 - 1.32 (m, 2H); 1.42 - 1.68 (m, 2H); 1.92 - 2.18 (m, 1H); 2.98 and 3.29 (2xtd, *J* = 4.5 & 9.9 Hz, total 1H); 4.82 and 4.85 (2xd, *J* = 4.5 Hz, total 1H); 4.90 - 4.93 and 4.95 - 4.99 (2xdd, *J* = 2.2, & 4.8 Hz, total 1H); 6.30 (bs, 1H); 7.20 - 7.49 (m, 5H).

IR : 3410, 1750 cm^{-1}.

1.6.10a Synthesis of 3-menthyloxy-4-phenylazetidin-2-one (1.19 or 1.20) from pure β-lactam 1.17 or 1.18

To a water solution (3 ml) of potassium per sulfate (0.162 g, 0.6 mmol), a solution of pure β-lactam **1.17** or **1.18** (0.1 g, 0.2 mmol) in acetonitrile (8 ml) was added and the reaction mixture was refluxed for 4 h. The usual work-up as described for compound **1.07** gave crude product, which was purified by column chromatography to give 39 mg (65%) of pure optically active NH-β-lactam (**1.19** or **1.20**) as a white solid.

M.p. : 173-174 °C.

^{1}H NMR : δ 0.26 (d, *J* = 8 Hz, 3H); 0.55 (d, *J* = 8 Hz, 3H); 0.76 (m, 2H); 0.88 (d, *J* = 8 Hz, 3H); 0.97 (m, 2H); 1.26 (m, 2H); 1.52 (m, 2H); 2.15 (m, 1H); 2.95 (td, *J* = 4. 5 &10.2, IH); 4.81 (d, *J* = 4.8 Hz, 1H); 4.88 (dd, *J* = 2.2, & 4.8 Hz, 1H); 6.30 (bs, 1H); 7.42 (m, 5H).

^{13}C NMR: : 15.87, 20.70, 22.21, 23.02, 24.68, 31.55, 34.28, 41.22, 47.61, 58.79, 81.37, 84.56, 127.80, 128.12, 136.48, 169.89.

$[a]^{D}_{23}$: : +25.51° (c 0.97, CH_2Cl_2).

IR: : 1759, 3413 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{19}H_{27}O_2N$

Calculated : C, 75.71; H, 9.03; N, 4.65%.

Found : C, 75.92; H, 9.15; N, 4.64%.

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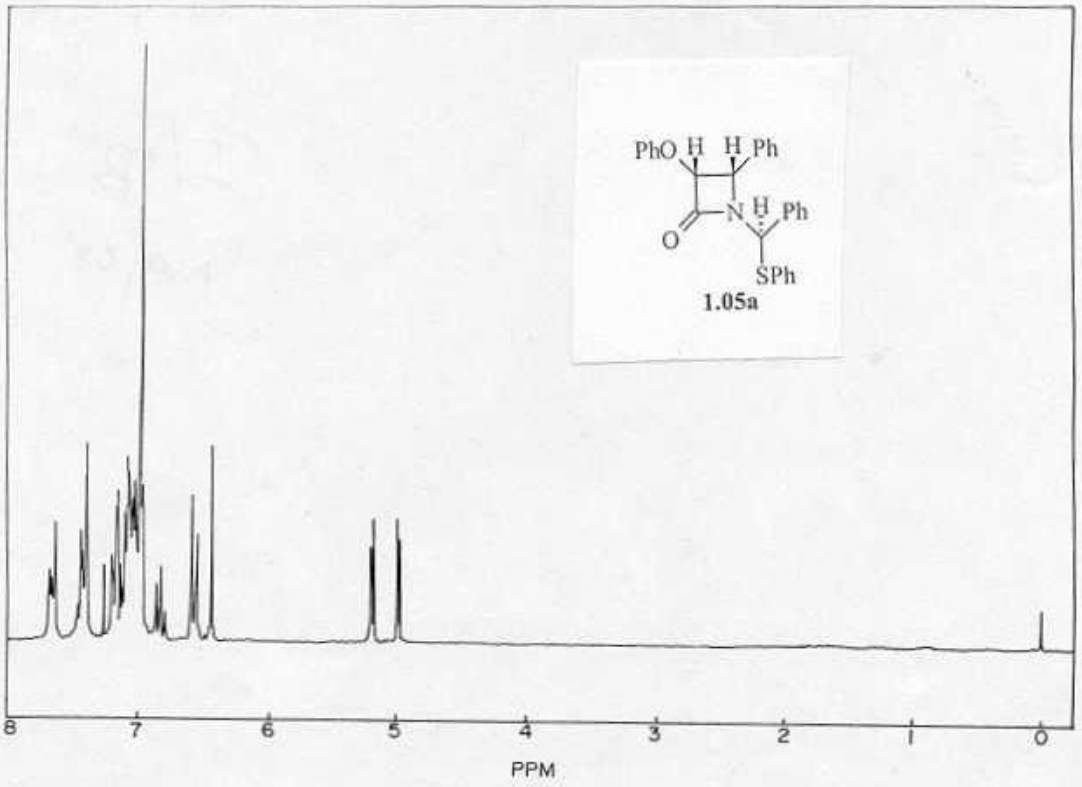
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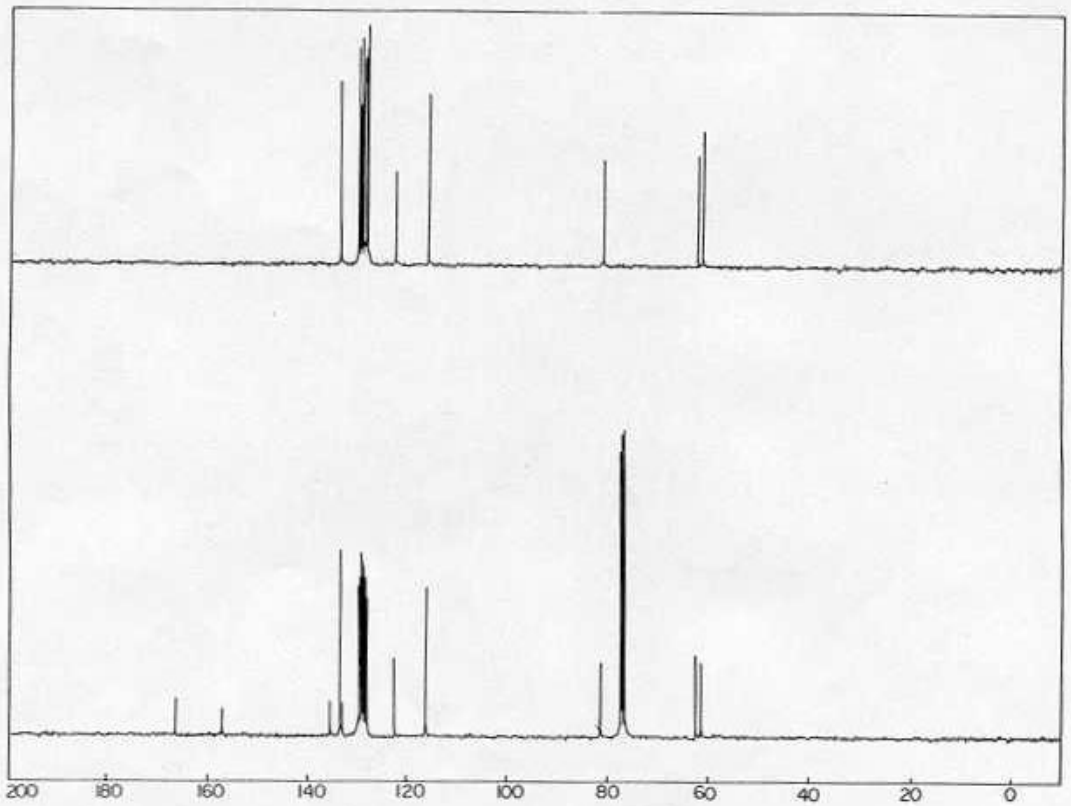
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120
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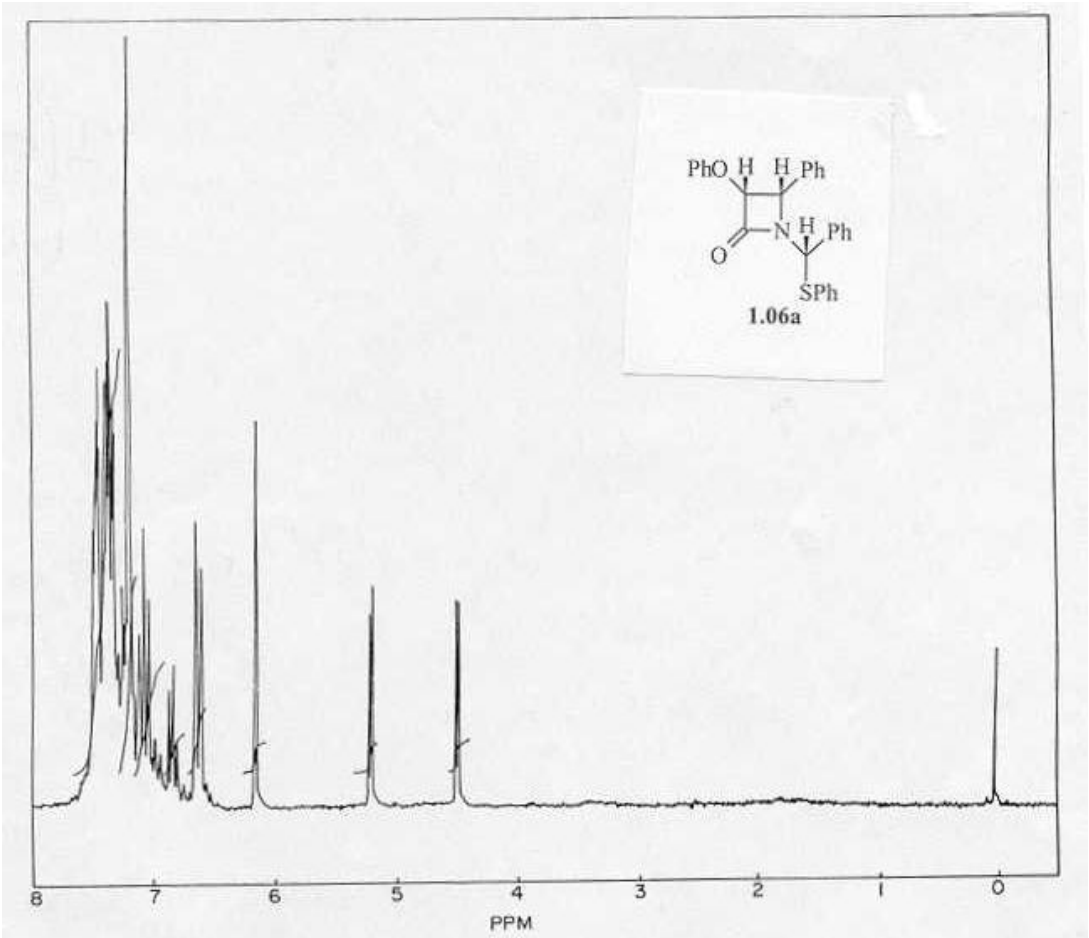
PPM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O
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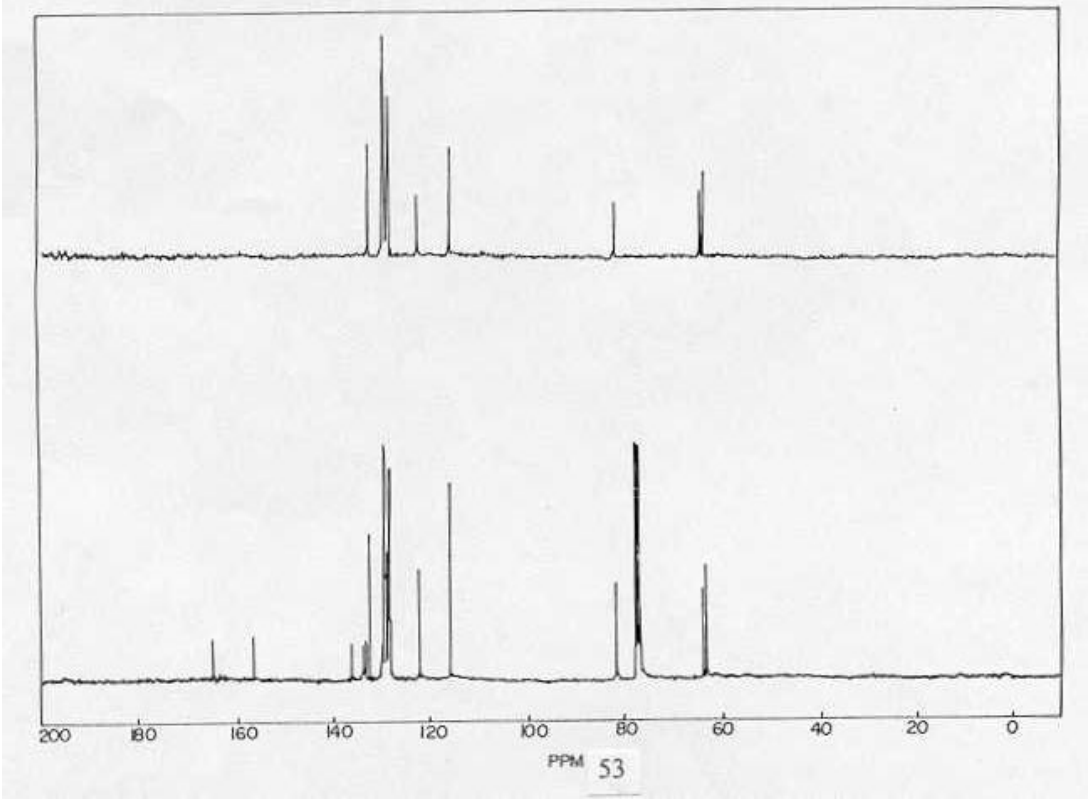
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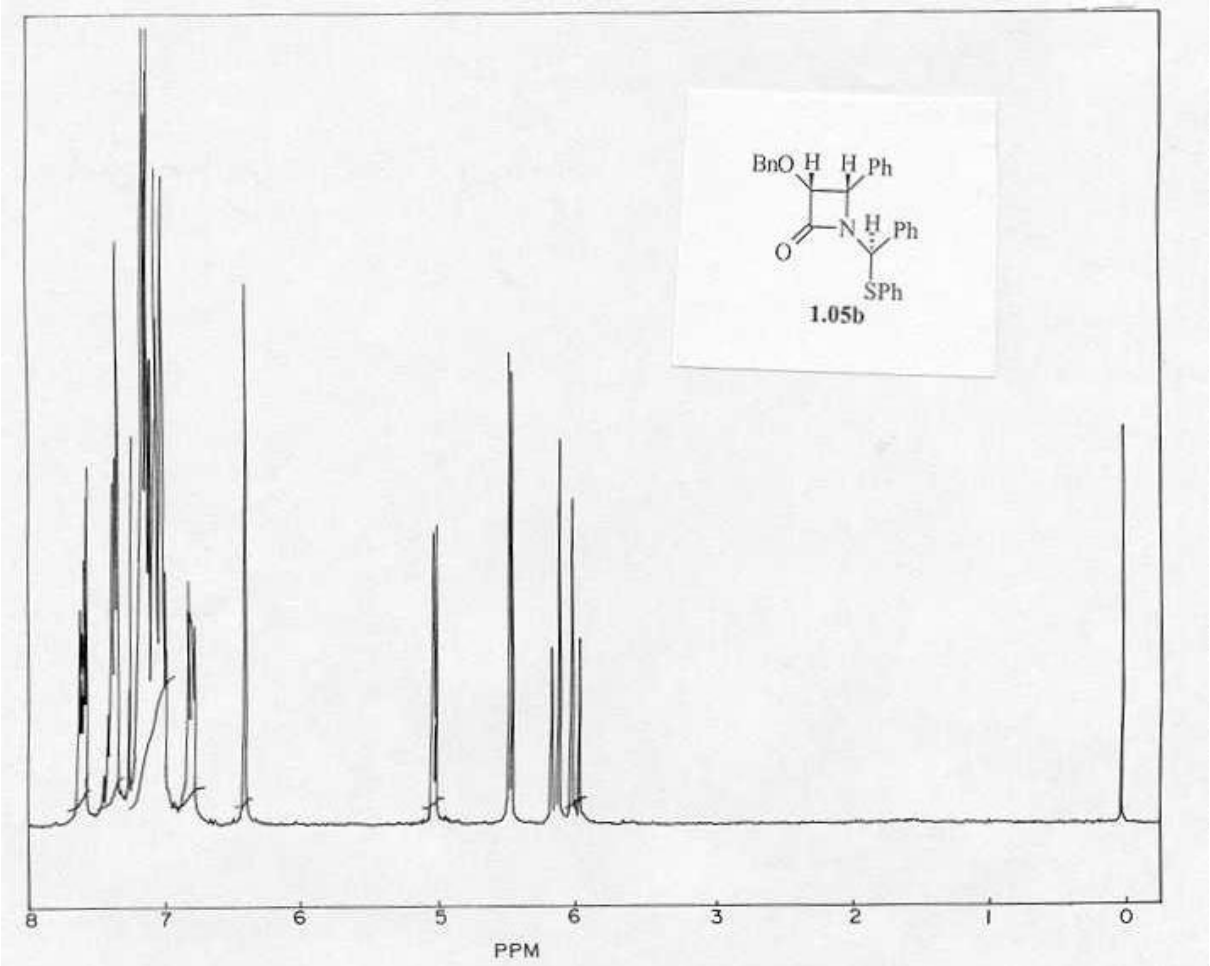
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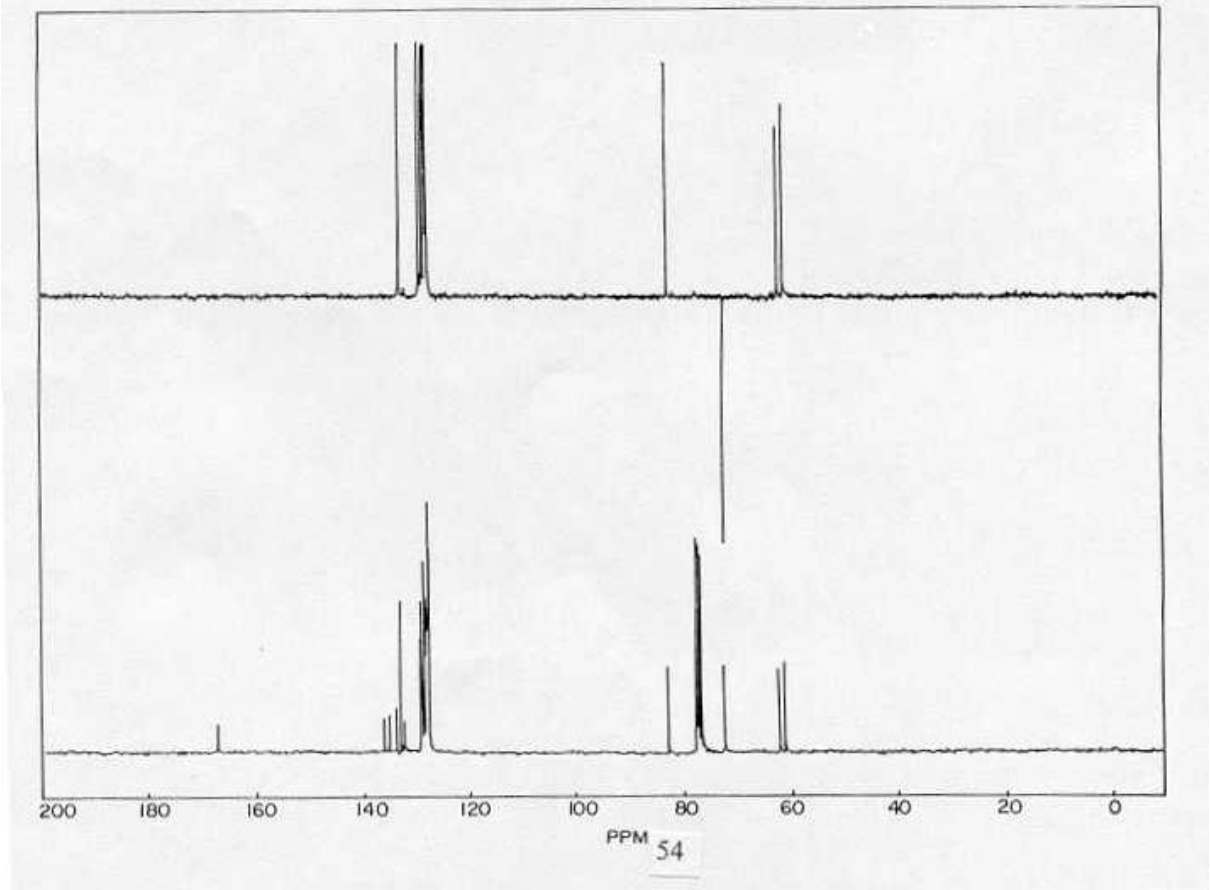
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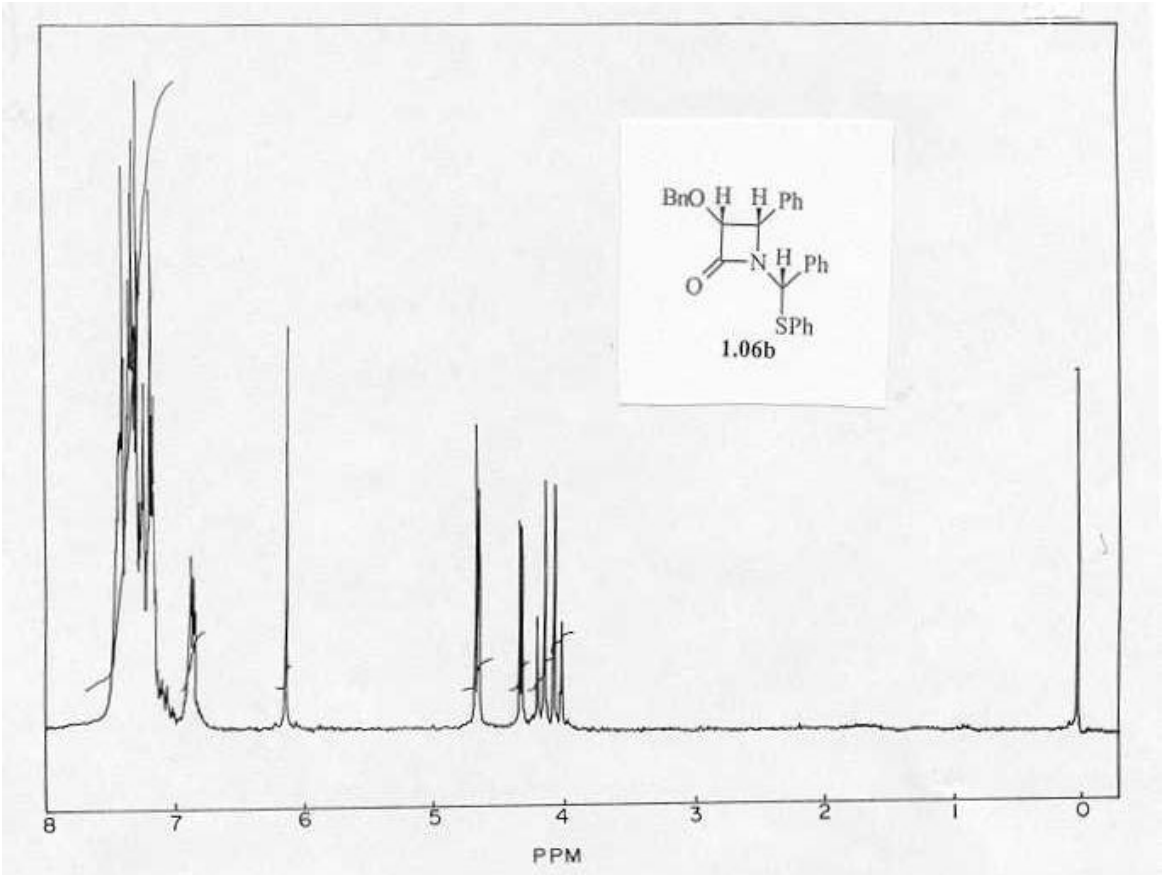
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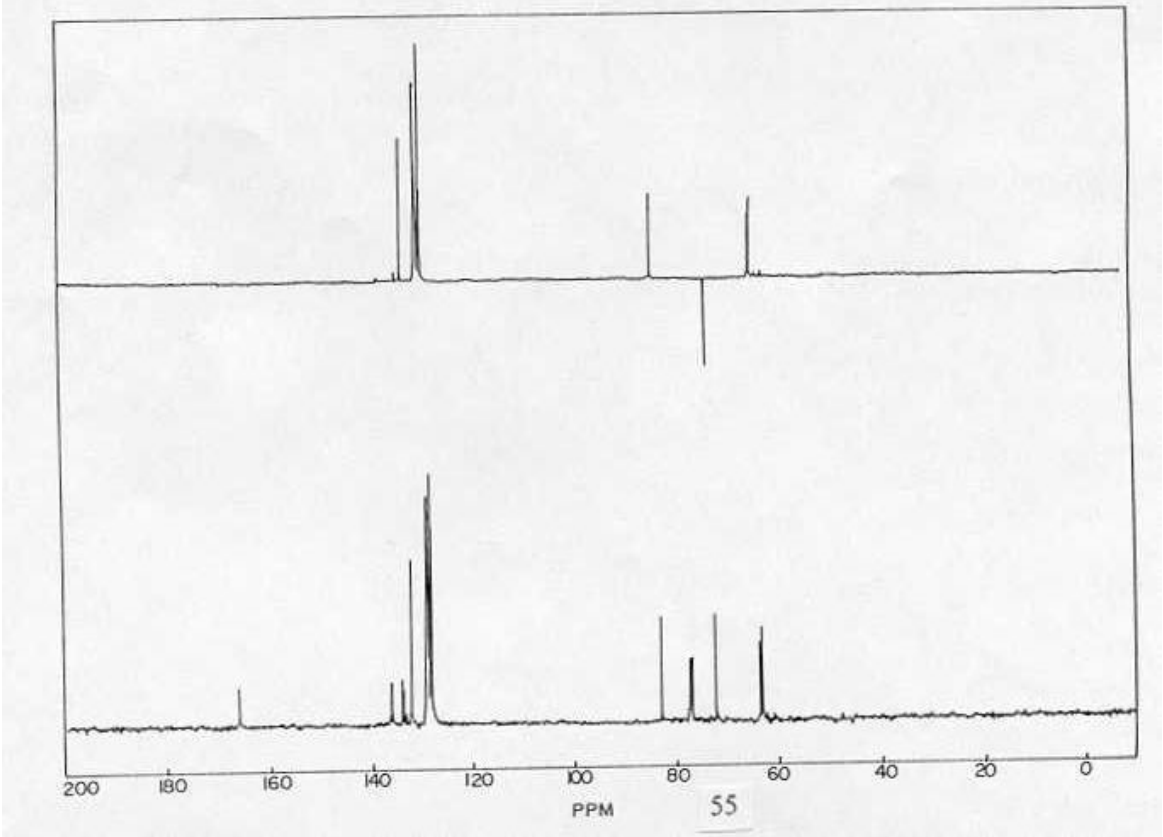
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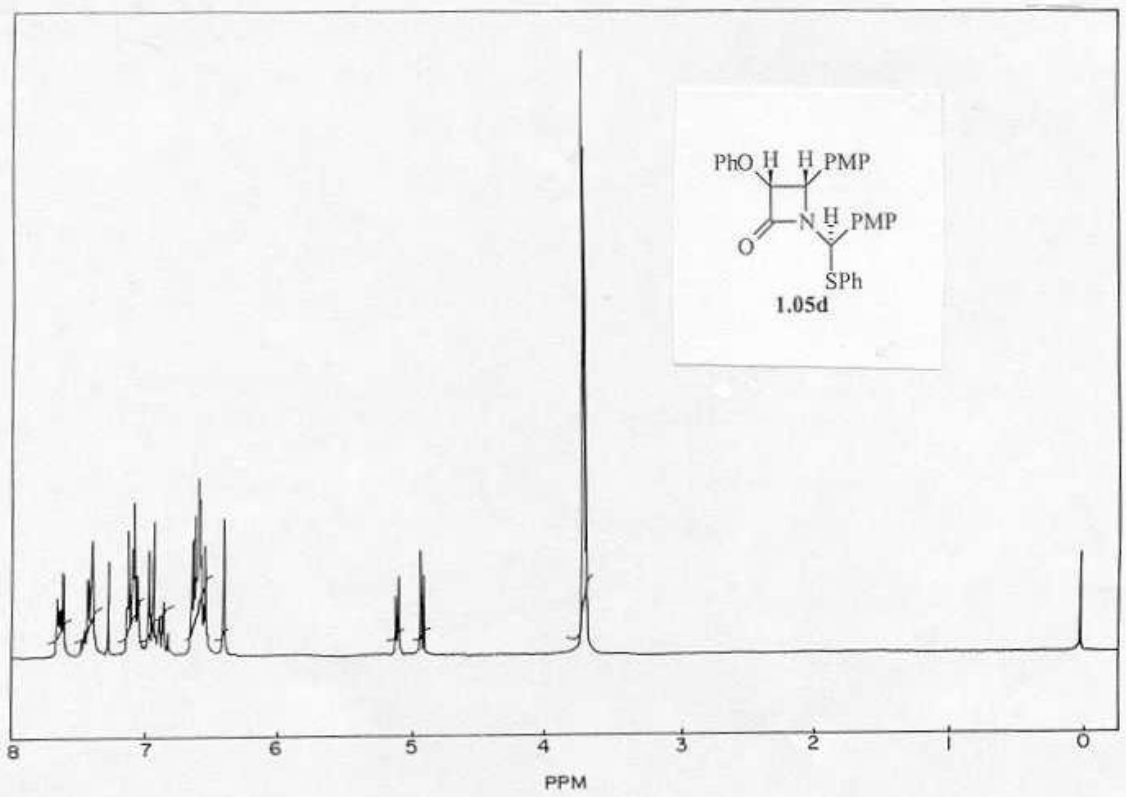
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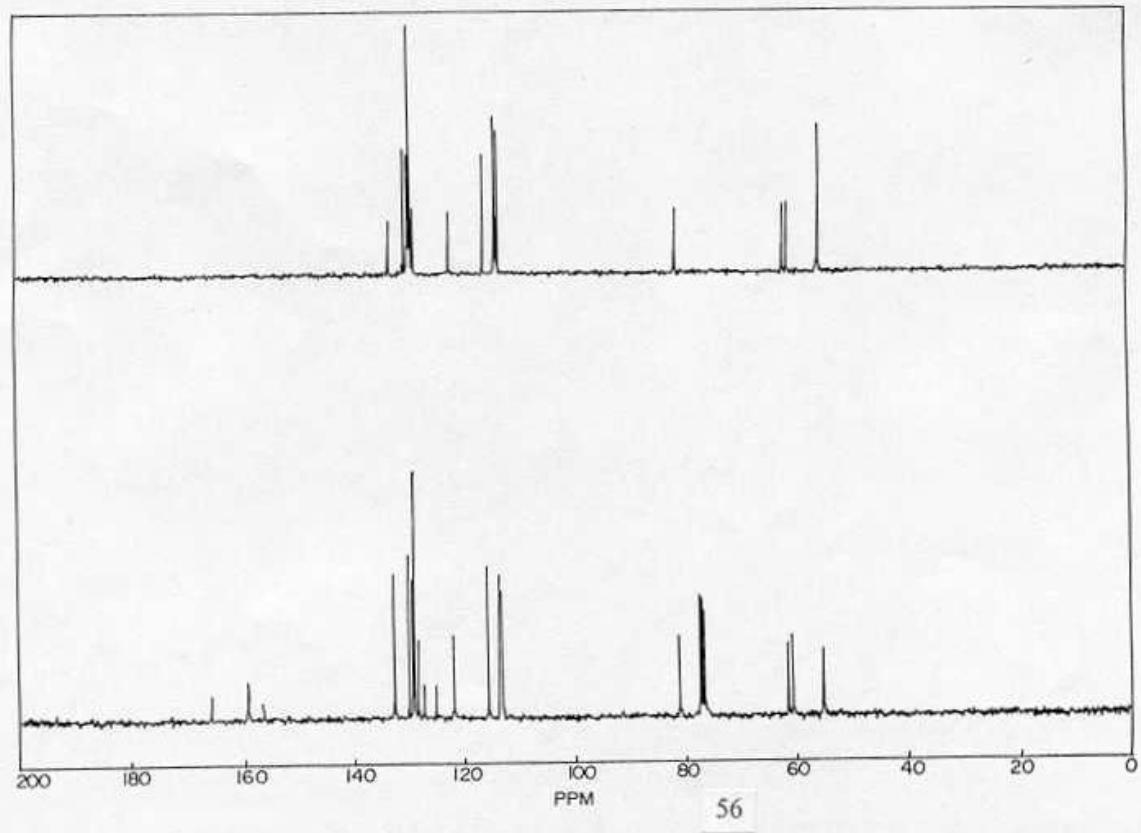
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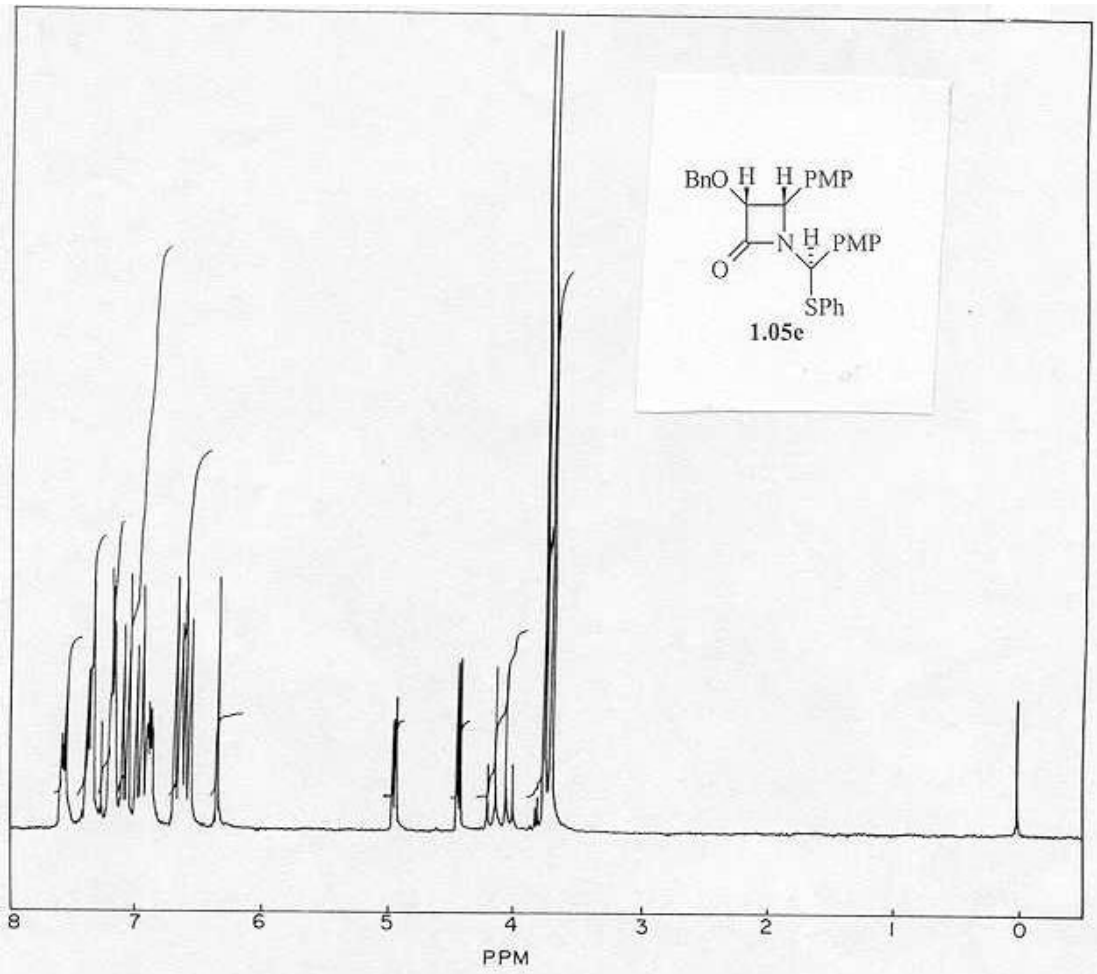
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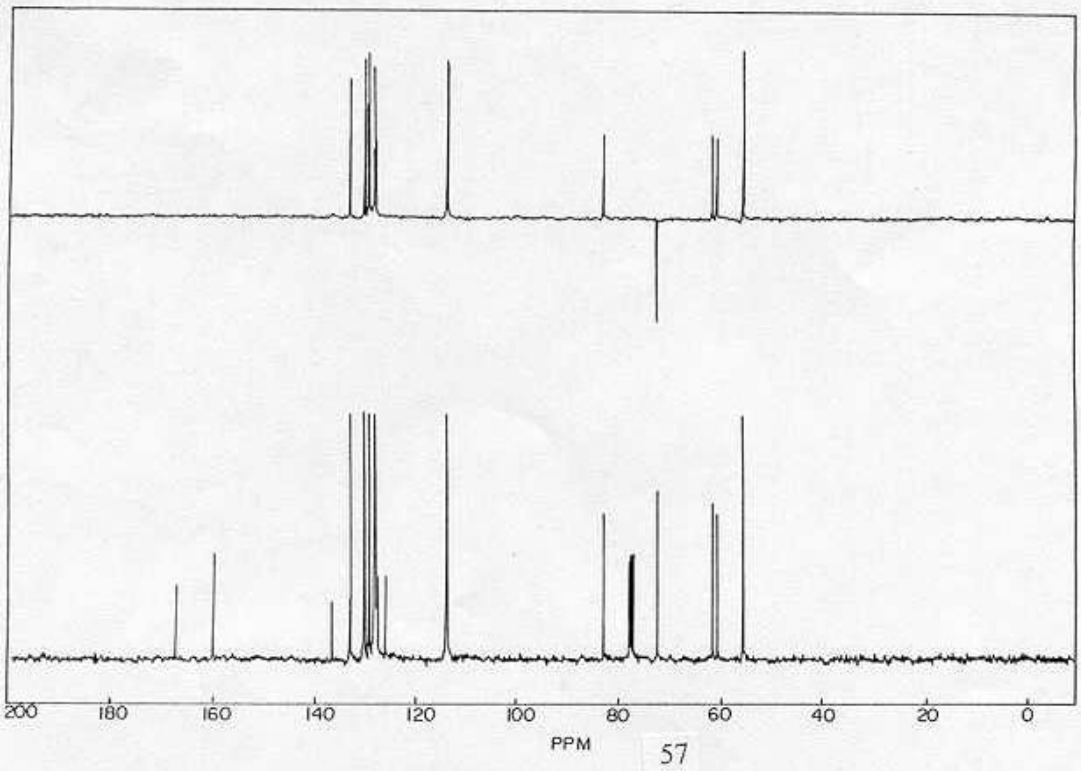
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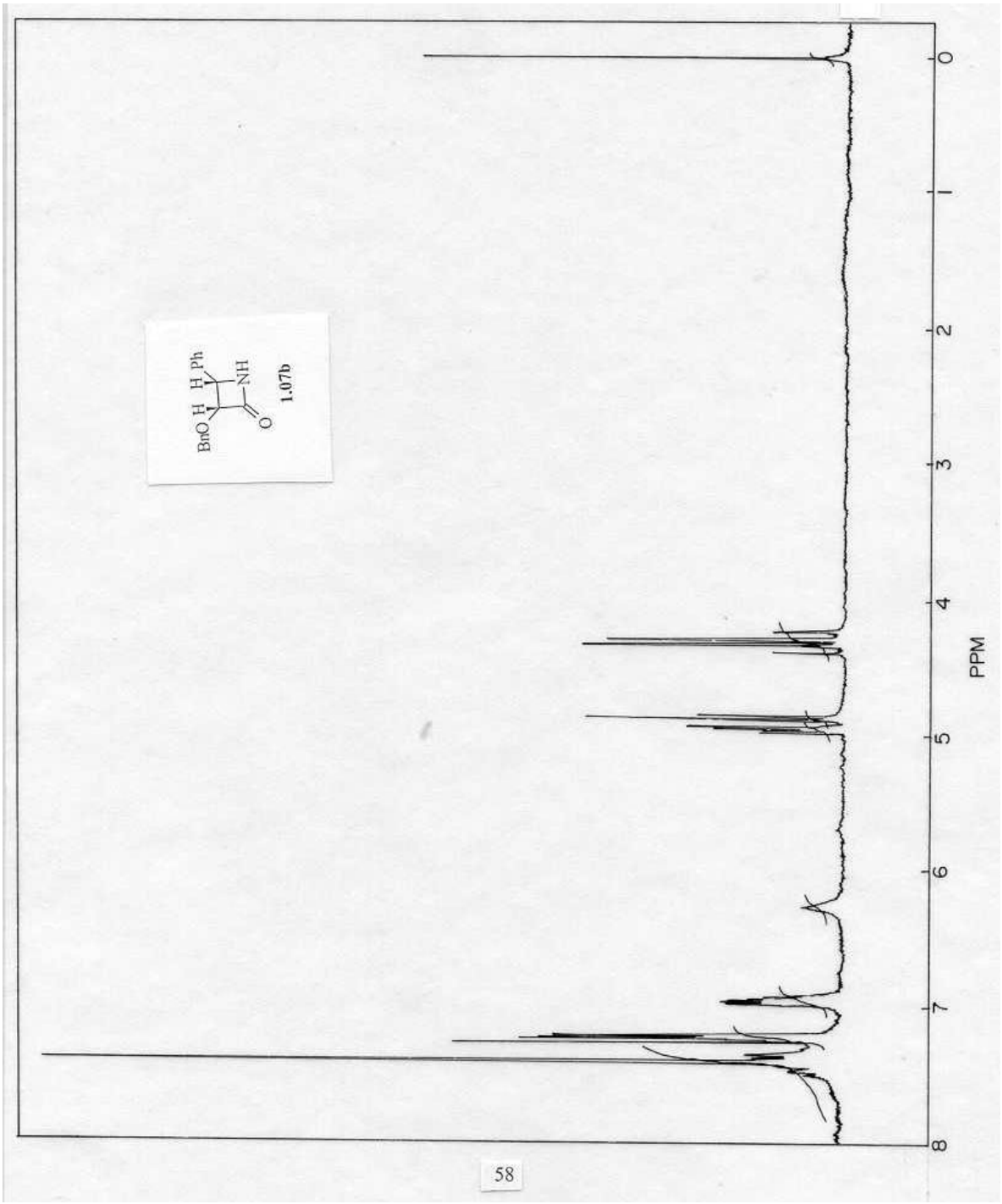
PPM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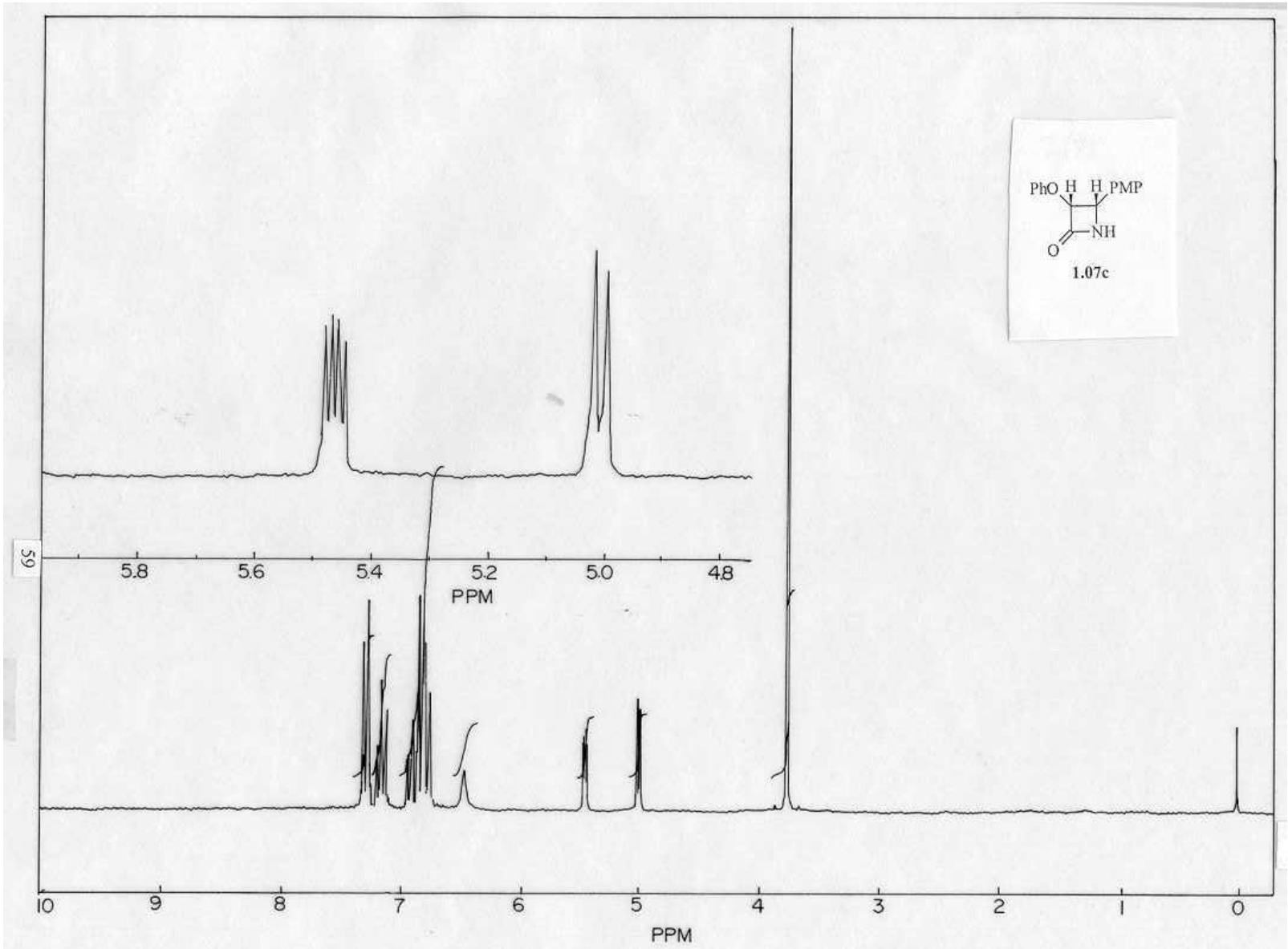
5
6
7
8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O
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5.8
5.6
5.4
5.2
5.0
4.8
PPM
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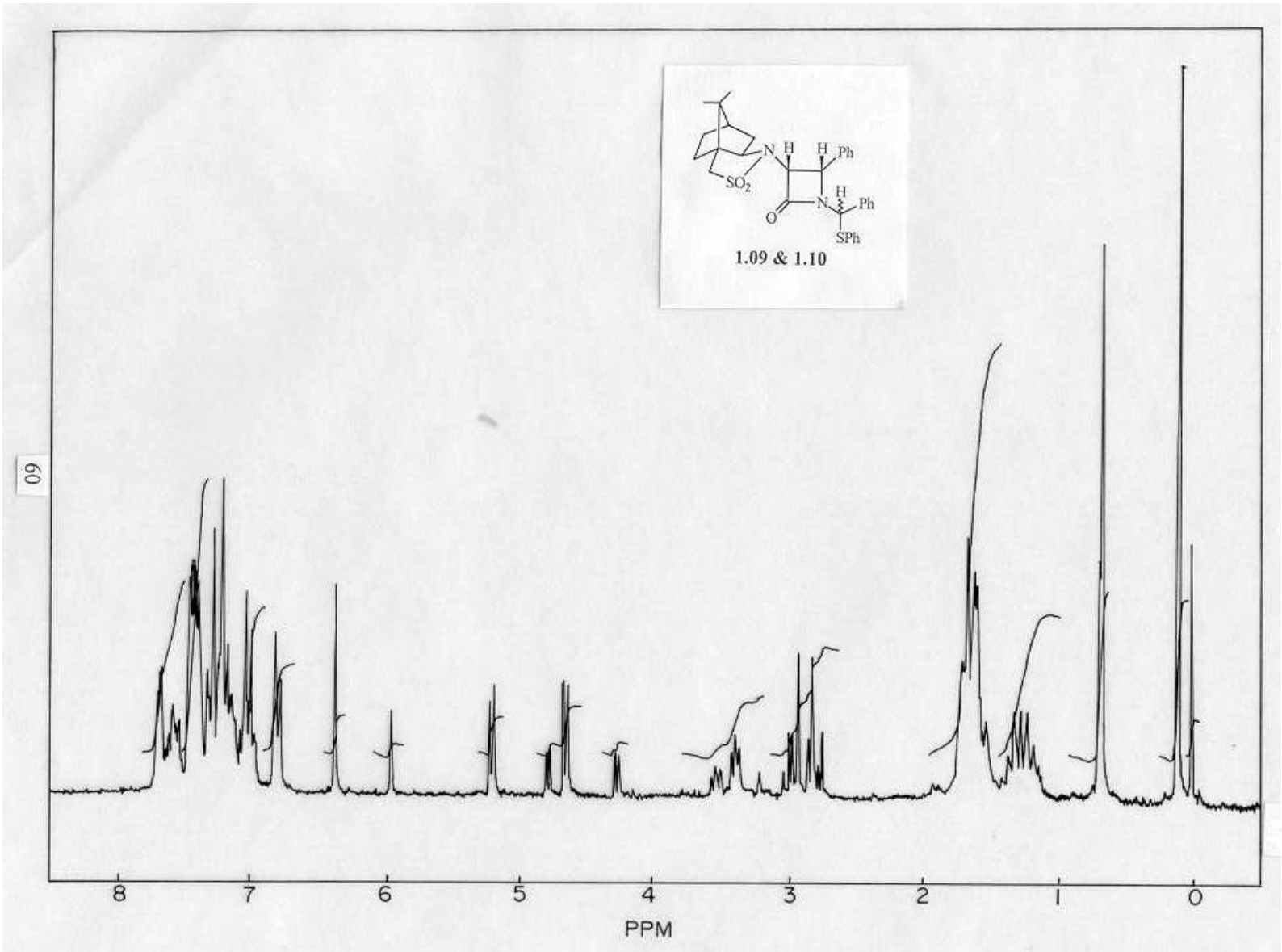
PPM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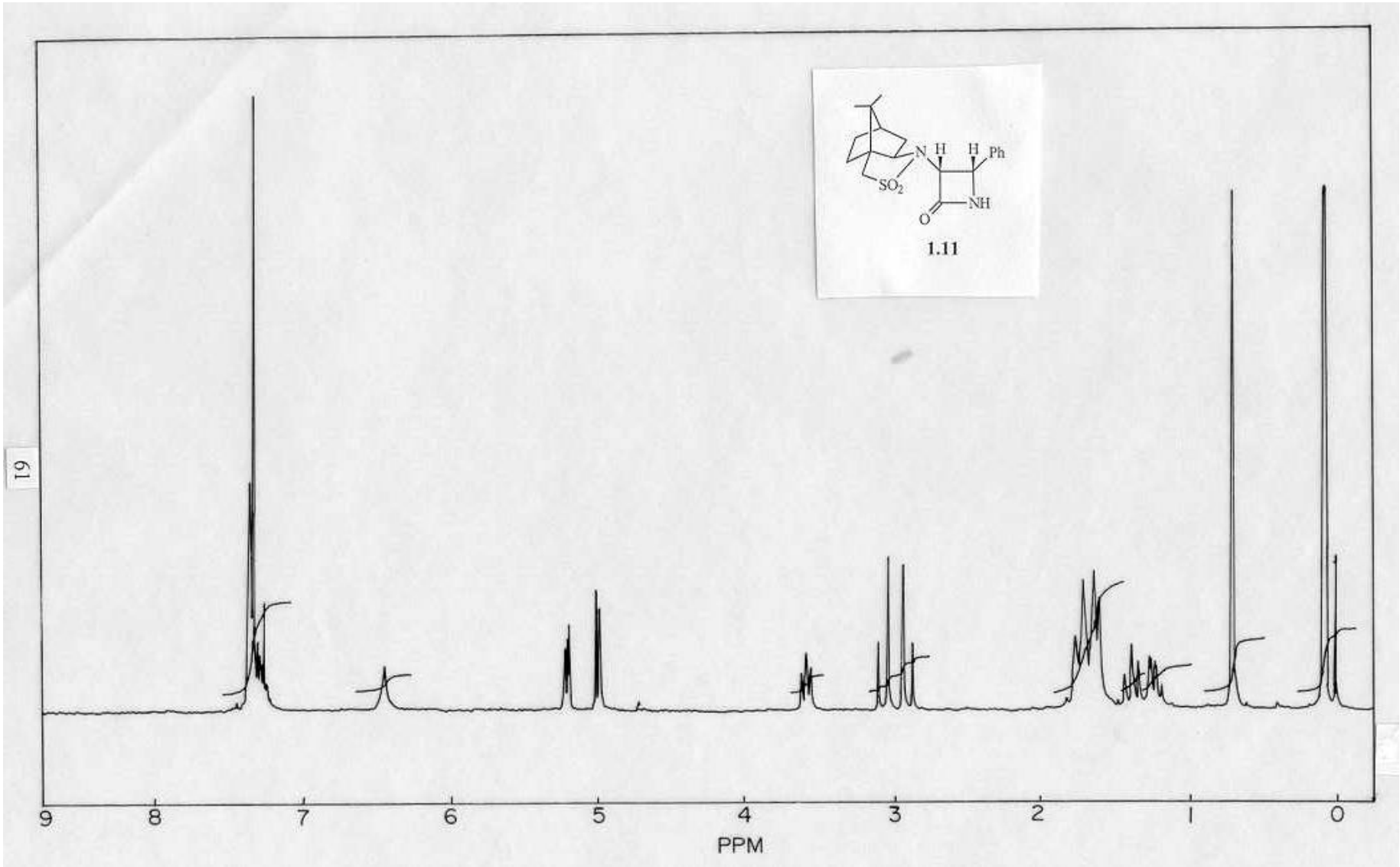
PPM
1.09 & 1.10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H Ph
SO2
NH
O
1.11
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8
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2
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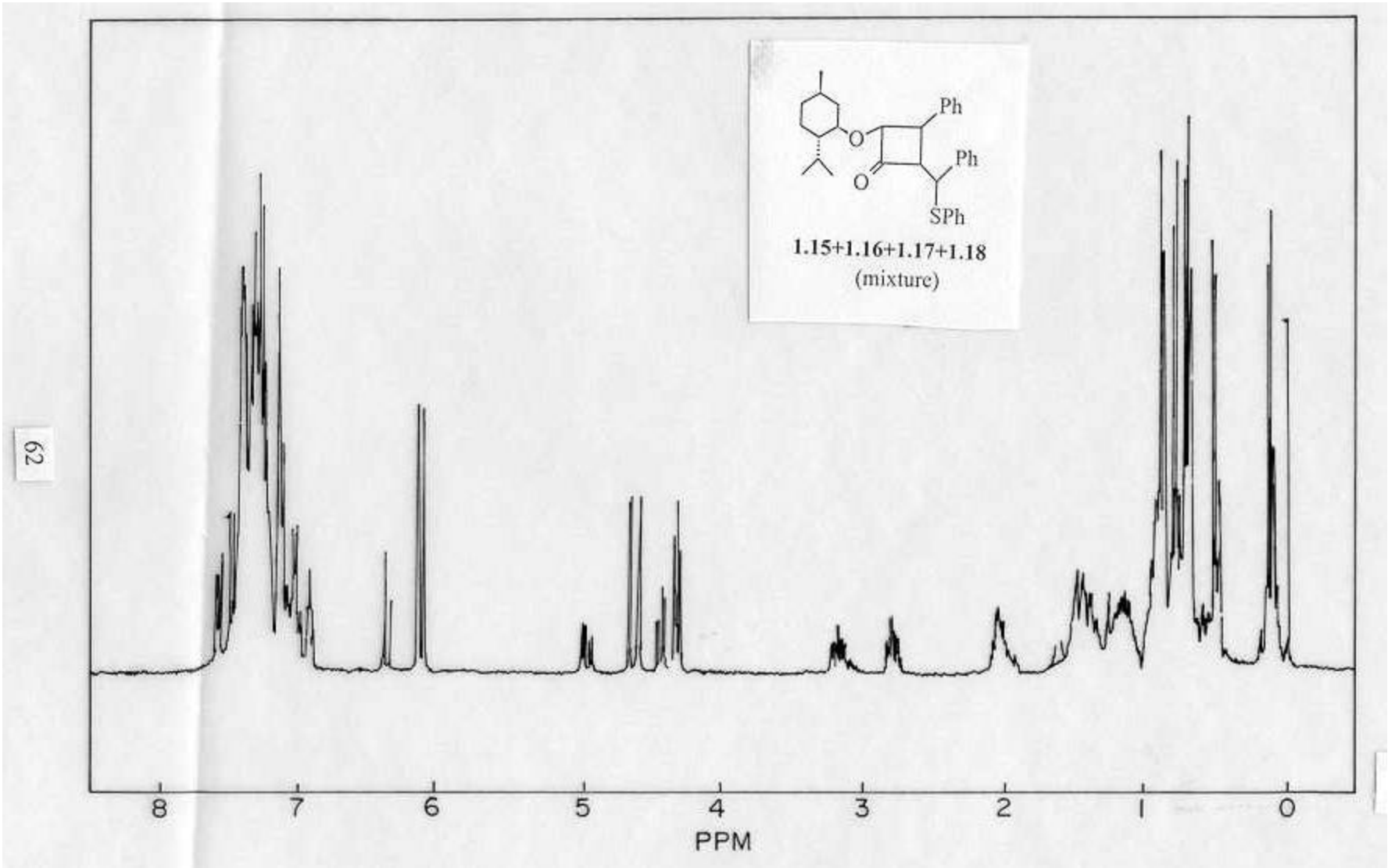
PPM


Ph
O
Ph
O
SPh
1.15+1.16+1.17+1.18
(mixture)
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5
4
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2
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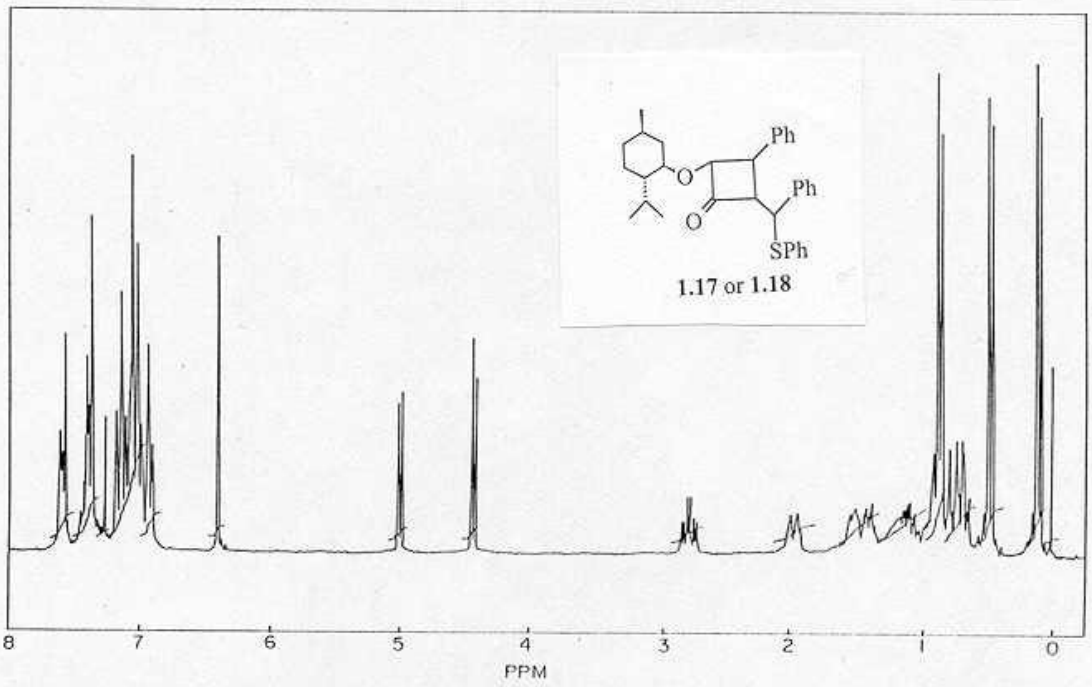
0
PPM


Ph
Ph
SPh
O
O
8
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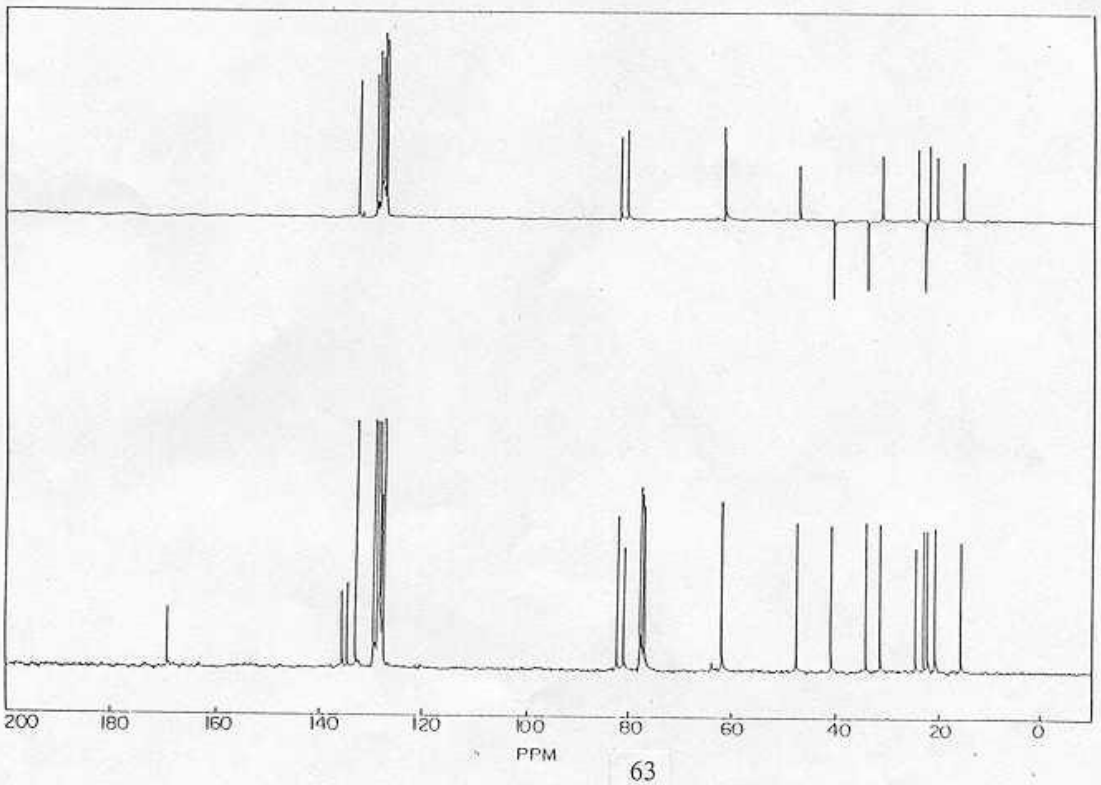
0
PPM

1.17 or 1.18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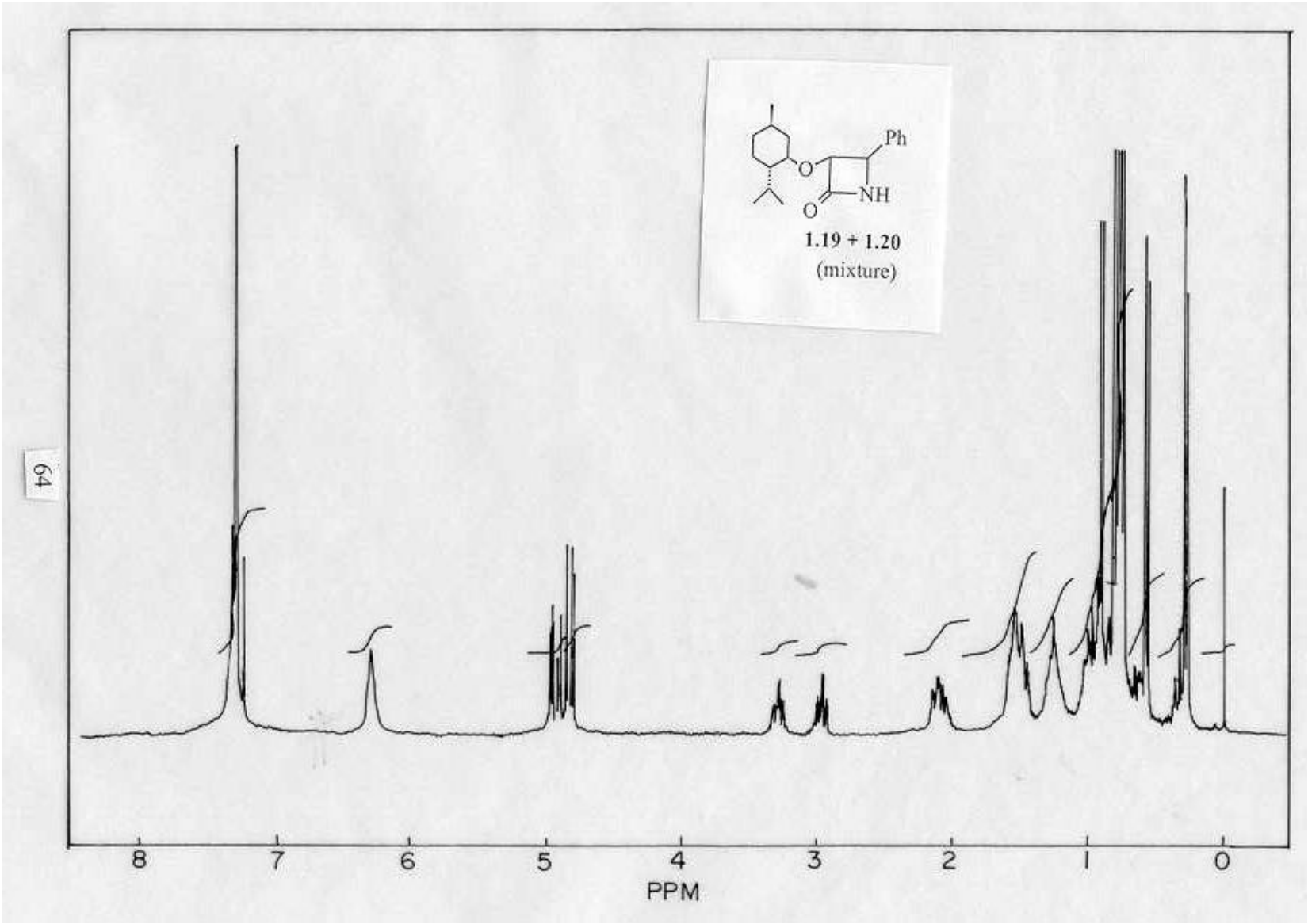
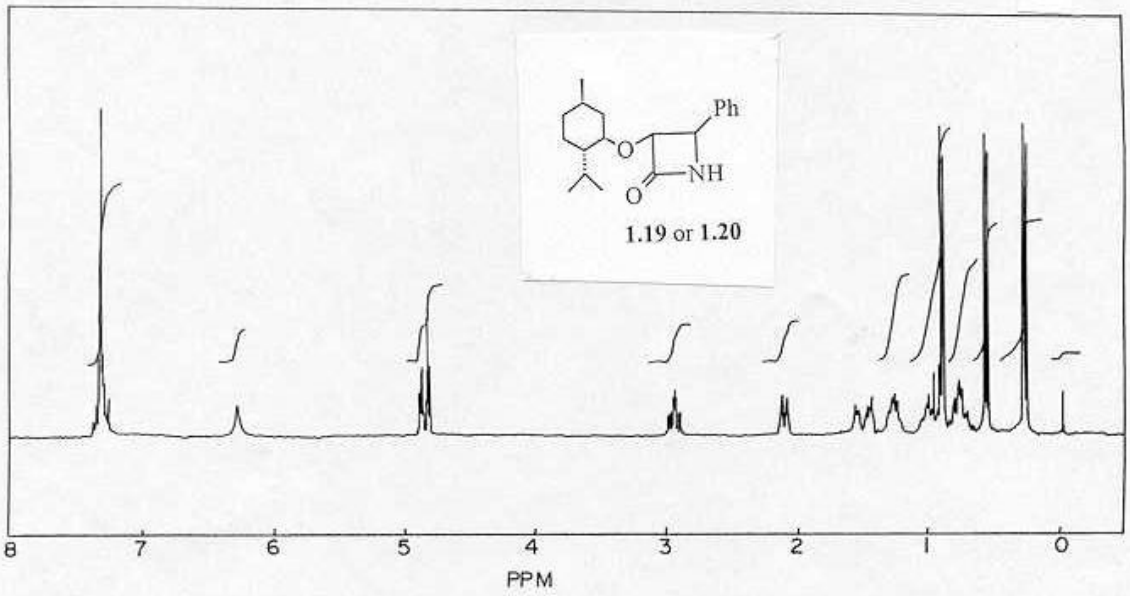
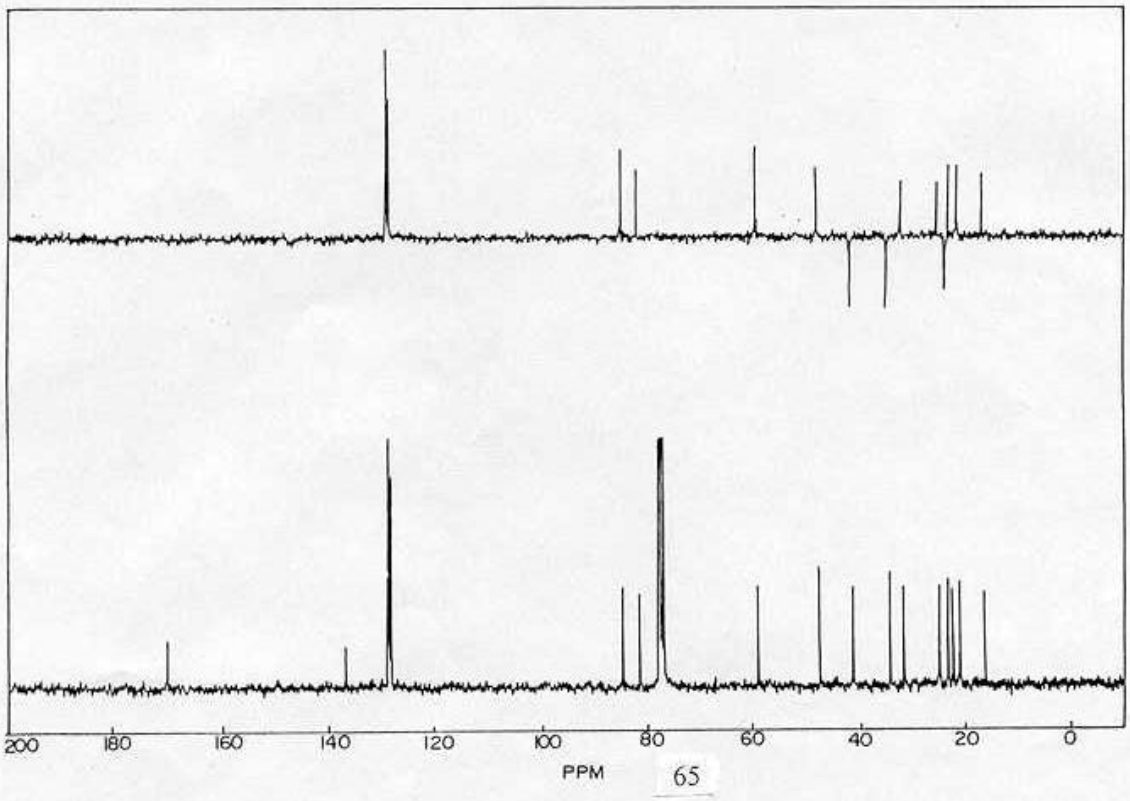


64



1.19 or **1.20**



Chapter II

Stereoselective synthesis of cis-bis-b-lactams linked with an ethylene bridge

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Part of this work has been published in

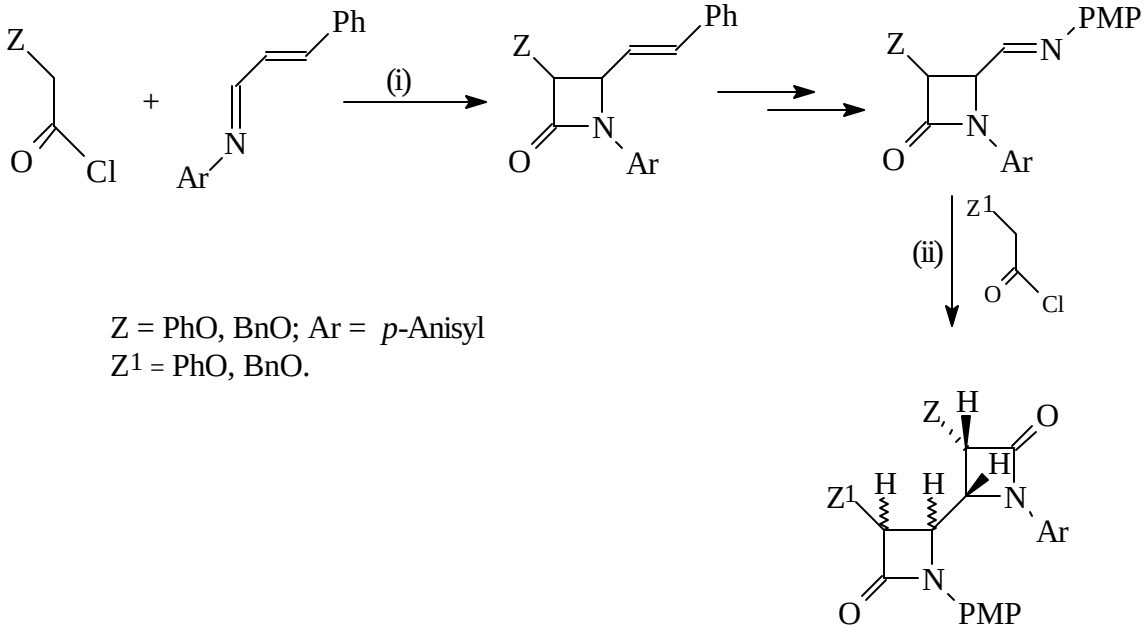
Tetrahedron, **2000**, *56*, 8555

2.1 Introduction

Although β-lactam derivatives are well known for their antibiotic activities[1] less attention has been drawn to those of bis-β-lactams. However, bis-β-lactams serves as an important intermediate for the synthesis[2] of synthetically useful compounds like bis-azetidines, enantiomerically pure diamines, amino alcohols, polyamino alcohols, polyamino ethers, and polyamines. Bis-azetidines are shown to exhibit various biological activities. Ojima has shown the utility of bis-β-lactams for the synthesis[3, 4, 5] peptides.

A step-wise synthesis of bis-β-lactams has been reported by Bose et al.[6] The first β-lactam ring was constructed by ketene-imine cycloaddition (Staudinger reaction) using styryl imine and an acid chloride. The Styryl group at 4 position was converted to aldehyde by oxidation. This imine derived from this aldehyde on Staudinger reaction with different acid chlorides gave bis-β-lactams in 2-45% over all yields (Scheme-2.01).

Scheme 2.01



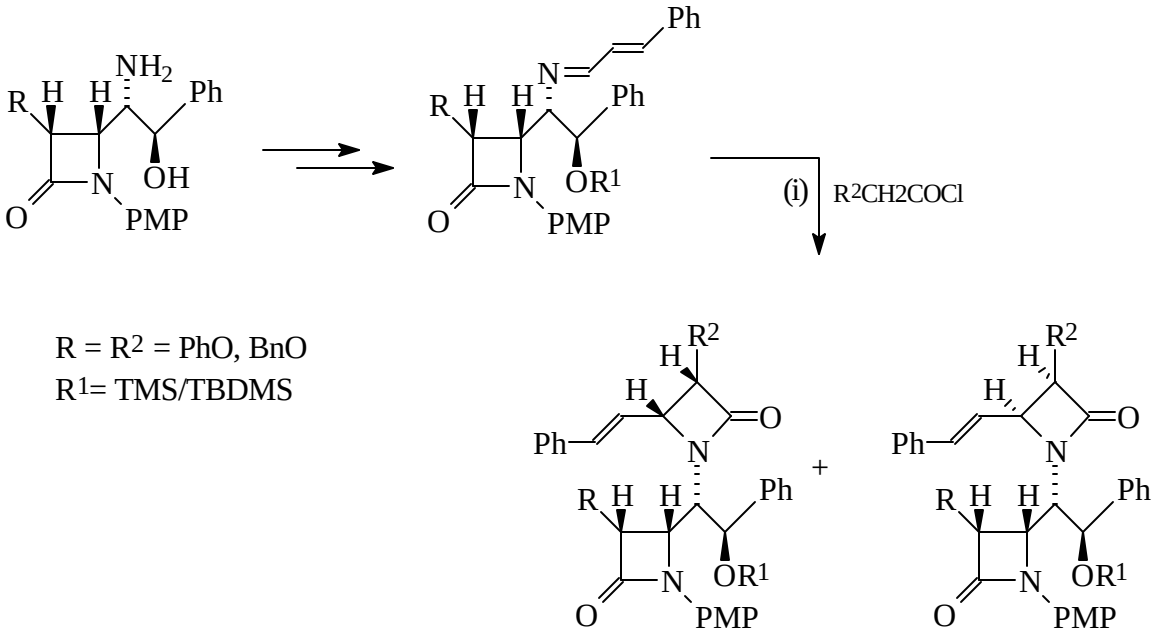
Z = PhO, BnO; Ar = *p*-Anisyl
Z^1 = PhO, BnO.

Reagents and reaction conditions (i): Et_3N/DCM, 0 °C-RT, Overnight.

The free amino group present at 3 position of optically pure β-lactam has also been utilized for the preparation of bis-β-lactams[7] by converting it to imine followed by cycloaddition reaction with ketene generated from various acid chlorides in presence of

tertiary amines (Scheme 2.02). This methodology gave moderate to high diastereoselectivity (65:35 - 95:5) in second β-lactam ring construction with good yield (69 – 96%).

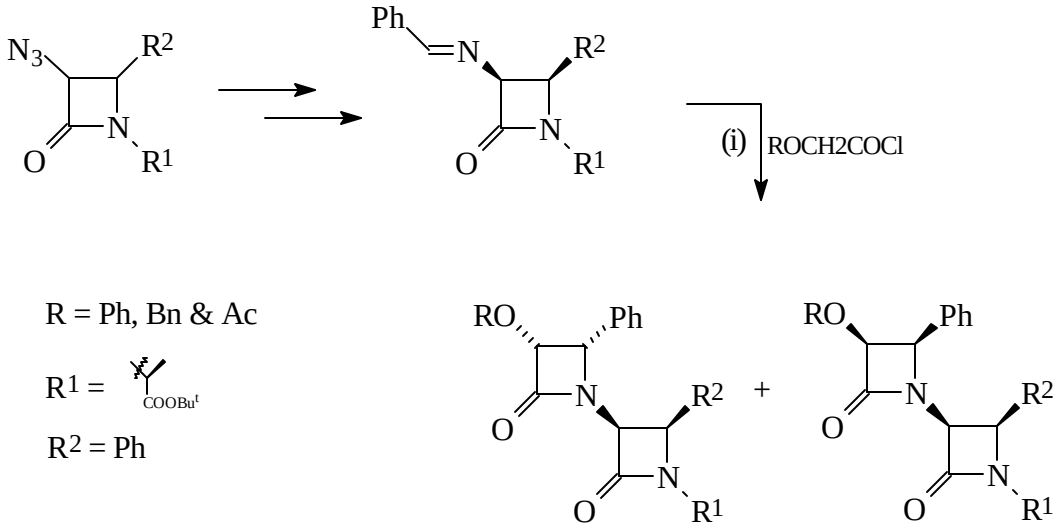
Scheme 2.02



Reagents and reaction conditions (i): Et_3N/DCM, –78 °C-RT, Overnight.

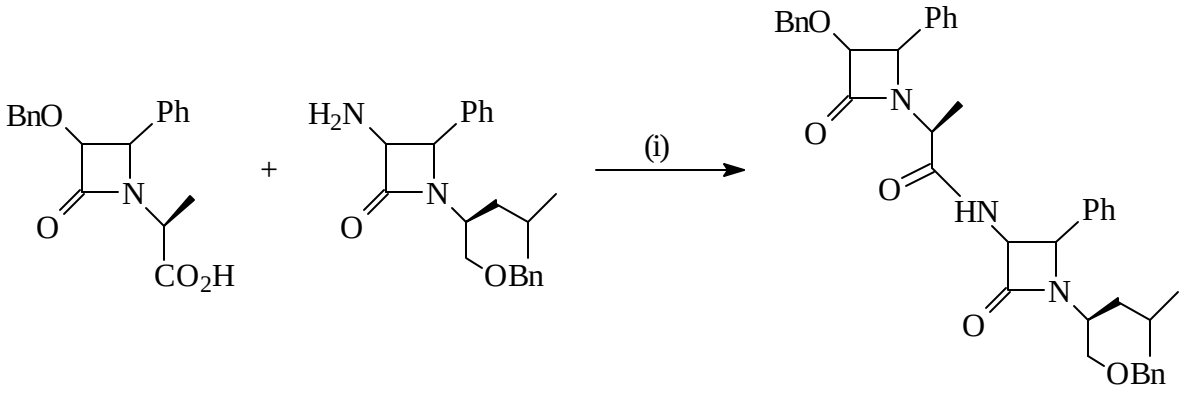
Ojima et al[2] have achieved synthesis of bis-β-lactams in 58 – 87% yield in two ways viz., (i) stepwise synthesis of bis-β-lactams and (ii) coupling of two mono β-lactams to give a bis-β-lactams (Scheme 2.03 and 2.04).

Scheme 2.03



Reagents and reaction conditions (i): Et_3N/DCM –15 °C-RT.

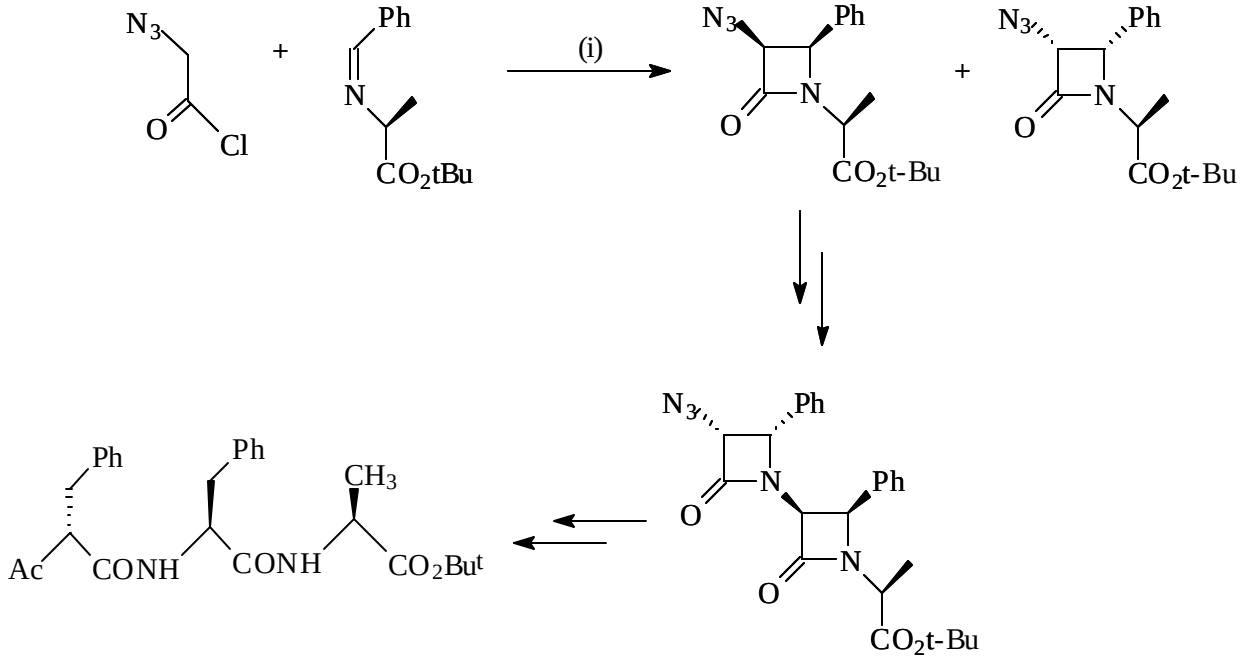
Scheme 2.04



Reagents and reaction conditions (i): DCC/HOBT (1-hydroxy benzotriazole), THF, 0 °C, Overnight.

A mono β-lactam with azido group at 3 position was prepared by Staudinger reaction of azidoacetyl chloride with imine. This azido group was transformed to imine and made to undergo [2+2] one more cycloaddition (Staudinger reaction) reaction with azidoacetyl chloride to give bis-β-lactams[3, 4,5] in 74% yield (Scheme 2.05). These bis-β-lactams have been utilized for the synthesis of peptides.

Scheme 2.05



Reagents and reaction conditions (i): Et_3N/DCM −78 °C-RT.

2.2 Present work

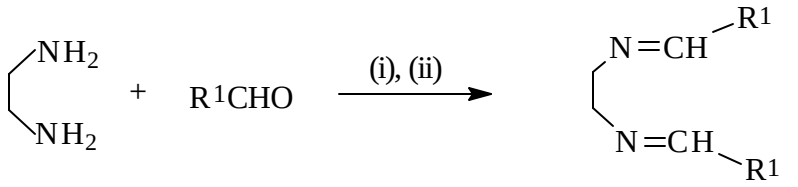
This chapter deals with one step synthesis of bis-β-lactams linked with an ethylene bridge starting from bis-imines derived from ethylene diamine *via* Staudinger reaction with *in situ* generated ketenes from various acid chlorides.

2.3 Results and discussion

2.3.1 *Preparation of bis-imines 2.01, 2.02 and 2.03*

The bis-imines (**2.01 – 2.03**) have been prepared in good yields from ethylene diamine and corresponding aromatic aldehydes by using reported procedures.[8, 9, 10]

Scheme 2.06



2.01 R^1 = *p*-Anisyl
2.02 R^1 = Ph
2.03 R^1 = -CH=CHPh

Reagents and Conditions (i) For bis imines **2.01** and **2.02** : anhyd. $MgSO_4$/DCM, r.t, 15h; (ii) For bis imine **2.03** : EtOH, reflux, 1h (**2.03**)

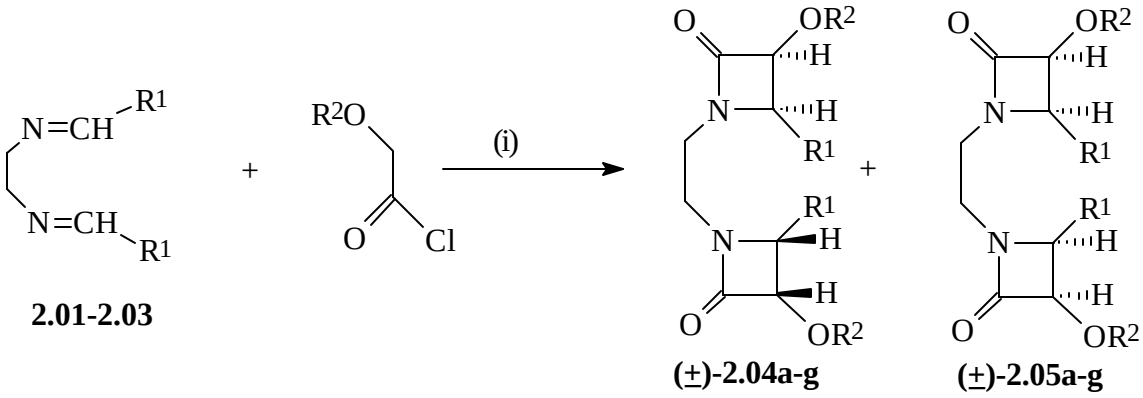
The imine **2.01** has been chosen as a representative compound for spectral discussion and characterization. The ^{1}H NMR spectrum of **2.01** showed a singlet at δ 3.74 corresponding to methyl group of *p*-methoxyphenyl. A singlet appeared at δ 3.84 was assigned to methylene protons of ethylene bridge. The aromatic protons appeared as a set of doublet at δ 6.78 and 7.50 with the *J* value of 8 Hz. A sharp singlet appeared at δ 8.06 was assigned to methyne protons of imine. The IR spectrum showed a band at 1630 cm^{-1} corresponding to C=N.

2.3.2 Preparation of bis-β-lactams 2.04a-g and 2.05a-g

A solution of acid chlorides was added to solution of bis-imines (**2.01-2.03**) and triethyl amine in dry DCM at 0°C. After the completion of reaction (TLC), the reaction mixture on usual work-up gave diastereomeric mixture two bis-β-lactams **2.04** and **2.05**

(Scheme-2.07). The diastereomeric ratio was determined by ^{1}H NMR spectral analysis of the crude reaction mixture. The diastereomers were separated by flash column chromatography to give pure bis-β-lactams **2.04** and **2.05** in very good yields.

Scheme 2.07



Reagents and conditions (i) R^2CH_2COCl/Et_3N, 0 °C, Overnight.

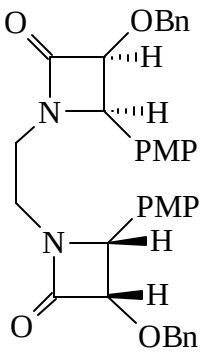
Table 1. Synthesis of bis-β-lactams **2.04** & **2.05**

Compd.	**R^1**	**R^2**	Compound **2.04** & **2.05**			
			Yield[a] (%)	Ratio[b] of **2.04** & **2.05**	m.p. of **2.04**[c] (^{o}C)	m.p. of **2.05**[c] (^{o}C)
a	Anisyl	Ph	80	42:58	204-205	182-183
b	Anisyl	Bn	86	55:45	138-139	227-228
c	Anisyl	Ac	75	51:49	184-185	194-195
d	Ph	Ph	79	38:62	212-213	195-196
e	Ph	Bn	85	30:70	128-129	242-243
f	Styryl	Bn	60	58:42	Semisolid	151-153
g	Styryl	Ph	66	61:39	196-198	195-196

[a] Isolated yields of diastereomeric mix of **2.04** & **2.05**. [b] The diastereomeric ratio of **2.04** & **2.05** was determined from ^{1}H NMR spectral data. [c] The diastereomers **2.04** & **2.05** were separated by flash column chromatography.

The compound **2.04b** was chosen as a representative of **2.04** series for spectral discussion and characterization.

^{1}H NMR spectrum of **2.04b** showed a set of doublets at δ 2.72 and 3.72 with the *J* values of 10.8 Hz for four methylene-protons of ethylene bridge. The six methyl-protons of *p*-methoxyphenyl group appeared together as a singlet at δ 3.81. A set of doublets appeared at δ 4.14 and 4.30 with the *J* values of 8.1 Hz were assigned to benzylic protons. The four β-lactam protons appeared together as a set of doublets. The C4 and C3 β-lactam protons appeared as set of doublets at δ 4.82 and 5.00



(±)-2.04b

respectively with the *J* value of 4.2 Hz. The stereochemistry for C3 and C4 centers of both β-lactam rings was assigned as *cis* from coupling constant values (*J* = 4.2 Hz) of protons at C3 and C4. The presence of only two doublets, integrating for two protons each, for β-lactam protons of both the ring and two doublets with geminal coupling (10.8 Hz) for methylene protons of the ethylene bridge indicates C_2 symmetry in the molecule. The eighteen aromatic protons appeared as a set of multiplets between δ 6.73–7.07 and 7.12–7.41. The IR spectrum showed β-lactam carbonyl stretching at 1735 cm^{-1}. This compound gave satisfactory microanalysis.

Table 2. ^{1}H NMR data for bis-β-lactams **2.04**.

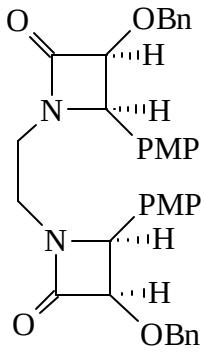
Compound No	Chemical shifts and *J* values for protons at C3 and C4 of β-lactam **2.04**	
	C4-H	C3-H
2.04a	5.17 (d, *J* = 6.5 Hz)	5.34 (d, *J* = 6.5 Hz)
2.04b	4.82 (d, *J* = 4.2 Hz)	5.00 (d, *J* = 4.2 Hz)
2.04c	5.13 (d, *J* = 4.5 Hz)	5.74 (d, *J* = 4.5 Hz)
2.04d	5.22 (d, *J* = 3.9 Hz)	5.38 (d, *J* = 3.9 Hz)
2.04e	4.90 (d, *J* = 4.4 Hz)	5.08 (d, *J* = 4.4 Hz)
2.04f	4.52 (dd, *J* = 4.4 & 9.2 Hz)	4.83 (d, *J* = 4.4 Hz)
2.04g	4.80 (dd, *J* = 4.9 & 9.3 Hz)	5.40 (d, *J* = 4.9 Hz)

All the other bis-β-lactams showed two characteristic doublets (Table 2) in the range of δ 4.52–5.74 for corresponding protons at C4 and C3 of β-lactam ring with the *J* values in

range between 3.9 and 6.5 Hz. The coupling constant indicates *cis* stereochemistry of these protons. The presence of C_2 symmetry in these compounds was further confirmed from X-ray crystal structure analysis of one of the compounds (**2.04b**) from this series (see Fig. 2).

The compound **2.05b** was chosen as a representative of **2.05** series for spectral discussion and characterization.

^{1}H NMR spectrum of **2.05b** showed a set of multiplets at δ 2.81-3.02 and δ 3.41-3.62 for four methylene protons of ethylene bridge. The six-methyl protons of *p*-methoxy phenyl group appeared together as a singlet at δ 3.82. A set of doublets appeared at δ 4.14 and 4.26 with the *J* values of 10.8 Hz was assigned to benzylic protons. Four β-lactam protons at C4 and C3 have appeared together as a set of doublets at δ 4.58 and 4.70



(±)-2.05b

respectively with the *J* value of 4.2 Hz. The stereochemistry of C3 and C4 of β-lactam centers were established as *cis* from coupling constant values (*J* = 4.2 Hz). The eighteen aromatic protons appeared as a set of multiplets between δ 6.78–7.02 and 7.12–7.33. The IR spectrum showed β-lactam carbonyls stretching at 1750 cm^{-1}. This compound gave satisfactory microanalysis.

Table 3. ^{1}H NMR data for bis-β-lactams **2.05**

Compound No	Chemical shifts and *J* values for protons at C3 and C4 of β-lactam **2.05**	
	C4-H	C3-H
2.04a	4.88(d, *J* = 5.4 Hz)	5.24 (d, *J* = 5.4 Hz)
2.04b	4.58(d, *J* = 4.2 Hz)	4.70 (d, *J* = 4.2 Hz)
2.04c	4.85(d, *J* = 5.4 Hz)	5.65 (d, *J* = 5.4 Hz)
2.04d	4.87(d, *J* = 4.2 Hz)	5.22 (d, *J* = 4.2 Hz)
2.04e	4.59(d, *J* = 4.3 Hz)	4.68 (d, *J* = 4.3 Hz)
2.04f	4.37(dd, *J* = 4.4, 9.5 Hz)	4.76 (d, *J* = 4.4 Hz)
2.04g	4.75(dd, *J* = 4.3, 9.2 Hz)	5.40 (d, *J* = 4.4 Hz)

All the other bis-β-lactams showed two characteristic doublets in the range of δ 4.37–5.65 for corresponding protons at C4 and C3 of β-lactam ring with the *J* values in range between 4.2 and 5.4 Hz (Table 3). The coupling constant is indicative of *cis* stereochemistry of these protons. The presence of two multiplets for the ethylene bridge protons suggests unsymmetrical structure for these compounds, which was further confirmed from X-ray crystal structure analysis of one of the compounds (**2.05c**) from this series (see Fig. 2).

X-ray Structure Analysis of 2.04b

In order to ascertain the relative stereochemistry of the bis-β-lactam **2.04**, the X-ray crystal analysis was undertaken. The bis-β-lactam **2.04b** was selected as a representative of **2.04** series.

Structure determination of bis-b -lactam 2.04b [$C_{37}H_{36}N_2O_8$]

Single crystals were grown from methylene chloride/pet. ether by slow evaporation of the solvent. Crystal of size 0.60 X 0.47 X 0.06 mm was used for data collection on Enaraf Nonius CAD-4 Single Crystal X-ray diffractometer using Cu-Kα radiation (λ = 1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M = 636.68, monoclinic, space group C 2/c, *a* = 23.944 (3), *b* = 10.716(3), c = 25.821(3) Å, β = 95.47(2)°, *V* = 6595(2) $Å^3$, Z = 8, Dc = 1.282 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by Full-matrix least-squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of scale, positional and anisotropic thermal parameters of non-hydrogen atom were carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 410, converged to R_1 = 0.0665, R_w = 0.190, $w=1/\sigma^2[(Fo^2)+(0.1513P)^2+1.199P]$ where $P=(Fo^2+2Fc^2)/3$ from 5977 unique reflections ([I>2σ(I)]), from a total of 6806 collected. The residual density in the difference map for peak and hole is 0.390 and -0.612 e. $Å^{-3}$ respectively.

The X-ray analysis of bis-β-lactam **2.04b** (Fig. 1) confirmed the relative stereochemistry of this compound 3S, 4R, 3′S, 4′R or 3R, 4S, 3′R, 4′S. The same relative stereochemistry of 3S, 4R, 3′S, 4′R or 3R, 4S, 3′R, 4′S was assigned to all other compounds of this series by comparing their spectral data with bis-β-lactam **2.04b**.

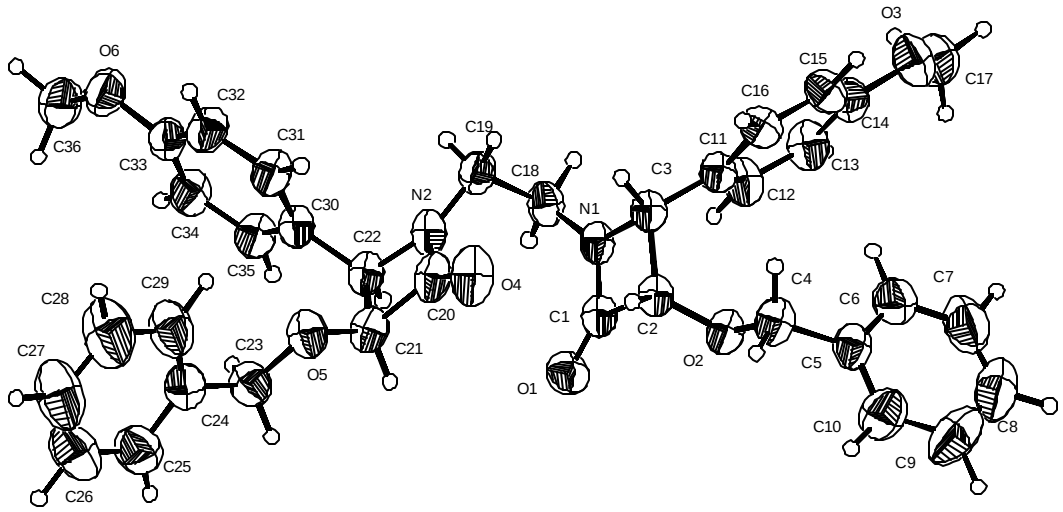


Fig. 1. ORTEP diagram of bis-β-lactam **2.04b**

X-ray Structure Analysis of 2.05c

The bis-β-lactam **2.05c** was selected as a representative of **2.05** series. The crystals were grown from dichloromethane/pet. ether.

Structure Determination of bis-b -lactam 2.05c [$C_{26}H_{28}N_2O_8$] :

Singles Crystals were grown by slow evaporation of the compound from methylene chloride/pet. ether. Crystal of size 0.62 X 0.5 X 0.2 mm was used for data collection on Enaraf Nonius CAD-4 Single Crystal X-ray diffractometer using Cu-Kα radiation (λ = 1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M = 496.50, Triclinic, space group P-1, a = 6.425 (2), b = 14.161 (2), c = 14.811(3) Å, α = 106.45 (2), β = 100.58 (2), γ = 98.76 (2)°, V = 1240.3 (5) $Å^3$, Z = 2, D_c = 1.330 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by Full-matrix least squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of scale, positional and anisotropic thermal parameters of non-hydrogen atom were carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 326, converged to R_1 = 0.0532, R_w = 0.168, $w=1/\sigma^2[(Fo^2)+(0.1075P)^2+0.5243P]$ where $P=(Fo^2+2Fc^2)/3$ from 3934 unique reflections

([I>2σ(I)]), from a total of 4516 collected. The residual density in the difference map for peak and hole is 0.362 and -0.252 e. $Å^{-3}$ respectively.

The X-ray analysis of bis-β-lactam **2.05c** (Fig. 2) confirmed the relative stereochemistry of this compound as 3S, 4R, 3′R, 4′S or 3R, 4S, 3′S, 4′R. The same relative stereochemistry of 3S, 4R, 3′R, 4′S or 3R, 4S, 3′S, 4′R was assigned to all other compounds of this series by comparing their spectral data with bis-β-lactam **2.05c**.

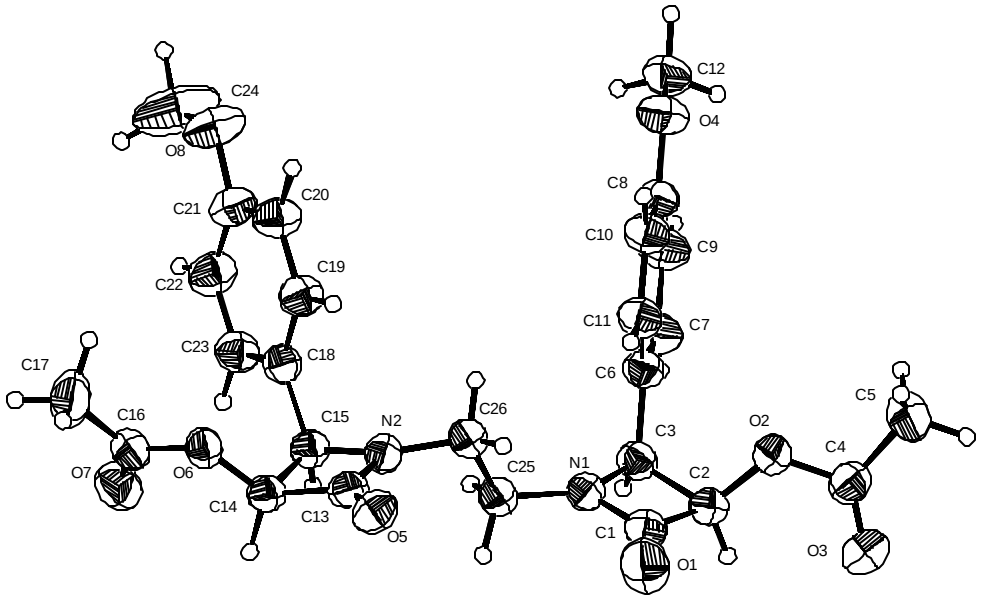


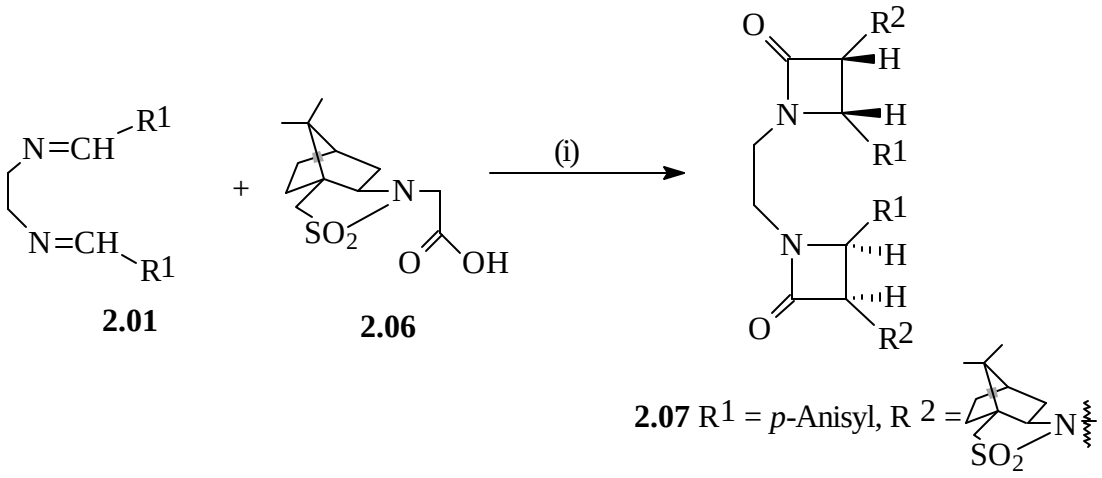
Fig. 2. ORTEP diagram of bis-β-lactam **2.04b**

2.3.3 Preparation of bis b-lactam 2.07

The methodology described for bis-β-lactams **2.04** & **2.05** was extended for asymmetric synthesis of bis-β-lactams. To achieve the diastereoselectivity in β-lactam ring formation *via* ketene-imine cycloaddition reaction, a sterically demanding chiral acid **2.06**, derived from camphor sultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **2.06** was obtained in overall 70% yield from camphor sultam in two steps using reported procedure.[11] The cycloaddition reaction of ketene derived from the acid **2.06** with imine **2.01** in presence of triethylamine and phenyldichlorophosphate furnished stereospecifically bis-β-lactam **2.07** in excellent yield (93%) (Scheme-2.08). The formation

of single diastereomer was evident from ^{1}H NMR & HPLC analysis of the crude reaction mixture.

Scheme 2.08



Reagents and conditions: i) $Ph(PO)Cl_2/Et_3N$, 0 °C Overnight

Spectral discussion and characterization of bis-β-lactam 2.07

^{1}H NMR spectrum of bis-β-lactam (**2.07**) showed two singlets at δ 0.36 and 0.76 for *gem*-dimethyl group of sultam moiety. The twenty protons of sultam part appeared as several multiplets at δ 1.15–3.62. The six methyl-protons of two *p*-methoxyphenyl groups appeared as a singlet at δ 3.78. The two methylene protons of ethylene bridge appeared as a doublet at δ 3.84 with *J* value of 10.8 Hz. As observed earlier, the presence of two doublets for the ethylene bridge protons indicates the C_2 symmetry in the molecule. The β-lactam protons at C4 and C3 appeared at δ 4.94 and 5.02 respectively as doublets integrating for two protons each with the *J* values of 4.8 Hz. The eight aromatic protons appeared as two doublets at δ 6.88 and 7.19 with the *J* values of 8.7 Hz. The IR spectrum showed β-lactam carbonyl stretching at 1757 cm^{-1}. This compound gave satisfactory microanalysis.

The stereochemical determination of bis-β-lactam (2.07)

The C_2 symmetric structure was assigned to bis-β-lactam **2.07** based on its ^{1}H NMR spectrum, which compares very well with the ^{1}H NMR spectra of C_2 symmetric bis-β-lactams **2.04** obtained earlier. The absolute stereochemistry for this bis-β-lactam **2.07** was assigned as

3*R*, 4*S*, 3′*R*, 4′*S* based on our earlier work on asymmetric synthesis of β-lactams[11] using ketene derived from Oppolzer's sultam and imines.

2.4 Summary

The formation of two β-lactam rings in single operation has been achieved by the cycloaddition reaction of bis-imines **2.01 – 2.03** with various acid chlorides in presence of base to get bis-β-lactams **2.04** and **2.05** in very good yield.

2.5 Experimental

2.5.1 General procedure for the preparation of imines 2.01 & 2.02

A mixture of freshly distilled aldehyde (0.15 mol), ethylenediamine (0.05 mol), anhydrous $MgSO_4$ (24 g) and dry dichloromethane (200 ml) was stirred for 15 h at room temperature. The reaction mixture was then filtered through a bed of celite and the solvent from the filtrate was removed by distillation under reduced pressure. The residue was then treated with a 10% solution of ethyl acetate in pet. ether to remove unreacted aldehyde and filtered to give required imines **2.01** and **2.02** in excellent yield as a crystalline solids.

2.5.1a Preparation of N,N′-Bis-(*p*-methoxyphenylmethylene)ethane diamine 2.01

The reaction of *p*-methoxybenzaldehyde (20.42 g, 0.15 mol) and ethylenediamine (3 g, 0.05 mol) gave crude product, which on crystallization from EtOAc: Pet. ether (90:10) gave 13 g (88%) of pure bis-imine **2.01** as white needles.

M.p. : 109-110°C [lit.[6] m.p. 110-111°C].

^{1}H NMR : δ 3.74 (s, 6H); 3.84 (s, 4H); 6.78 (d, *J* = 8 Hz, 4H); 7.50 (d, *J* = 8 Hz, 4H); 8.06 (s, 2H).

IR : 830, 1010, 1450, 1630 cm^{-1}.

2.5.1b Preparation of N,N′-Bis-(phenylmethylene)ethane diamine 2.02

The reaction of benzaldehyde (15.9 g, 0.15 mol) and ethylenediamine (3 g, 0.05 mol) gave crude product, which on crystallization from EtOAc: Pet. ether (90:10) gave 9.92 g (84%) of pure bis-imine **2.02** as white crystalline slid.

M.p. : 52-53°C [lit.[7] m.p. 51.5-53°C].

^{1}H NMR : δ 3.88 (s, 4H); 6.92–7.88 (m, 10H); 8.14 (s, 2H).

IR : 960, 1000, 1350, 1430, 1610 cm^{-1}

2.5.2 Preparation of N,N′-Bis(styrylmethylene)ethane diamine 2.03

A solution of freshly distilled cinnamaldehyde (14.18 g, 0.107 mol) and ethylenediamine (3 g, 0.05 mol) in ethanol (40 ml) was refluxed for 1h. The solvent was removed by distillation under reduced pressure and the residue was purified by crystallization

from ethylacetate: pet-ether (90:10) to give 14.38 g (100%) of pure bis-imine **2.03** as a crystalline pale yellow solid.

M.p. : 108-109°C [lit.[8] m.p. 109°C].

^{1}H NMR : δ 3.80 (s, 4H); 6.70-6.95 (m, 4H); 7.15-7.55 (m, 10H); 7.95 (d, *J* = 6.6 Hz, 2H).

IR : 979, 1164, 1218, 1450, 1635, 2846, 2939 cm^{-1}.

2.5.3 General procedure for the synthesis of b-lactams 2.04a-g & 2.05a-g

A solution of the acid chlorides (8.85 mmol) in dry CH_2Cl_2 (15 ml) was slowly added to a solution of imines **2.01 – 2.03**, (2.53 mmol) and triethylamine (26.5 mmol) in CH_2Cl_2 (15 ml) at 0 ^oC. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. It was then washed with water (2 x 20 ml), satd. $NaHCO_3$ (15 ml), brine (15 ml), and dried over anhydrous Na_2SO_4. It was filtered and filtrate on removal of organic solvent by distillation under reduced pressure gave crude product of a diastereomeric mixture. The diastereomers were separated by flash column chromatography (pet. ether: ethyl acetate, 3:1) to give pure β-lactams (**2.04 a-g** & **2.05a-g**) in very good yields. The less polar C_2-symmetric β-lactam (**2.04**) eluted first followed by more polar meso β-lactam (**2.05**).

2.5.3a Synthesis of b-lactams 2.04a and 2.05a

The phenoxy acetyl chloride (1.5 g, 8.85 mmol) on treatment with imine **2.01** (0.75 g, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^oC gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 1.14 g (80%, total yield) of pure β-lactams **2.04a** (minor) and **2.05a** (major) as white solids.

1, 2–Bis[3¢-phenoxy-4¢-(*p*-methoxyphenyl)azetidin-2¢-one-1¢-yl]ethane 2.04a

M.p. : 204-205 ^oC.

^{1}H NMR : δ 2.80 (d, *J* = 11.4 Hz, 2H); 3.75 (s, 6H); 3.82 (d, *J* = 11.4 Hz, 2H); 5.17 (d, *J* = 6.5 Hz, 2H); 5.34 (d, *J* = 6.5 Hz, 2H); 6.60–6.93 (m, 12H); 7.02–7.33 (m, 6H).

^{13}C NMR : 37.36, 55.24, 60.76, 82.55, 113.93, 116.86, 129.16, 129.80, 155.37, 160.14, 166.82.

MS (*m/z*) : 121(100%), 134, 148, 161, 226.

IR : 1735 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{34}H_{32}N_2O_6$.

Calculated : C, 72.32; H, 5.71, N, 4.96%.

Found : C, 72.40; H, 5.49; N, 4.69%.

1-[3¢-Phenoxy–4¢-(*p*-methoxyphenyl)azetidin-2¢-one-1¢-yl]-2-[3¢¢-Phenoxy-4¢¢-(*p*-methoxyphenyl)azetidin-2¢¢-one-1¢¢-yl]ehtane 2.05a

M.p. : 182-183 ^oC.

^1H NMR : δ 3.00-3.24 (m, 2H); 3.50 -3.75 (m, 2H); 3.78 (s, 6H); 4.88 (d, *J* = 5.4 Hz, 2H); 5.24 (d, *J* = 5.4 Hz, 2H); 6.57-7.42 (m, 18H).

^{13}C NMR : 38.24, 55.27, 61.68, 82.16, 113.99, 116.80, 129.16, 129.86, 155.37, 160.23, 165.84.

MS (*m/z*) : 245 (100%), 148, 161, 226, 254.

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{34}H_{32}N_2O_6$.

Calculated : C, 72.32; H, 5.71, N, 4.96%.

Found : C, 72.50; H, 5.76; N, 4.76%.

2.5.3b Synthesis of b-lactams 2.04b and 2.05b

The benzyloxy acetyl chloride (1.63 g, 8.85 mmol) on treatment with imine **2.01** (0.75 g, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^oC gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 1.29 g (86%, total yield) of pure β-lactams **2.04b** (major) and **2.05b** (minor) as white solids.

1,2-Bis[3¢-benzyloxy-4¢-(*p*-methoxyphenyl)azetidin-2¢-one-1¢-yl]ethane 2.04b

M.p. : 138-139 ^oC.

^1H NMR : δ 2.72 (d, *J* = 10.8 Hz, 2H); 3.72 (d, 10.79Hz, 2H); 3.81 (s, 6H); 4.14 (d, *J* = 8.1 Hz, 2H); 4.30 (d, *J* = 8.1 Hz, 2H); 4.82 (d, *J* = 4.2 Hz, 2H); 5.00 (d, *J* = 4.2 Hz, 2H); 6.73 - 7.04 (m, 8H); 7.12 – 7.41 (m, 10H).

^{13}C NMR : 37.34, 55.64, 60.99, 72.65, 84.69, 114.34, 125.77, 128.16, 128.39, 128.52, 130.12, 136.85, 160.32, 168.32.

MS (*m/z*) : 91(100%), 149, 261, 281, 331, 484, 501(M^+-Bn).

IR : 1735cm^{-1}.

Elemental analysis

Molecular Formula : $C_{36}H_{36}N_2O_6$.

Calculated : C, 72.95; H, 6.12, N, 4.72%.

Found : C, 72.69, H, 6.22, N, 4.58%.

1-[3¢-Benzyloxy–4¢-(*p*-methoxyphenyl)azetidin-2¢-one-1¢-yl]-2-[3¢¢-Benzyloxy-4¢¢-(*p*-meth-oxyphenyl)azetidin-2¢¢-one-1¢¢-yl]ehtane 2.05b

M.p. : 227 – 228 ^{o}C.

^{1}H NMR : δ 2.81-3.02 (m, 2H); 3.41-3.62 (m, 2H); 3.82 (s, 6H); 4.14 (d, *J* = 10.8 Hz, 2H); 4.26 (d, *J* = 10.8 Hz, 2H); 4.58 (d, *J* = 4.2 Hz, 2H); 4.70 (d, *J* = 4.2 Hz, 2H); 6.78-7.02 (m, 8H); 7.12-7.33 (m, 10H).

^{13}C NMR : 37.81, 55.48, 61.59, 72.33, 83.77, 114.17, 125.22, 128.00, 128.24, 128.36, 129.92, 136.54, 160.22, 167.34

MS (*m/z*) : 90 (100%), 148, 240, 268, 501 (M^{+} -Bn).

IR : 1750 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{36}H_{36}N_2O_6$.

Calculated : C, 72.95; H, 6.12, N, 4.72%.

Found : C, 72.76; H, 6.17; N, 4.85%.

2.5.3c Synthesis of b -lactams 2.04c and 2.05c

The acetoxy acetyl chloride (1.21 g, 8.85 mmol) on treatment with imine **2.01** (0.75 g, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^{o}C gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 0.94 g (75%, total yield) of pure β-lactams **2.04c** (major) and **2.05c** (minor) as white solids.

1,2-Bis-[3¢-acetoxy-4¢-(*p*-methoxyphenyl)azetidin-2¢one-1¢-yl]ethane 2.04c

M.p. : 184-185 ^{o}C.

^{1}H NMR : δ 1.72 (s, 6H); 2.88 (d, *J* = 10.3 Hz, 2H); 3.79 (d, *J* = 10.27Hz, 2H); 3.82 (s, 6H); 5.13 (d, *J* = 4.53Hz, 2H); 5.74 (d, *J* = 4.55 Hz, 2H); 6.89 (d, *J* = 8.69 Hz, 4H); 7.17 – 7.32 (m, 4H).

^{13}C NMR : 19.98, 38.23, 38.77, 39.18, 39.59, 40.01, 40.43, 40.85, 41.27, 55.36, 60.13,

76.26, 77.26, 77.62, 113.98, 124,97, 129.74, 159.85, 161.39, 165.40, 168.66.

MS (*m/z*) : 121(100%), 161, 262, 304.

IR : 1755 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{26}H_{28}N_2O_8$.

Calculated : C, 62.89; H, 5.68, N, 5.64%.

Found : C, 62.77; H, 5.72; N, 5.77%.

1-[3¢-Acetoxy–4¢-(*p*-methoxyphenyl)azetidin-2¢-one-1¢-yl]-2-[3¢¢-Acetoxy-4¢¢-(*p*-methoxyphenyl)azetidin-2¢¢-one-1¢¢-yl]ehtane 2.05c

M.p. : 194 – 195 ^oC.

^1H NMR : δ 1.73 (s, 6H); 3.02 – 3.18 (m, 2H); 3.46 – 3.67 (m, 2H); 3.83 (s, 6H); 4.85 (d, *J* = 5.4 Hz, 2H); 5.65 (d, *J* = 5.4 Hz, 2H); 6.92 (d, *J* = 9.7 Hz, 4H); 7.14 – 7.30 (m, 4H).

^{13}C NMR : 19.84, 38.45, 55.24, 61.31, 77.43, 113.93, 123.82, 129.65, 160.14, 165.26, 168.92.

MS (*m/z*) : 150 (100%), 121, 135.

IR : 1758 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{26}H_{28}N_2O_8$.

Calculated : C, 62.89; H, 5.68, N, 5.64%.

Found : C, 62.62; H, 5.69; N, 5.50%.

2.5.3d Synthesis of b-lactams 2.04d and 2.05d

The phenoxy acetyl chloride (1.5 g, 8.85 mmol) on treatment with imine **2.02** (598 mg, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^oC gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 1.0 g (79%, total yield) of pure β-lactams **2.04d** (minor) and **2.05d** (major) as white solids.

1,2-Di-[3¢-Phenoxy-4¢-phenylazetidin-2¢-one-1¢-yl]ethane 2.04d

M.p. : 212-213 ^oC.

^1H NMR : δ 2.86 (d, J = 8.6 Hz, 2H); 3.88 (d, J = 8.6 Hz, 2H); 5.22 (d, *J* = 3.9 Hz, 2H);

5.38 (d, *J* = 3.9 Hz, 2H); 6.58-7.39 (m, 20H).

^{13}C NMR : 37.54, 61.16, 82.62, 115.64, 116.92, 128.49, 129.01, 129.13, 132.45, 155.28, 166.85.

MS (*m/z*) : 230 (100%), 196, 224.

IR : 1752 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{32}H_{28}N_2O_4$.

Calculated : C, 76.17; H, 5.59; N, 5.55%.

Found : C, 76.05; H, 5.30; N, 5.40%.

1-[3¢-Phenoxy-4¢-phenylazetidin-2¢-one-1¢-yl]-2-[3¢¢-phenoxy-4¢¢-phenylazetidin-2¢¢-one-1¢¢-yl]ehtane 2.05d

M.p. : 195 - 196 ^{o}C.

^{1}H NMR : δ 3.00 – 3.23 (m, 2H); 3.55 – 3.79 (m, 2H); 4.87 (d, *J* = 4.2Hz, 2H); 5.22 (d, *J* = 4.2Hz, 2H); 6.52 – 6.73 (m, 4H); 6.97 – 7.20 (m, 4H); 7.20–7.43 (m, 12H).

^{13}C NMR : 38.30, 62.08, 82.16, 116.80, 128.55, 129.16, 132.27, 155.28, 165.81.

MS (*m/z*) : 230 (100%), 196.

IR : 1729 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{32}H_{28}N_2O_4$.

Calculated : C, 76.17; H, 5.59; N, 5.55%.

Found : C, 76.30; H, 5.36; N, 5.31%.

2.5.3e Synthesis of b -lactams 2.04e and 2.05e

The benzyloxy acetyl chloride (1.63 g, 8.85 mmol) on treatment with imine **2.02** (598 mg, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^{o}C gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 1.14 g (85%, total yield) of pure β-lactams **2.04e** (minor) and **2.05e** (major) as white solids.

1,2-Di[3¢-benzyloxy-4¢-phenylazetidin-2¢-one-1¢-yl]ethane 2.04e

M.p. : 128-129 ^{o}C.

^{1}H NMR : δ 2.75 (d, *J* = 10.9 Hz, 2H); 3.80 (d, *J* = 10.9 Hz, 2H); 4.12 (d, *J* =10.8 Hz, 2H);

4.29 (d, *J* = 10.8 Hz, 2H); 4.90 (d, *J* = 4.4 Hz, 2H); 5.08 (d, *J* = 4.4 Hz, 2H); 6.94 (m, 4H); 7.18-7.46 (m, 16H).

^{13}C NMR : 37.29, 61.32, 69.19, 72.64, 80.16, 81.13, 82.98, 83.11, 84.73, 86.08, 90.09, 128.03, 128.25, 128.38, 128.72, 133.90, 136.56, 166.11, 168.21, 175.39.

IR : 1740 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{34}H_{32}N_2O_4$.

Calculated : C, 76.67; H, 6.05; N, 5.26%.

Found : C, 76.43; H, 6.16; N, 4.98%.

1-[3¢-Benzyloxy-4¢-phenylazetidin-2¢-one-1¢-yl]-2-[3¢¢-benzyloxy-4¢¢-phenylazetidin-2¢¢-one-1¢¢-yl] ehtane 2.05e

M.p. : 242 – 243 ^{o}C.

^{1}H NMR : δ 2.90-3.10 (m, 2H); 3.51-3.71 (m, 2H); 4.12 (d, *J* = 10.3 Hz, 2H); 4.24 (d, *J* = 10.3 Hz, 2H); 4.59 (d, *J* = 4.3 Hz, 2H); 4.68 (d, *J* = 4.3 Hz, 2H); 6.84-6.97 (m, 4H); 7.14-7.54 (m, 16H).

^{13}C NMR : 37.72, 61.95, 72.24, 83.71, 127.88, 128.21, 128.46, 128.58, 128.79, 133.34, 136.24, 167.09.

IR : 1750 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{34}H_{32}N_2O_4$.

Calculated : C, 76.67; H, 6.05; N, 5.26%.

Found : C, 76.51; H, 6.31; N, 5.27%.

2.5.3f Synthesis of b-lactams 2.04f and 2.05f

The benzyloxy acetyl chloride (1.63 g, 8.85 mmol) on treatment with imine **2.03** (728 mg, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^{o}C gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 0.89 g (60%, total yield) of pure β-lactams **2.04f** (major) and **2.05f** (minor).

1-[3¢-Benzyloxy-4¢-styrylazetidin-2¢-one-1¢-yl]-2-[3¢¢-benzyloxy-4¢¢-styrylazetidin-2¢¢-one-1¢¢-yl] ehtane 2.04f

M.p. : Isolated as a semisolid material.

^{1}H NMR : δ 3.00 (d, *J* = 11.2 Hz, 2H); 3.62 (d, *J* = 11.8 Hz, 2H); 4.52 (dd, *J* = 4.4, 9.2 Hz, 2H); 4.62 (d, *J* = 7.3 Hz, 2H); 4.68 (d, *J* = 7.3 Hz, 2H); 4.83 (d, *J* = 4.4 Hz, 2H); 6.23 (dd, *J* = 9.2, 16.1 Hz, 2H); 6.72 (d, *J* = 16.1 Hz, 2H); 7.15-7.50 (m, 20H).

^{13}C NMR : 37.89, 60.53, 72.59, 83.65, 122.69, 126.37, 127.84, 128.02, 128.31, 135.44, 136.40, 167.17

MS (*m/z*) : 494 (M^+-90), 236, 91(100%).

IR : 1747 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{38}H_{36}N_2O_4$.

Calculated : C, 78.06; H, 6.20; N, 4.79%.

Found : C, 78.17; H, 6.13; N, 4.54%.

1-[3¢-Benzyloxy-4¢-styrylazetidin-2¢-one-1¢-yl]-2-[3¢¢-benzyloxy-4¢¢-styrylazetidin-2¢¢-one-1¢¢-yl] ehtane 2.05f

M.p. : 158-159 ^oC.

^{1}H NMR : δ 3.10-3.27 (m, 2H); 3.39-3.50 (m, 2H); 4.37 (dd, *J* = 4.4, 9.5 Hz, 2H); 4.53 (d, *J* = 11.0 Hz, 2H); 4.64 (d, *J* = 10.8 Hz, 2H); 4.76 (d, *J* = 4.4 Hz, 2H); 6.30 (dd, *J* = 9.5, 15.7 Hz, 2H); 6.63 (d, *J* = 15.4 Hz, 2H); 7.15-7.50 (m, 20H).

^{13}C NMR : 38.39, 61.31, 72.82, 83.68, 123.54, 126.87, 128.00, 128.21, 128.39, 128.73, 135.93, 136.51, 136.76, 167.31

MS (*m/z*) : 494 (M^+-90), 236, 91 (100%).

IR : 1747 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{38}H_{36}N_2O_4$.

Calculated : C, 78.06; H, 6.20; N, 4.79%.

Found : C, 77.87; H, 6.41; N, 4.84%.

2.5.3g Synthesis of b -lactams 2.04g and 2.05g

The phenoxy acetyl chloride (1.5 g, 8.85 mmol) on treatment with imine **2.03** (728 mg, 2.53 mmol) in presence of triethylamine (2.68 g, 26.5 mmol) at 0 ^{o}C gave mixture of two β-lactams. This mixture was separated by flash column chromatography to give 0.93 g (66%, total yield) of pure β-lactams **2.04g** (major) and **2.05g** (minor) as white solids.

1-[3¢-Phenoxy-4¢-styrylazetidin-2¢-one-1¢-yl]-2-[3¢¢-phenoxy-4¢¢-styrylazetidin-2¢¢-one-1¢¢-yl] ehtane 2.04g

M.p. : 196-198 ^{o}C.

^{1}H NMR : δ 3.12 (d, *J* = 11.3 Hz, 2H); 3.76 (d, *J* = 11.7 Hz, 2H); 4.80 (dd, *J* = 4.9, 9.3 Hz, 2H); 5.40 (d, *J* = 4.9 Hz, 2H); 6.25 (dd, *J* = 9.3, 16.1 Hz, 2H); 6.80 (d, *J* = 15.6 Hz, 2H); 6.90-7.60 (m, 20H).

^{13}C NMR : 37.57, 38.67, 38.94, 39.22, 59.70, 81.15, 114.42, 121.13, 121.34, 125.65, .127.36, 127.60, 128.46, 134.65, 136.12, 156.14, 164.93

MS (*m/z*) : 292, 222, 128 (100%).

IR : 1755 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{36}H_{32}N_2O_4$.

Calculated : C, 77.67; H, 5.79; N, 5.03%.

Found : C, 77.56; H, 5.71; N, 4.89%.

1-[3¢-Phenoxy-4¢-styrylazetidin-2¢-one-1¢-yl]-2-[3¢¢-phenoxy-4¢¢-styrylazetidin-2¢¢-one-1¢¢-yl] ehtane 2.05g

M.p. : 195-196 ^{o}C.

^{1}H NMR : δ 3.27-3.67 (m, 4H); 4.75 (dd, *J* = 4.3, 9.2 Hz, 2H); 5.42(d, *J* = 4.4 Hz, 2H); 6.37 (dd, *J* = 9.2, 15.9 Hz, 2H); 6.75 (d, *J* = 15.6 Hz, 2H); 6.88-7.55 (m, 20H).

^{13}C NMR : 38.33, 39.31, 3958, 39.86, 60.89, 81.61, 114.17, 115.09, 121.68, 122.20, 126.35, 127.94, 128.18, 128.97, 135.32, 136.64, 156.78, 165.63.

MS (*m/z*) : 292, 222, 128(100%).

IR : 1757 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{36}H_{32}N_2O_4$.

Calculated : C, 77.67; H, 5.79; N, 5.03%.

Found : C, 77.45; H, 5.68; N, 4.81%.

2.5.4 Synthesis of bis-β-lactam 2.07

To a stirred mixture of bis imine **2.01** (0.75 g, 2.53 mmol), acid**2.06** (2.418 g, 8.86 mmol), triethylamine (0.6 ml) and dry CH_2Cl_2 (10 ml), a solution of phenyl dichlorophosphate (2 mL, 0.013 mol) in dry CH_2Cl_2 (40 ml) was added at 0°C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and successively washed with water (30 ml), satd. $NaHCO_3$ solution (30 ml), brine (30 ml), and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to give the crude product, which was column chromatographed (silica gel, 60-120, pet. ether/ethyl acetate) to furnish 1.9 g (93%) of pure β-lactam (**2.07**) as a white crystalline solid.

$[\alpha]_D$: + 96.56 (1, $CHCl_3$)

M.p. : 229-231°C.

^{1}H NMR : δ 0.36 (s, 6H); 0.76 (s, 6H); 1.15-1.52 (m, 4H); 1.60-1.90 (m, 12H); 2.80 -3.12 (m, 6H); 3.47-3.62 (m, 2H); 3.78 (s, 6H); 3.84 (d, *J* = 10.8 Hz, 2H); 4.94 (d, *J* = 4.8 Hz, 2H); 5.02 (d, *J* = 4.8 Hz, 2H); 6.88 (d, *J* = 8.7 Hz,4H); 7.19 (d, *J* = 8.7 Hz, 4H).

^{13}C NMR : 19.97, 20.27, 26.99, 32.94, 38.27, 39.10, 45.41, 47.62, 48.92, 50.30, 55.62, 59.71, 63.60, 66.36, 114.38, 126.53, 129.24, 160.17, 165.15.

MS (*m/z*) : 121 (100%), 228, 459.

IR : 1757 cm^{-1}.

Elemental analysis

Molecular Formula : $C_{42}H_{54}N_4O_8S_2$.

Calculated: C, 62.51; H, 6.74; N, 6.94%.

Found : C, 62.32; H, 6.54; N, 6.85%.

2.6 References

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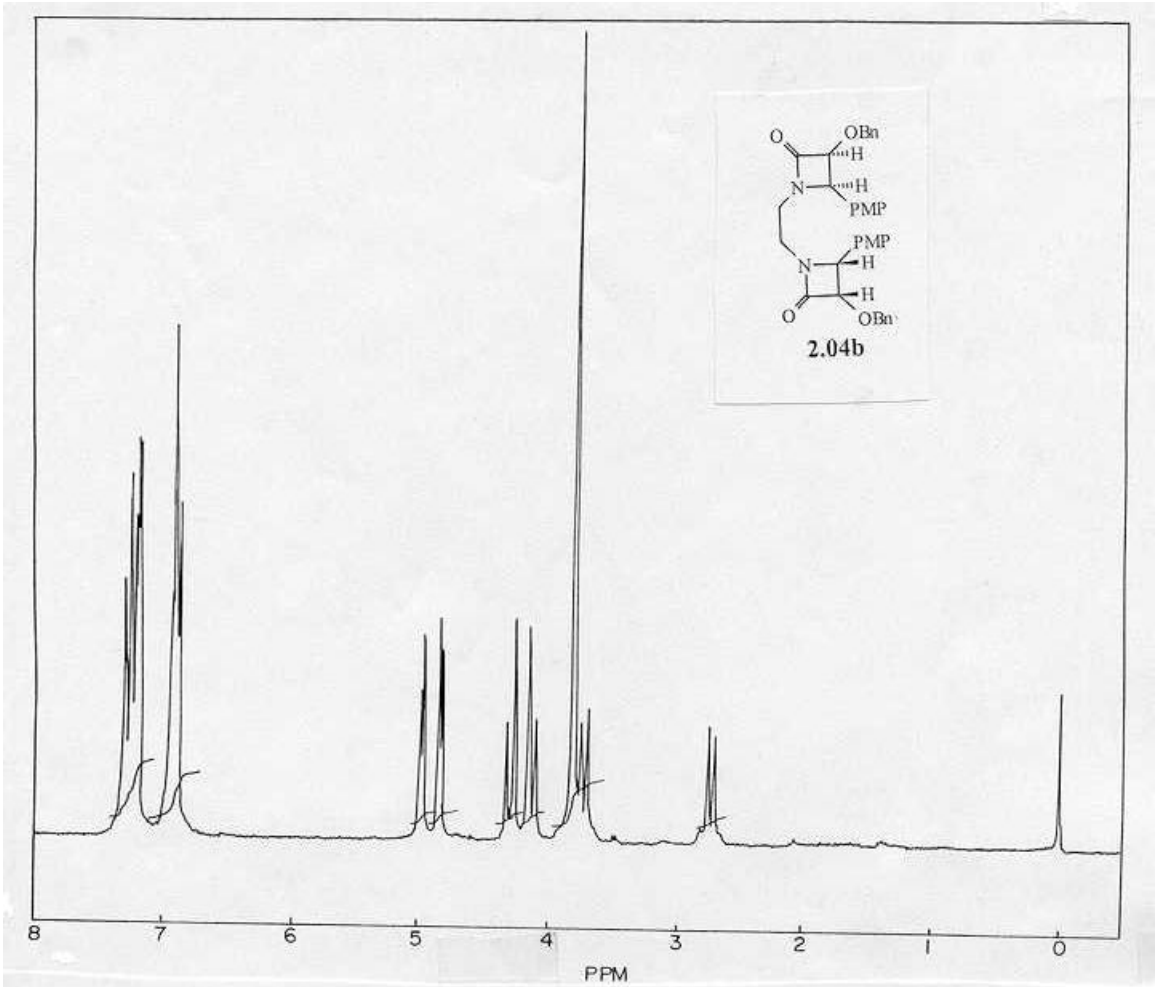
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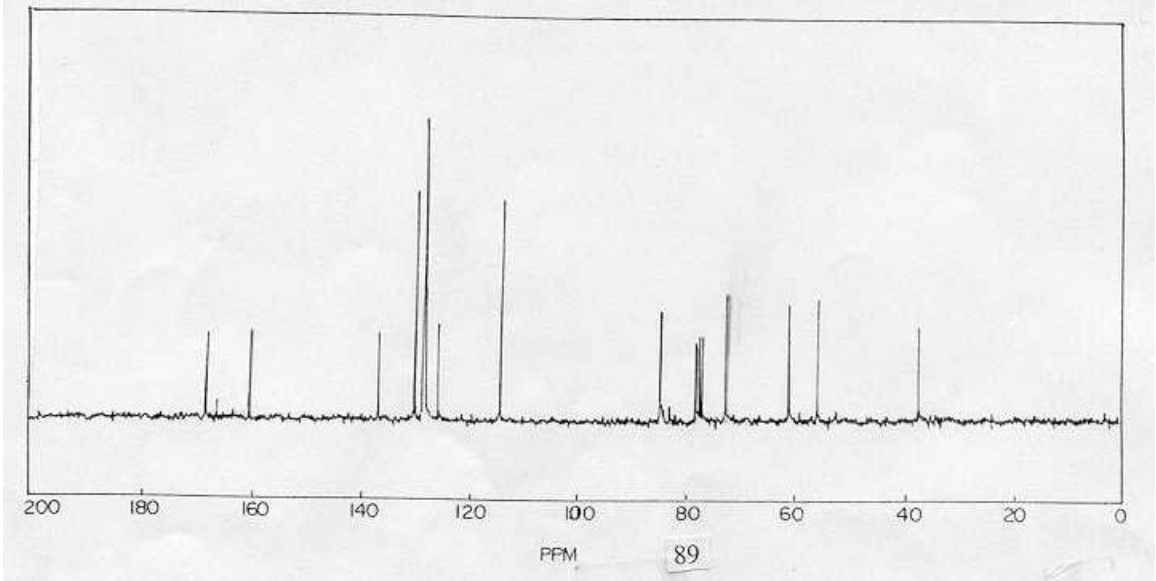
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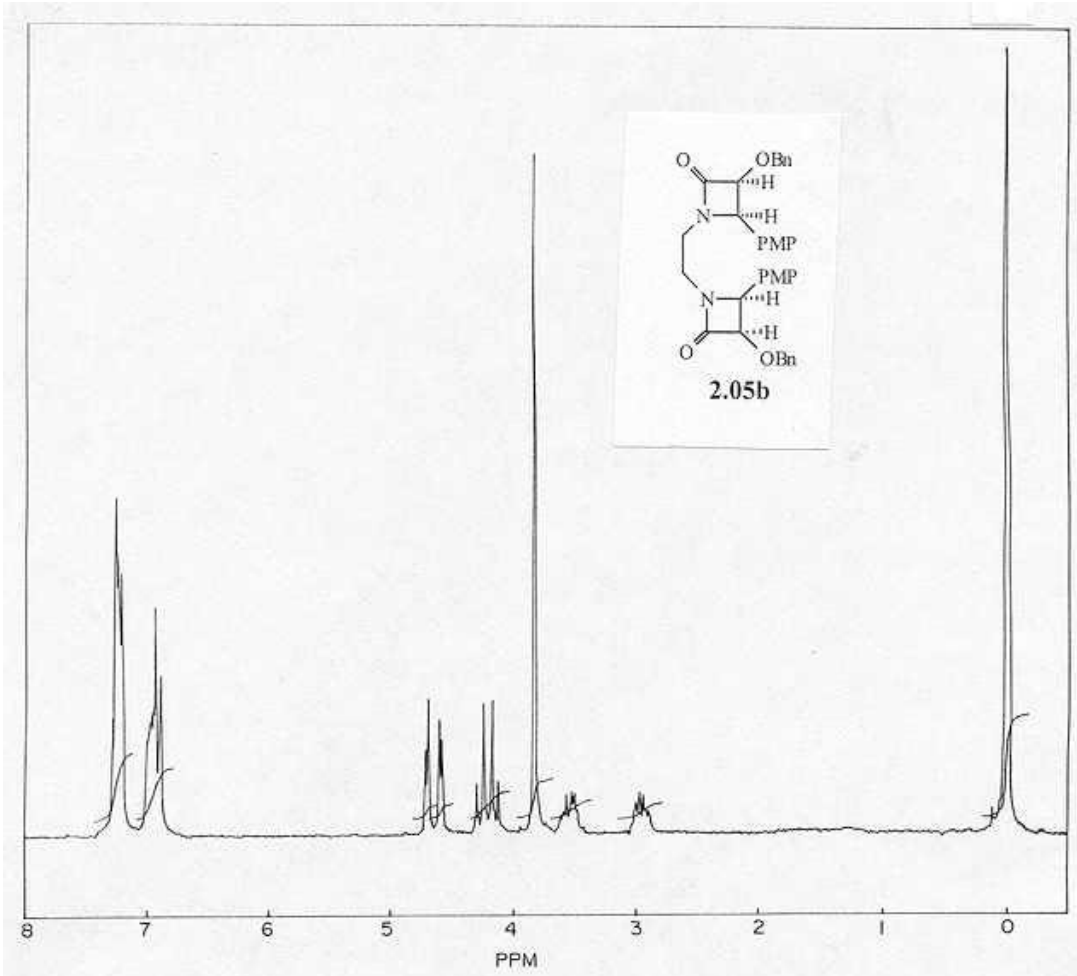
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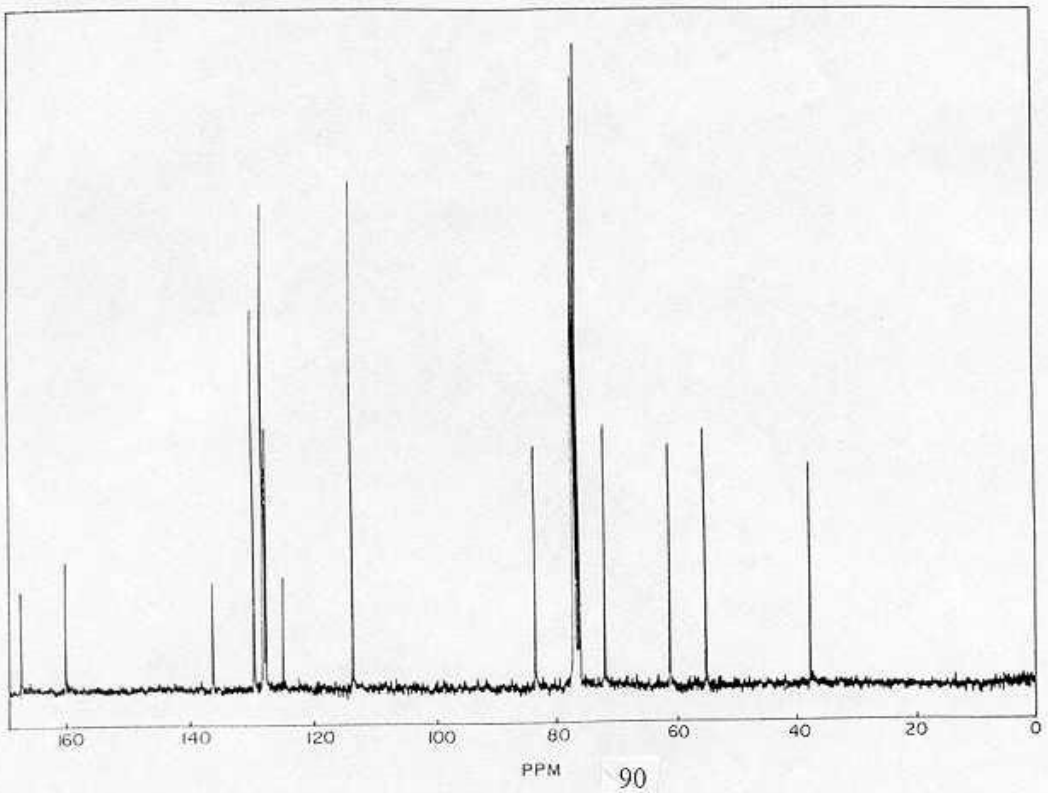
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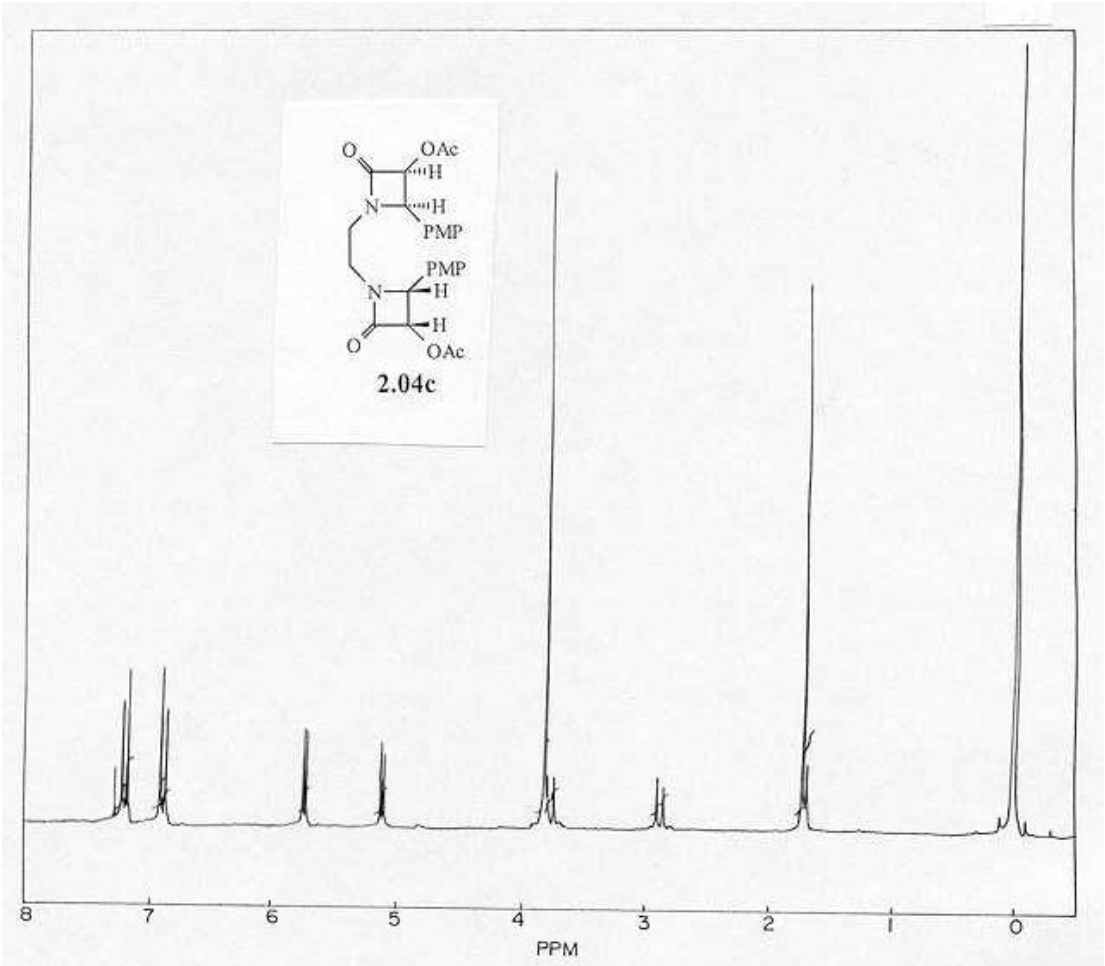
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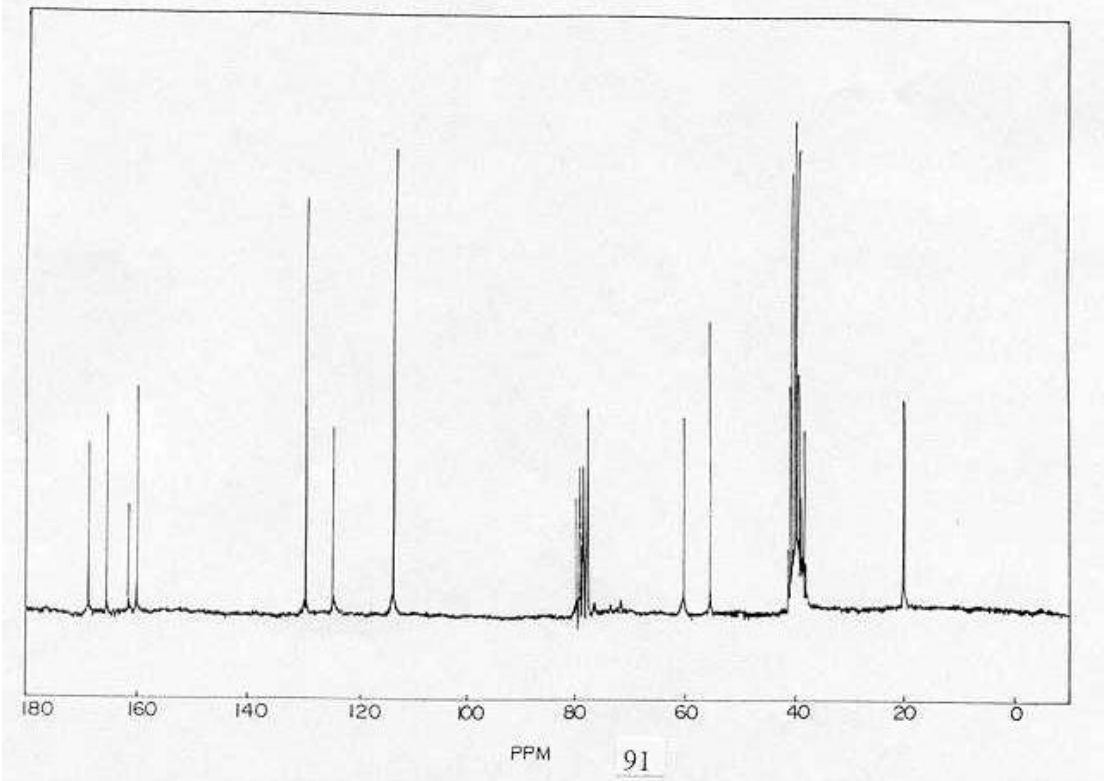
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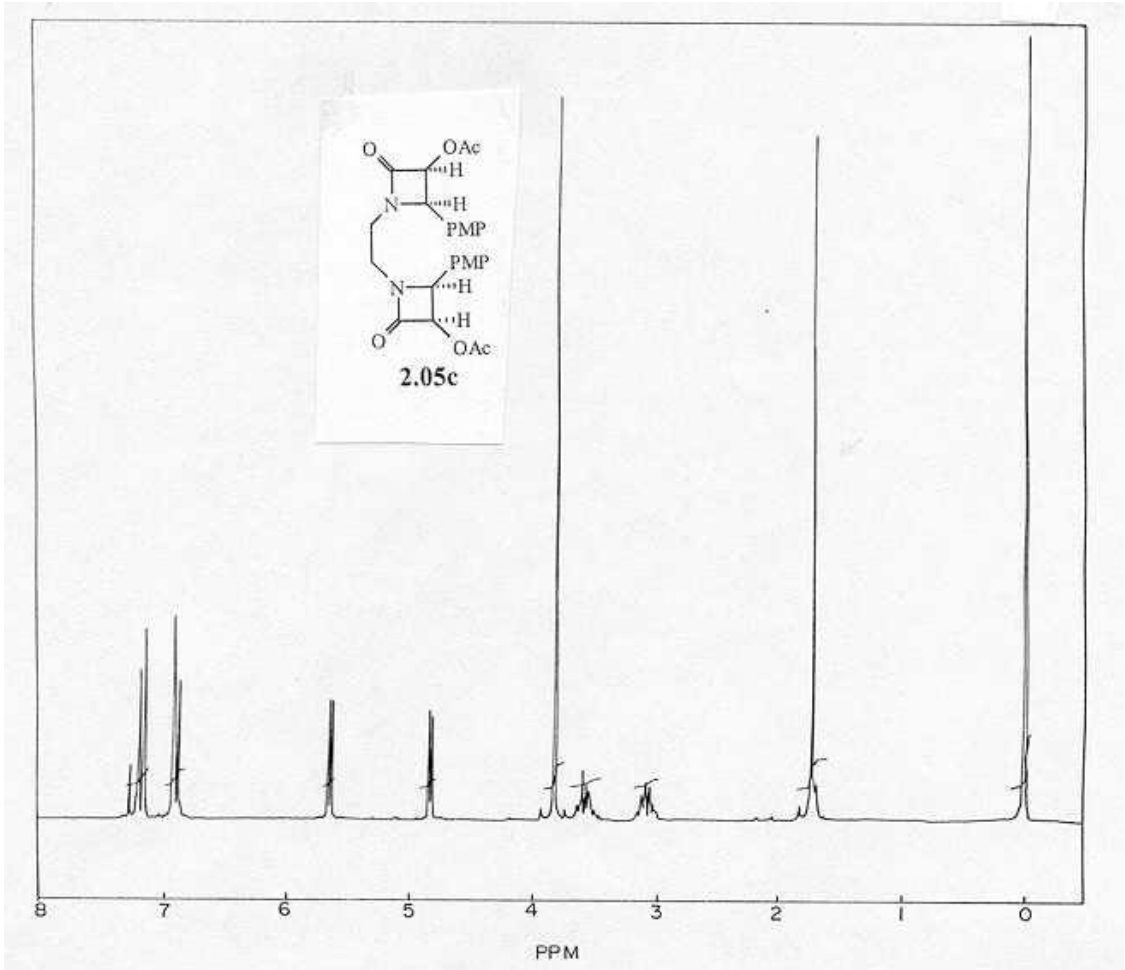
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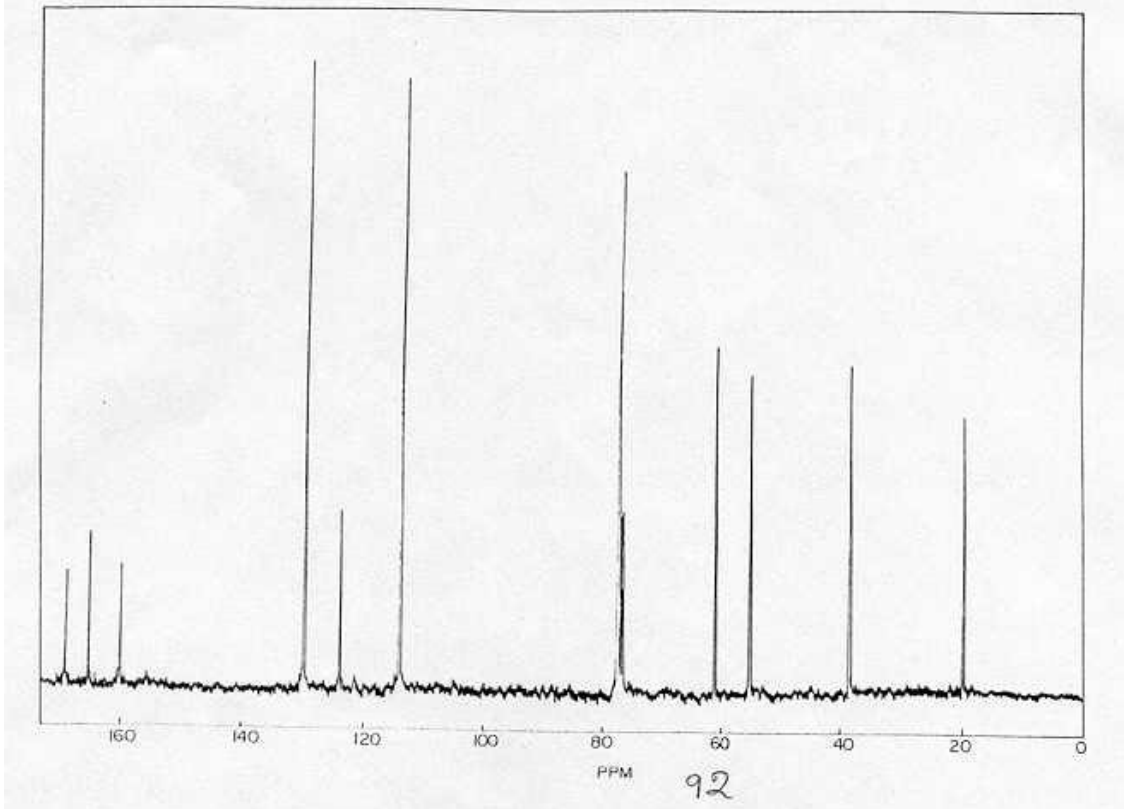
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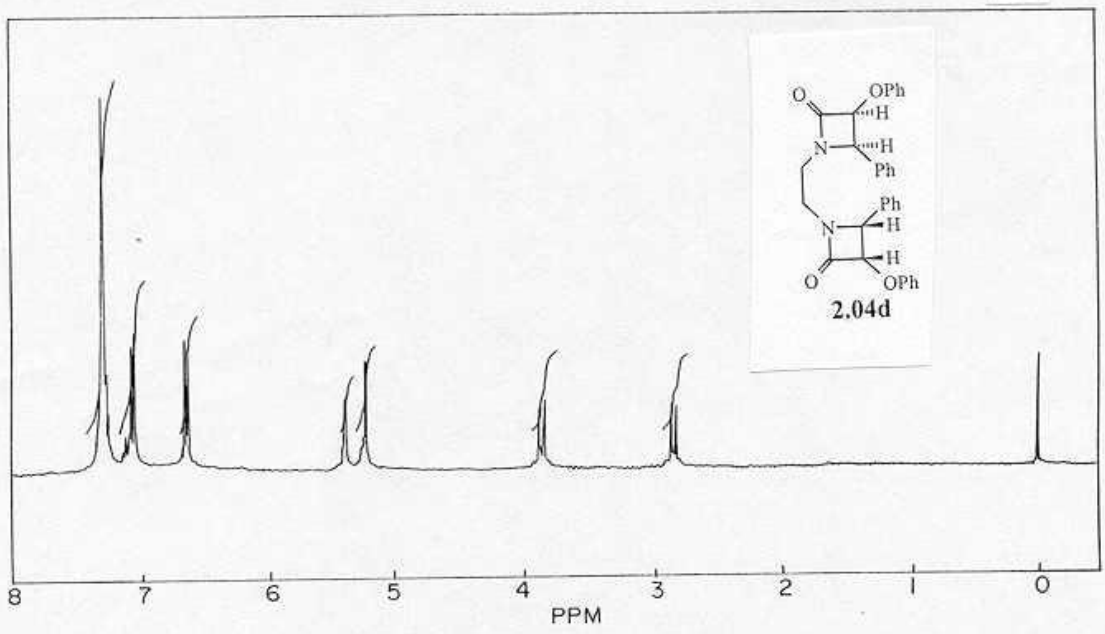
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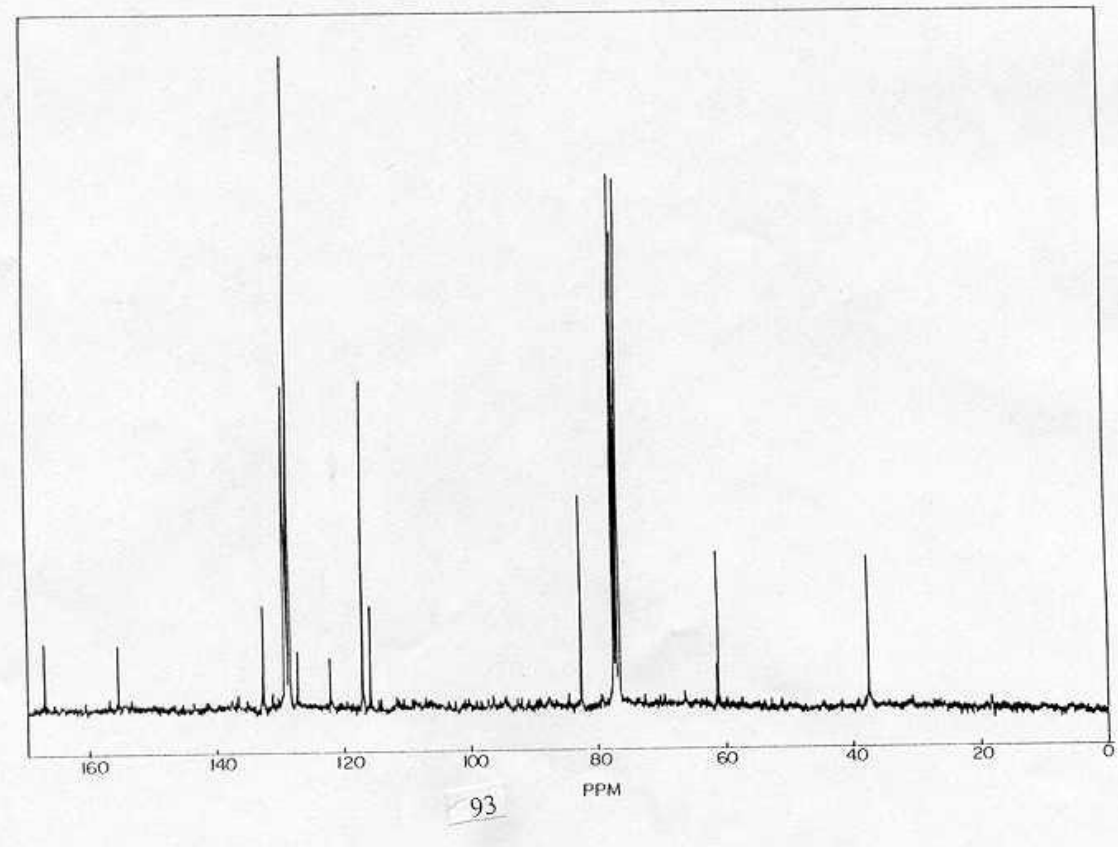
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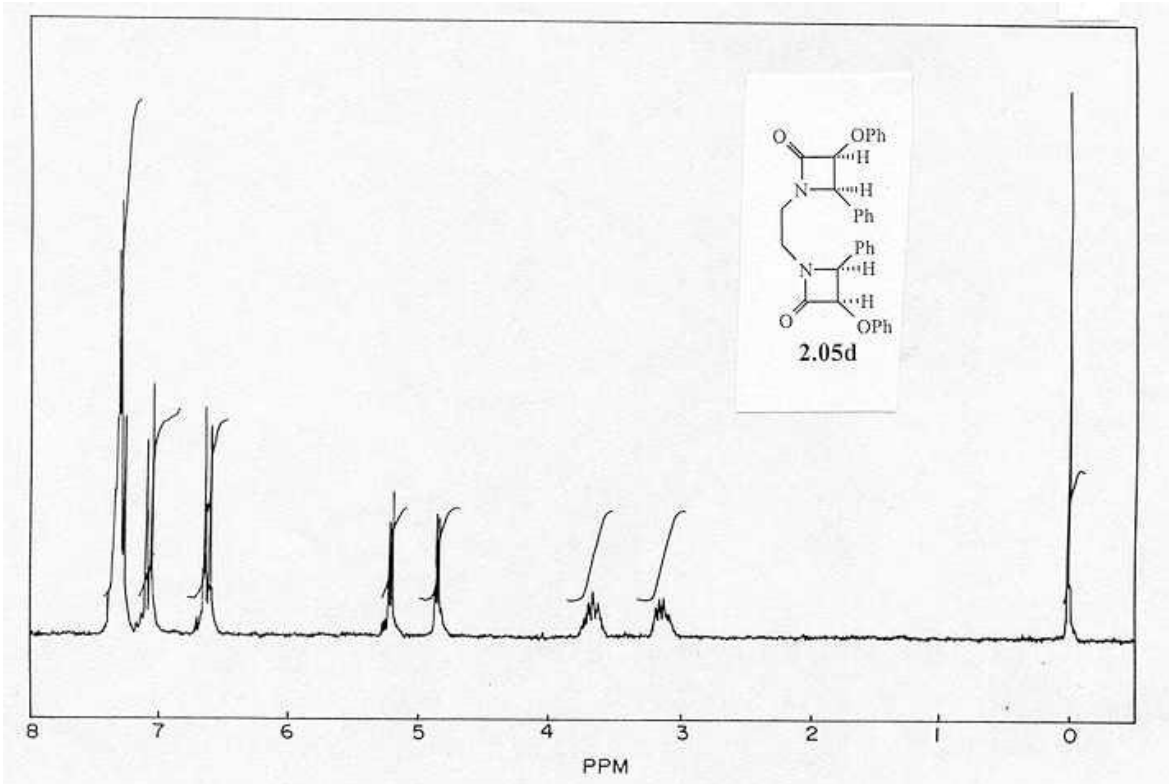
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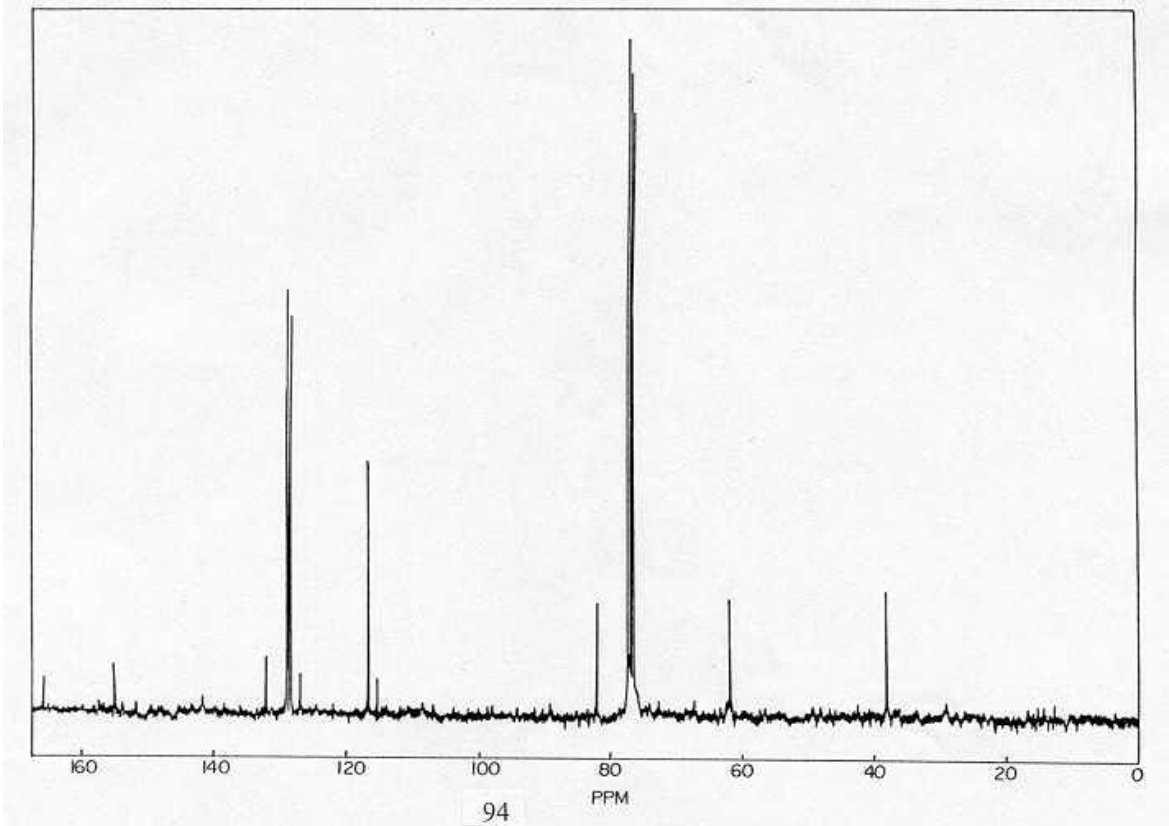
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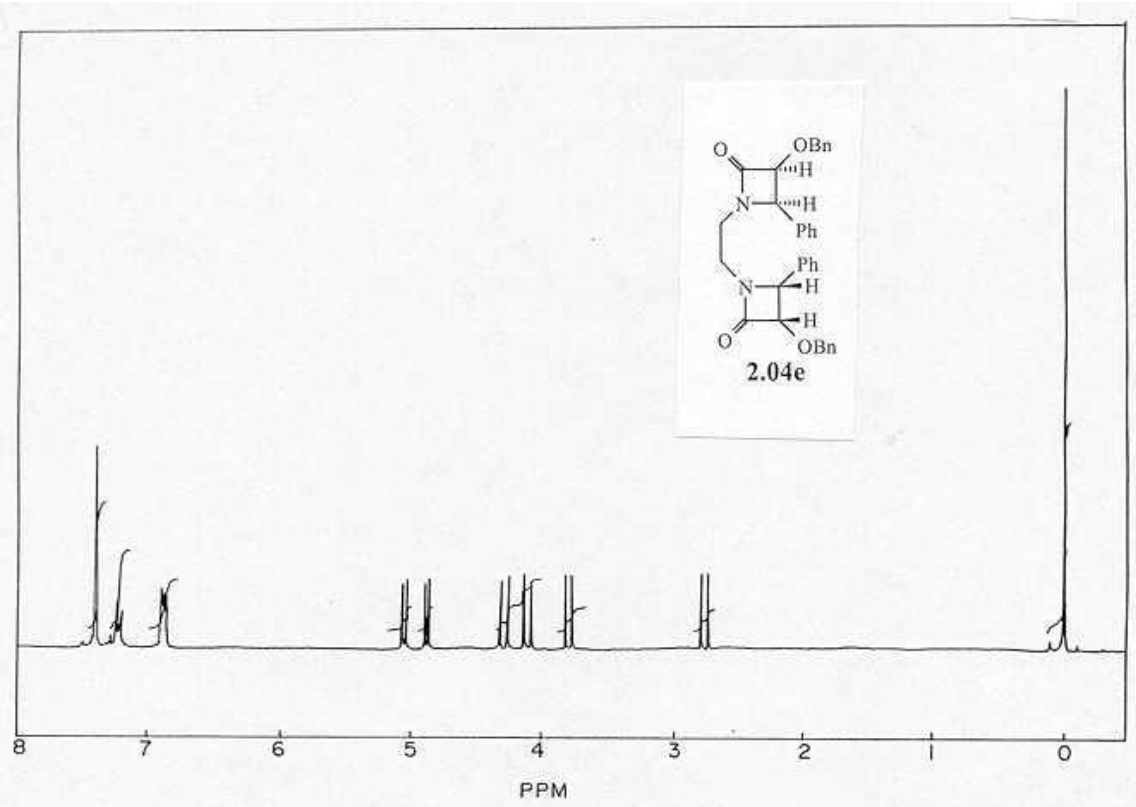
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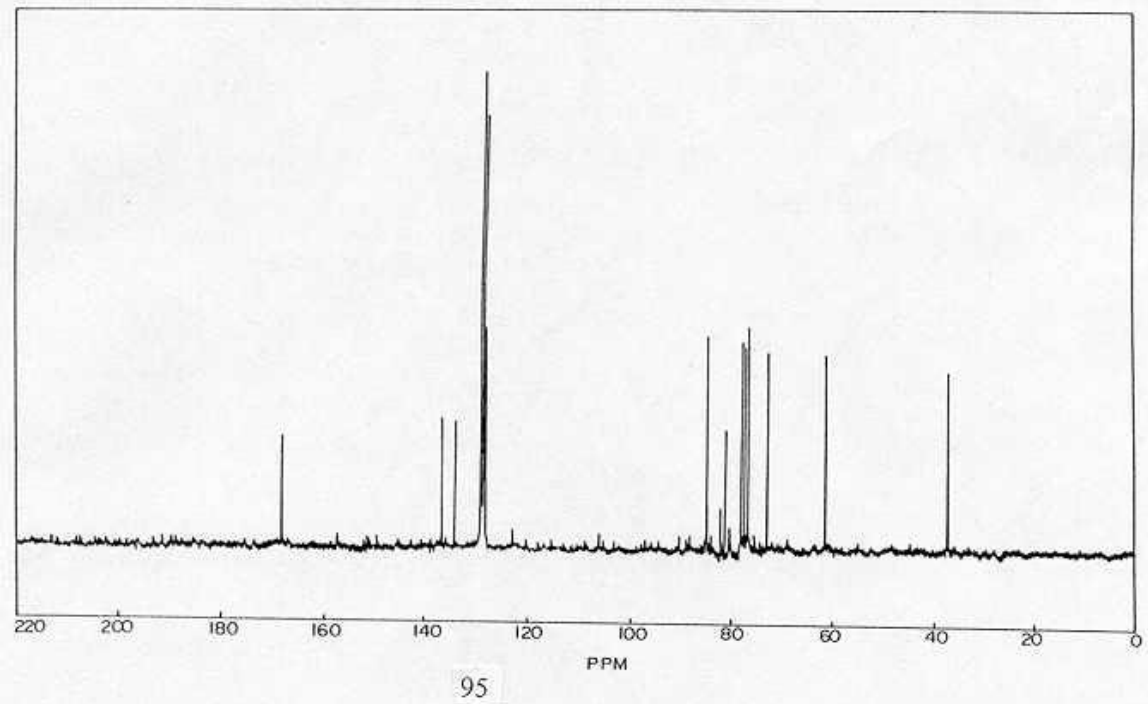
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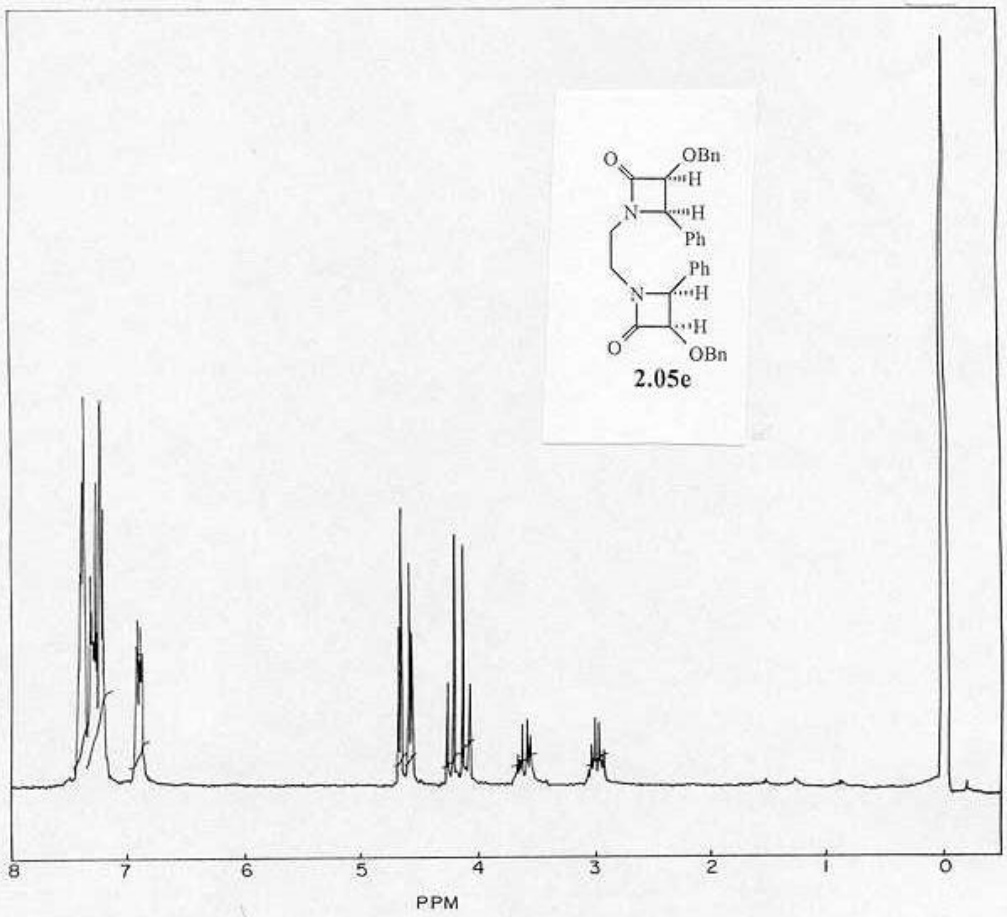
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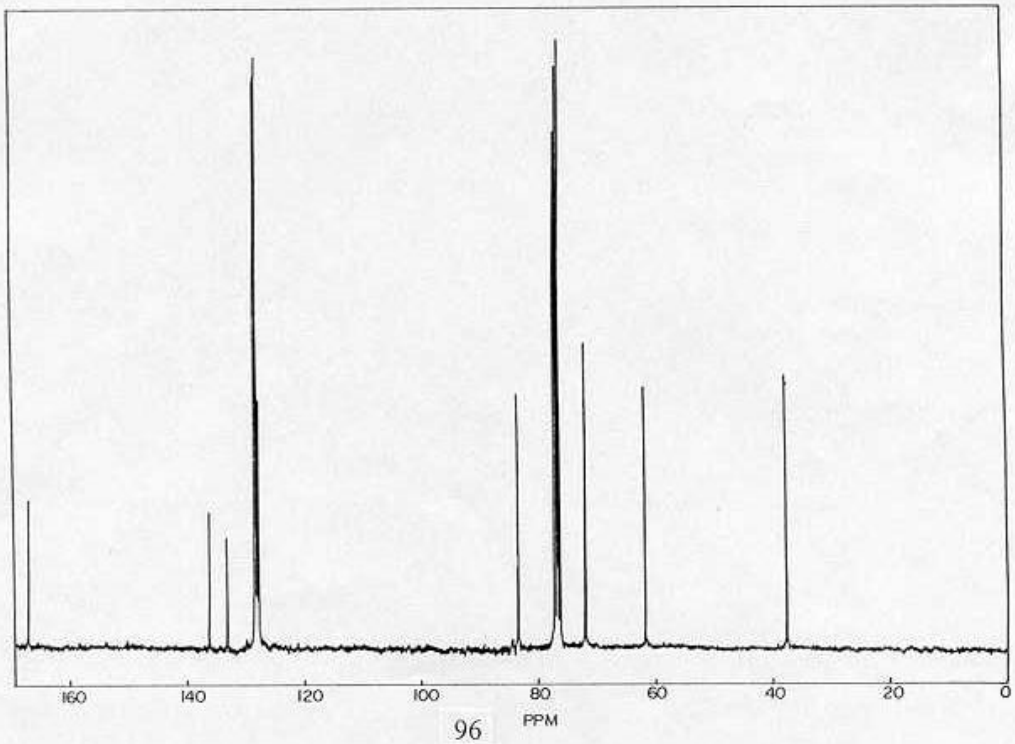
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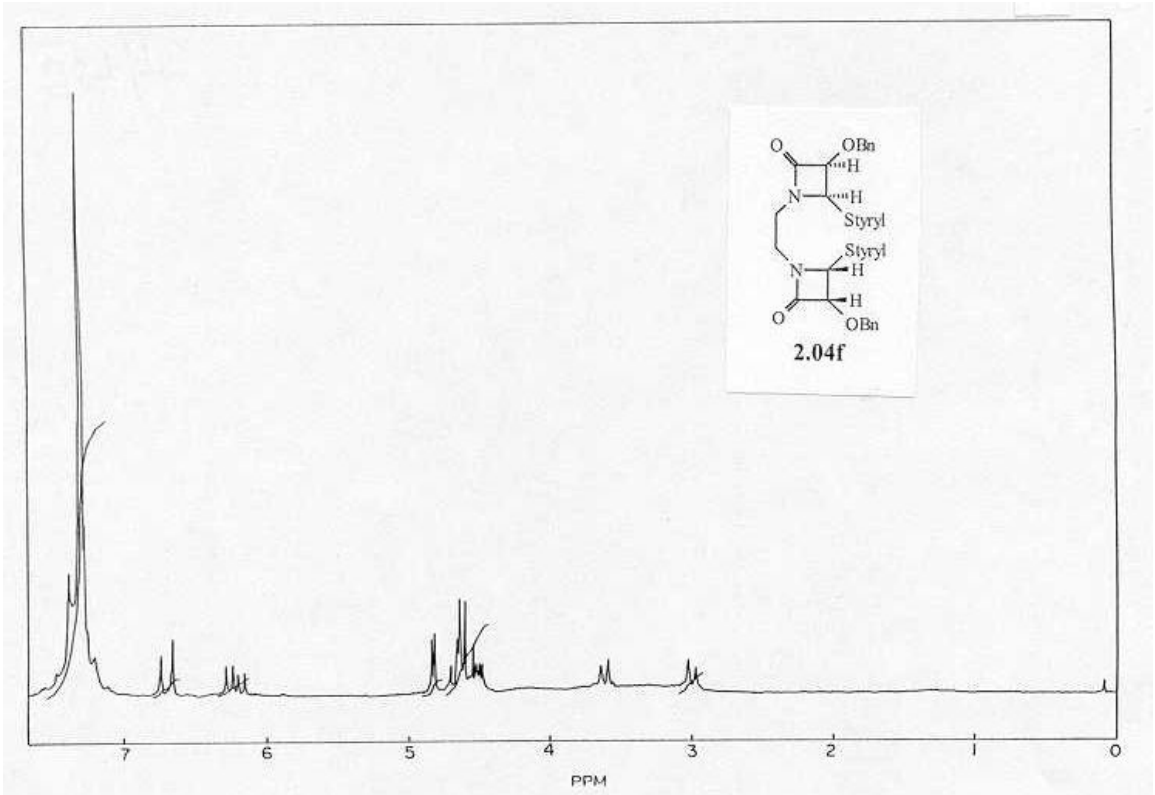
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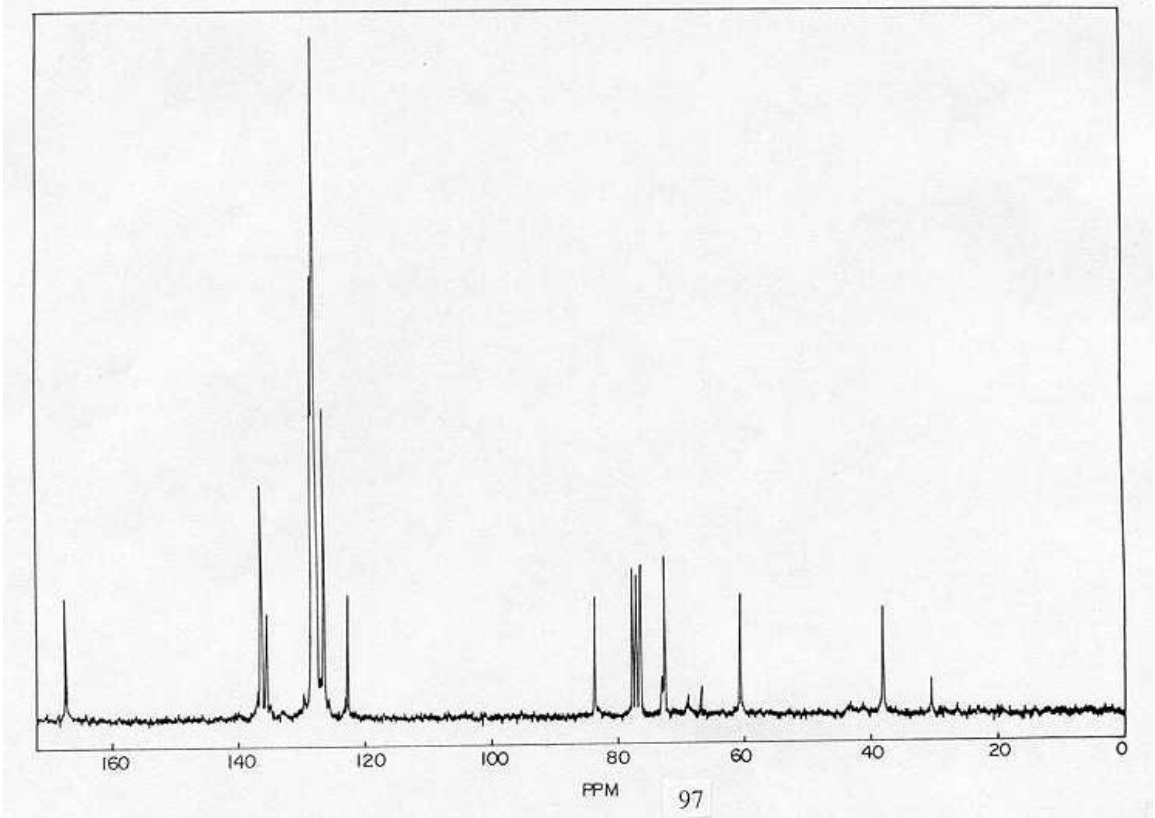
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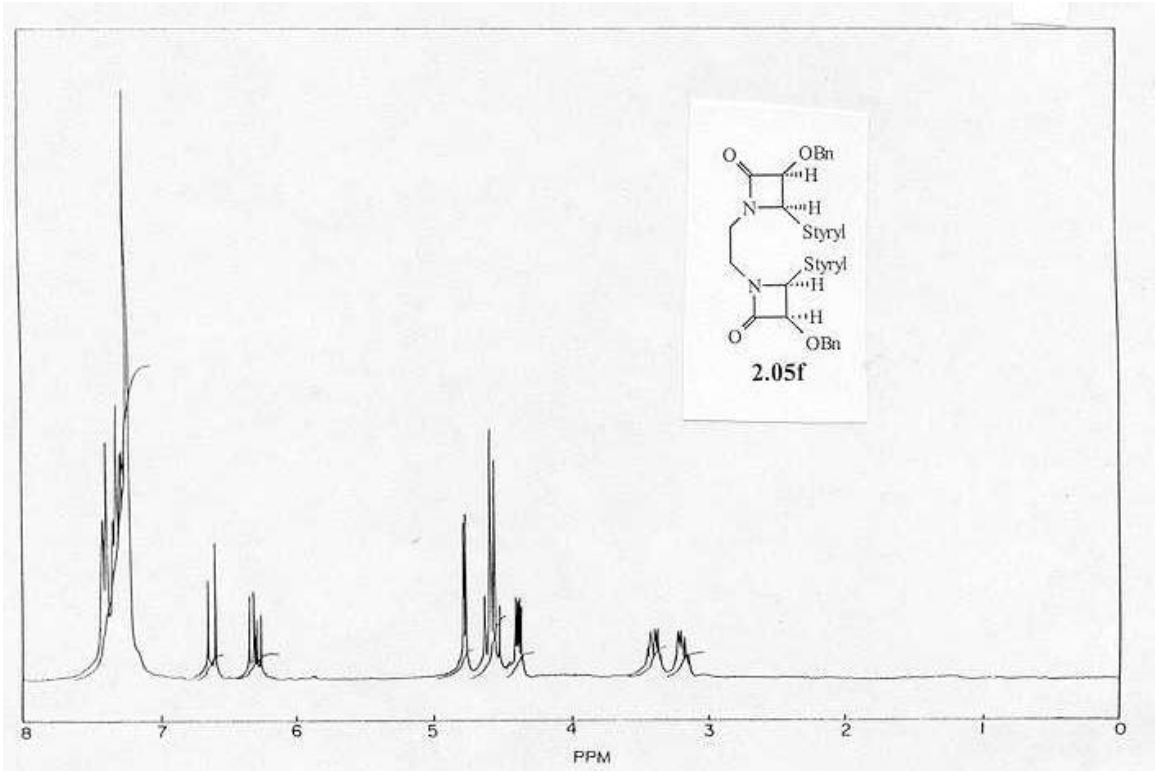
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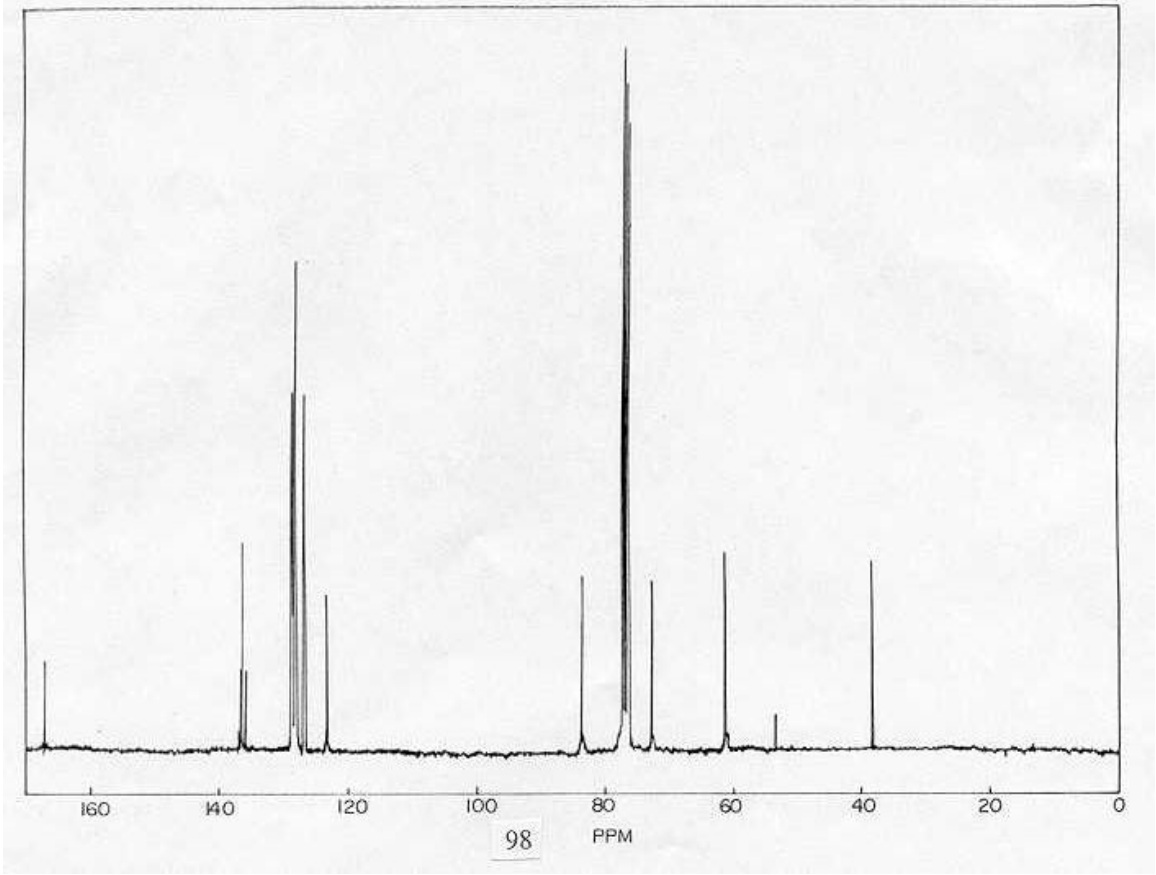
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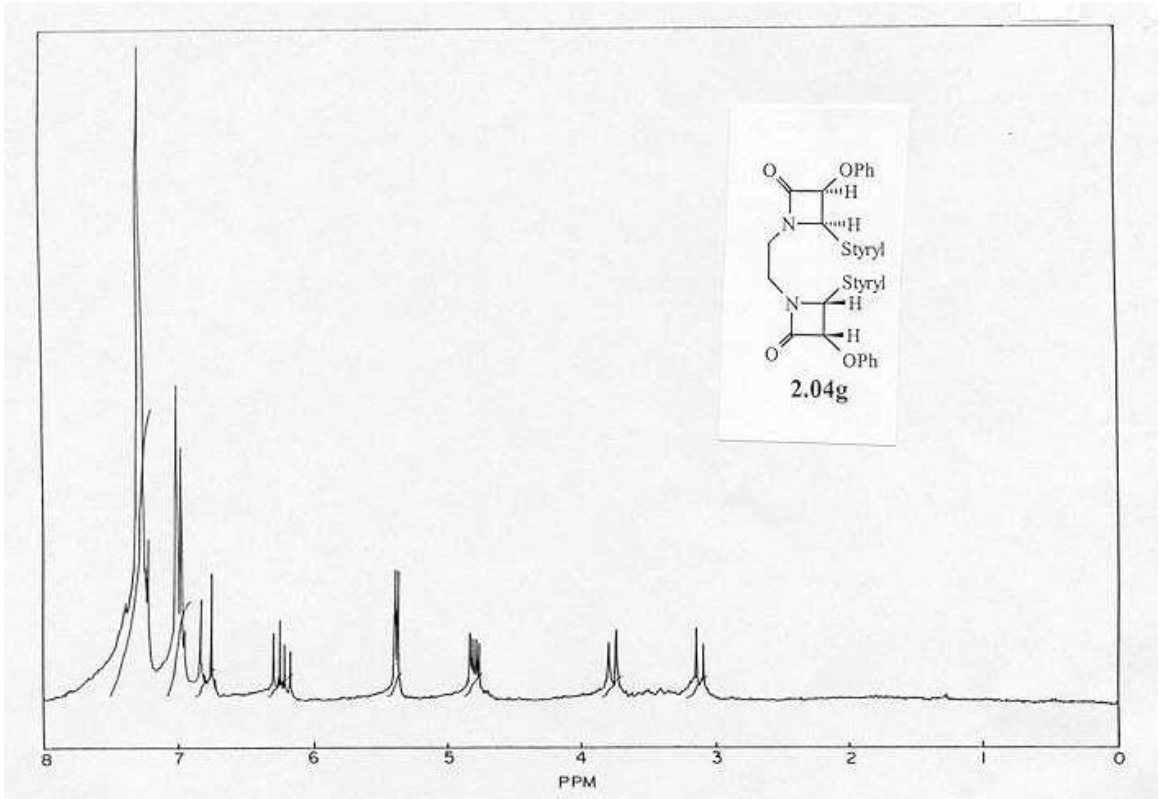
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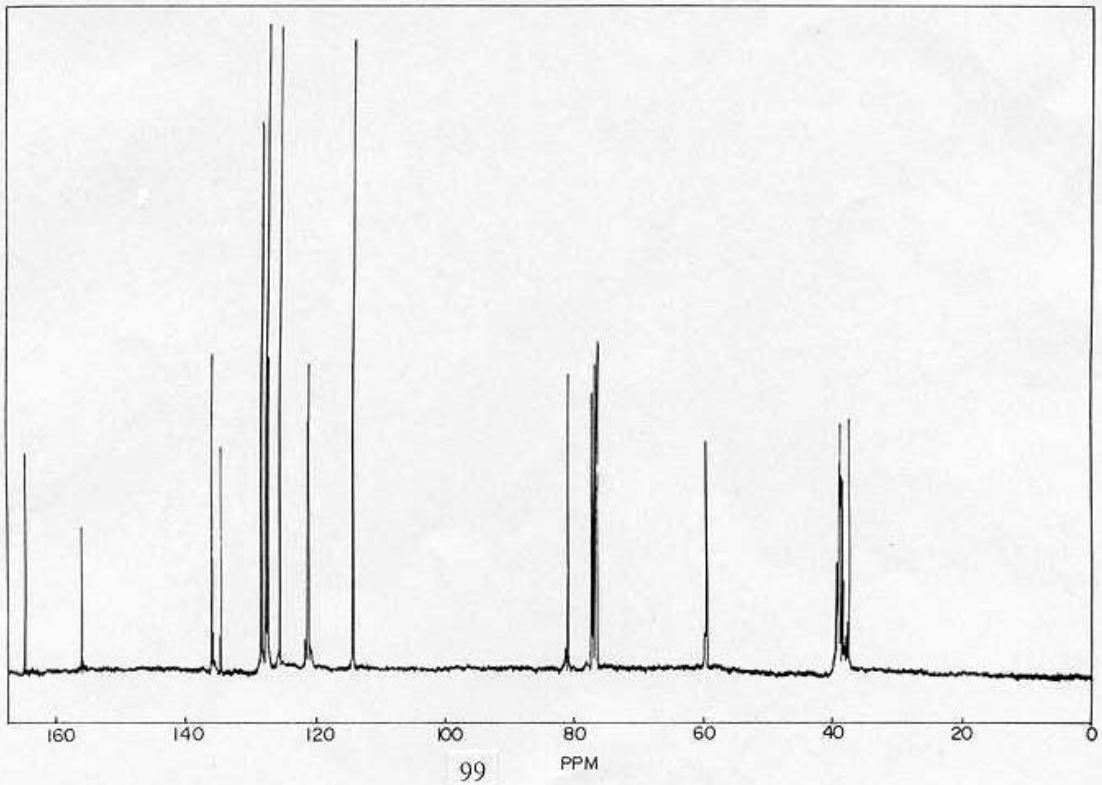
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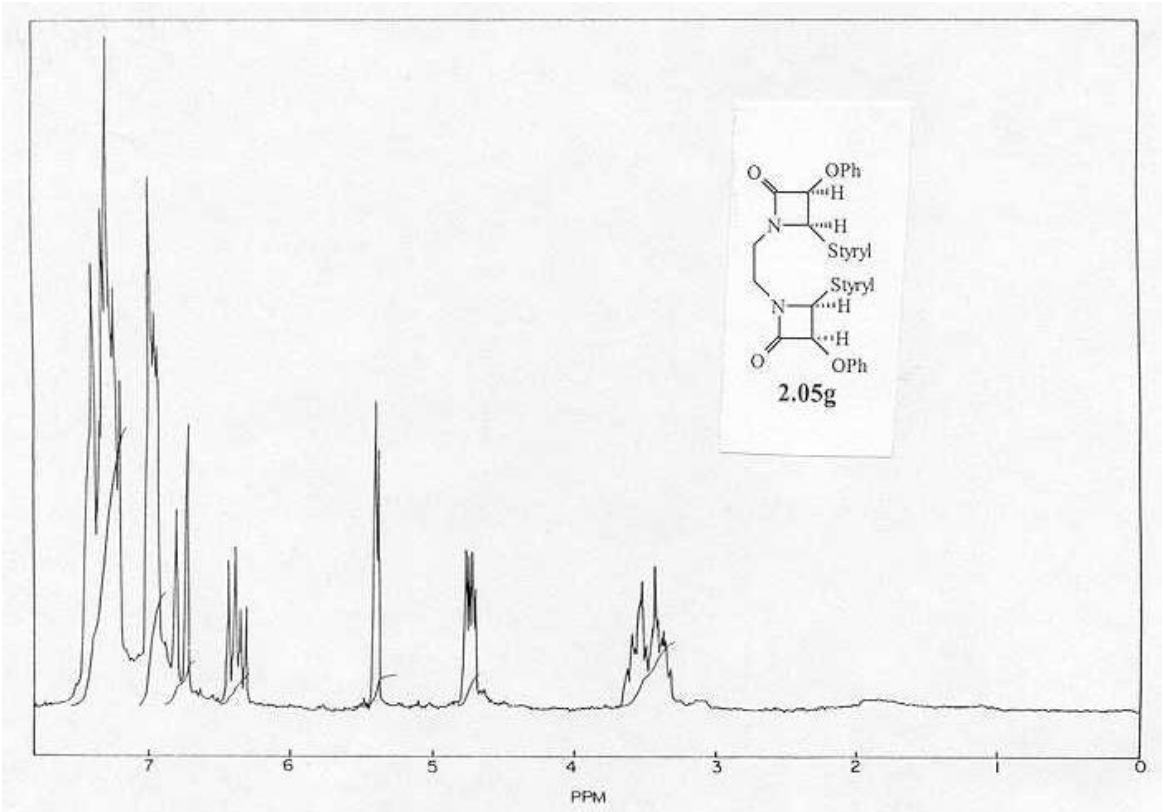
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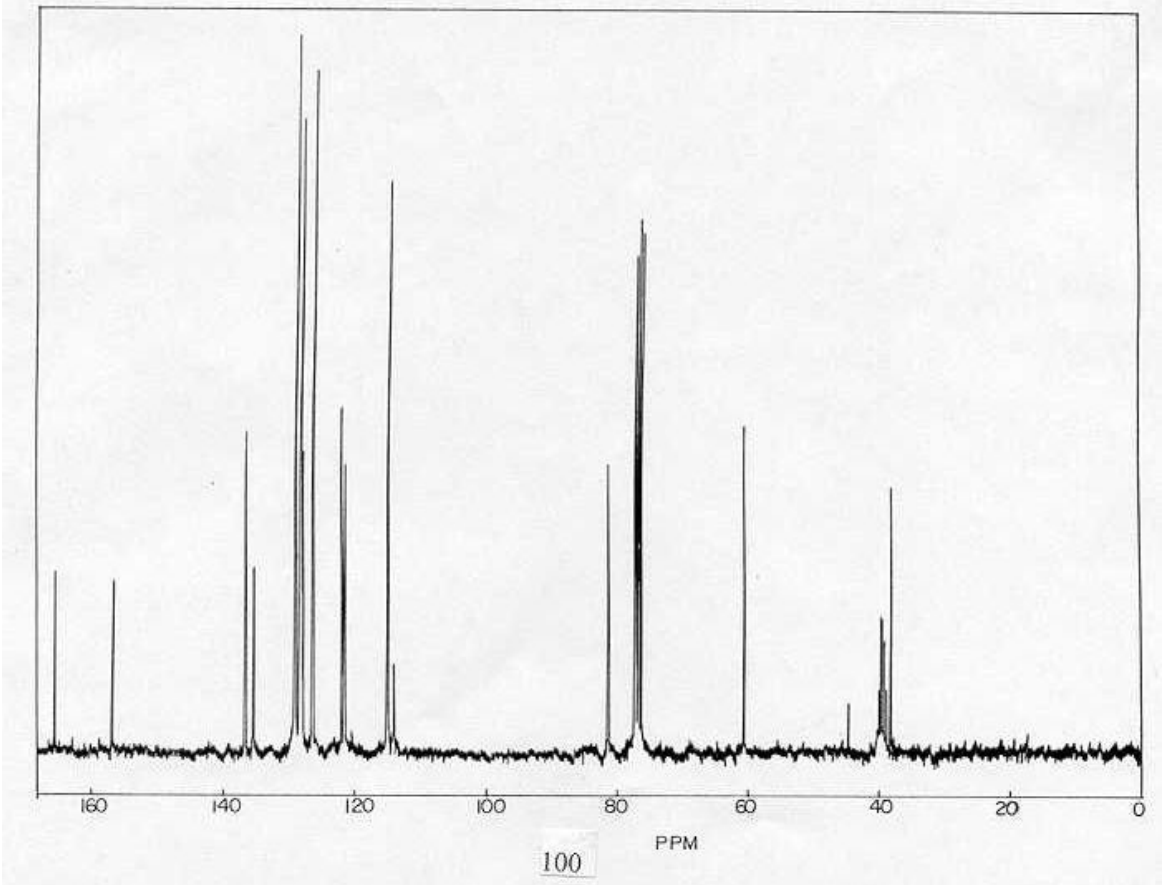
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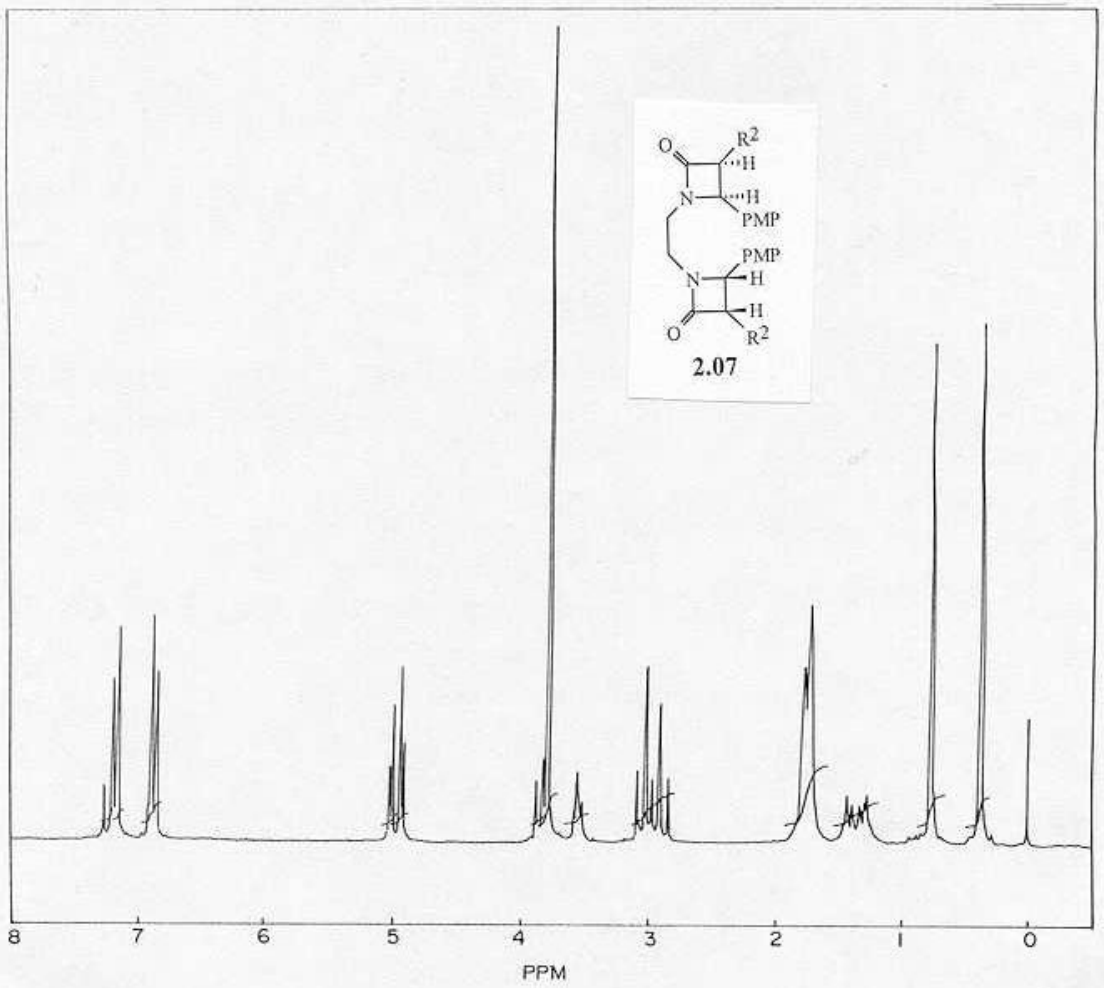
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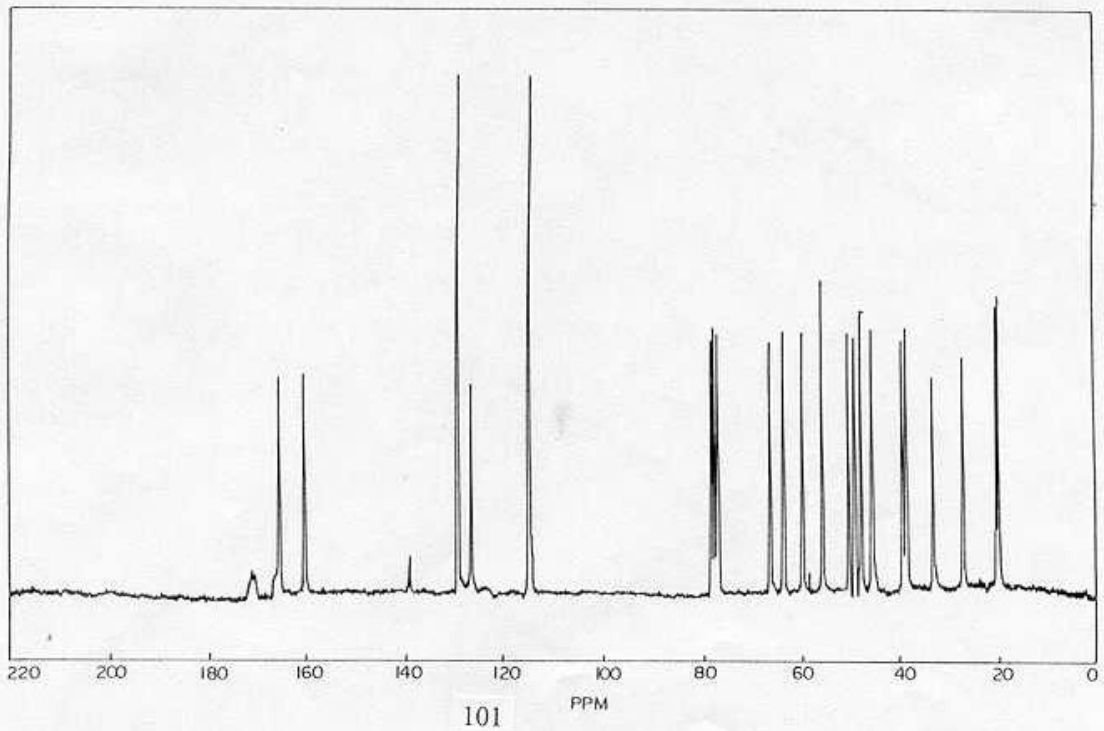
2.07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Chapter III

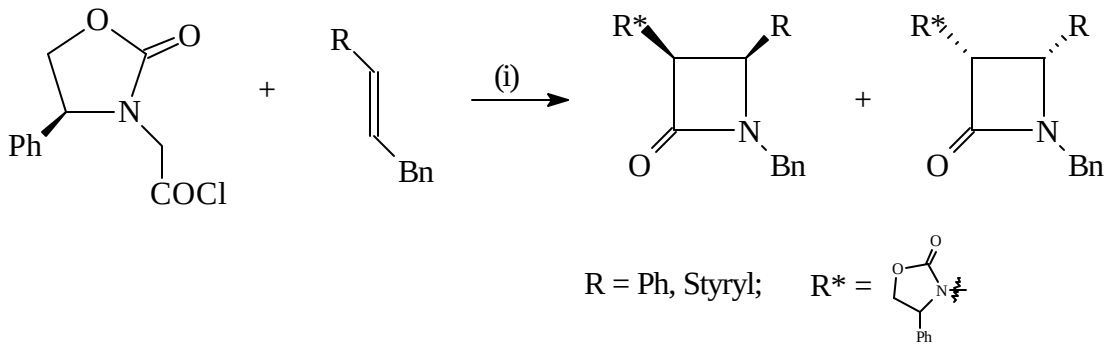
Synthesis of chiral acid from camphor-10-sulfonic acid and its attempted application for the synthesis of b-lactam

3.1 Introduction

Of the various methodologies reported for the synthesis of β-lactams, ketene-imine cycloaddition reaction (Staudinger reaction) is the widely used method due its simplicity and predictability of stereochemical outcome. It has also been reported that various levels of diastereoselectivity in β-lactams ring construction could be achieved by using chiral ketene precursors. Following is a brief review of the asymmetric synthesis of β-lactams *via* the Staudinger reaction using chiral ketenes.

Evans and Sjogren have reported used of chiral oxazolidine derived from (S)-phenylglycine as a ketene component for cycloaddition reaction[1] and shown excellent asymmetric induction (97:3) in the *cis*-β-lactam ring formation (Scheme 3.01) with 90% yield.

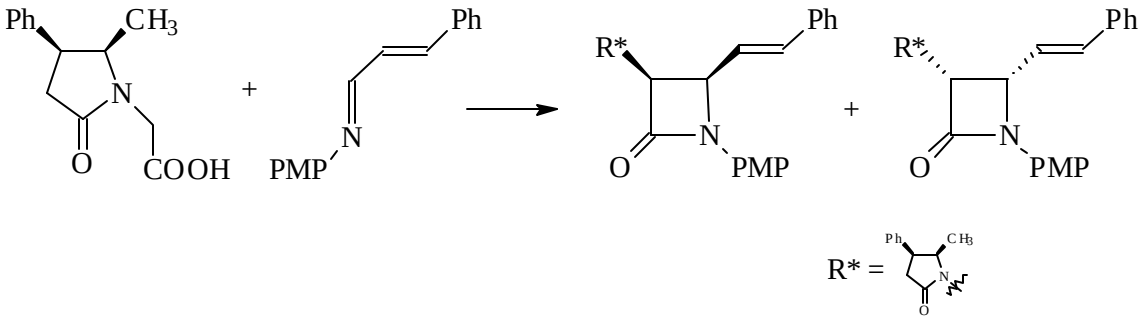
Scheme 3.01



Reagents and conditions (i): Et_3N/DCM: Toluene, −78 °C, 2h.

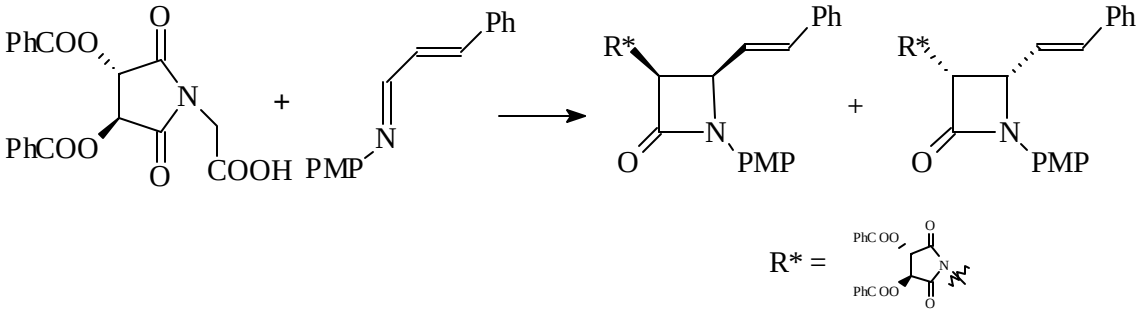
A chiral ketene component derived from nor-ephedrine has been reported to give very high selectivity (>95%) in *cis*-β-lactam ring formation *via* ketene-imine cycloaddition[2] (Staudinger reaction) reaction (Scheme 3.02).

Scheme 3.02



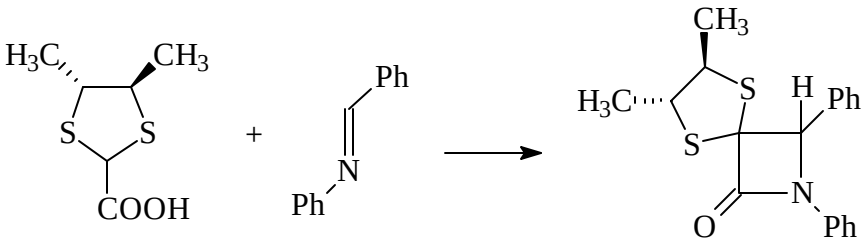
The tartarimidoacetic acid derived from S, S-tartaric acid has been used as a chiral ketene precursor for diastereoselective synthesis[2] of β-lactams (Scheme 3.03). Though this chiral auxiliary has γ-chiral center with respect to newly forming chiral center of β-lactam ring, the diastereoselectivity obtained in this reaction is quite high (86:14).

Scheme 3.03



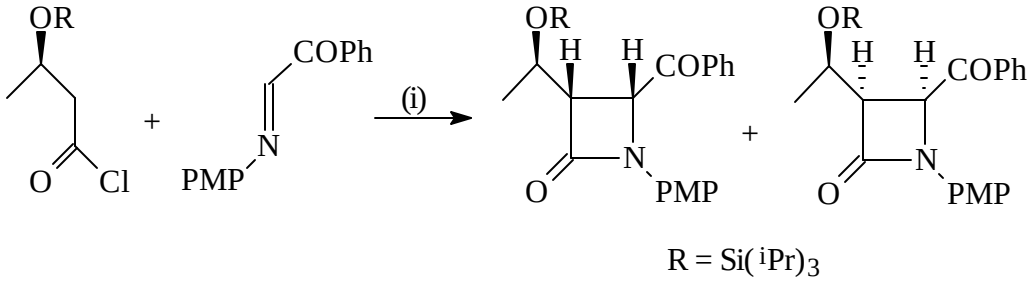
The use of chiral ketene derived from 1,3-dithioline-2-carboxylic acid in cycloaddition reaction to form spiro β-lactam has been reported to give poor diastereoselectivity[3] (de 20%) (Scheme 3.04).

Scheme 3.04



An acid chloride derived from O-protected 3-hydroxybutyric acid was used in cycloaddition reaction,[4] to give β-lactams in 66% yield with 1:4 diastereoselectivity (Scheme 3.05).

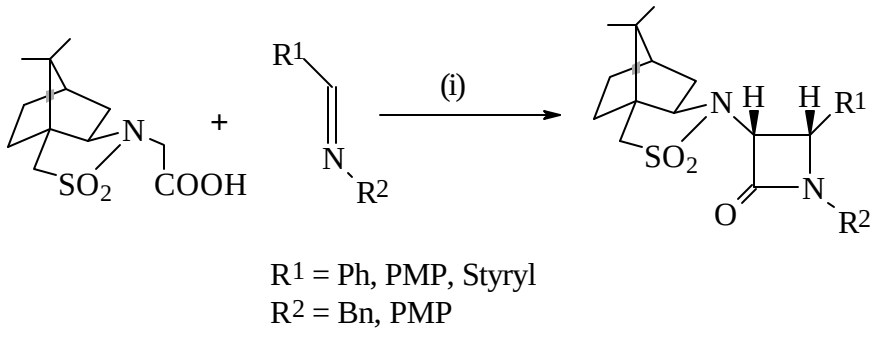
Scheme 3.05



Reagents and conditions (i): DIEA/DCM, –20 °C, 16 h.

The sterically hindered chiral acid derived from Oppolzer's sultam on [2+2] cycloaddition[5] (Staudinger reaction) reaction with various imines has been reported to give diastereospecifically only one isomer with yields ranging from 60-91% (Scheme 3.06).

Scheme 3.06



Reagents and conditions (i): Et_3N/DCM, –23 °C, 15 h.

3.2 Present Work

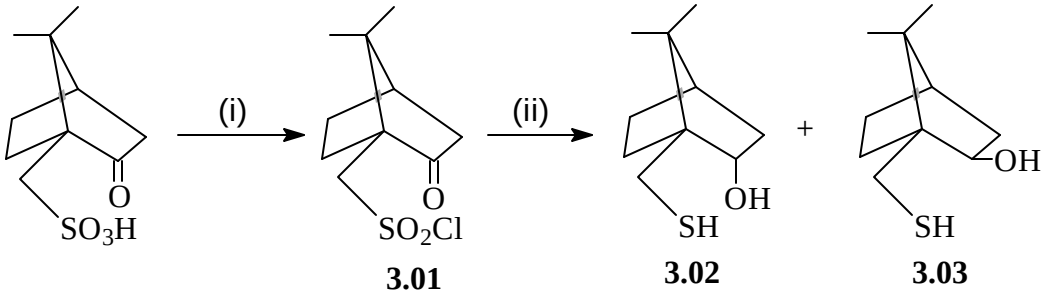
The camphor-10-sulphonic acid derived chiral auxiliaries have been used successfully for very high chiral induction in the product. We, therefore, thought that a chiral acid derived from camphor-10-sulphonic acid would provide necessary steric bulk for ketene-imine cycloaddition reaction. The designed synthesis of this chiral acid **3.08** has been discussed in the following results and discussion section.

3.3 Results and Discussions

3.3.1 Preparation of camphor thiols 3.02 and 3.03

The camphor-10-sulfonyl chloride (**3.01**)[6] prepared from camphor-10-sulphonic acid on reduction[7a, 7b] with LAH gave a endo/exo mixture of the thio alcohols **3.02** and **3.03** in good yield. The pure exo-thiol (**3.03**) was obtained by crystallization.

Scheme 3.07

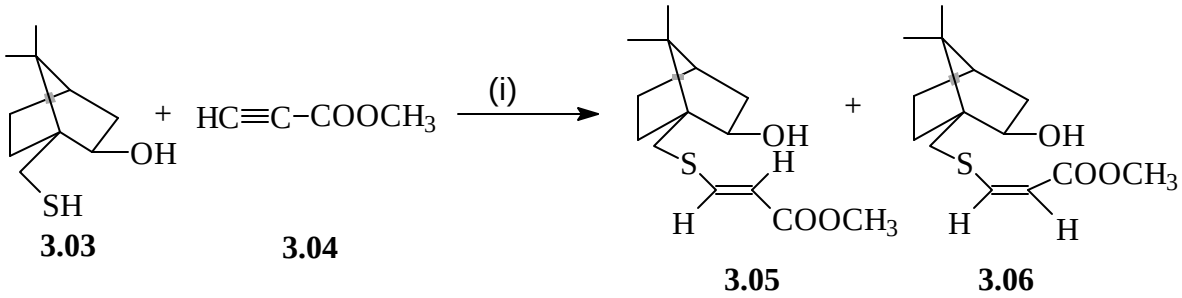


Reagents and reaction conditions: (i) $SOCl_2$/ref.4h; (ii) LAH/ EtOEt, −78°C, overnight ref.

3.3.2 Preparation of E/Z adducts 3.05 and 3.06

The exo-thiol **3.03** on treatment[6] with methyl propiolate (**3.03**)[8a,8b] in presence of few drops of triethylamine gave a mixture of E/Z adducts **3.05** and **3.06** in 82% yield. These E/Z isomers were separated by fractional crystallization from ethanol-water.

Scheme 3.08



Reagents and reaction conditions: (i) Et_3N/ EtOH-H_2O, 0 °C, 3 h.

Spectral characterization of E-isomer (3.05)

The ^{1}H NMR spectrum of E-isomer (**3.05**) showed two-gem dimethyl groups of camphor part separately as two sharp singlets at δ 0.86 and 1.04. A multiplet at δ 0.95-1.85 was assigned to seven protons of camphor moiety. The methylene protons attached to S were appeared as a set of doublets at δ 2.80, 3.20 with geminal coupling constant of 13.5 Hz. A multiplet at δ 3.58-3.70 was assigned to CH proton attached to free OH group of camphor moiety. The two CH protons of S-CH=CH-CO_2Me were appeared together as multiplet at δ 3.90-4.04.

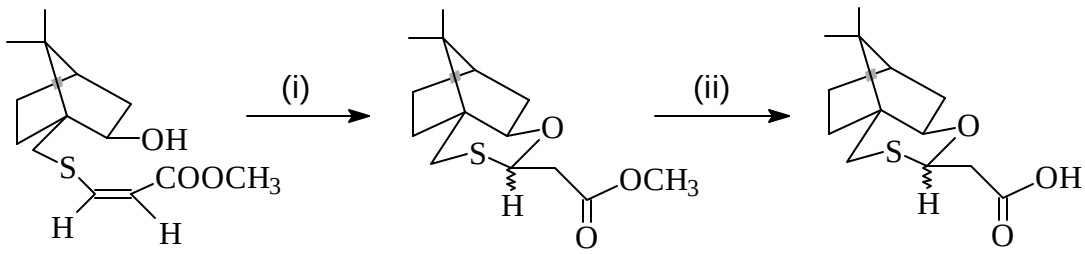
Spectral discussion and characterization of Z-isomer (3.06)

The ^{1}H NMR spectrum of Z-isomer (**3.06**) showed two-gem dimethyl groups of camphor part separately as two sharp singlets at δ 0.87 and 1.00. A multiplet at δ 0.95-1.83 was assigned to seven of camphor protons. The alcoholic proton has appeared as a broad singlet at δ 1.99. Two doublets appearing at δ 2.77 and 3.20 with the coupling constant of 11.7 Hz were assigned to two methylene protons attached to sulphor (CH_2-S). The methyl proton of methoxy group has resonated at δ 3.74 as a sharp singlet. The CH-proton attached to OH has appeared as a triplet at δ 3.95 with the coupling constant of 4.9 Hz. A set of doublets appearing at δ 5.85 (S-CH=), δ 7.24 (=CH-COOMe) with the coupling constant of 9.75 Hz were assigned to the vicinal protons of double bond. The IR spectrum showed ester-carbonyl stretching at 1675 cm^{-1} and O-H stretching at 3440 cm^{-1}.

3.3.3 Preparation of ester 3.07 and acid 3.08

The Z-isomer (**3.06**) on acid catalyzed cyclization in the presence of PTSA gave ester (**3.07**) in very good yield. The ester **3.07** on alkaline hydrolysis using MeOH/KOH yielded corresponding acid (**3.08**) in good yield (Scheme 3.08).

Scheme 3.09



3.06 **3.07** **3.08**

Reagents and reaction conditions: (i) PTSA/r.t.3h; (ii) MeOH/KOH, r.t. Overnight.

Spectral discussion and characterization of ester (3.07)

The ^{1}H NMR spectrum of ester **3.07** showed a set of sharp singlets at δ 0.90 and 1.29 for two *gem* dimethyl groups of camphor part. Two multiplets appeared between δ 0.79-1.95 and δ 2.55-2.96 were assigned to seven protons camphor unit and two methylene protons adjacent to carboxylic group. A doublet resonated at δ 3.14 with the coupling constant of 13.5 Hz was assigned to one of the methylene protons attached to sulphor (CH_2-S). A multiplet appearing between δ 3.60-3.87 was assigned to CH proton attached to oxygen of camphor moiety. The methyl protons of methoxy group appeared as a sharp singlet at δ 3.80. A dd (doublet of doublet) appeared at δ 5.10 with the coupling constant of 8.1 and 4.3 Hz was assigned to methyne proton on a carbon flanked by O, S and CH_2. The IR spectrum of this ester **3.07** showed carbonyl stretching at 1700 cm^{-1}.

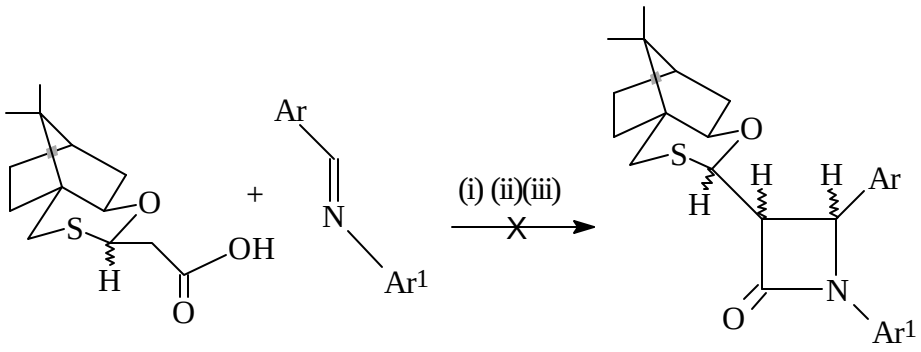
Spectral discussion and characterization of acid (3.08)

The ^{1}H NMR spectrum of acid **3.08** showed two sharp singlets at δ 0.90 and 1.30 for *gem*-dimethyl of camphor part. A multiplet appeared at δ 0.80-1.98 was assigned to eight protons of camphor unit. Both the protons of methylene attached to carboxylic group were appeared together as a multiplet at δ 2.62-2.98. The CH proton of camphor ring carbon attached to oxygen was seen as a triplet at δ 2.73 with the coupling constant of 8.1 Hz. The methylene protons attached to sulphor (CH_2-S) appeared as a doublet at δ 3.16 with the coupling constant of 13.5 Hz. A doublet of doublet appeared at δ 3.67 with the coupling constant of 13.5 & 4.0 Hz was assigned to the methyne (CH) proton of camphor moiety bearing oxygen atom. A doublet of doublet appeared at δ 5.08 with the coupling constant of 8.6 & 5.4 Hz was assigned to the CH of methyne group attached to S, O & CH_2. The IR spectrum showed carbonyl stretching at 1680 cm^{-1} and O-H stretching at 2900 cm^{-1}.

3.3.4 Attempted synthesis of β-lactam 3.10

The acid **3.08** on treatment with different imines in the presence of an acid activator (Phenyl dichlorophosphate) and triethylamine failed to give corresponding β-lactams. Alternatively, the acid chloride generated from acid (**3.08**) by the treatment of oxalyl chloride [$(COCl)_2$] in dry DCM or $SOCl_2$/benzene when reacted with imine in presence of triethylamine did not give expected β-lactam.

Scheme 3.10



3.08 **3.09** **3.10**

	Ar	**Ar 1**
a	Ph	PMP
b	Ph	Styryl

Reagents and reaction conditions (i): $Ph(PO)Cl_2/Et_3N$, DCM, 0 °C/Toluene-ref. or (ii): $SOCl_2/Et_3N$, or (iii) $(COCl)_2/Et_3N$.

3.4 Summary

A novel chiral acid had been successfully synthesized from camphor-10-sulfonic acid. However, it failed to under go cycloaddition reaction with imines under normal Staudinger reaction conditions.

3.5 Experimental

3.5.1 Preparation of Sulfonyl chloride 3.01

The camphor-10-sulfonic acid (10g, 0.045 mol) was refluxed with thionyl chloride (50 ml) until the HCl gas ceases (5 h). Then the excess thionyl chloride was distilled off under reduced pressure. The residue obtained was crystallized from ethyl acetate to give 9.82 g (85%) of pure camphor-10-sulfonyl chloride (**3.01**), m.p. 81-83 °C [Lit[6]. 83-84 °C].

3.5.2 Preparation of thio alcohols 3.02 and 3.03

To a mixture of LAH (4.08g, 108 mmol) and ether (100 ml), a solution of (1S)-d-10-camphorsufonyl chloride (**3.01**) (13.46g, 54 mmol) in ether (100 ml) was added at –78 °C under nitrogen in small portions. The mixture was first stirred at room temperature and then at reflux overnight. The reaction mixture was cooled to room temperature and excess LAH was cautiously quenched with ethyl acetate and finally with dilute hydrochloric acid (ca. 1-2%). The resulting reaction mixture was filtered through a celite pad and washed thoroughly with ether. The filtrate was then washed with brine and dried over anhydrous sodium sulfate. It was filtered and filtrate on evaporation of solvent gave strongly smelling oily residue, which was purified by flash column chromatographed under medium pressure eluting with pet. ether-ethyl acetate, 98:2 to give 8.2 g (82%, total yield) of thio alcohols **3.03** & **3.04**. The first eluted less polar product was found to be (1S)-d-10-mercaptoisoborneol (**3.03**).

M.p. : 75 °C [Lit. [7a, 7b] 70/76-78 °C].

^{1}HNMR : δ 0.83 (s, 3H); 1.00 (s, 3H); 2.13 (bs, 1H); 2.56 (dd, *J*= 10.25 & 5.13 Hz, 1H); 2.80 (dd, *J*= 12.82 & 7.69 Hz, 1H); 3.99 (t, *J*= 5.13 Hz, 1H).

IR : 3400 cm^{-1}.

$[\alpha]_D$: –56.31 (c, 1 $CHCl_3$). [Lit. [7a, 7b] –57.44/-55.4 (c, 10 $CHCl_3$)].

The second eluted more polar product was found to be (1S)-d-10-mercaptoborneol (**3.02**)

M.p. : 68 °C [Lit. [7a, 7b] 66/70 °C].

^{1}H NMR : δ 0.81(s, 3H); 0.86 (s, 3H); 0.92-3.22 (m, 8H); 3.92 (dd, *J*= 10.81 & 5.4 Hz, 1H); 4.33 (dd, *J*= 13.51 & 2.7 Hz, 1H);

IR : 3410 cm^{-1}.

$[\alpha]_D$: –11.5 (c, 1 $CHCl_3$). [Lit. [7a, 7b] –11.76 (c, 10 $CHCl_3$).

3.5.3 Preparation of (1S)-d-10-mercaptoisoborneol Adducts to Methyl Propiolate (3.05 & 3.06)

To a stirred solution of (1S)-d-10-mercaptoisoborneol (**3.03**) (4.0g; 21.5 mmol) and methyl propiolate (1.8 g, 21.4 mmol) in ca. 50 ml of a 9:1 mixture ethanol-water was cooled to 0 °C, a few drops of triethylamine was added. The reaction was allowed to warm-up to room temperature. White precipitates of the *cis* adduct **3.06** formed after 3 h was filtered and the filtrate extracted with DCM, dried over anhydrous sodium sulfate. It was filtered and filtrate was concentrated to ca. 4-5 ml. The concentrated solution on addition of petroleum ether gave white crystals, which were filtered. The two crops of crystalline materials were combined and recrystallized from pet. ether-dichloromethane to give 4.17 g (72%) of pure ester **3.06**.

M.p. : 121 °C [Lit.[7a] 121 °C].

^{1}H NMR : δ 0.87 (s, 3H); 1.00 (s, 3H); 0.95-1.83 (m, 7H); 1.99 (bs, 1H); 2.77 (d, *J*= 11.70 Hz, 1H); 3.20 (d, *J*= 11.70 Hz, 1H); 3.74 (s, 3H); 3.95 (t, *J*= 4.87 Hz, 1H); 5.85 (d, *J*= 9.75 Hz, 1H); 7.24 (d, *J*= 9.75 Hz, 1H).

^{13}C NMR : 167.32, 152.08, 112.27, 76.38, 52.78, 51.34, 47.95, 45.61, 40.49, 36.25, 30.97, 27.15, 20.80, 20.27.

IR : 3440, 1675, 1560, 1430 cm^{-1}.

MS (m/z) : 270(M^+), 252, 152, 118(100%).

$[\alpha]_D$: –9.50 (c, 1 $CHCl_3$) [Lit.[7a] –9.43 (c, 0.3 $CHCl_3$).

The mother liquor from above was evaporated to dryness and the residue was purified by column chromatography eluting with pet. ether-ethyl acetate (98:2) to afford 1.04 g (18%) of ester **3.05** as a colorless oil.

^{1}H NMR : δ 0.86 (s, 3H); 1.04 (s, 3H); 0.95-1.85 (m, 7H); 2.80 (d, *J* = 13.5 Hz, 1H); 3.20 (d, *J* = 13.5 Hz, 1H); 3.58-3.70 (m, 1H); 3.90-4.04 (m, 2H).

3.5.4 Preparation of ester 3.07

Solutions of adduct **3.06** (Z-isomer, 1 g, 3.7 mmol) and a pinch of PTSA in DCM (30 ml) was stirred at room temperature for 3 h. The reaction mixture was filtered through a bed of silica gel and the solvent was rotaevaporated to give 0.95g (95%) of pure ester **3.07**.

M.p. : Oil.

^{1}H NMR : δ 0.90 (s, 3H); 1.29 (s, 3H); 0.79-1.95 and 2.55-2.96 (m, 9H); 3.14 (d, *J*= 13.5 Hz, 2H); 3.60-3.87 (m, 1H); 3.80 (s, 3H); 5.10 (dd, *J* = 8.1 & 4.3 Hz, 1H).

^{13}C NMR : 170.49, 85.55, 77.88, 51.95, 46.79, 45.68, 42.00, 40.93, 37.88, 34.46, 28.86, 27.41, 23.37, 20.56.

IR : 1700, 1560 cm^{-1}.

MS (m/z) : 270(M^{+}), 153, 135, 93(100%).

$[\alpha]_D$: −122.80 (c, 1 $CHCl_3$).

Elemental analysis

Molecular Formula : $C_{14}H_{22}O_3S$.

Calculated : C, 62.22; H, 8.15; S, 11.85%.

Found : C, 61.47; H, 8.38; S, 12.52%.

3.5.5 Preparation of Acid 3.08

To a solution of ester **3.07** (1 g, 3.7 mmol) in methanol (30 ml), solid KOH (622 mg, 0.01 mol) was added portion wise at ice-water temperature. The reaction mixture was then allowed to attain room temperature and stirred for overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in water (30 ml) and was extracted with ethyl acetate (2x20 ml). The aq. solution was acidified with 10% HCl. This slightly acidic solution was extracted with ethyl acetate (3x30 ml). The combined organic extracts were washed successively with water (2x20 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. It was filtered and filtrate on evaporation of solvent under reduced pressure gave 825 mg (87%) of sufficiently pure acid **3.08** as a white solid.

M.p. : 113-115 °C

^{1}H NMR : δ 0.90 (s, 3H); 1.30 (s, 3H); 0.80-1.98 (m, 7H); 2.62-2.98 (m, 2H); 3.16 (d, *J*= 13.5 Hz, 1H); 3.67 (dd, *J*= 13.5 & 4.05Hz, 1H); 5.08 (dd, *J* = 8.6 & 5.4 Hz, 1H).

^{13}C NMR : 19.84, 20.06, 22.86, 26.90, 28.33, 32.89, 33.92, 37.04, 40.46, 41.49, 44.58, 45.13, 46.27, 73.21, 76.12, 85.05, 175.40.

IR : 1680, 2900 cm^{-1}.

MS (m/z) : 256(M^{+}), 168, 93 (100%).

$[\alpha]_D$: −104.54 (c, 1 $CHCl_3$).

3.5.6 Attempted general procedure for the synthesis of b-lactam 3.10

To a stirred mixture of acid **3.08** (0.5g, 1.95mmol), imines (**3.09**) (2.53 mmol), triethylamine (0.8 ml, 5.86 mmol) and dry CH_2Cl_2 (15 ml), a solution of phenyl dichlorophosphate (0.45 ml, 2.93 mmol) in dry CH_2Cl_2 (15 ml) was added at 0 °C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and successively washed with water (15 ml), satd. $NaHCO_3$ solution (10 ml) and brine (10 ml) and dried (Na_2SO_4). It was filtered and the filtrate on evaporation of solvent gave the crude product, the IR spectrum of which showed a peak corresponding to amide carbonyl (1700 cm^{-1}). The crude product was column chromatographed (silica gel, 60-120, 15% ethyl acetate/pet. ether) to furnish a pale yellow solid, the proton NMR of which showed no β-lactam present.

3.5.7 Preparation of acid chloride from acid 3.08 using oxalyl chloride and its attempted use for the synthesis of β-lactam **3.10**

The acid **3.08** (0.5 g, 1.95 mmol) in 10 ml of dry DCM was slowly added oxalyl chloride (0.248 g, 1.95 mmol) in 3 ml dry DCM at 0 °C. The reaction mixture was allowed to warm-up to room temperature and stirring continued till the reaction goes to completion (TLC, 1h). This reaction mixture as such was added to 10 ml dry DCM solution of imines **3.09** (2.93 mmol) and triethylamine (0.8 ml, 5.8 mmol) at 0 °C. The reaction mixture was allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with 30 ml of DCM and successively washed with water (5 ml), sat. $NaHCO_3$ (2x5 ml) and brine (5 ml). This DCM solution was dried over anhydrous sodium sulfate and filtered. The filtrate on evaporation of solvent gave a residue, the IR spectrum of which did not show presence of β-lactam.

3.5.8 Preparation of acid chloride from acid 3.08 using thionyl chloride and its attempted us for the synthesis of β-lactam **3.10**

A mixture of acid **3.08** (0.5 g, 1.95 mmol) and $SOCl_2$ (5 ml, 68.5 mmol) in 15 ml of dry benzene was refluxed for 5h. The excess $SOCl_2$ and solvent benzene have been distilled out under reducer pressure to give a gummy residue. This residue was dissolved in 15 ml of dry DCM and was added to imines **3.09** (2.93 mmol) and triethylamine (0.8 ml, 5.8 mmol) at 0 °C. The reaction mixture was allowed to warm-up to room temperature and stirred further

for 15 h. It was diluted with 30 ml of DCM and successively washed with water (5 ml), sat. $NaHCO_3$ (2x5 ml) and brine (5 ml). The DCM solution was dried over anhydrous sodium sulfate and filtered. The filtrate on evaporation of solvent gave a residue, the IR spectrum of which did not show presence of β-lactam.

3.6 References

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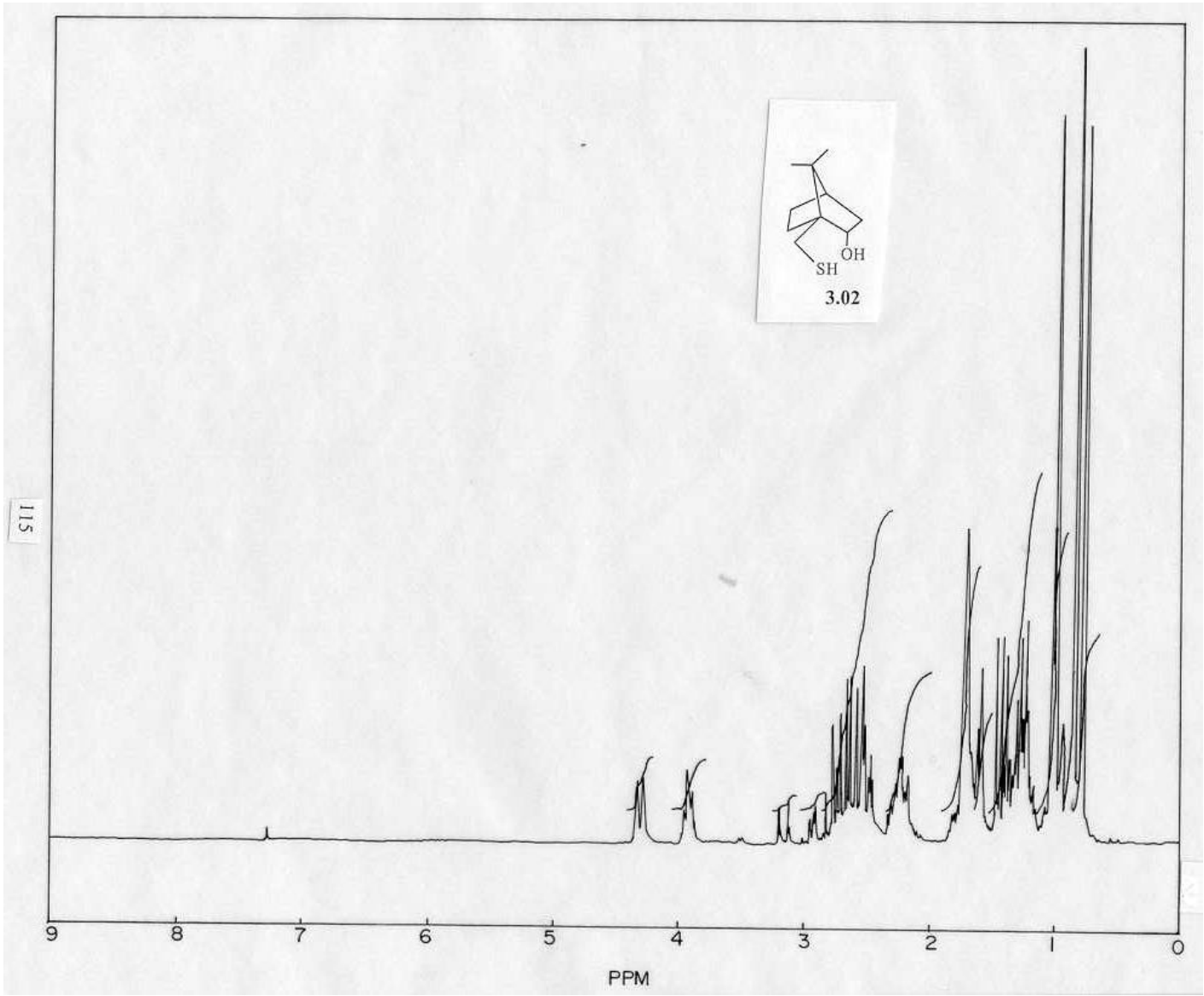
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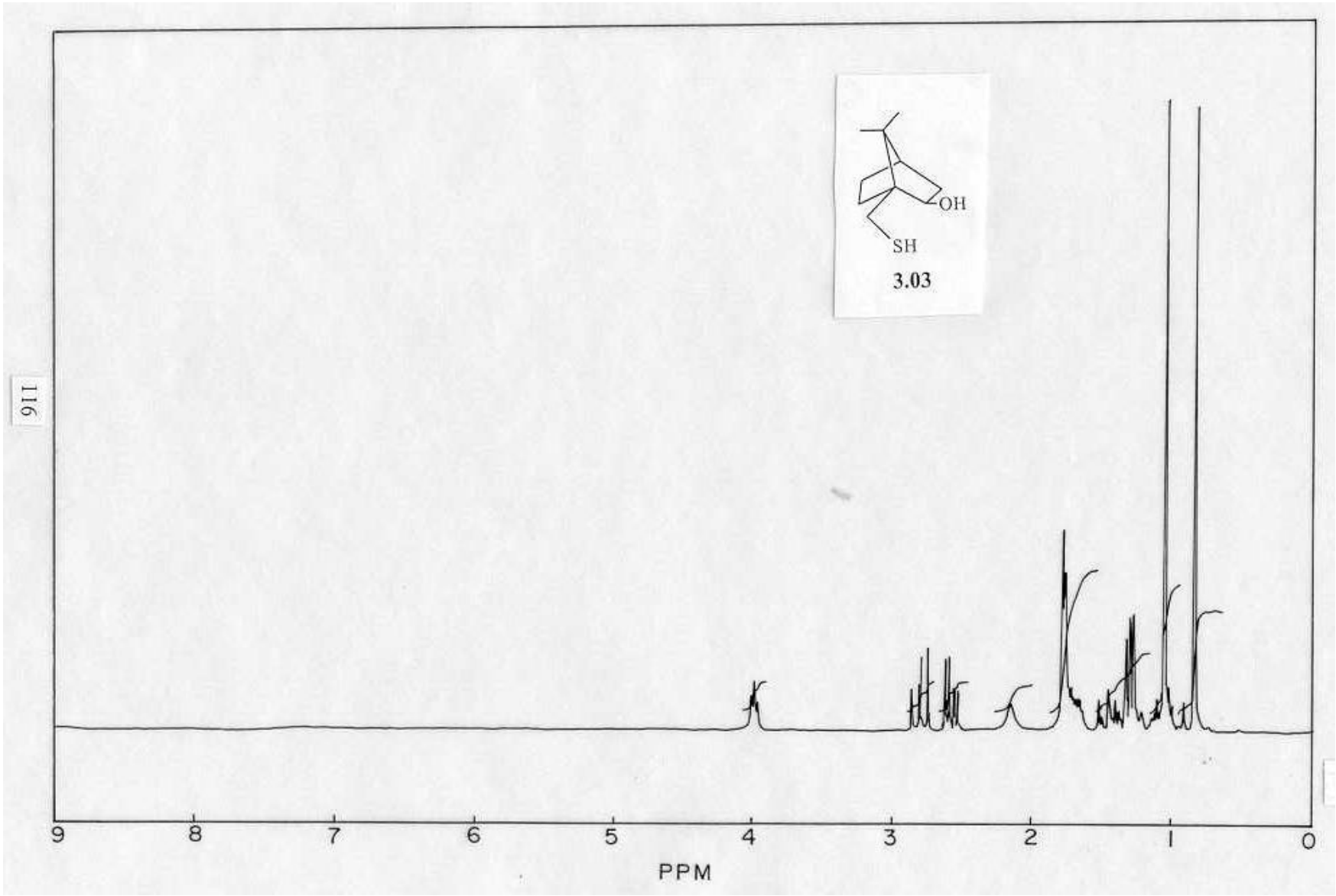
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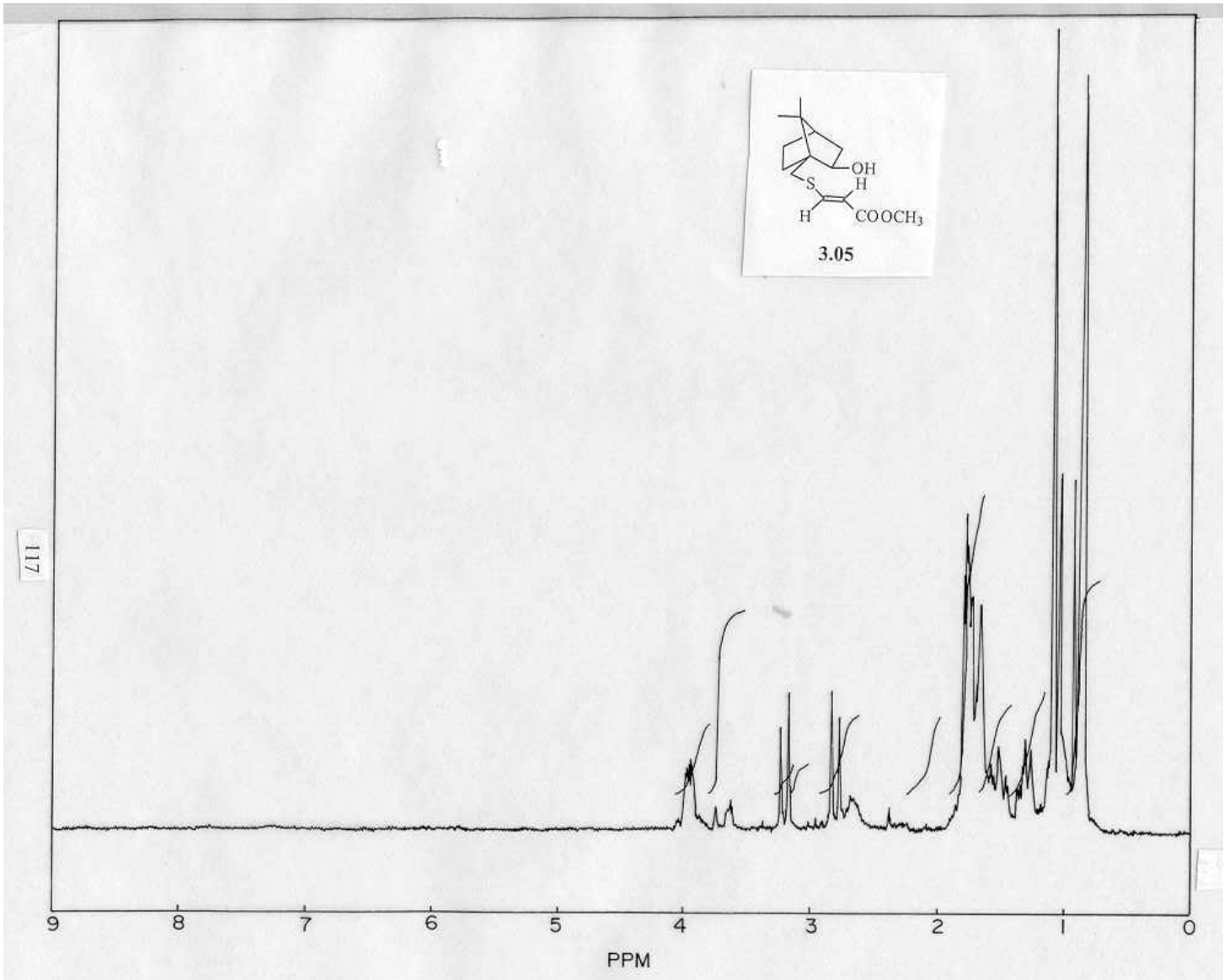
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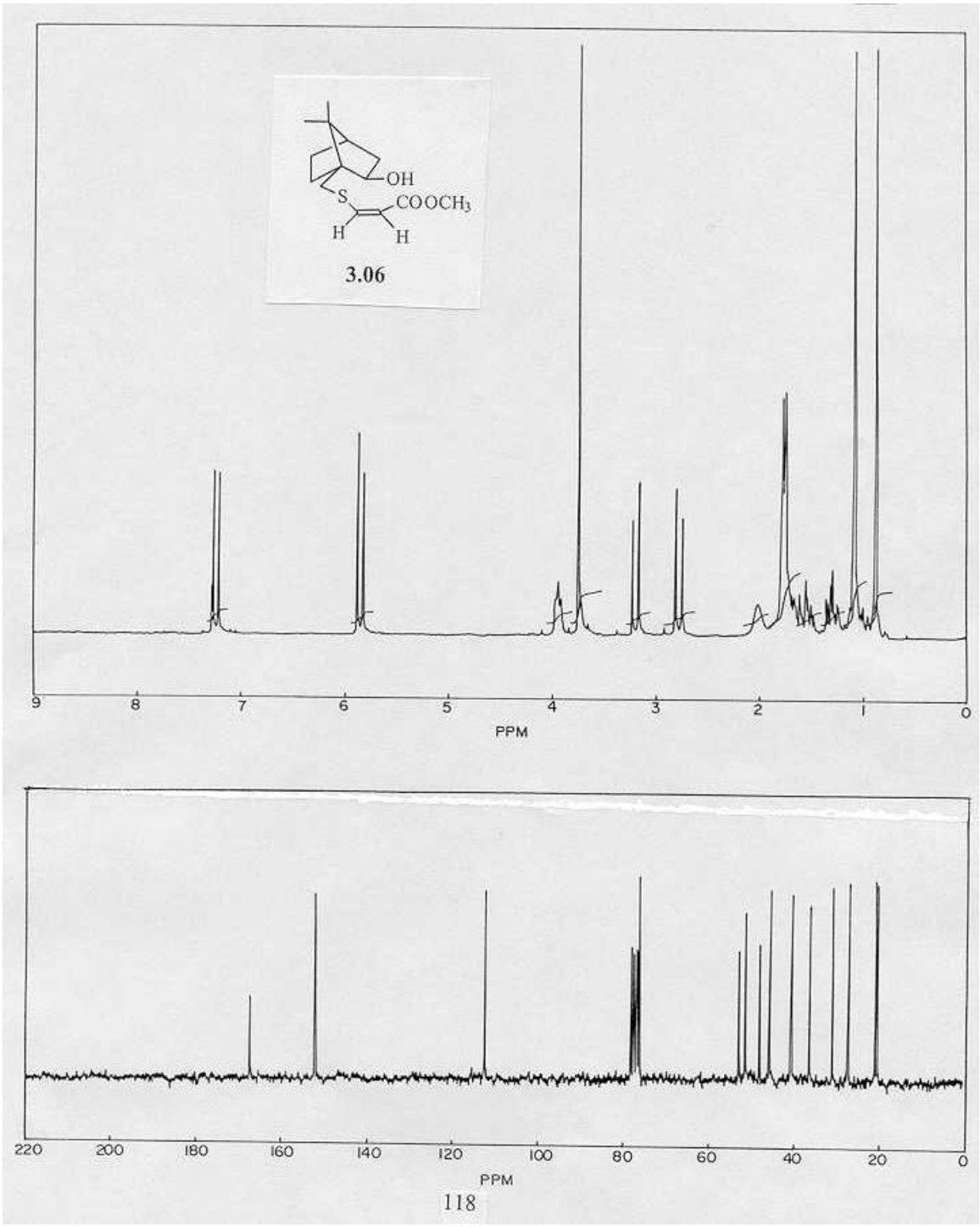
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PPM
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200
180
160
140
120
100
80
60
40
20
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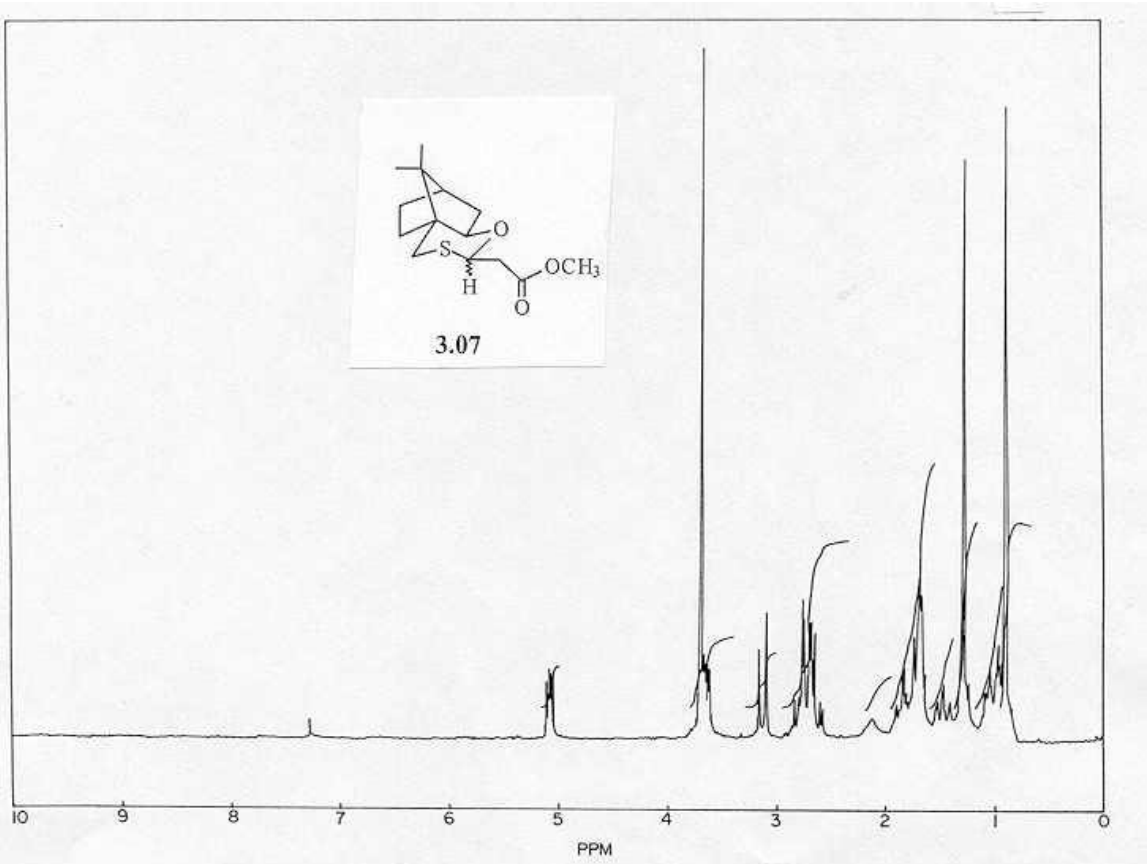
PPM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H
OCH3
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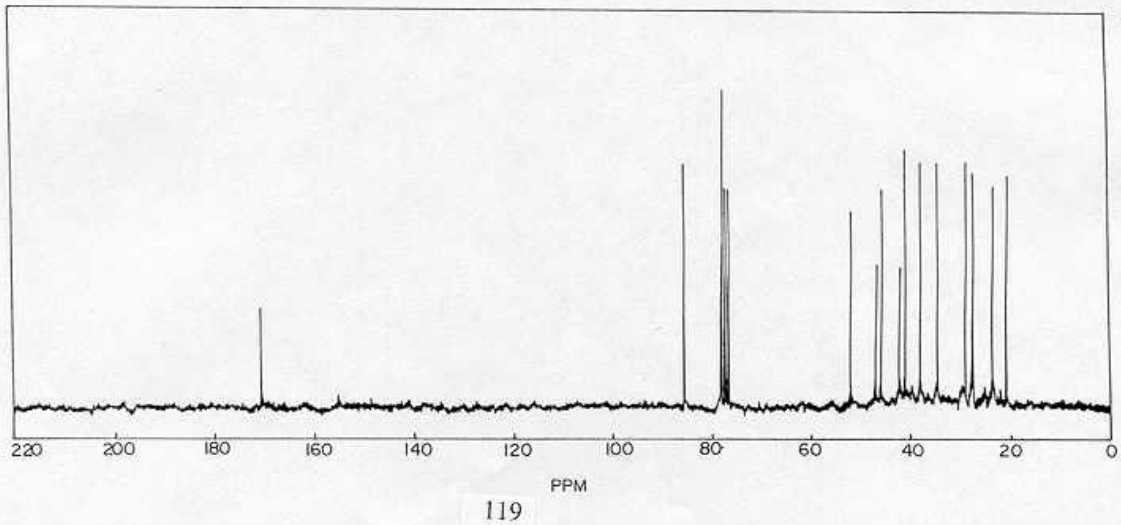
PPM

3.07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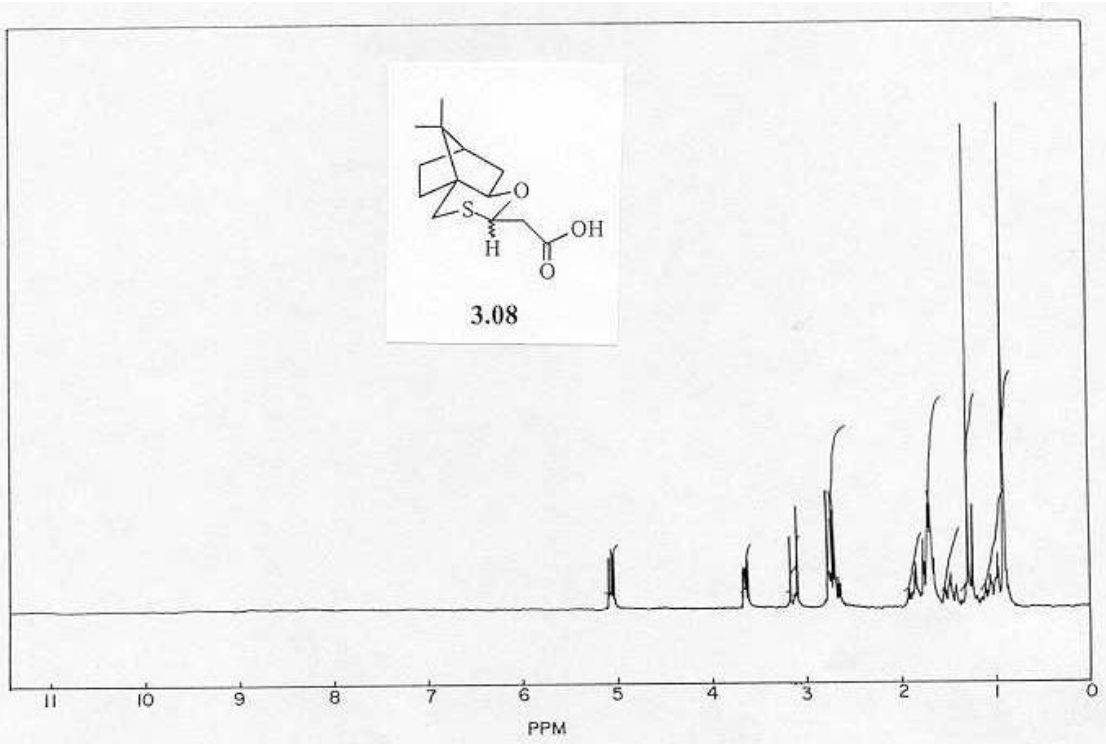
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OH
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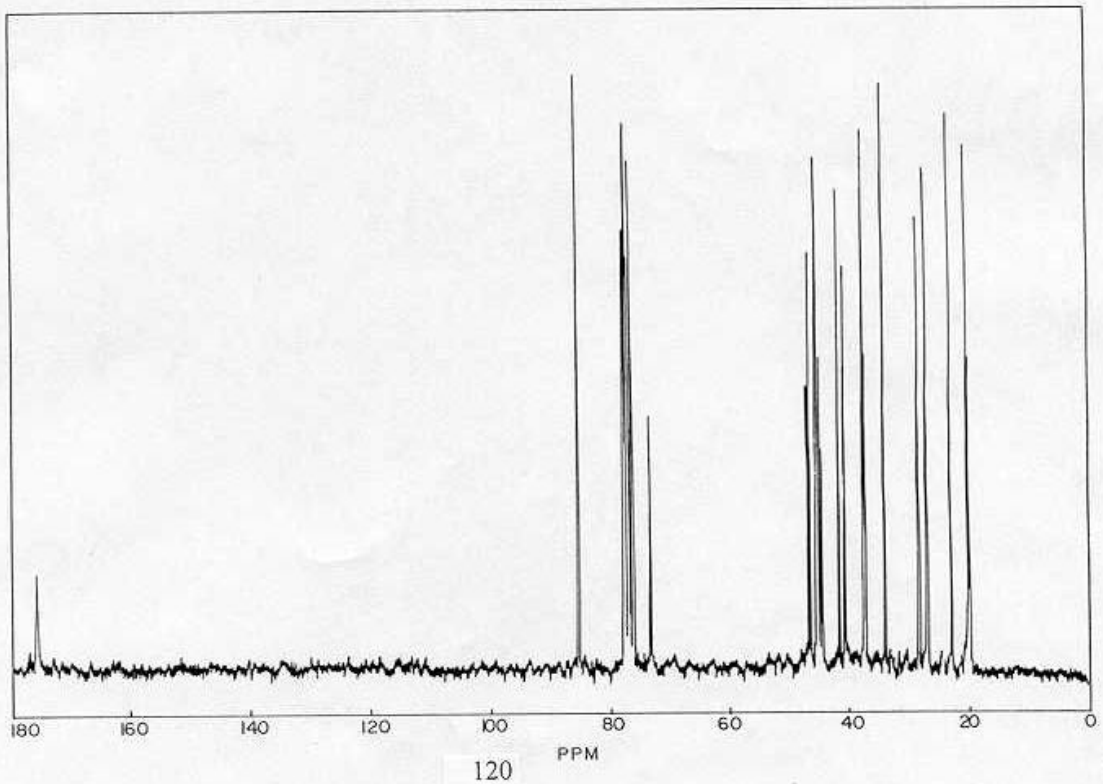
3.08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160
140
120
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40
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0
PPM

Chapter IV

The use of chiral acid derived from D-glucose for diastereoselective synthesis of b-lactam

4.1 Introduction

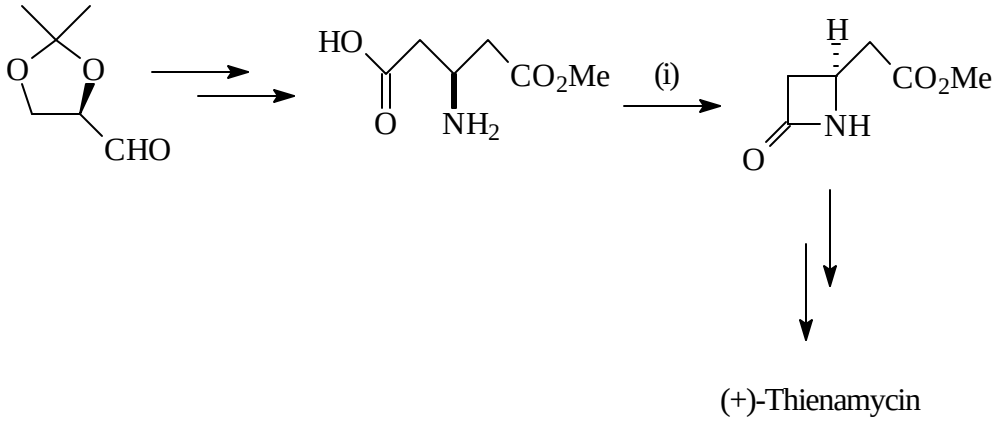
Carbohydrates, a cheap and naturally occurring *chiral pool,* have been extensively used as a chiral auxiliary for the synthesis of various optically active natural priducts.[2] The carbohydrate derived chiral auxiliaries have also been used for the synthesis of unnatural amino acids *via* opening of β-lactam ring.[1]

Carbohydrates have been used as chiral auxiliary in various forms viz. aldehyde, amine and ketene in ketene-imine cycloaddition reaction leading to the formation of β-lactams.

Asymmetric synthesis of b-lactams

The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into β-amino ester, which on cyclization[3] with 2,2'-dipyridyl disulphide and triphenyl phosphene gave 3-unsubtituted β-lactam (Scheme 4.01). This β-lactam has been converted into (+)-thienamycin in several steps.

Scheme 4.01

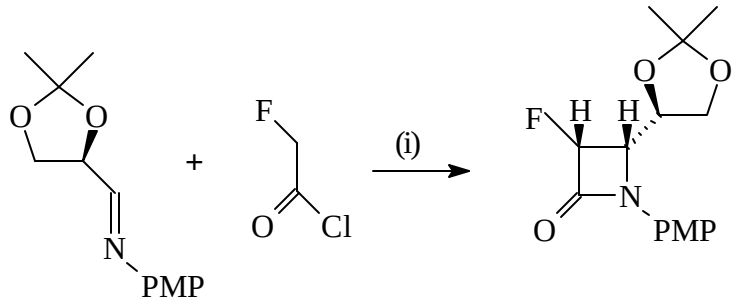


(+)-Thienamycin

Reagents and conditions (i): Ph_3P-$(PyS)_2$/ CH_3CN

The imine derived from (R)-glyceraldehyde and *p*-anisidine, was made to undergo [2+2] cycloaddition[4] (Staudinger reaction) reaction with the ketene obtained from flouro aetylchloride in presence of triethylamine to give diastereospecically only one β-lactam in 68% yield (Scheme 4.02).

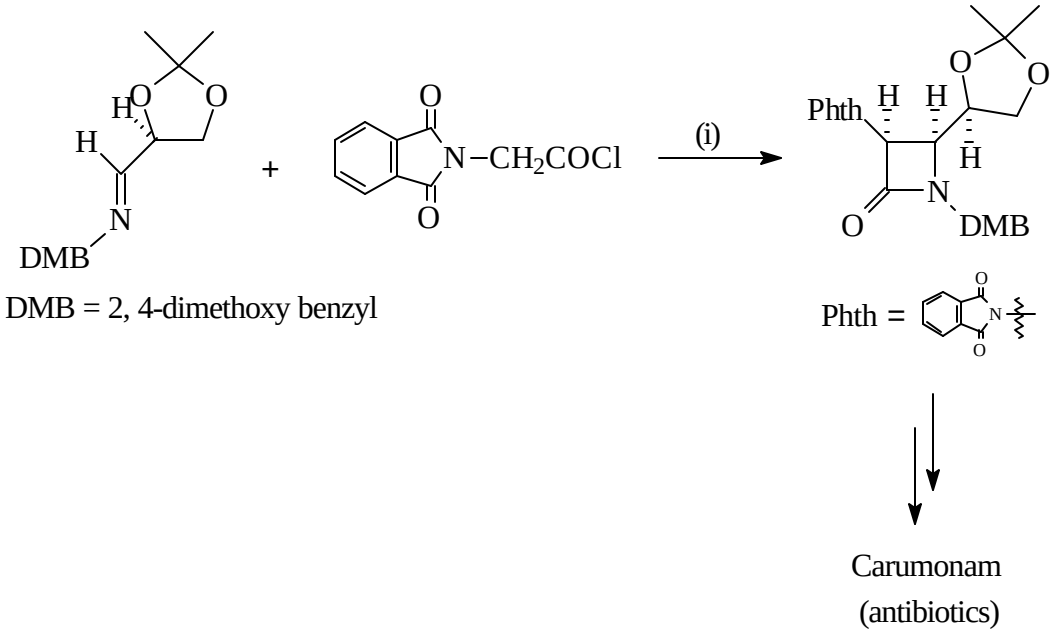
Scheme 4.02



Reagents and conditions (i): Et_3N/DCM, r.t. 16 h.

The imine derived from L-(S)-glyceraldehyde and 2,4-dimethoxybenzylamine, and phthalimidoaetyl chloride underwent Staudinger reaction[5] to give β-lactam, which is key intermediate for the synthesis carumonam antibiotics (Scheme 4.03).

Scheme 4.03

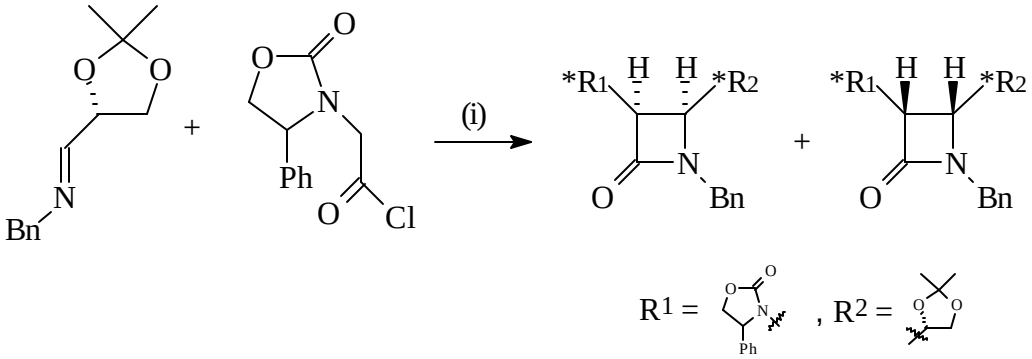


DMB = 2, 4-dimethoxy benzyl

Reagents and conditions (i): Et_3N/DCM, 0 ºC 2 h.

J. Palomo et al[6] have treated the imine derived from L-(S)-glyceraldehyde and benzylamine with oxazolidine acid chloride to give *cis*-β-lactams in good yield with 40:60 diastereomeric ratio (Scheme 4.04).

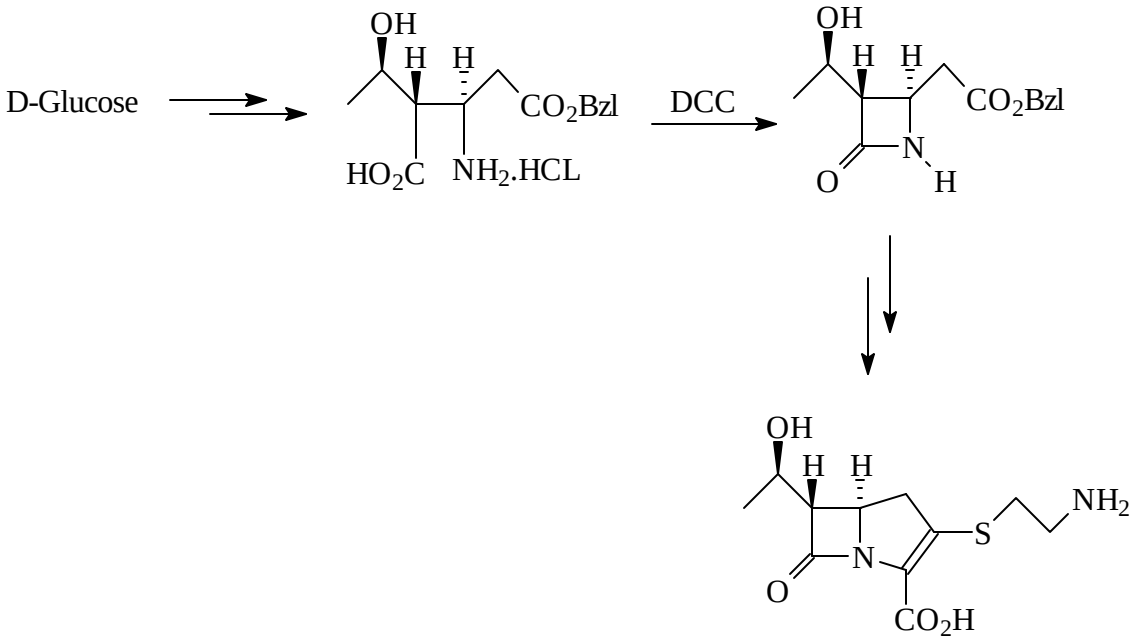
Scheme 4.04



Reagents and conditions (i): Et_3N/DCM, -78 °C, 20 h.

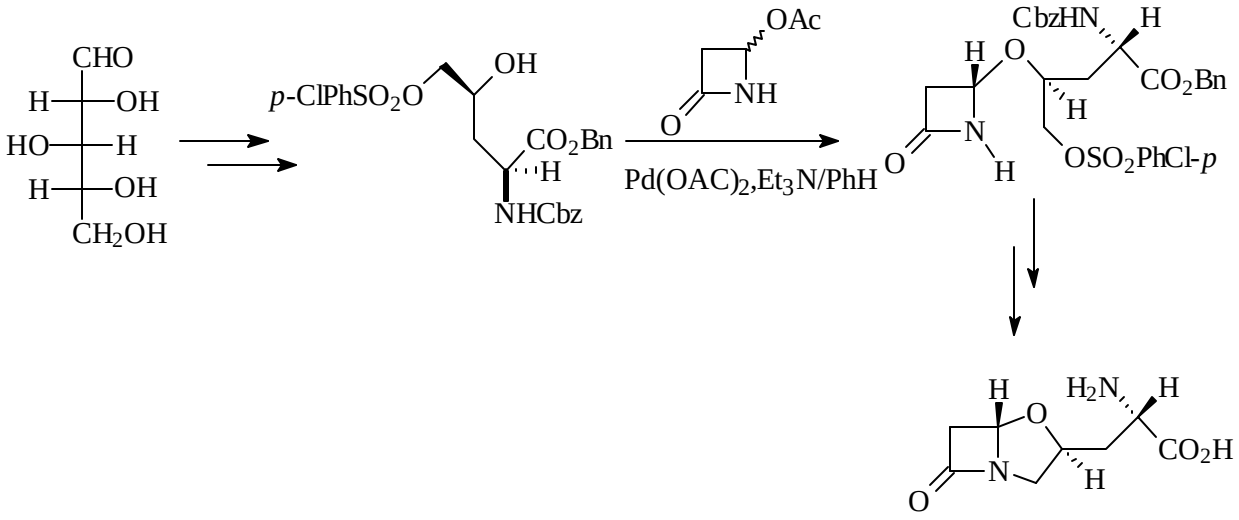
The β-amino acid, derived from D-glucose on cyclization[7] in presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotics in several steps (Scheme 4.05).

Scheme 4.05



A chiral amino alcohol derived[8] from D-xylose was coupled with racemic 4-acetyloxy N-unsubstituted-β-lactam in presence of palladium acetate-Et_3N to give diastereomeric mixture (70:30) of β-lactams in 65% yield. The major isomer has been converted to clavamine **Ro 22-5417** antibiotic (Scheme 4.06).

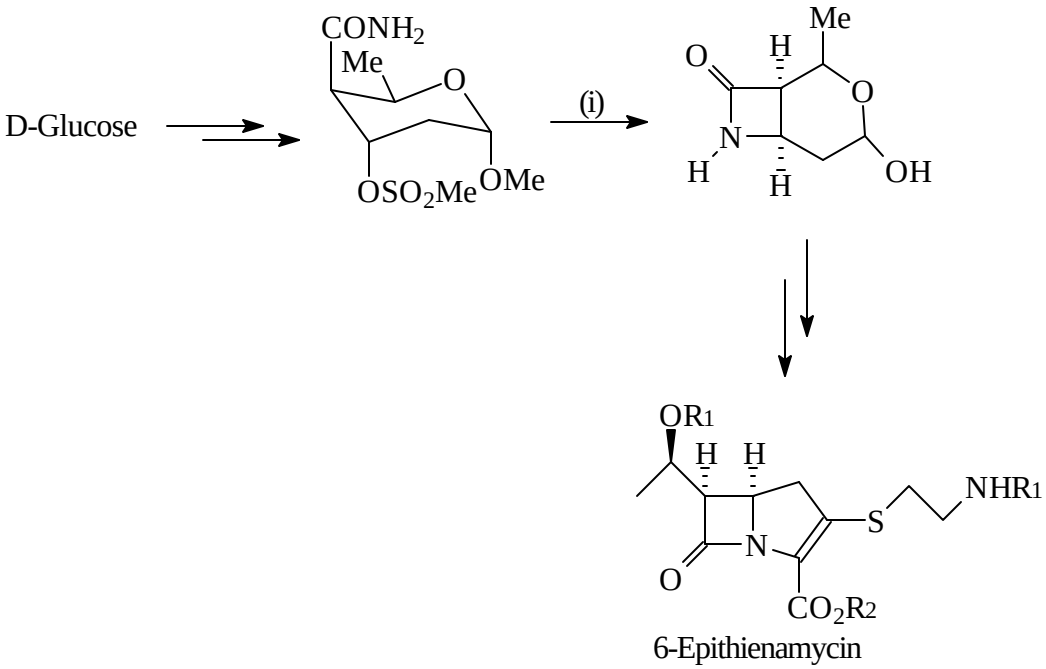
Scheme 4.06



Ro 22-5417

The amide derived from D-glucose has been cyclised[9] in presence of potassium *tert*-butoxide, to give bicyclic β-lactam in 45% yield. This bicyclic β-lactam has been transformed into 6-epithienemycin in a multi steps process (Scheme 4.07).

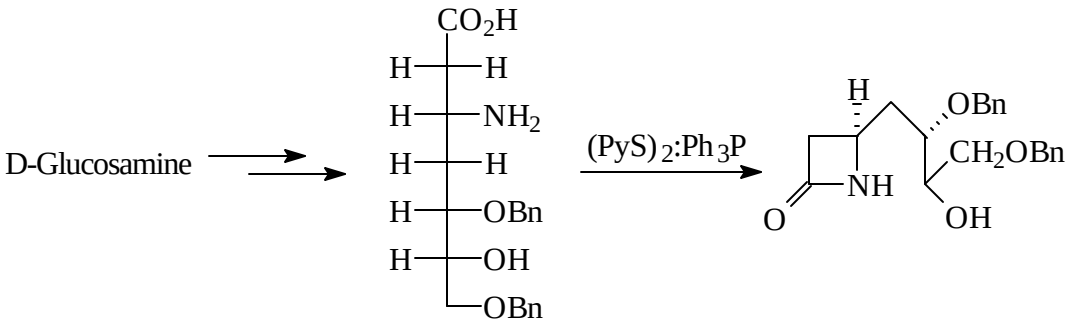
Scheme 4.07



Reagents and conditions (i): Bu^{t}OK, 18-crown ether/DMF, 0 °C, 3 h.

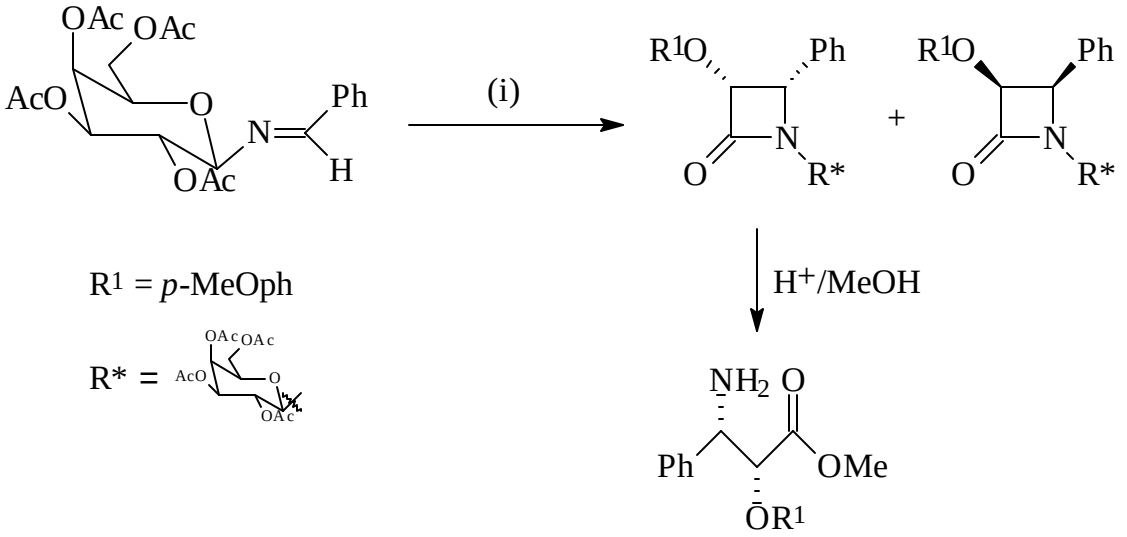
The β-amino acid derived[10] from D-glucosamine has been cyclised to N-unsubstituted β-lactam in presence of 2,2'-dipyridyl disulfide/Ph_3P. This N-unsubstituted β-lactam serves as a intermediate for the synthesis of (+)- thienamycin (Scheme 4.08).

Scheme 4.08



Georg. G. I et al[11] 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 60:40 diastereomeric mixture of β-lactams in 90% yield. The α-isomer was transformed to β-amino esters (Scheme 4.09).

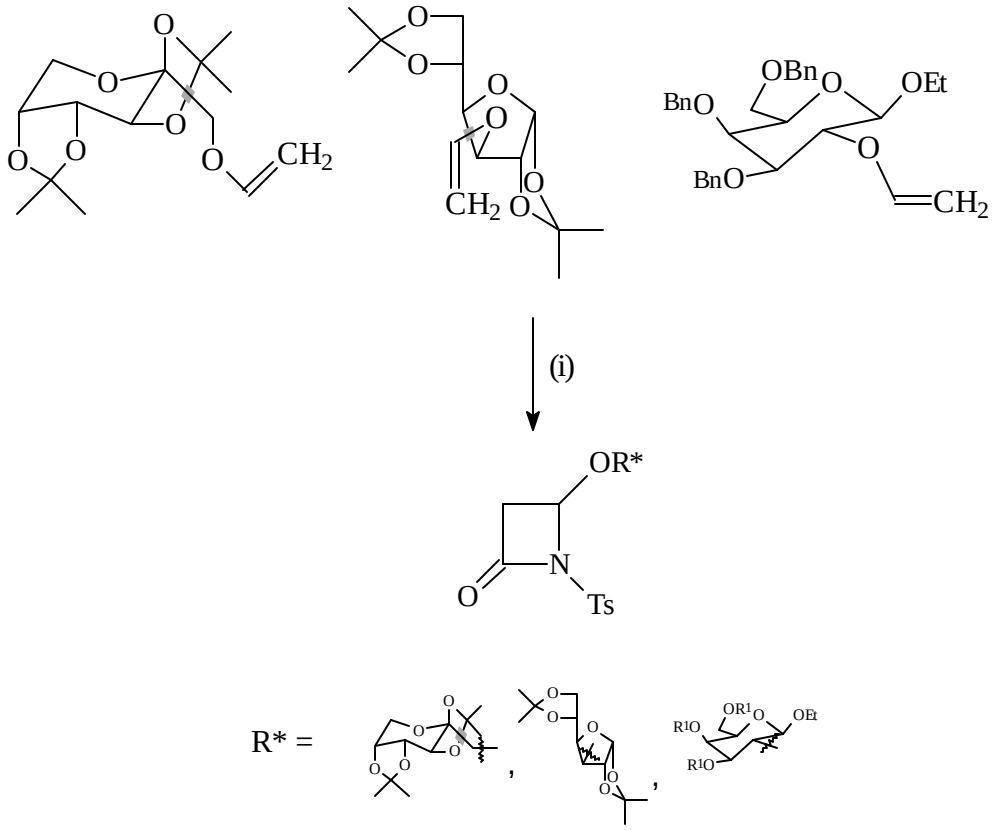
Scheme 4.09



Reagents and conditions (i): R^1OCH_2COCl,Et_3N/DCM, 25 °C, Overnight.

The vinyl ethers derived[12a] from protected glucose have been treated with tosyl isocyanate to give 3-unsubstituted β-lactams in good yields with maximum diastereoselectivity of 6:1 (Scheme 4.10a).

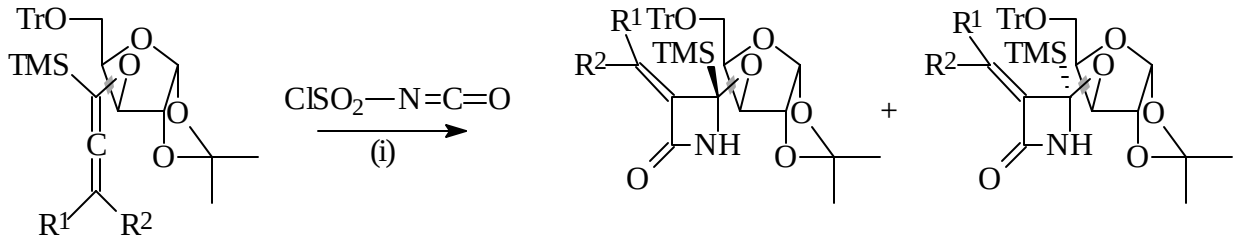
Scheme 4.10a



Reagents and conditions (i): Ts-N=C=O/EtOEt, 25 °C, Overnight.

Similarly, the allenyl ethers of sugar have also been reported to undergo [2+2] cycloaddition reaction with chlorosulfonyl isocyanate (CSI) to give NH-β-lactam with high selectivity of 89:11[12b] (Scheme 4.10b).

Scheme 4.10b

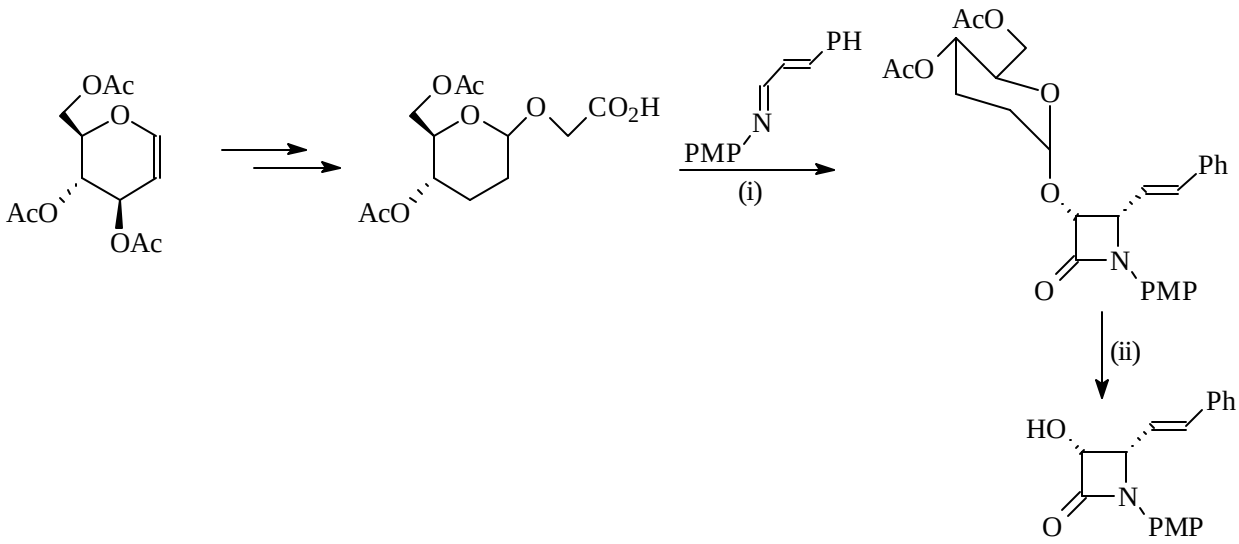


$R^1 = R^2 = H$

Reagents and conditions (i): Na_2CO_3/Toluene, –70 °C, 1.5 h.

B. C. Borer et al[13] have used tri-O-acetyl-D-glucal derived chiral acid as ketene precursor for diastereoselective synthesis of β-lactams (Scheme 4.11). They obtained diastereoselectivity of 70:30 in this reaction. The sugar moiety was deprotected by the treatment of acetic acid/water to give 3-hydroxy-β-lactam.

Scheme 4.11



Reagents and conditions (i): $(COCl)_2$, cat. DMF, Et_3N/DCM, –78 °C, 2 h.; (ii): AcOH: H_2O: THF.

4.2 Present Work

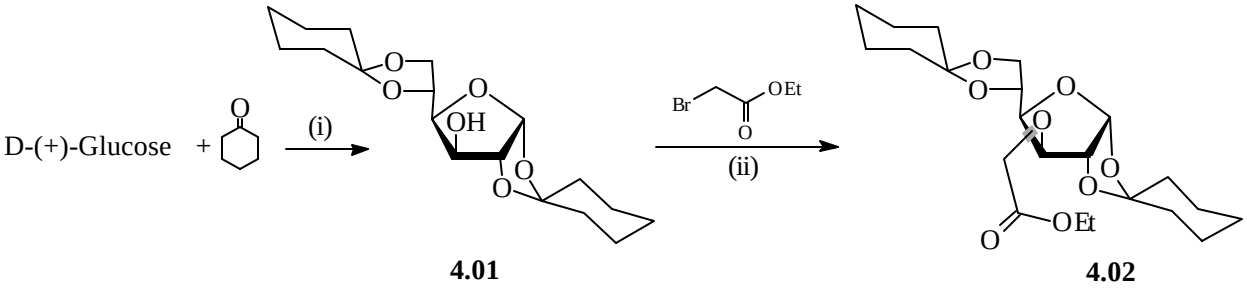
This chapter deals with the stereoselective synthesis of *cis*-β-lactams using chiral acid derived from 1,2:5,6-dicyclohexylidine glucofuranoside and 1,2:5,6-diisopropylidine glucofuranoside.

4.3 Results and Discussion

4.3.1 Preparation of ester 4.02

The alcohol 4**.01** was prepared as per the reported procedure,[14] which was alkylated[15] with ethyl bromoacetate in presence NaH to give ester **4.02** in 87% yield.

Scheme 4.12



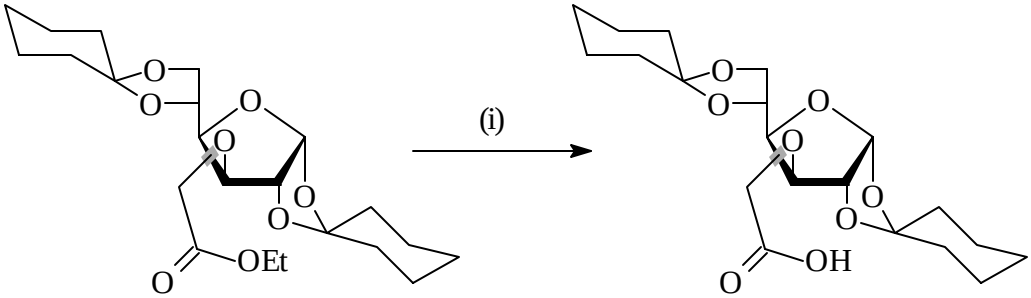
4.01 **4.02**

Reagents and conditions (i) Conc. H_2SO_4, ice-cold water. (ii) NaH/THF, reflux, 15 h.

4.3.2 Preparation of acid 4.03

The ester **4.02** on alkaline hydrolysis using methanolic KOH gave required acid **4.03** in excellent yield (92%).

Scheme 4.13



4.02 **4.03**

Reagents and conditions (i): MeOH/KOH, r.t., overnight.

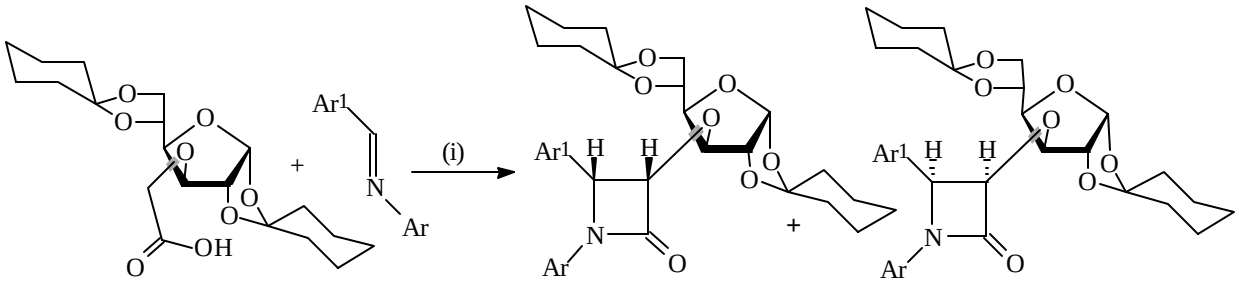
Spectral discussion and characterization of acid 4.03

^{1}H NMR spectrum of acid **4.03** showed several multiplets between δ 1.13 and 1.85 due to twenty methylene-protons of cyclohexyl part. Other multiplets appearing between δ 3.80 and 4.46 were due to five protons of glucose unit and two methylene-protons adjacent to the acid carbonyl. One of the glucose unit protons appeared as doublet at δ 4.54 with *J* value of 3.6 Hz. A doublet at δ 5.96 with *J* value of 3.6 Hz was assigned to anomeric proton of glucose unit. The IR spectrum showed carbonyl stretching at 1737 cm^{-1}.

4.3.3 Preparation of β-lactams 4.04 a-e and 4.05 a-e

The acid **4.03** when treated with imines (**4.04**) in presence of triethyl amine and an acid activator (phenyl dichlorophosphate) at 0 °C gave a diastereomeric mixture of *cis*-β-lactams **4.05** and **4.06** in moderate yields (Scheme 4.14, Table 1). The crude reaction mixture on purification by column chromatography gave a diastereomeric mixture of β-lactams **4.05** and **4.06**, which could not be separated either by extensive column chromatography or by fractional crystallization. The diastereomeric ratio was determined from ^{1}H & ^{13}C NMR spectral analysis, which showed presence of two diastereomers in almost equal amounts.

Scheme 4.14



Reagents and conditions (i): $Ph(PO)Cl_2$, Et_3N/DCM, 0 °C, 15 h.

Table 1. Synthesis of β-lactams **4.05** and **4.06**

Compound No	**Ar**[1]	**Ar**	Compounds **4.05** and **4.06**		
			Yield[a] (%)	Ratio[b]	M.p[c] (°C)
a	Ph	PMP	54	~1:1	180-182
b	PMP	PMP	51	~1:1	114-115
c	Styryl	PMP	66	~1:1	137-138
d	PMP	Ph	57	~1:1	89-90
e	Fu	PMP	55	~1:1	100-101

[a] Isolated yield of β-lactam mixture (**4.05** and **4.06**). [b] The diastereomeric ratio determined from ^{13}C NMR spectrum. [c] M.p of pure β-lactam mixture (**4.05** and **4.06**), which was purified by column chromatography.

The cycloaddition reaction of ketene derived from acid **4.03** with imine **4.04a** when carried out at –40 and –15 °C under went cycloaddition reaction to give a diastereomeric mixture of β-lactams **4.05a** and **4.06a** in relatively low yields (see Table 2, Entry No. 2 & 3) with no improvement in diastereoselectivity. A little improvement in yield of β-lactam ring formation was achieved by using triphosgene [$CO(OCCl_3)_2$] in place of phenyl dichlorophosphate (see Table 2, Entry No. 4 & 5). However, no improvement in diastereoselectivity was observed.

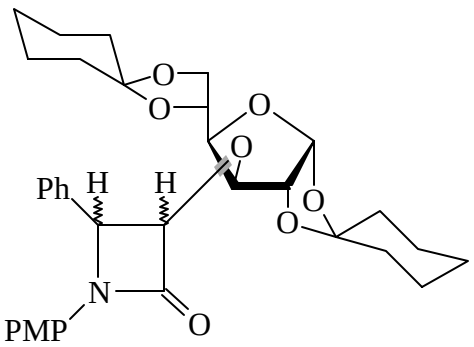
Table 2. Synthesis of β-lactams **4.05a** and **4.06a** at different reaction conditions

Entry No.	Temperature (°C)	Acid activator	Compounds **4.05a** and **4.06a**	
			Yield[a] (%)	Ratio[b]
1	0	$Ph(PO)Cl_2$	54	~1:1
2	–15	$Ph(PO)Cl_2$	31	~1:1
3	–40	$Ph(PO)Cl_2$	27	~1:1
4	0	$CO(OCCl_3)_2$	58	~1:1
5	–40	$CO(OCCl_3)_2$	42	~1:1

[a] Isolated yield of diastereomeric mixture of β-lactams **4.05** and **4.06**. [b] The diastereomeric ratio determined from ^{1}H & ^{13}C NMR spectrum.

The diastereomeric mixture of β-lactams **4.05a** and **4.06a** could not be separated either by column chromatography or fractional crystallization. This diastereomeric mixture was chosen as a representative compound of this series for spectral discussion.

The ^{1}H NMR spectrum of the diastereomeric mixture of β-lactams **4.05a** and **4.06a** showed several multiplets between δ 1.05 and 1.75 due to methylene-protons of cyclohexyl part of both the diastereomers. A doublet appearing at δ 3.06 with *J* = 3.4 Hz was due to one of the protons glucose unit of one of the diastereomers. The other protons from glucose units of both the diastereomers were seen as several multiplets in between δ 3.15-3.30, 3.45-3.60 3.65- 4.15, and 4.25-4.45. Methyl-protons of two *p*-methoxyphenyl groups from both the diastereomers were appeared as a singlet at δ 3.75. A doublet appeared at δ 4.90 with *J* value of 3.4 Hz, accounting for one proton, was due to one of the glucose unit protons. One β-lactam proton of one of the diastereomer was seen as a doublet at δ 5.02 with *J* value of 5.4 Hz indicating the *cis* stereochemistry of the β-lactam protons. Other β-lactam protons along with anomeric proton of glucose unit of one of the diastereomer were appeared as a multiplet at δ 5.29-5.35. Anomeric proton of glucose unit of other diastereomer appeared as a doublet at δ 5.83 with *J* value of 3.9 Hz. A doublet appeared at δ 6.80 with *J* value of 8.8 Hz was assigned to aromatic protons of *p*-methoxyphenyl group. Several multiplets appeared between δ 7.20 and 7.47 were due to rest of the aromatic protons. The ^{13}C NMR spectrum showed two peaks at 162.31 and 163.96 corresponding to two β-lactam carbonyl carbons. The mass spectrum was well supporting the compounds' structure. The IR spectrum of diastereomeric mixture showed presence of β-lactam carbonyl stretching at 1749 cm^{-1}.



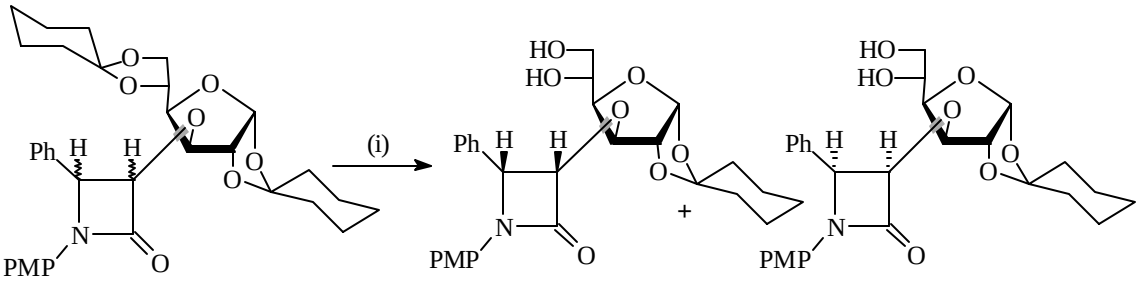
4.05a & **4.06a**

4.3.4 Preparation of diols 3.06 and 3.07

Since the β-lactam mixture **4.05** and **4.06** could not be separated either by column chromatography or by crystallization, it was decided to deprotect one of the ketal groups selectively. The β-lactam mixture **4.05a** and **4.06a** on treatment with 75% aq. acetic acid under went smooth deprotection[16] of 5,6-O-cyclohexylidine group yielding a diastereomeric

mixture of diols **4.07** and **4.08** in excellent yield (98%). These diastereomeric diols were separated by flash column chromatography using 30% ethyl acetate-pet. ether. The less polar diol **4.07** eluted first followed by more polar diol **4.08**. The structure of these diols was confirmed from their IR and ^{1}H NMR spectral analysis. The *cis* stereochemistry was assigned to β-lactam protons based on coupling constant (~5 Hz) for these protons. However, the absolute stereochemistry of these diols could not be determined, as X-ray quality crystals could not be obtained from these compounds. The absolute stereochemistry shown for the structures in the Scheme-4.15 is tentative and could interchange between the diols **4.07** and **4.08**.

Scheme 4.15



4.05a & 4.06a **4.07** **4.08**

Reagents and conditions (i): aq. AcOH, 80 ºC, 2.5 h.

Spectral discussion and characterization of diol 4.07

^{1}H NMR spectrum of diol **4.07** showed a multiplet at δ 1.22-1.75 for ten methylene-protons of cyclohexyl part. A broad singlet appeared at δ 1.85 was assigned to two OH-protons. A multiplet appeared between δ 3.20 3.62, accounting for three protons, was due to protons of glucose unit. A singlet appeared at δ 3.77 was assigned to methyl-protons of *p*-methoxy phenyl group. A multiplet appeared between δ 3.87 and 4.05, accounting for two protons, was due to protons of glucose unit. A doublet appeared at δ 4.57 with *J* value of 3.4 Hz, was assigned to one of glucose unit protons. The C4 and C3 β-lactam protons appeared as set of doublets at δ 5.10 and 5.30 respectively with the *J* values of 4.9 Hz. A doublet appeared at δ 5.90 with *J* value of 3.4 Hz was assigned to anomeric proton of glucose unit. A doublet appeared at δ 6.80 with *J* value of 8.8 Hz was assigned to two aromatic protons of *p*-methoxy phenyl group. Several multiplets appeared between δ 7.15 and 7.56 were assigned to

other seven aromatic protons. ^{13}C NMR spectrum showed a peak at 163.96 for β-lactam carbonyl carbon. The IR spectrum showed β-lactam carbonyl stretching at 1749 cm^{-1} and O-H stretching at 3579 cm^{-1}.

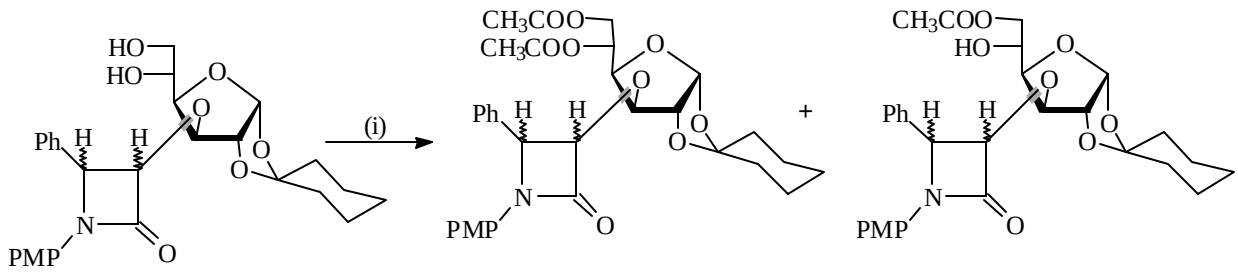
Spectral discussion and characterization of diol 4.08

^{1}H NMR spectrum of other diol **4.08** showed a multiplet at δ 1.10-1.61 for ten methylene-protons of cyclohexyl part. A broad singlet appeared at δ 3.14 was assigned to two OH-protons. One of the glucose unit protons appeared as a doublet at δ 3.40 with the coupling constant of 3.4 Hz. The two multiplets appeared at δ 3.47-3.85 and 3.85-4.08, integrating for five protons, were assigned to other five protons of glucose unit. A sharp singlet appeared at δ 3.67 was assigned to methyl-protons of *p*-methoxy phenyl group. The C4 and C3 β-lactam protons have appeared as two separate shoulders at δ 4.95-5.10 and δ 5.15-5.26 respectively. The *cis* stereochemistry was assigned to these protons based on the coupling constant coupling constant observed for their O-diacetyl derivative (see discussion for **4.09, 4.10** and **4.11**). The anomeric proton of glucose unit was seen as a doublet at δ 5.12 with the coupling constant of 3.4 Hz. Two of aromatic protons were appeared as doublet at δ 6.70 with the coupling constant of 8.8 Hz. The rest of aromatic protons were appeared as several multiplets between δ 7.10 and 7.45. A peak observed at 164.13 ppm in ^{13}C NMR spectrum of this compound was assigned to the carbonyl carbon of β-lactam ring. The IR spectrum showed β-lactam carbonyl stretching at 1739 cm^{-1} and OH stretching at 3409 cm^{-1}.

4.3.5 Preparation of acetates[17] 4.09 and 4.10 from diol 4.08

The diol **4.08** was acetylated using acetyl chloride in presence of triethylamine at 0 °C to give mixture of mono and di acetates. These two acetates were separated by column chromatography to give pure di and monocetates **4.09** and **4.10** respectively in very good yield.

Scheme 4.16



4.08 **4.09** **4.10**

Reagents and conditions (i): $AcCOCl/Et_3N$, 0 °C, 3.5 h.

Spectral discussion and characterization of mono acetate 4.10

^1H NMR spectrum of mono acetate **4.10** showed several multiplets between δ 0.25 and 1.72 for ten methylene-protons of cyclohexyl part. A singlet appeared at 2.10 was assigned to acetoxy methyl protons. One of the glucose protons appeared as a doublet at δ 3.44 with *J* value of 3.4 Hz. A sharp singlet appeared at δ 3.75 was assigned to methyl-protons of *p*-methoxy phenyl group. The three glucose unit protons were appeared as a multiplet between δ 3.99 and 4.25. A doublet appeared at δ 4.37 with *J* value of 9.2 Hz, integrating for two protons, was due to other two protons of glucose unit. The two doublets appeared at δ 5.12 and 5.28 with the *J* values of 4.9 Hz were assigned to respectively. The coupling constant of 4.9 Hz indicates the *cis* stereochemistry for the C4 and C3 of β-lactam protons. A doublet appeared at δ 5.19 with *J* value of 3.4 Hz was assigned to anomeric proton of glucose unit. A doublet appeared at δ 6.80 with *J* value of 8.8 Hz was assigned to two aromatic protons of *p*-methoxyphenyl group. Several multiplets appeared between δ 7.17 and 7.50 were due to seven aromatic protons. The IR spectrum showed carbonyl stretching at 1738 cm^{-1} and OH stretching at 3462 cm^{-1}. The mass spectrum was well supporting the compound's structure.

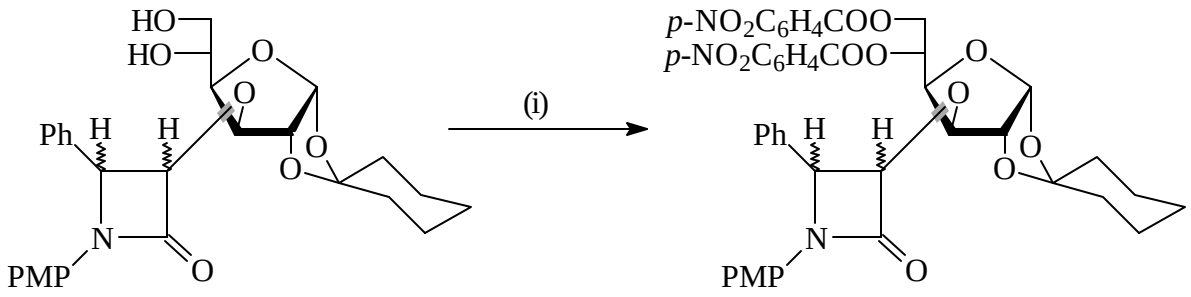
Spectral discussion and characterization of diacetate (4.09)

^{1}H NMR spectrum showed several multiplets between δ 0.7 and 1.75 for ten methylene-protons of cyclohexyl part. Two singlets appeared at δ 2.05 and 2.17 were assigned to methyl protons of two acetoxy groups. A sharp singlet appeared at δ 3.74 was assigned to methyl-proton of *p*-methoxyphenyl group. One of the glucose unit protons appeared as a doublet at δ 3.84 with *J* value of 3.4 Hz. Several multiplets appeared between δ 3.88 and 4.65, integrating for five protons, were assigned to glucose unit protons. The two doublets appeared at δ 4.97 and 5.17 with the *J* values of 4.9 Hz were assigned to C4 and C3 β-lactam protons respectively. A doublet appeared at δ 5.08 with *J* value of 2.9 Hz was assigned to anomeric proton of glucose unit. A doublet appeared at δ 6.75 with *J* value of 8.8 Hz was assigned to two aromatic protons of *p*-methoxyphenyl group. Several multiplets appeared between δ 7.12 and 7.46 due to seven aromatic protons. The IR spectrum showed carbonyl stretching at 1749 cm^{-1}. The mass spectrum was well supporting the compound's structure.

4.3.6 Preparation of p-nitro benzoate 4.11 of diol 4.08

The diol **4.08** on treatment with *p*-nitrobenzoyl chloride in presence of triethylamine gave dibenzoate 4.11 in good yield.

Scheme 4.17



4.08 **4.11**

Reagents and conditions (i): *p*-O_2NPhCOCl/Et_3N, 0 °C, 3.5 h.

Spectral discussion and characterization of dibenzoate (4.11)

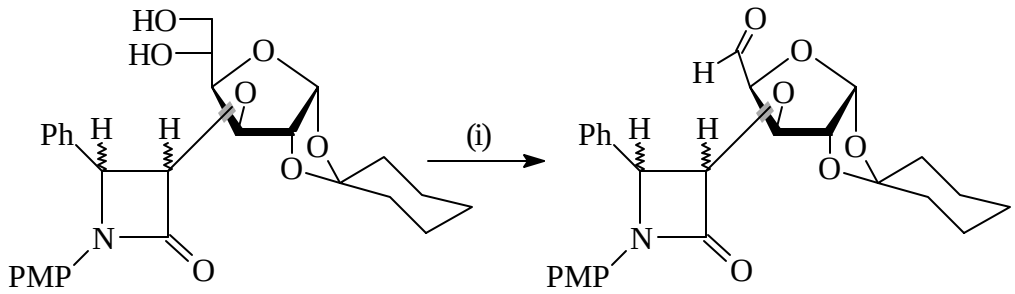
^{1}H NMR spectrum of dibenzoate **4.11** showed several multiplets between δ 1.39 and 1.75 for ten methylene-protons of cyclohexyl part. A singlet appeared at δ 3.76 was assigned

to three methyl-protons of *p*-methoxy phenyl group. Two glucose unit protons were appeared as the two doublets, accounting for one proton each, at δ 3.88 and 4 .32 with the *J* values of 3.4 Hz. The two multiplets appeared between δ 4.39-4.65 and δ 4.80-5.00, integrating for two and one proton respectively, were assigned to other three glucose unit protons. The two doublets appeared at δ 4.45 and 5.20 with *J* values of 4.9 Hz were assigned to C4 and C3 β-lactam protons respectively. A doublet appeared at δ 5.15 with *J* value of 3.4 Hz was assigned to anomeric proton of glucose unit. One of the glucose unit protons was appeared as a multiplet between δ 5.55 and 5.70,. The two doublets appeared at δ 6.75 and 7.13 with the *J* values of 9.3 Hz were assigned to four aromatic protons. The two multiplets between δ 7.33-7.50 and δ 8.12-8.39, integrating for four and nine protons respectively, were due to aromatic protons. The IR spectrum showed carbonyls' stretching at 1689 (w), 1736 and 1757 cm-^{1}. This compound gave satisfactory microanalysis.

4.3.7 Preperation[18] of aldehydes 4.12 and 4.13 from diols 4.07 and 4.08 respectively

Both the diols **4.07** and **4.08** were separately cleaved to corresponding aldehydes (**4.12** and **4.13**) on treatment with powdered $NaIO_4$. The crude product was filtered through silica gel column to give pure aldehyde in excellent yield (98%).

Scheme 4.18



4.07 or **4.08** **4.12** or **4.13**

Reagents and conditions (i): $NaIO_4$/MeOH: H_2O, RT, overnight.

Spectral discussion and characterization of aldehyde 4.12

^{1}H NMR spectrum aldehyde **4.12** showed several multiplets between δ 1.13 and 1.85 for ten methylene-protons of cyclohexyl part. A singlet appeared at δ 3.70 was assigned to methyl-protons of *p*-methoxy phenyl group. A multiplet appeared between δ 3.99 and 4.13, integrating for one proton, was assigned to one of the glucose unit protons. Three doublets

appeared at δ 4.20, 4.26, 4.90 accounting for one proton each with the coupling constants of 3.4, 4.3, and 3.4 Hz respectively were assigned to other glucose unit protons. The C4 and C3 of β-lactam protons were seen as set of doublets at δ 4.85 and 5.17 with the coupling constant of 5.4 Hz respectively. A doublet at δ 6.00 with *J* value of 3.4 Hz was assigned to anomeric proton of glucose unit. A doublet appeared at δ 6.75 with *J* value of 9.3 Hz was assigned to two aromatic protons of *p*-methoxyphenyl group. The other seven aromatic protons have appeared as several multiplets between δ 7.10 and 7.45. A singlet appeared at δ 8.55 was assigned to aldehyde proton. The IR spectrum showed carbonyl stretching at 1747 cm^{-1}. Mass spectrum was well supporting the compound's structure.

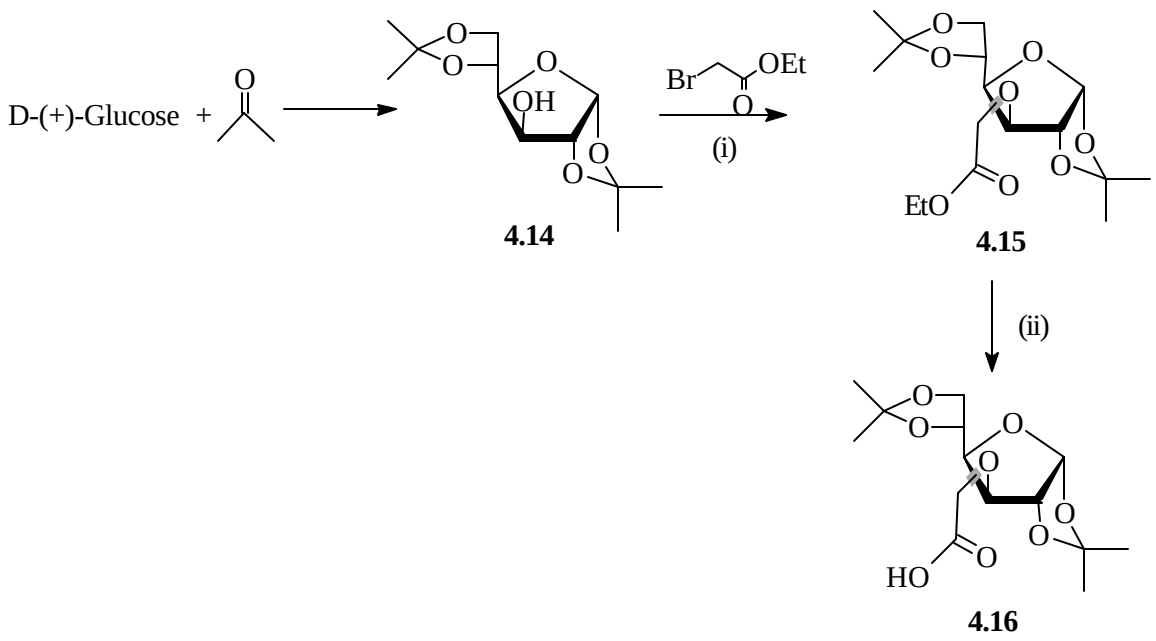
Spectral discussion and characterization of aldehyde 4.13

^{1}H NMR spectrum showed several multiplets between δ 1.06 and 1.85 for ten methylene-protons of cyclohexylidine part. A doublet appeared at δ 3.47 with the coupling constant of 3.5 Hz was due to one of the glucose unit protons. A sharp singlet appeared at δ 3.70 was assigned to methyl-protons of *p*-methoxy phenyl group. The two doublets appeared at δ 4.26 and 4.35 with *J* values of 3.4 and 4.3 Hz respectively were due to two of glucose unit protons. The C4 and C3 β-lactam protons have appeared as set of doublets at δ 4.94 and 5.14 with *J* values of 4.9 Hz. The anomeric proton of glucose unit was resonated at δ 5.26 with the coupling constant of 3.4 Hz. The nine aromatic protons have appeared as several multiplets between δ 7.10 and 7.45. The aldehyde proton has resonated at δ 9.45 as a singlet. Mass spectrum was well supporting the compound's structure.

4.3.8 ***Preparation of acid 4.16***

As discussed above the acid **4.03** derived from D-glucose did not give diastereoselectivity in β-lactam ring formation. Therefore, it was decided to prepare other the acids from D-glucose and study their effect of on the diastereoselective β-lactam ring formation *via* ketene-imine cycloaddition reaction. The acid **4.16** was prepared from 1,2:5,6-di-O-isopropylidine (**4.14**)[19] by following similar procedure as described earlier (Scheme – 4.19).

Scheme 4.19



Reagents and conditions (i): NaH/THF, reflux, 15 h. (ii): MeOH/KOH, overnight, rt.

Spectral discussion and Characterization of acid 4.16

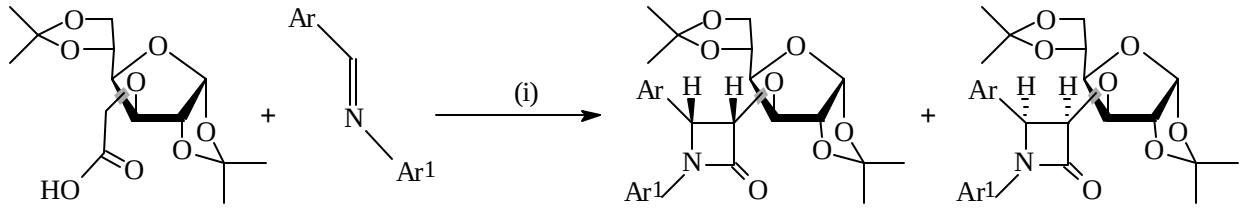
^{1}H NMR spectrum of acid **4.16** showed merged signal for nine protons of three methyl groups belonging to acetonide *gem*-dimethyls δ 1.20 and 1.55. The other methyl group of one of the acetonide appeared separately as a sharp singlet at δ 2.10. Several multiplets between δ 3.64 and 4.44 were seen for four protons of the glucose unit. One proton of glucose unit was appeared as doublet at δ 4.53 with the coupling constant of 3.6 Hz. The anomeric proton of glucose unit was resonated as a doublet at δ 4.61 with the coupling constant of 3.7 Hz. A multiplet appeared at δ 5.86-6.00, integrating for one proton, was due to one of the glucose unit protons. A broad singlet appearing at δ 8.00-8.70 was assigned to the proton of acid-hydroxyl group. The IR spectrum showed carbonyl stretching at 1736 cm^{-1} and OH stretching at 3425 cm^{-1}.

4.3.9 Preparation of b-lactams 4.18a,b & 4.19a,b

The acid **4.16** on treatment with different imines (**3.17**) under similar reaction conditions as described for the preparation of β-lactams **4.05** and **4.06**, gave crude β-lactam as a diastereomeric mixture. This crude reaction mixture after purification by column chromatography gave inseparable diastereomeric mixture of β-lactams **4.18** and **4.19** in almost equal quantities. These diastereomers could not be separated either by column

chromatography or by crystallization. The β-lactam protons were found to be *cis* to each other from ^{1}H NMR coupling constants.

Scheme 4.20



4.16 **4.17** **4.18** **4.19**

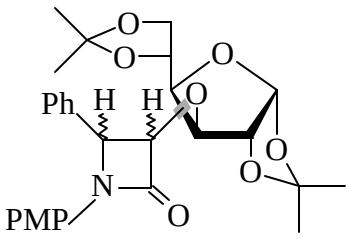
Reagents and conditions (i): $CO(OCCl_3)_2/Et_3N$, 0° C, 15h.

Table 3. Synthesis of β-lactams **4.18** and **4.19**

Compound No:	**Ar**	**Ar^1**	Compounds **4.18** and **4.19**		
			Yield[a]	Ratio[b]	M.p[c] °C
a	Ph	PMP	56	~1:1	156-157
b	PMP	PMP	54	~1:1	160-161

[a] Isolated yield of β-lactam mixture (**4.18** and **4.19**). [b] The diastereomeric ratio determined from ^{1}H NMR spectrum. [c] M.p of pure β-lactam mixture (**4.18** and **4.19**).

The β-lactam mixture **4.18a** and **4.19a** was chosen as representative pair for spectral discussion and characterization.



4.18a & **4.19a**

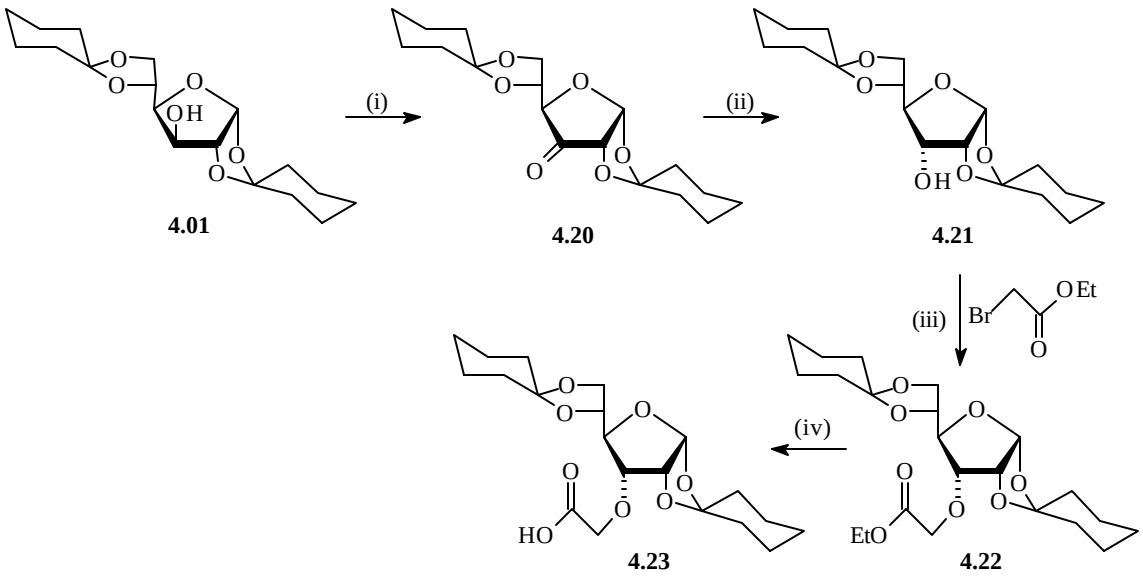
^{1}H NMR spectrum of the diastereomeric mixture showed a multiplet at 0.90-1.50 for twenty-four protons of *gem*-dimethyl groups. One of the glucose unit protons was seen as a doublet at δ 3.10 with a coupling constant of 3.4 Hz. The two methoxy groups of *p*-methoxyphenyl from diastereomeric β-lactams **4.18a** and **4.19a** appeared together as a singlet at δ 3.65. Several multiplets appeared between δ 3.15 and 4.45 were due to glucose unit protons. The two doublets appeared at δ 4.55 and 4.86 with the coupling constant of 3.9 and 3.4 respectively were due to two of glucose unit protons. The two doublets appeared at δ 4.92 and 5.21 with the coupling constant of 5.3 and 5.4 respectively

were due to two of β-lactam protons. One of the β-lactam ring protons and anomeric proton from one diastereomer were merged and appeared as a multiplet at δ 5.07-5.18. A doublet appeared at δ 5.77 with the coupling constant of 4.0 Hz was due to one of the anomeric protons of the glucose unit. The other anomeric proton resonated at δ 5.88 with the coupling constant of 3.9 Hz. The two multiplets appeared at δ 6.60-6.86 and δ 7.00-7.46 were due to total of eighteen aromatic protons. The IR spectrum showed carbonyl stretching at 1743 cm^{-1}.

4.3.10 Preparation of acid 4.23

The acids **4.03** and **4.16** derived from 4-β-hydroxy derivative of glucose did not give appreciable diastereoselectivity in β-lactam ring formation as these acid derivatives fail to provide necessary steric discrimination in ketene-imine cycloaddition reaction. It was, therefore, decided to synthesize the acid by inverting the chiral center bearing hydroxy group at C-3 and study its effect on the diastereoselectivity in β-lactam ring formation.

Scheme 4. 21



Reagents and reaction conditions (i): PCC, 3A° MS, neutral alumina/DCM, RT, 15 h. (ii): $NaBH_4$/MeOH:H_2O. (iii): NaH/THF, ref. 15 h. (iv): MeOH/KOH, overnight.

The alcohol **4.01** on oxidation with PCC by reported procedure[20] gave ketone **4.20**, which on reduction[21] with $NaBH_4$ yielded C-3 inverted alcohol **3.21** in good over all yield

(Scheme-4.21). This alcohol **4.21** on alkylation with ethyl bromoacetate in presence of sodium hydride gave ester **4.22** in 76% yield. The ester **4.22** on alkaline hydrolysis gave corresponding acid **4.23** in very high yield (92%).

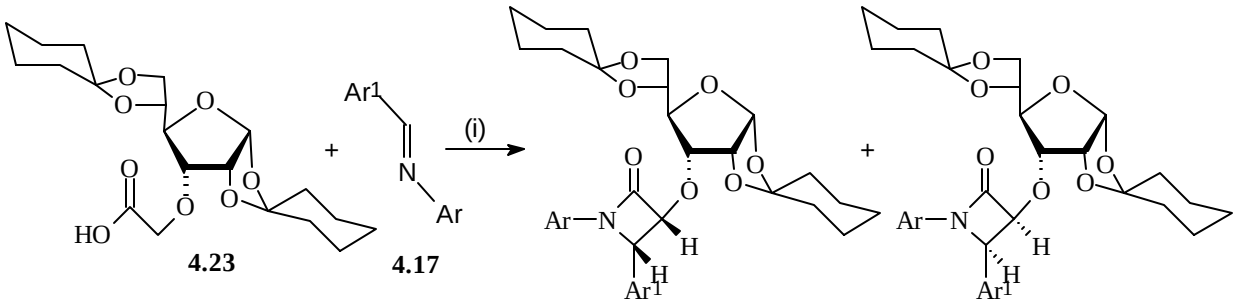
Spectral discussion and characterization of acid 4.23

^{1}H NMR spectrum of acid **4.23** showed a multiplet at δ 1.20-1.90 for ten cyclohexylidine-protons. A doublet appeared at δ 2.06 with the coupling constant of 12.7 Hz, accounting for two protons. Several multiplets appeared between δ 3.60 and 4.50 were due to five of glucose unit protons. One of the glucose unit protons at C-4 appeared as triplet at δ 4.70 with the coupling constant of 3.9 Hz. The anomeric proton of glucose unit has resonated at δ 5.80 with the coupling constant of 3.5 Hz. A broad singlet appeared at δ 7.96 was assigned to the proton of carboxylic OH group. The IR spectrum showed carbonyl stretching at 1738 cm^{-1} and OH stretching at 3491cm^{-1}.

4.3.11 Preparation of β-lactams 4.24a,b & 4.25a,b

The acid **4.23** on reaction with imines **4.17** in presence of triethylamine and triphosgene at 0 °C gave a diastereomeric mixture of β-lactams **4.24** and **4.25** in good yield (Scheme-4.22). The HPLC analysis of the crude reaction mixture showed a maximum diastereomeric ratio of 59:41 by using imine derived from benzaldehyde and *p*-methoxyaniline. These β-lactams could be separated easily by column chromatography using 15% ethyl acetate-pet. ether. The C4 and C3 β-lactam protons were found to be *cis* to each other from ^{1}H NMR coupling constant. The reaction carried out at –15 °C using imine **3.17a** also could not improve the diastereoselectivity on the contrary gave lower yield (55%). The absolute stereochemistry of these compounds could not be determined, as these derivatives also did not give quality crystal required for X-ray analysis.

Scheme 4. 22



4.23 **4.17** **4.24** **4.25**

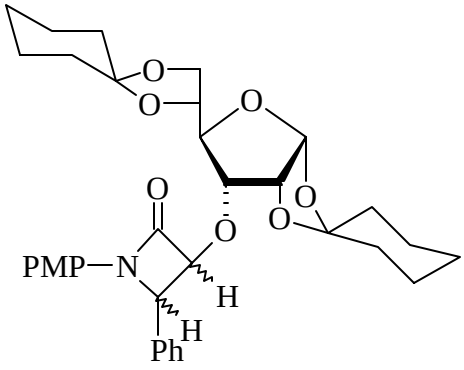
Reagents and reaction conditions (i): $CO(OCCl_3)_2$, Et_3N/DCM, 0 °C, Overnight.

Table 4. Synthesis of β-lactams **4.24** and **4.25**

Compd No.	**Ar[1]**	**Ar**	Yield[a] (%)	Ratio[b] of **4.24** & **4.25**	M.p.[c] (°C)	
					4.24a	**4.25a**
a	Ph	PMP	67	59:41	103-105	151-152
b	PMP	PMP	58	53:47	Semisolid	140-141

[a] Isolated yield of β-lactam mixture (**4.24** and **4.25**). [b] The diastereomeric ratio determined from ^{1}H NMR coupling constant and HPLC analysis. [c] The β-lactam mixture was separated by column chromatography.

The β-lactam **4.24a** was chosen as a representative of β-lactams **4.24a** and **4.24b** for spectral discussion and characterization.



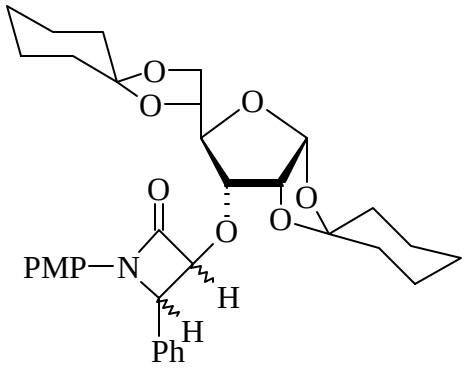
4.24a

The ^{1}H NMR spectrum of β-lactam **4.24a** showed several multiplets at δ 1.05-1.80 due to cyclo-hexylidine-protons. Several multiplets appeared between δ 3.22 and 3.95 were due to 5 protons of glucose part. A singlet appeared at δ 3.66 was assigned to methyl protons of *p*-methoxyphenyl group. The glucose unit proton at C-4 resonated at δ 4.63 as a triplet with the coupling constant of 4.1 Hz. The C-4 and C-3 β-lactam protons appeared as a set of doublets at δ 5.05 and 5.10 respectively with the coupling constant of 5.1 Hz, , indicating the *cis* stereochemistry of these protons. The anomeric proton of glucose unit has resonated at δ 5.67 as a doublet with the

coupling the constant of 3.6 Hz. A doublet appeared at δ 6.70 with the coupling constant of 9.2 Hz was due to two of 9 aromatic protons. The other seven aromatic protons have appeared as multiplet between δ 7.06 and 7.45. The IR spectrum showed β-lactam carbonyl stretching at 1749 cm^{-1}.

The β-lactam **4.25a** was chosen as a representative of β-lactams **4.25a** and **4.25b** for spectral discussion and characterization.

The ^{1}H NMR spectrum of β-lactam **4.25a** showed several multiplets at δ 1.05-1.85 due to cyclo-hexylidine protons. The glucose unit proton at C-4 appeared as a triplet at δ 3.48 with the coupling constant of 4.2 Hz. A sharp singlet appeared at δ 3.68 was assigned to methyl protons of *p*-methoxy phenyl group. A set of multiplets appeared between δ 3.60- 3.80 and 3.95-4.15 were due to five glucose



4.25a

unit protons. The C-4 and C-3 β-lactam protons have appeared as a set of doublets at δ 5.12 and 5.24 respectively with the coupling constant of 5.1 Hz, indicating the *cis* stereochemistry of these protons. The anomeric proton of glucose unit has resonated at δ 5.56 as a doublet with the coupling constant of 3.7 Hz. A doublet appeared at δ 6.73 with the coupling constant of 9.1 Hz was due to two of 9 aromatic protons. The other seven aromatic protons have appeared as multiplets between δ 7.08 and 7.40. The IR spectrum showed β-lactam carbonyl stretching at 1745 cm^{-1}.

4.4 Summary

The acid derived from 1,2:5, 6-di-O-cyclohexylidine glucofuranoside (**4.01**) has been subjected to Staudinger reaction ([2+2] cycloaddition) in presence of acid activators and triethylamine for diastereoselective synthesis of optically pure *cis*-β-lactams and their derivatives. The acid derived from 1,2:5,6-di-O-disopropylidine glucofuranoside (**4.14**) has also been subjected to the above reaction to check its effect on diastereoselectivy. In most of the cases the almost 1:1 diastereomeric mixture was obtained. The inversion of the chiral center at the C-3 position also did not show appreciable improvement in diastereoselectivity in the formation of β-lactam ring.

4.5 **Experimental**

4.5.1 Preparation of ester 4.02

Slurry of alcohol **4.01** (10 g, 0.0294 mol) and NaH (~50%) (1.55 g, 0.032) in dry THF (175 ml) was refluxed for 2 h. The reaction mixture was then cooled to 0 °C and a solution of ethyl bromoacetate (3.3 ml, 0.0294 mol) in dry THF (30 ml) was then added slowly over a period of 30 min. The reaction mixture was allowed to warmed-up to room temperature and then it was refluxed for 15 h. The reaction mixture was then cooled to 0 °C and the excess NaH was quenched with methanol and the solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The ethyl acetate extract was washed with water (3x25 ml), brine (25 ml) and dried over anhydrous Na_2SO_4. It was then filtered and filtrate on evaporation of solvent gave 8.89 g (76%) of ester **4.02** as viscous oil.

MS (m/z) : 426 (M^+), 397, 99 (100%).

IR: 1749 cm^{-1}.

4.5.2 Preparation of acid 4.03

To a solution of ester **4.02** (8.76 g, 0.02 mol) in methanol (100 ml), potassium hydroxide (3.5 g, 0.0625 mol) was added portion wise. The reaction mixture was stirred for overnight at room temperature. The solvent was removed by distillation under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate to remove trace amount of unreacted ester present. The reaction mixture was acidified with 2N HCl and extracted with ethyl acetate (3x50 ml). The ethyl acetate extract was washed with water (3x20 ml), brine (20 ml) and dried over Na_2SO_4. It was then filtered and filtrate on evaporation of solvent gave 7.32 g (92%) of required acid **4.03** as thick syrup.

^{1}H NMR : δ 1.13-1.85 (m, 20H; 3.80-4.46 (m, 8H); 4.54 (d, *J* = 3.6 Hz, 1H); 5.96 (d, *J* = 3.6 Hz, 1H).

MS (m/z) : 398 (M^+), 83 (100%).

IR : 1737 cm^{-1}.

$[\alpha]_D$: −22.83° (c, 1 $CHCl_3$).

4.5.3 General procedure for the synthesis of β-lactams 3.04 a-e and 3.05 a-e

To a stirred mixture of acid **4.03** (0.85 g, 2.135 mmol), imines (**4.04**) (2.77 mmol), triethylamine (0.9 ml, 6.46 mmol) and dry CH_2Cl_2 (15 ml), a solution of phenyl dichlorophosphate (0.5 ml, 3.2 mmol) in dry CH_2Cl_2 (15 ml) was added at 0 °C over a period of 20 min. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and successively washed with water (15 ml), satd. $NaHCO_3$ solution (15 ml) and brine (15 ml) and dried over anhydrous Na_2SO_4. It was then filtered and filtrate on evaporation of solvent gave crude product, which was column chromatographed (silica gel, 60-120, 15% ethyl acetate/pet. ether) to furnish a pure mixture of β-lactams **4.05a-e** and **4.06a-e** in moderate yields.

4.5.3a Synthesis of β-lactams 4.05a & 4.06a

The acid **4.03** (0.85 g, 2.135 mmol) on treatment with imine **4.04a** (0.584 g, 2.77 mmol) in presence of triethylamine (0.9 ml, 6.46 mmol) and phenyl dichlorophosphate (0.5 ml, 3.2 mmol) at 0 °C gave crude product. This was column chromatographed to give 732 mg (58%) of diastereomeric mixture of β-lactams **4.05a** & **4.06a** as a white solid. The diastereomers could not be separated either by crystallization or column chromatography.

M.p. : 180-182 °C.

^{1}H NMR : δ 1.05-1.75 (m, 40H); 3.06 (d, *J* = 3.4 Hz, 1H); 3.15-3.30 (m, 1H); 3.45-3,60 (m, 1H); 3.65-4.15 (m, 7H); 3.75 (s, 6H); 4.25-4.45 (m, 1H); 4.90 (d, *J* = 3.4 Hz, 1H); 5.02 (d, *J* = 5.4 Hz, 1H); 5.29-5.35 (m, 4H); 5.83 (d, *J* = 3.9 Hz, 1H); 6.80 (d, *J* = 8.8 Hz, 4H); 7.20-7.47 (m, 14H).

^{13}C NMR : 23.37, 23.69, 25.01, 34.42, 36.07, 36.30, 55.15, 61.49, 61.97, 65.76, 66.74, 71.62, 71.74, 80.53, 81.02, 81.89, 82.14, 82.90, 83.31, 84.09, 84.46, 104.28, 104.62, 109.41, 111.95, 112.22, 114.17, 118.55, 127.57, 127.80, 128.32, 128.54, 130.32, 133.25, 133.74, 156.25, 162.31, 163.96.

MS (m/z) : 591 (M^+), 563, 493, 211, 54 (100%).

IR : 1749 cm^{-1}.

4.5.3b Synthesis of β-lactams 4.05b & 4.06b

The acid **4.03** (0.85 g, 2.135 mmol) on treatment with imine **4.04b** (0.667 g, 2.77 mmol) in presence of triethylamine (0.9 ml, 6.46 mmol) and phenyl dichlorophosphate (0.5

ml, 3.2 mmol) at 0 °C gave crude product. This was column chromatographed to give 677 mg (51%) of pure β-lactam mixture **4.05b** & **4.06b** as a white solid. This mixture could not be separated either by crystallization or by column chromatography.

M.p. : 114 – 115 °C.

^{1}H NMR : δ 1.05-1.75 (m, 40H); 3.21 (d, *J* = 3.7 Hz, 1H); 3.25-3.38 (m, 1H); 3.45-4.17 (m, 11H); 3.71 (s, 3H); 3.78 (s, 3H); 3.80 (s, 3H); 4.27-4.45 (m, 1H); 4.87 (d, *J* = 3.7Hz, 1H); 4.97 (d, *J* = 5.1 Hz, 1H); 5.10-5.25 (m, 3H); 5.34 (d, *J* = 2.9 Hz, 1H); 5.84 (d, *J* = 3.6 Hz, 1H); 6.55-7.36 (m, 16H).

MS (m/z) : 281, 241 and 108 (100%).

IR : 1749 cm^{-1}.

4.5.3c Synthesis of b-lactams 4.05c & **4.06c**

The acid **4.03** (0.85 g, 2.135 mmol) on treatment with imine **4.04c** (0.656 g, 2.77 mmol) in presence of triethylamine (0.9 ml, 6.46 mmol) and phenyl dichlorophosphate (0.5 ml, 3.2 mmol) at 0 °C gave crude product. This was column chromatographed to give 870 mg (66%) of diastereomeric mixture of pure β-lactams **4.05c** & **4.06c** as a white solid. These diastereomers could not be separated either by column chromatography or by crystallization.

M.p. : 137 – 138 °C.

^{1}H NMR : δ 1.12-1.80 (m, 40H); 3.77 (s, 6H); 3.86-4.30 (m, 10H); 4.40-4.60 (m, 2H); 4.76-5.03 (m, 5H); 5.24 (d, *J* = 6.8 Hz, 1H); 5.76 (d, *J* = 3.4 Hz, 1H); 5.95 (d, *J* = 3.4 Hz, 1H); 6.20-6.42 (m, 2H); 6.72-6.95 (m, 4H); 7.20-7.55 (m, 14H).

IR : 1747 cm^{-1}.

4.5.3d Synthesis of b-lactams 4.05d & **4.06d**

The acid **4.03** (0.85 g, 2.135 mmol) on treatment with imine **4.04d** (0.584 g, 2.77 mmol) in presence of triethylamine (0.9 ml, 6.46 mmol) and phenyl dichlorophosphate (0.5 ml, 3.2 mmol) at 0 °C gave crude product. This was column chromatographed to give 720 mg (57%) of diastereomeric mixture of pure β-lactams **4.05d** & **4.06d** as a white solid. These diastereomers could not be separated either by column chromatography or by crystallization.

M.p. : 89 – 90 °C.

^{1}H NMR : δ 1.15-1.82 (m, 40H); 3.21 (d, *J* = 3.7 Hz, 1H); 3.27-3.43 (m, 1H); 3.53-4.27

(m, 8H); 3.79 (s, 3H); 3.80 (s, 3H); 4.27-4.50 (m, 1H); 4.88 (d, *J* = 3.6 Hz, 1H); 5.00 (d, 5.5 Hz, 1H); 5.18-5.32 (m, 3H); 5.37 (d, 3.7 Hz, 1H); 5.84 (d, *J* = 3.7 Hz, 1H); 6.80-7.47 (m, 18H).

^{13}C NMR : : 23.31, 23.39, 23.62, 23.69, 23.86, 24.03, 24.70, 25.01, 34.38, 35.13, 35.49, 36.07, 36.24, 36.33, 55.03, 55.09, 61.18, 61.53, 65.94, 66.81, 71.62, 71.76, 80.55, 80.64, 81.08, 81.92, 82.17, 82.85, 83.20, 84.11, 84.24, 104.34, 104.63, 108.85, 109.49, 112.02, 112.3, 113.82, 113.99, 117.36, 121.32, 124 29, 124.81, 125.24, 128.64, 128.95, 129.06, 136.78, 159.75, 159.98, 163.08, 164.71.

MS (m/z) : 591 (M^+), 563, 251(100%), 211.

IR : 1751 cm^{-1}.

4.5.3e Synthesis of b -lactams 4.05e & **4.06e**

The acid **4.03** (0.85 g, 2.135 mmol) on treatment with imine **4.04e** (0.556 g, 2.77 mmol) in presence of triethylamine (0.9 ml, 6.46 mmol) and phenyl dichlorophosphate (0.5 ml, 3.2 mmol) at 0 °C gave crude product. This was column chromatographed to give 681 mg (55%) of diastereomeric mixture of pure β-lactams **4.05e** & **4.06e** as a white solid. These diastereomers could not be separated either by column chromatography or by crystallization.

M.p. : 100 – 101 °C.

^{1}H NMR : δ 1.05-1.85 (m, 40H); 3.60-4.20 (m, 11H); 3.72 (s, 3H); 3.77 (s, 3H); 4.35-4.48 (m, 1H); 4.90 (d, *J* = 3.7 Hz, 1H); 5.03 (d, *J* = 5.9 Hz, 1H); 5.20-5.35 (m, 3H); 5.56 (d, *J* = 3.7 Hz, 1H); 5.89 (d, *J* = 3.7 Hz, 1H); 6.40 (d, *J* = 9.6 Hz, 2H); 6.65 (d, *J* = 9.6 Hz, 2H); 6.75 (d, *J* = 9.6 Hz, 2H); 6.82 (d, *J* = 9.6 Hz, 2H); 7.20-7.55 (m, 6H);

IR : 1755 cm^{-1}.

4.5.4 General procedure or the preparation of diols 4.07 and 4.08

The β-lactam mixture **4.05a** and **4.06a** (0.985g, 1.66mmol) was taken in 10 ml of 75% aq. acetic acid and kept at 75-80 °C for 2.5 h. with intermittened shaking. After the completion of reaction (TLC), the acetic acid was removed under reduced pressure and the residue was taken 25 ml of dichloromethane. Which was then washed with sat. bicarbonate (2x5 ml) and brine (5 ml), dried over anhydrous sodium sulfate. It was filtered and filtrate on evaporation of organic solvent under reduced pressure gave crude product **4.07** and **4.08**.

These diols (**4.07** and **4.08**) were separated by flash column chromatography using 30% ethyl acetate/pet. ether to give 831 mg (98%, total yield) of pure product as a white solid.

diol 4.07

M.p. : 102-121 °C.

^{1}H NMR : δ 1.22-1.75 (m, 10H); 1.85 (bs, 2H); 3.20-3.62(m, 3H); 3.77 (s, 3H); 3.87-4.05 (m, 2H); 4.57 (d, *J* = 3.4 Hz, 1H); 5.10 (d, *J* = 4.9 Hz, 1H); 5.30 (d, *J* = 4.9 Hz, 1H); 5.90 (d, *J* = 8.8 Hz, 2H); 7.15- 7.56 (m, 7H).

^{13}C NMR : 23.73, 24.02, 25.01, 35.82, 36.48, 55.60, 62.29, 64.31, 68.83, 80.15, 82.28, 83.35, 84.38, 104.74, 112.72, 114.67, 119.08, 127.83, 129.26, 130.40, 133.74, 156.86, 163.96.

MS (m/z) : 511 (M^+), 362, 149, 99 (100%

IR : 1749 and 3579 cm^{-1}.

$[\alpha]_D$: +80.99° (c, 1 $CHCl_3$).

diol 4.08

M.p. : 193 – 194 °C.

^{1}H NMR : δ 1.10-1.61 (m, 10H); 3.14 (bs, 2H); 3.40 (d, *J* = 3.4 Hz, 1H); 3.47-3.85 (m, 3H); 3.67 (s, 3H); 3.85-4.08 (m, 2H); 4.95-5.10 (m, 1H); 5.15-5.26 (m, 1H); 5.12 (d, J= 3.4 Hz, 1H); 6.70 (d, *J* = 8.8 Hz, 2H); 7.10-7.45 (m, 7H).

^{13}C NMR : 23.33, 23.62, 24.64, 35.31, 36.10, 55.23, 62.77, 64.67, 68.23, 80.04, 81.93, 84.86, 85.01, 104.31, 112.17, 114.21, 118.85, 127.88, 128.58, 128.72, 129.93, 133.30, 156.48, 164.13.

MS (m/z) : 511 (M^+), 362, 149, 99 (100%).

IR : 1739 and 3409 cm^{-1}.

$[\alpha]_D$: –32.77° (C, 0.01 $CHCl_3$).

4.5.5 General procedure for the preparation of acetates 4.09 and 3.10 from diol 3.07

To a methylene chloride (25 ml) solution of diol **4.08** (0.2 g 0.38 mmol) and triethyl amine (0.2 g, 1.97 mmol), a methylene chloride (5 ml) solution of acetyl chloride (0.1 ml, 1.37 mmol) was added drop wise at 0°C over a period of 10 min. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 3.5 h at the same temperature. After the starting material disappeared (TLC), the reaction mixture was diluted with methylene chloride, successively washed with water (10 ml), bicarbonate (2x10 ml) and

brine (10 ml). This solution was dried over anhydrous Na_2SO_4. It was filtered and the filtrate on evaporation of solvent gave crude product. The two spots seen on TLC were separated by column chromatography using 15% ethyl acetate/pet. ether to give pure di and monocetates **4.09** and **4.10** respectively in 86% yield as a white solid.

Diacetate 4.09

M.p. : Semi solid.

^{1}H NMR : δ 0.70-1.75 (m, 10H); 2.05 (s, 3H); 2.17 (s, 3H); 3.74 (s, 3H); 3.84 (d, *J* = 3.4 Hz, 1H); 3.88-4.65 (m, 5H); 4.97 (d, *J* = 4.9 Hz, 1H); 5.08 (d, *J* = 2.9 Hz, 1H); 5.17 (d, *J* = 4.9 Hz, 1H); 6.75 (d, *J* = 8.8 Hz, 2H); 7.12-7.46 (m, 7H).

MS (m/z) : 595(M^+), 446, 211(100%), 149.

IR : 1637(w) and 1749 cm^{-1}.

Monoacetate 4.10

M.p. : 116 – 117 °C.

^{1}H NMR : δ 0.25-1.72 (m, 10H); 2.10 (s, 3H); 3.44 (d, *J* = 3.4 Hz, 1H); 3.75 (s, 3H); 3.99-4.25 (m, 3H); 4.37 (d, *J* = 9.2 Hz, 2H); 5.12 (d, *J* = 4.4 Hz, 1H); 5.19 (d, *J* = 3.4 Hz, 1H); 5.28 (d, *J* = 4.9 Hz, 1H); 6.80 (d, *J* = 8.8 Hz, 2H); 7.17-7.50 (m, 7H).

MS (m/z) : 553(M^+), 211(100%), 149.

IR : 1738 and 3462 cm^{-1}.

$[\alpha]_D$: –38.02° (c, 1 DCM).

4.5.6 Preparation of dibenzoate 4.11 of diol 4.08

To a methylene chloride (10 ml) solution of diol **4.08** (0.1 g, 0.19 mmol) and triethyl amine (0.1 g, 0.988 mmol), a methylene chloride (5 ml) solution of *p*-nitro benzoylchoride (0.109 g, 0.587 mmol) was added drop wise at 0 °C over a period of 10 min. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 3.5 h. After the consumption of starting diol (TLC), the reaction mixture was diluted with methylene chloride (20 ml) and it was successively washed with water (5 ml), bicarbonate (2x5 ml) and brine (5 ml). The organic solution was dried over anhydrous $NaSO_4$ and filtered. The filtrate on evaporation of solvent gave crude product, which was purified by column chromatography (silica gel, 60 – 120 mesh) using 25% ethyl acetate/pet. ether to give 152 mg (99%) of dibenzoate **4.08** as white solid.

M.p. : 2.03 – 204 °C.

^{1}H NMR : δ 1.30-1.75 (m, 10H); 3.76 (s, 3H); 3.88 (d, *J* = 3.4 Hz, 1H); 4.32 (d, *J* = 3.4 Hz, 1H); 4.39-4.65 (m, 2H); 4.80-5.00 (m, 1H); 4.45 (d, *J* = 4.9 Hz, 1H); 5.15 (d, *J* = 3.4 Hz, 1H); 5.20 (d, *J* = 4.4 Hz, 1H); 5.55-5.70 (m, 1H); 6.75 (d, *J* = 9.3 Hz, 2H); 7.13 (d, *J* = 9.3 Hz, 2H); 7.33-7.50 (m, 4H); 8.12-8.39 (m, 9H).

IR : 1689 (w), 1736 and 1757 cm^{-1}.

$[\alpha]_D$: : −115.2° (C, 0.01 DCM).

Elemental analysis:

Molecular Formula : $C_{42}H_{39}N_3O_{14}$.

Calculated : C, 62.29; H, 4.85; N, 5.18%

Found : C, 62.01, H, 4.90, N, 4.88%

4.5.7 General procedure for the preparation of aldehydes 4.12 and 4.13 from diols 4.07 and 4.08 respectively

To a 10 ml methanol/water (10:3) solution of diol (0.23 g, 0.45 mmol), powdered $NaIO_4$ (0.289 g, 1.35mmol) was added at room temperature and the reaction mixture was stirred overnight. After the completion of reaction (TLC), the reaction mixture was filtered and the residue was washed with methanol and the combined filtrates were concentrated on rotaevaporator. The residue was treated with water and extracted with methylene chloride (3x15 ml). The combined organic layer was dried over anhydrous $NaSO_4$. It was then filtered and filtrate on evaporation of solvent gave crude product, which was filtered through column to give pure aldehyde (**4.12** or **4.13)** as a white solid.

Aldehyde 4.12

Yield : 98%

M.p. : 90–91 °C.

^{1}H NMR : δ 1.13-1.85 (m, 10H); 3.70 (s, 3H); 3.99-4.13 (m, 1H); 4.20 (d, *J* = 3.4 Hz, 1H); 4.26 (d, *J* = 4.3 Hz, 1H); 4.85 (d, *J* = 4.9 Hz, 1H); 4.90 (d, *J* = 3.4 Hz, 1H); 5.17 (d, *J* = 5.4 Hz, 1H); 6.00 (d, *J* = 3.4 Hz, 1H); 6.75 (d, *J* = 9.3 Hz, 2H); 7.10-7.45 (m, 7H); 8.55 (s, 1H).

MS (m/z) : 479 (M^+), 330, 269, 240, 149, 91 (100%).

IR : 1747 cm^{-1}.

Aldehyde 4.13

Yield : 98%.

M.p. : 94–95 °C.

^{1}H NMR : δ 1.06-1.85 (m, 10H); 3.47 (d, *J* = 3.5 Hz, 1H); 3.67 (s, 3H); 4.26 (d, *J* = 3.4 Hz, 1H); 4.35 (d, *J* = 4.3 Hz, 1H); 4.94 (d, *J* = 4.9 Hz, 1H); 5.14 (d, *J* = 4.9 Hz, 1H); 5.26 (d, *J* = 3.4 Hz, 1H); 7.10-7.45 (m, 9H); 9.45 (s, 1H).

MS (m/z) : 479 (M^+), 330, 269, 240, 149, 91 (100%).

IR : 1749 cm^{-1}.

4.5.8 Preparation of Ester 4.15

Slurry of alcohol **4.14** (10 g, 0.0384 mol) and NaH (~50%) (2.0 g, 0.042) in dry THF (175 ml) was refluxed for 2 h. The reaction mixture was cooled to 0 °C and a solution of ethyl bromoacetate (4.3 ml, 0.0384 mol) in dry THF (30 ml) was added at this temperature over a period of 30 min. The reaction mixture was allowed to warm-up to room temperature and then it was refluxed for 15 h. The Reaction mixture was again cooled to 0 °C and excess NaH was quenched with methanol. The solvent from the reaction mixture was then removed by distillation under reduced pressure. The residue so obtained was treated with water (40 ml) and extracted with ethyl acetate (3x50 ml). The organic layer was washed successively with water (2x20 ml) and brine (15 ml) and dried over anhydrous Na_2SO_4. It was filtered and filtrate on concentration gave 9.96 g (75%) of ester **4.15** as viscous oil.

IR: 1751 cm^{-1}.

4.5.9 Preparation of acid 4.16

To a solution of ester **4.15** (6.92 g, 0.02 mol) in methanol (100 ml), potassium hydroxide (3.5 g, 0.0625 mol) was added in portions. The reaction mixture was stirred overnight at room temperature. The solvent was removed on a rotaevaporator. The residue so obtained was dissolved in water and extracted with ethyl acetate (2x25 ml) to remove trace amount of unreacted ester present. The aqueous layer was acidified with 2N HCl and extracted with ethyl acetate (3x50 ml). The combined organic extracts were washed with water (2x20 ml) and brine (15 ml) and dried over anhydrous Na_2SO_4. It was filtered and filtrate on concentration gave 5.72 g (90%) of acid **4.16** as thick syrup.

M.p. : Thick syrup.

^{1}H NMR : δ 1.20-155 (m, 9H); 2.10 (s, 3H); 2.20 (s, 2H); 3.64-4.44 (m, 4H); 4.53 (d, *J* = 3.6 Hz, 1H); 4.61 (d, *J* = 3.7 Hz, 1H); 5.86-6.00 (m, 1H); 8.0-8.70 (bs, OH).

IR : 3425, 1736, 1633 cm^{-1}.

MS (m/z) : 318(M^+), 141 (100%).

$[\alpha]_D$: −54.6 (c, 1 $CHCl_3$).

4.5.10a Synthesis of β-lactams 4.18a & 4.19a

The acid **4.16** (0.85 g, 2.67 mmol) on treatment with imine **4.17a** (0.845 g, 4.0 mmol) in presence of triethylamine (2.2 ml, 16.02 mmol) and triphosgene (729 g, 2.67 mmol) at 0 °C gave crude product. This was column chromatographed to give 764 mg (56%) of diastereomeric mixture of β-lactams **4.18a** & **4.19a** as a white solid. These diastereomers could not be separated either by column chromatography or by crystallization.

M.p : 156-157 °C.

^{1}H NMR : δ 0.90-1.50 (m, 24H); 3.10 (d, *J* = 3.4 Hz, 1H); 3.65 (2xs, 6H); 3.15-4.45 (m, 9H); 4.55 (d, *J* = 3.9 Hz, 1H); 4.86 (d, *J* = 3.4 Hz, 1H); 4.92 (d, *J* = 5.3 Hz, 1H); 5.07-5.18 (m, 2H); 5.21 (d, *J* = 5.4 Hz, 1H); 5.77 (d, *J* = 4.0 Hz, 1H); 5.88 (d, *J* = 3.9 Hz, 1H); 6.60-6.86 (m, 8H); 7.0-7.46 (m, 10H.

IR : 1743 cm^{-1}.

4.5.10b Synthesis of β-lactams 4.18b & 4.19b

The acid **4.16** (0.85 g, 2.67 mmol) on treatment with imine **4.17a** (0.964 g, 4.0 mmol) in presence of triethylamine (2.2 ml, 16.02 mmol) and triphosgene (729 g, 2.67 mmol) at 0 °C gave crude product. This was column chromatographed to give 780 mg (54%) of diastereomeric mixture of β-lactam **4.18b** & **4.19b** as a white solid. These diastereomers could not be separated either by column chromatography or by crystallization.

β-lactam mixture (**4.18b** and **4.19b**)

M.p : 160-161 °C.

^{1}H NMR : 0.90-1.50 (m, 24H); 3.10 (d, *J* = 3.4 Hz, 1H); 3.65 (2xs, 6H); 3.15-3.45 (m, 9H); 4.55 (d, *J* = 3.9 Hz, 1H); 4.86 (d, *J* = 3.4 Hz, 1H); 4.92 (d, *J* = 5.3 Hz,

1H); 5.07-5.18 (m, 2H); 5.21 (d, *J* = 5.4 Hz, 1H); 5.77 (d, *J* = 4.0 Hz, 1H); 5.88 (d, *J* = 3.9 Hz, 1H); 6.60-6.86 (m, 8H); 7.00-7.46 (m, 10).

IR : 1745 cm^{-1}

4.5.11 Preparation of ketone 4.20

A mixture of 1,2:5,6 di-O-cyclohexylidine-α-D-glucofuranoside (**4.01**) (15 g, 0.044 mol), PCC (12.3 g, 0.057 mol), activated molecular sieves (3A) (44 g), activated neutral alumina (22 g) and anhydrous dichloromethane (250 ml) was vigorously stirred with the help magnetic stirrer. The reaction mixture was stirred further for 15 h at room temperature. The supernatant dichloromethane layer from the reaction mixture was decanted and the residue was washed with dichloromethane (3x200 ml). The combined dichloromethane solution was filtered though a sintered glass funnel containing silica-gel (60-120 mesh). The residue was washed with ether (3x100 ml) and ether-DCM (9:1, 3x100 ml). The combined filtrate was concentrated under vacuum to give12 g (85%) ketone **4.20** as pale yellow syrup, which on standing solidified to a pale yellow solid.

M.p. : 66-67 °C.

^{1}H NMR : δ 1.20-1.85 (m, 20H); 3.85-4.47 (m, 4H); 4.40 (d, *J*=3.8Hz, 1H); 6.15 (d, *J*=3.8Hz, 1H).

IR : 1774, 1633 cm^{-1}.

MS (m/z) : 338(M^+), 141(100%).

$[\alpha]_D$: +108.1 (c, 1, $CHCl_3$).

4.5.12 Preparation of alcohol 4.21

To an ice-cold solution of ketone **4.20** (7.0 g, 0.021 mol) in ethanol-water (7:3, 75 ml), $NaBH_4$ (0.91 g, 0.024 mol) was added in portions. After 1h, ice bath was removed and stirring was continued further for 1h. Ethanol was removed under reduced pressure and residue was extracted with DCM. The combined organic extract was washed with water, dried over anhydrous Na_2SO_4. It was filtered and filtrate on evaporation of solvent gave 6.28 g (85%) of C-3 inverted alcohol **4.21** as a white solid. It was crystallized from pet. ether.

M.p : 120 °C.

^{1}H NMR : δ 1.15-1.85 (m, 20H); 2.60 (d, *J*=8.3 Hz, 1H); 3.80 (dd, 4.4 & 8.3 Hz, 1H); 3.92-4.15 (m, 2H); 4.30 (dd, *J*= 6.3 & 11.25 Hz, 1H); 4.61 (t, *J*= 4.9 Hz, 1H);

5.82 (d, *J*=3.9 Hz, 1H).

IR : 3493, 1625 cm^{-1}.

MS (m/z) : 340(M^+), 199, 141(100%).

$[\alpha]_D$: +36.53(c, 1 CHCl3).

4.5.13 Preparation of Ester 4.2

Slurry of alcohol **4.21** (10 g, 0.0294 mol) and NaH (~50%) (1.55 g, 0.032) in dry THF (175 ml) was refluxed for 2 h. It was then cooled to 0 °C and a solution of ethyl bromoacetate (3.3 ml, 0.0294 mol) in dry THF (30 ml) was added over a period of 30 min. The reaction mixture was allowed to warm-up to room temperature and then it was refluxed for 15 h. The reaction mixture was again cooled to 0 °C and the excess NaH was quenched by the addition of methanol. The solvent was removed by distillation under reduced pressure. The residue so obtained was treated with water (40 ml) and extracted with ethyl acetate (3x50 ml). The ethylacetate solution was dried over anhydrous Na2SO_4. It was then filtered and filtrate on evaporation of organic solvent gave 8.89 g (76%) of ester **4.22** as viscous oil.

M.p. : Viscous oil.

IR : 1755, 1633 cm^{-1}.

MS (m/z) : 426(M^+), 409, 141(100%).

$[\alpha]_D$: +47.65 (c, 1 $CHCl_3$).

4.5.14 Preparation of acid 4.23

To a solution of ester **4.22** (8.76 g, 0.02 mol) in methanol (100 ml), potassium hydroxide (3.5 g, 0.0625 mol) was added portion-wise. The reaction mixture was stirred overnight at room temperature. The solvent was removed on rotaevaporator. The residue was dissolved in water (40 ml) and extracted with ethyl acetate (2x2 ml) to remove trace amount of unreacted ester present. The aqueous solution was acidified with 2N HCl and extracted with ethyl acetate (3x50 ml). The organic extract was successively washed with water (2x30 ml) and brine (15 ml). This ethylacetate extract was dried over anhydrous Na_2SO_4. It was filtered and filtrate on removal of solvent by distillation under reduced pressure gave 7.32 g (92%) of required acid **4.23** as thick syrup, which solidified on standing.

M.p. : 109-110 °C.

^{1}H NMR : δ 1.20-1.80 (m, 20H); 2.06 (d, *J*= 12.7 Hz, 2H); 3.60-4.50 (m, 5H); 4.70 (t,

J= 3.9 Hz, 1H); 5.80 (d, *J*= 3.5 Hz, 1H); 7.96 (bs, 1H).

IR : 3491, 1738, 1633 cm^{-1}

MS (m/z) : 398(M^+), 141 (100%).

$[\alpha]_D$: +71.23 (c, 1 $CHCl_3$).

4.5.15a Synthesis of b-lactams 4.24a & 4.25a

To a solution of acid **4.23** (0.85 g, 2.135 mmol), imine **4.17a** (0.656 g, 2.77 mmol), and triethylamine (1.8 ml, 12.8 mmol) in dichloromethane (20 ml), a solution of triphosgene (583 mg, 2.135 mmol) in dichloromethane (10 ml) was added at 0 °C over a period of 30 min. The reaction mixture was allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with dichloromethane (40 ml) and it was washed successively with water (15 ml), satd. $NaHCO_3$ (15 ml), brine (10 ml), and dried (Na_2SO_4). It was filtered and filtrate on removal of solvent by distillation under reduced pressure gave diastereomeric mixture of β-lactams **4.24a** & **4.25a**. These diastereomers were separated by column chromatography (silica gel 100-200) using 15% ethylacetate-pet. ether to give 846 mg (67%, total yield) of pure product as a white solid. The less polar major isomer was tentatively called β-lactam **4.24a** and more polar as β-lactam **4.25a**.

b-lactam 4.24a

M.p. : 103-105 °C.

^{1}H NMR : δ 1.05-1.80 (m, 20H); 3.22-3.95(m, 5H); 3.66 (s, 3H); 4.63 (t, *J*= 4.1 Hz, 1H); 5.05 (d, *J*= 5.1 Hz, 1H); 5.1 (d, *J*= 5.1 Hz, 1H); 5.67 (d, *J*= 3.6 Hz, 1H); 6.70 (d, *J*= 9.2 Hz, 2H); 7.06-7.45 (m, 7H).

^{13}C NMR : 23.93, 25.03, 34.30, 35.71, 36.23, 55.27, 61.50, 64.21, 74.47, 77.95, 82.28, 103.77, 109.87, 113.68, 114.23, 118.63, 128.24, 128.43, 128.58, 133.43, 163.28.

IR : 1749 cm^{-1}.

MS (m/z) : 591(M^+), 149, 211(100%).

$[\alpha]_D$: -2.99 (c, 1 $CHCl_3$).

b-lactam 4.25a

M.p : 151-152°C

^{1}H NMR : δ 1.05-1.85 (m, 20H); 3.48 (t, *J*= 4.2 Hz, 1H); 3.60-3.80 (m, 2H); 3.68 (s, 3H); 3.95-4.15 (m, 3H); 5.12 (d, *J*= 5.1Hz, 1H); 5.24 (d, *J*= 5.1Hz, 1H);

5.56 (d, *J*= 3.7 Hz, 1H);6.73 (d, *J*= 9.1 Hz, 2H); 7.08-7.40 (m, 7H).

^{13}C NMR : 23.96, 24.95, 25.17, 29.66, 35.83, 36.31, 55.42, 61.38, 65.05, 74.79, 78.84, 81.67, 103.58, 110.38, 113.5, 114.5, 118.76, 128.17, 128.39, 130.81, 133.72, 156.51, 163.42.

IR : 1745 cm^{-1}.

MS (m/z) : 591(M^+), 149, 211(100%).

$[\alpha]_D$: +130.66 (c, 1 $CHCl_3$).

4.5.15b Synthesis of b-lactams 4.24b & 4.25b

The acid **4.23** (0.85 g, 2.135 mmol) on treatment with imine **4.17b** (0.667 g, 2.77 mmol) in presence of triethylamine (1.8 ml, 12.8 mmol) and triphosgene (583 mg, 2.135 mmol) at 0 °C gave 769 mg (58%, total yield) of β-lactams **4.24b** & **4.25b** as white solid. These β-lactams were separated by column chromatography (silica gel 100-200) using 15% ethylacetate-pet. ether. The less polar major isomer was tentatively called β-lactam **4.24b** and more polar as β-lactam **4.25b**.

b-lactam 4.24b

M.p : Semisolid.

^{1}H NMR : δ 0.55-1.86 m, 20H); 3.30-4.35 (m, 5H); 3.66 (s, 3H); 3.75 (s, 3H); 4.55-4.70 (m, 1H); 5.00 (d, *J*= 5.4 Hz, 1H); 5.07 (d, *J*= 5.4 Hz, 1H); 5.68 (d, *J*= 3.9 Hz, 1H); 6.70 (d, *J*= 9.3 Hz, 2H); 6.80 (d, *J*= 8.8 Hz, 2H); 7.18 (d, *J*= 8.8 Hz, 2H); 7.31 (d, *J*= 12.6 Hz, 2H).

IR : 17 45 cm^{-1}.

Mass m/z : 621(M^+), 472, 241, 149, 141(100%).

$[\alpha]_D$: –4.41 (c, 1 $CHCl_3$).

b-lactam 4.25b

M.p : 140-141°C.

^{1}H NMR : δ 0.65-1.85 (m, 20H); 3.50-3.85 (m, 3H); 3.66 (s, 3H); 3.73 (s, 3H); 3.92-4.18 m, 2H); 5.08 (d, *J*= 5.1 Hz, 1H); 5.20 (d, *J*= 5.1 Hz, 1H); 5.57 (d, *J*= 3.6 Hz, 1H); 6.50-6.90 (m, 4H); 7.08-7.30 (m, 4H).

IR : 17 45 cm^{-1}.

Mass m/z : 621(M+), 472, 241, 149, 141(100%).

$[\alpha]_D$: +95.64 (c, 1 $CHCl_3$).

4.6 References

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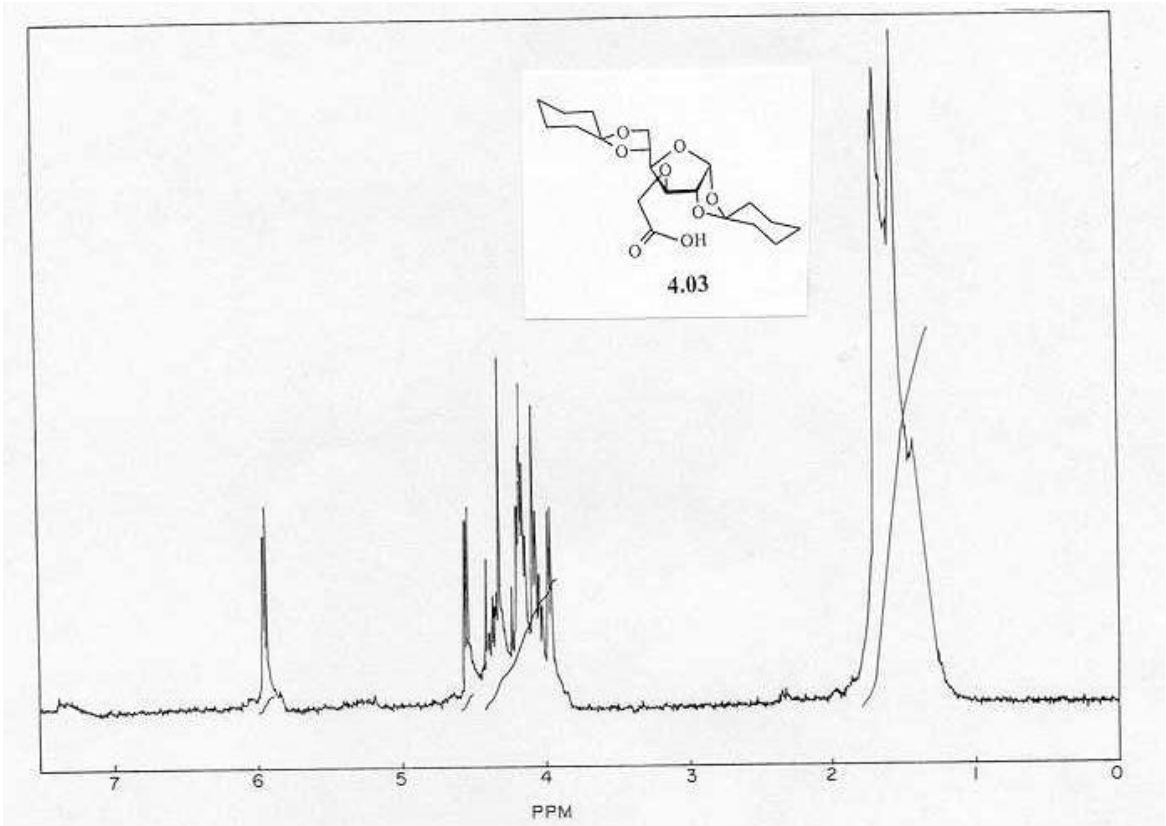

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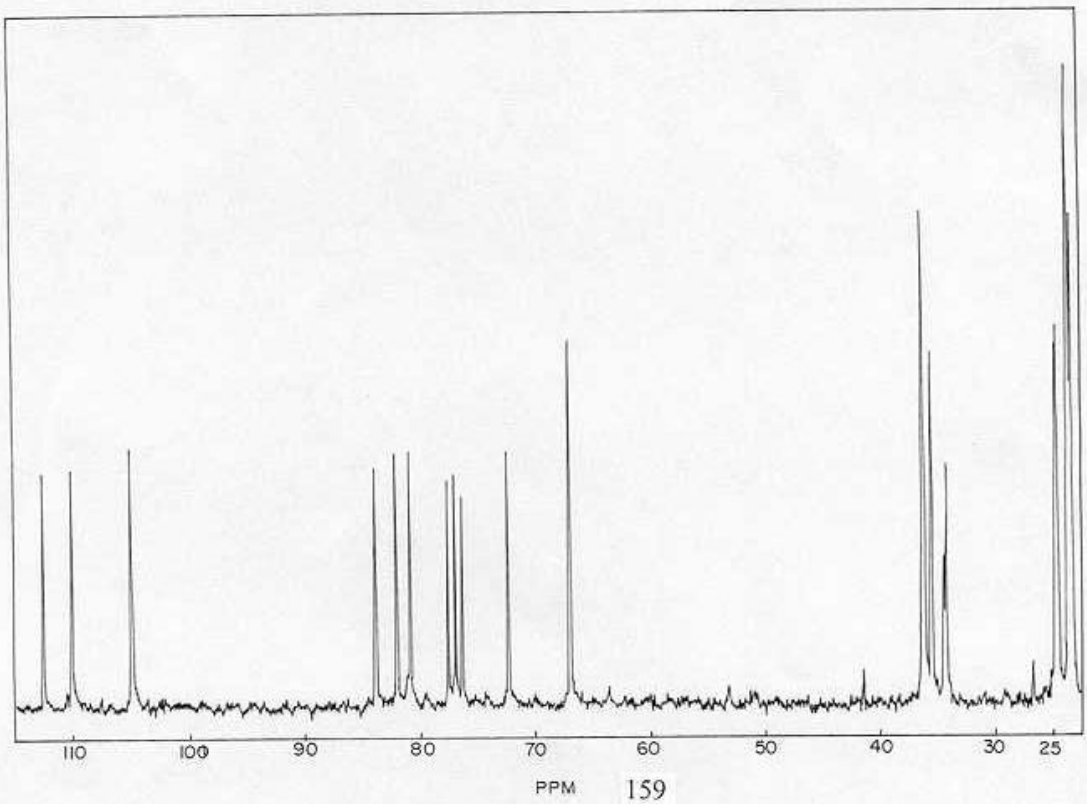
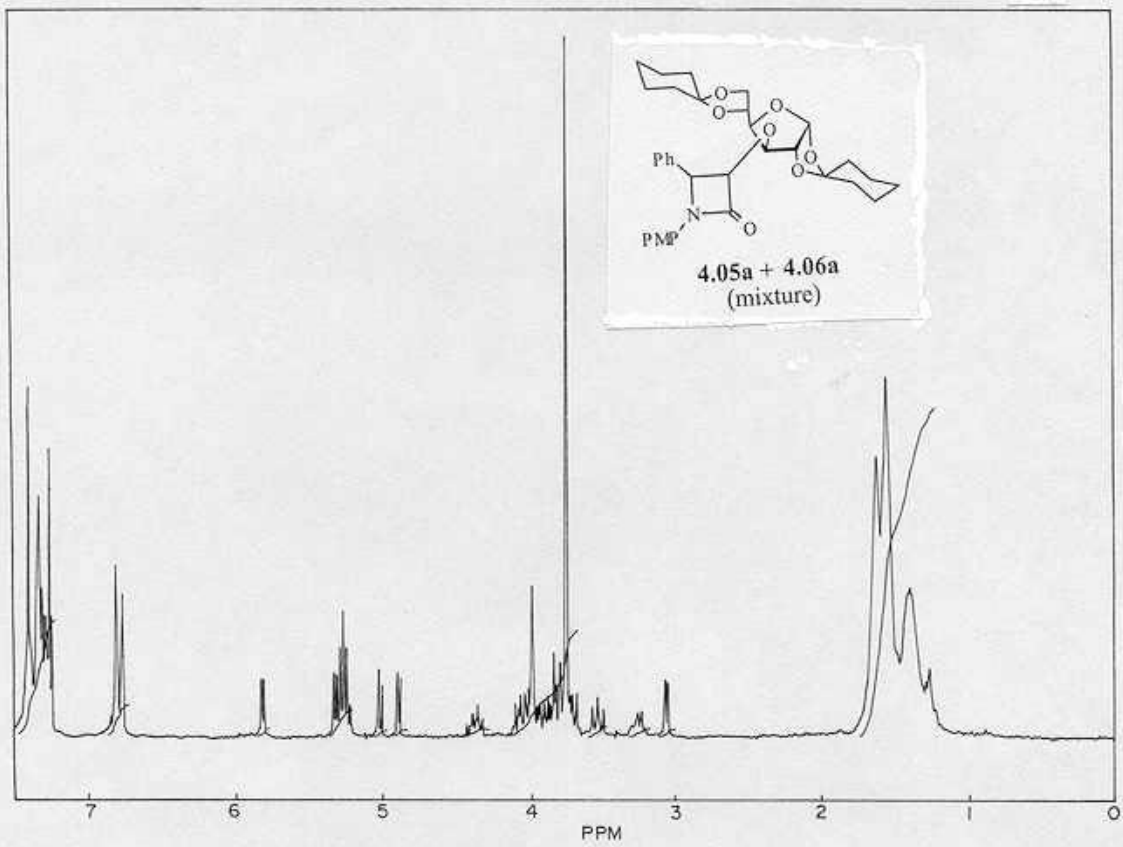
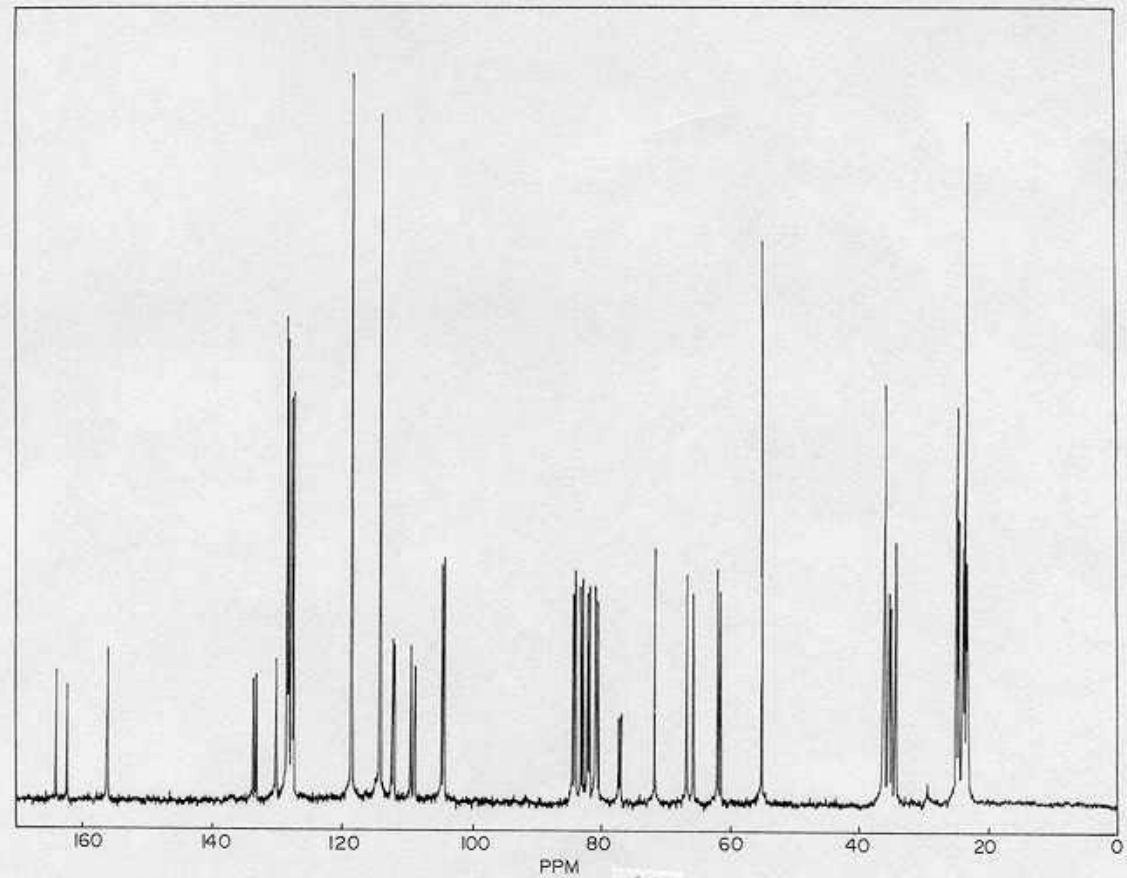
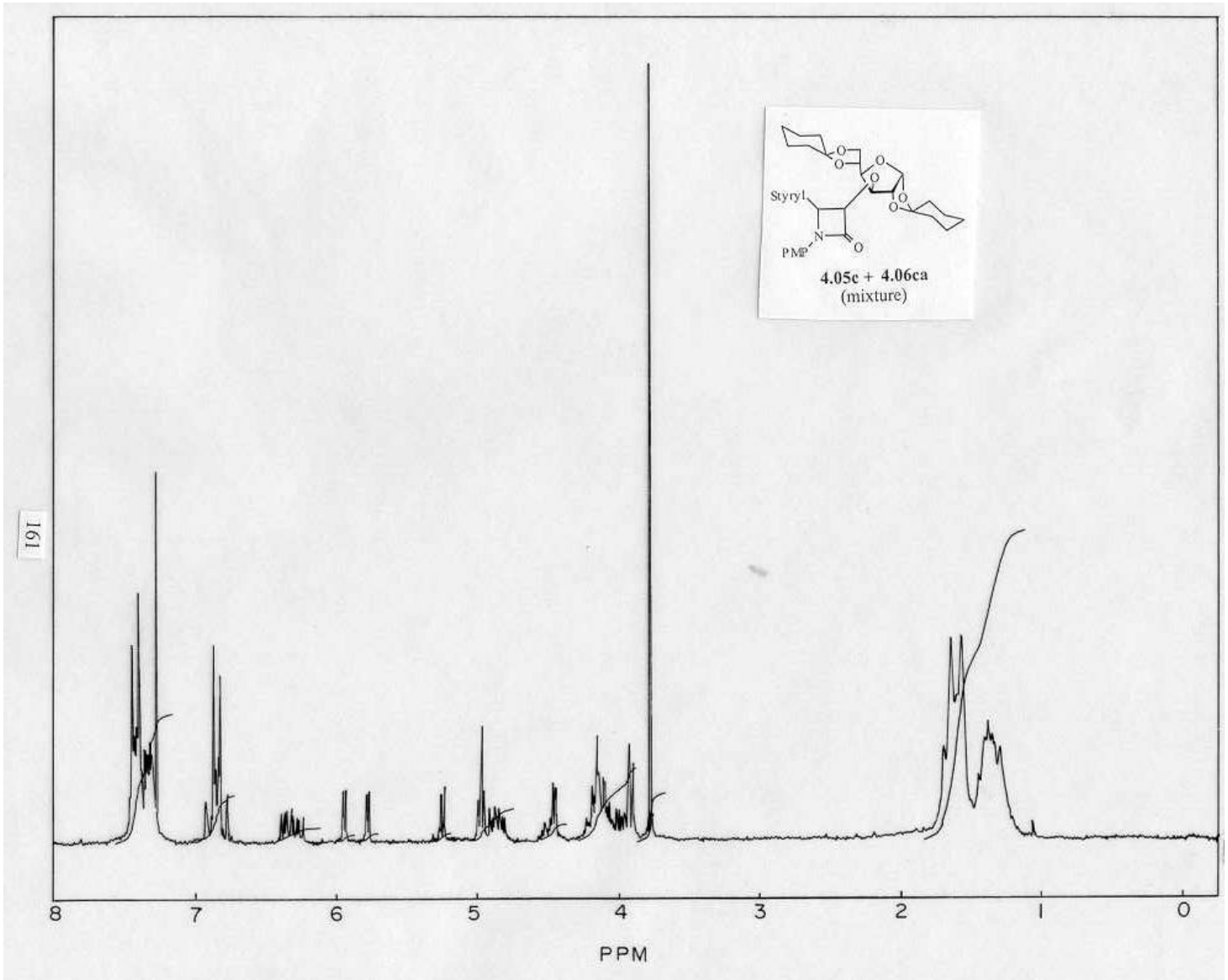




4.05a + 4.06a
(mixture)

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4.05c + 4.06ca
(mixture)
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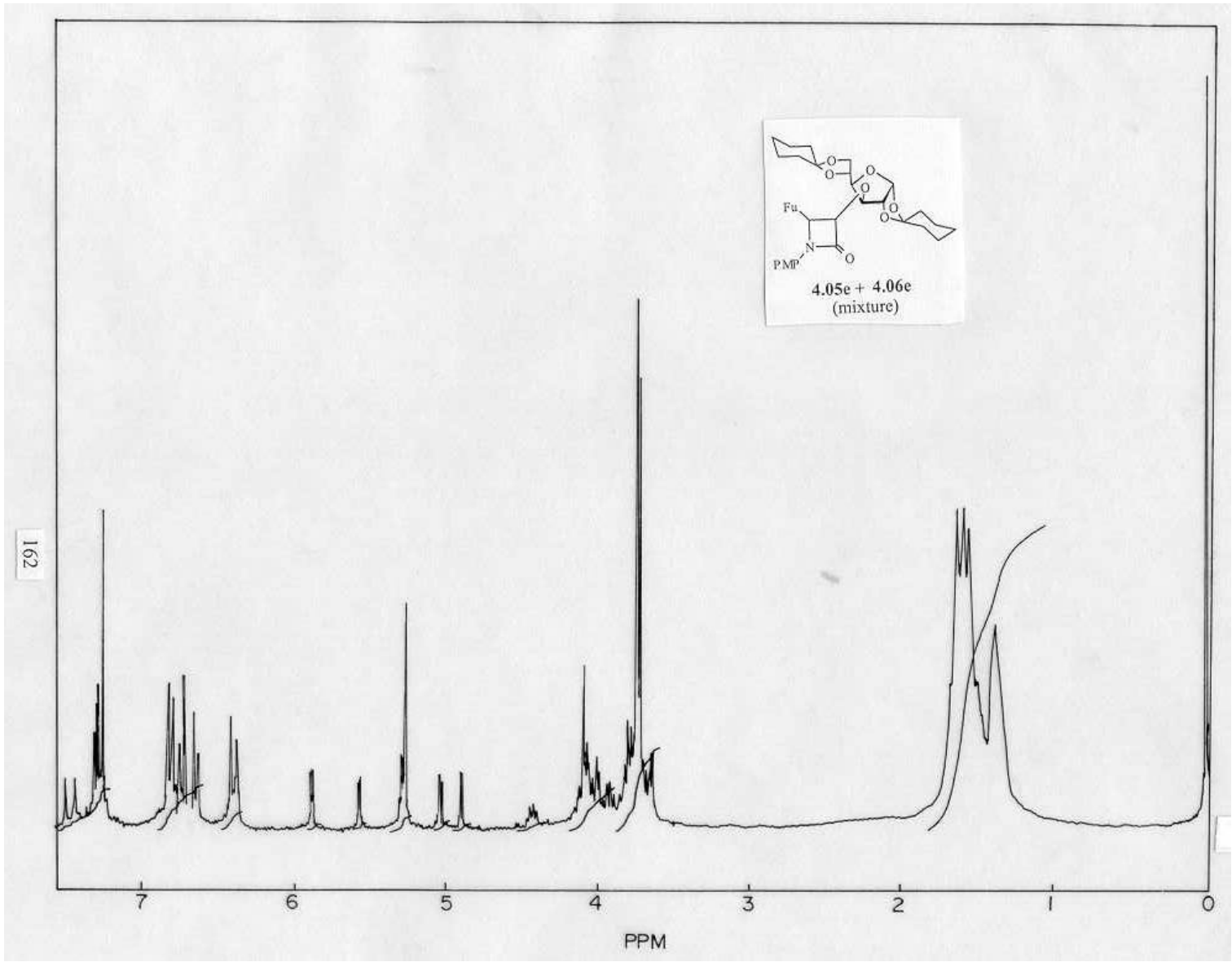
PPM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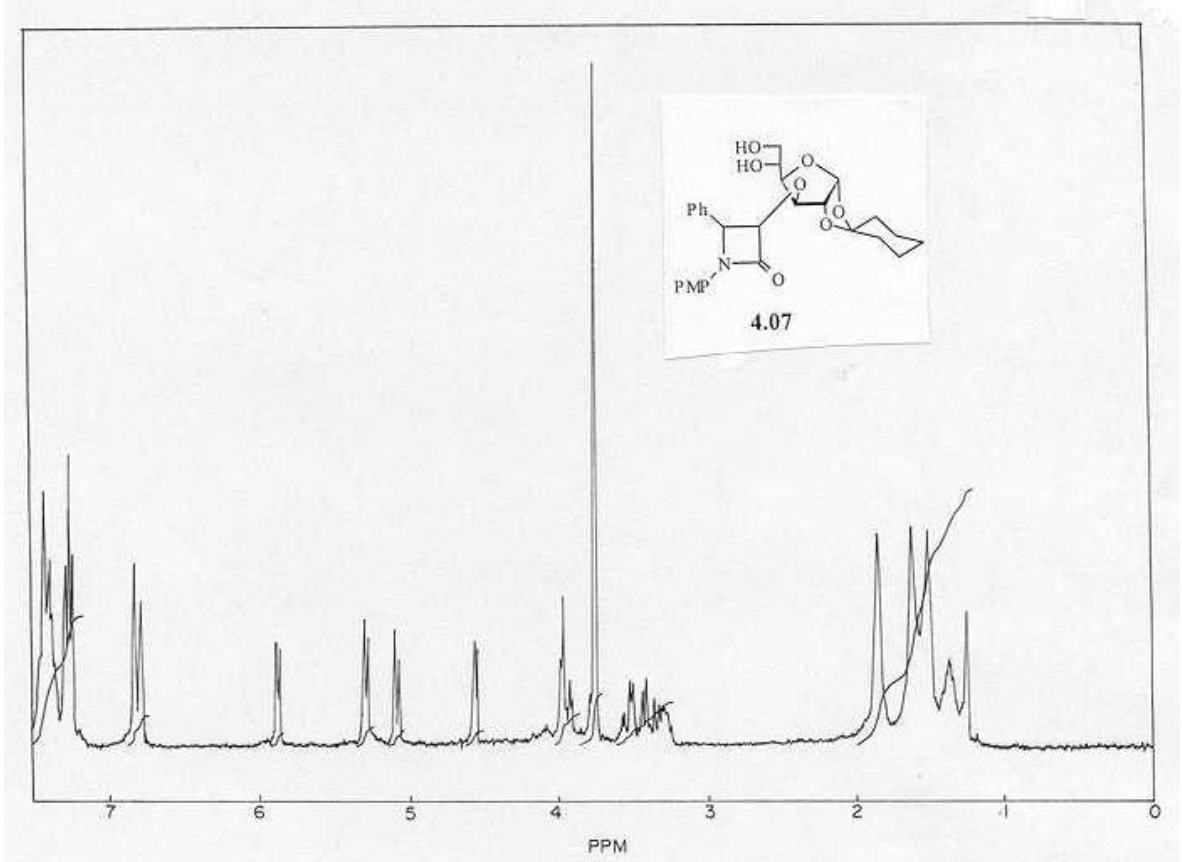
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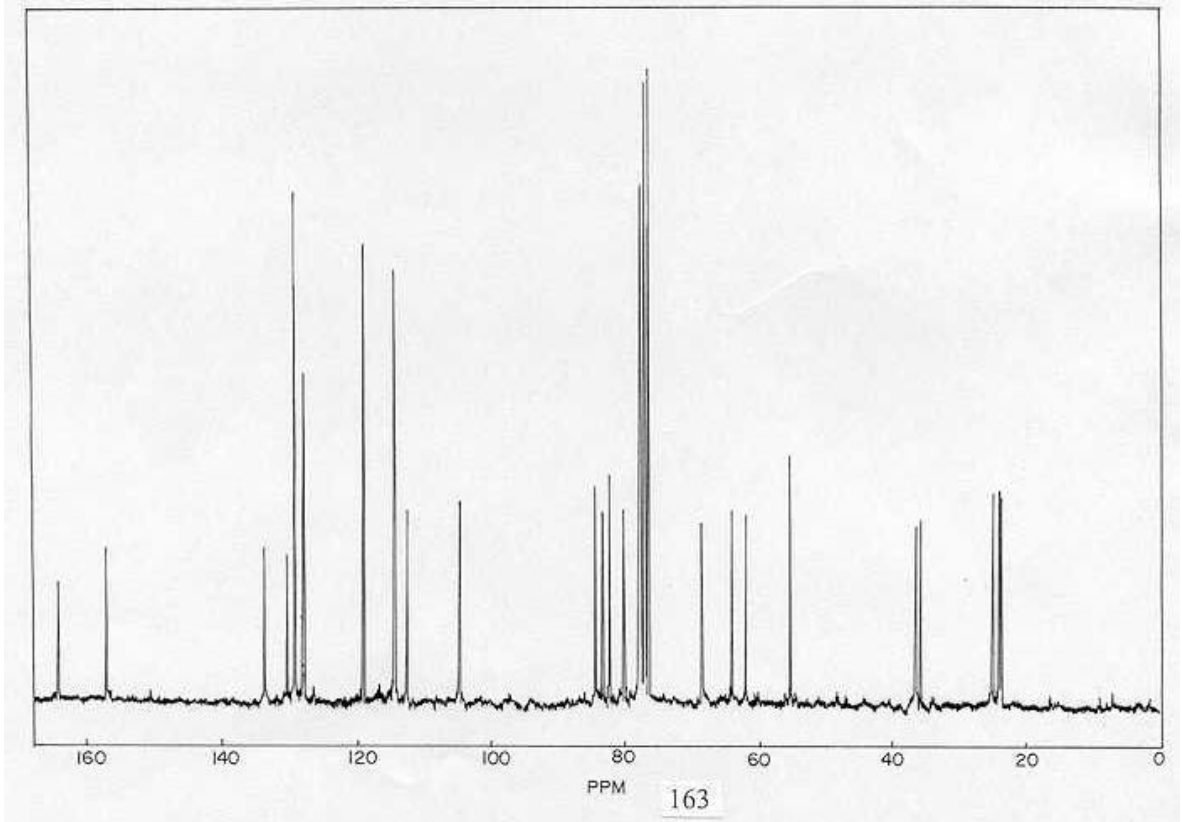
4.07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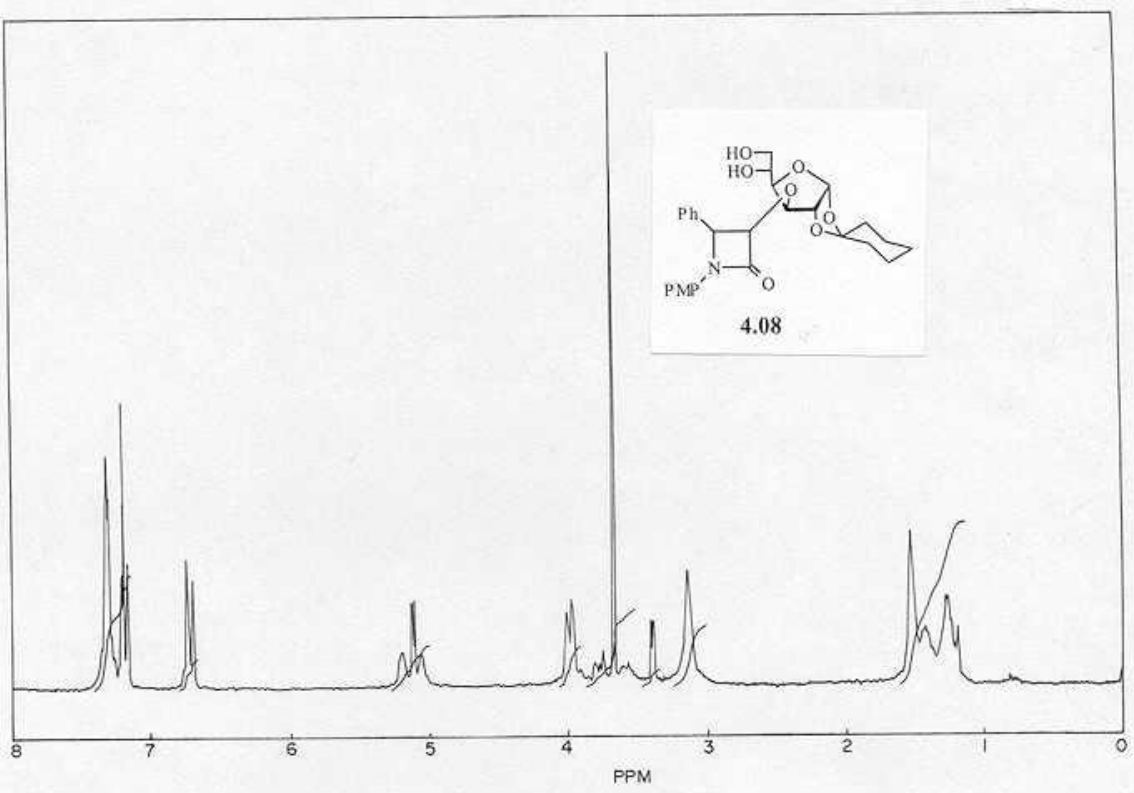
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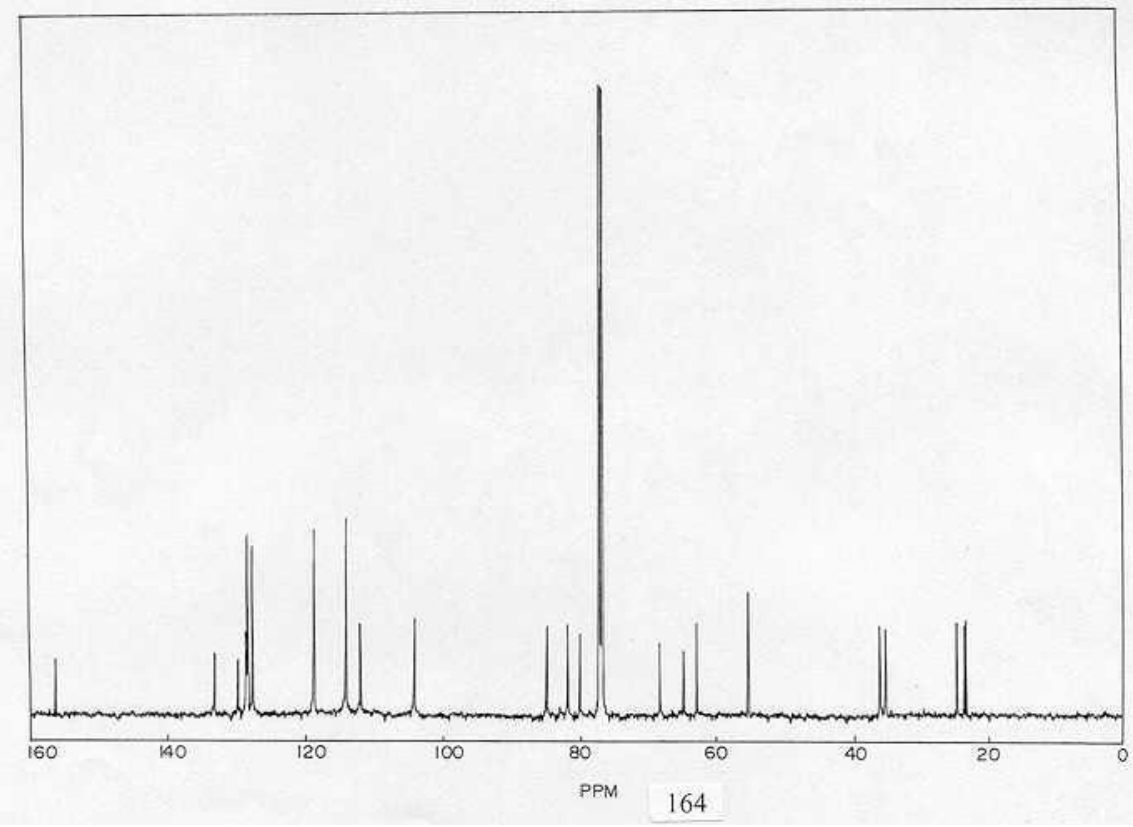
4.08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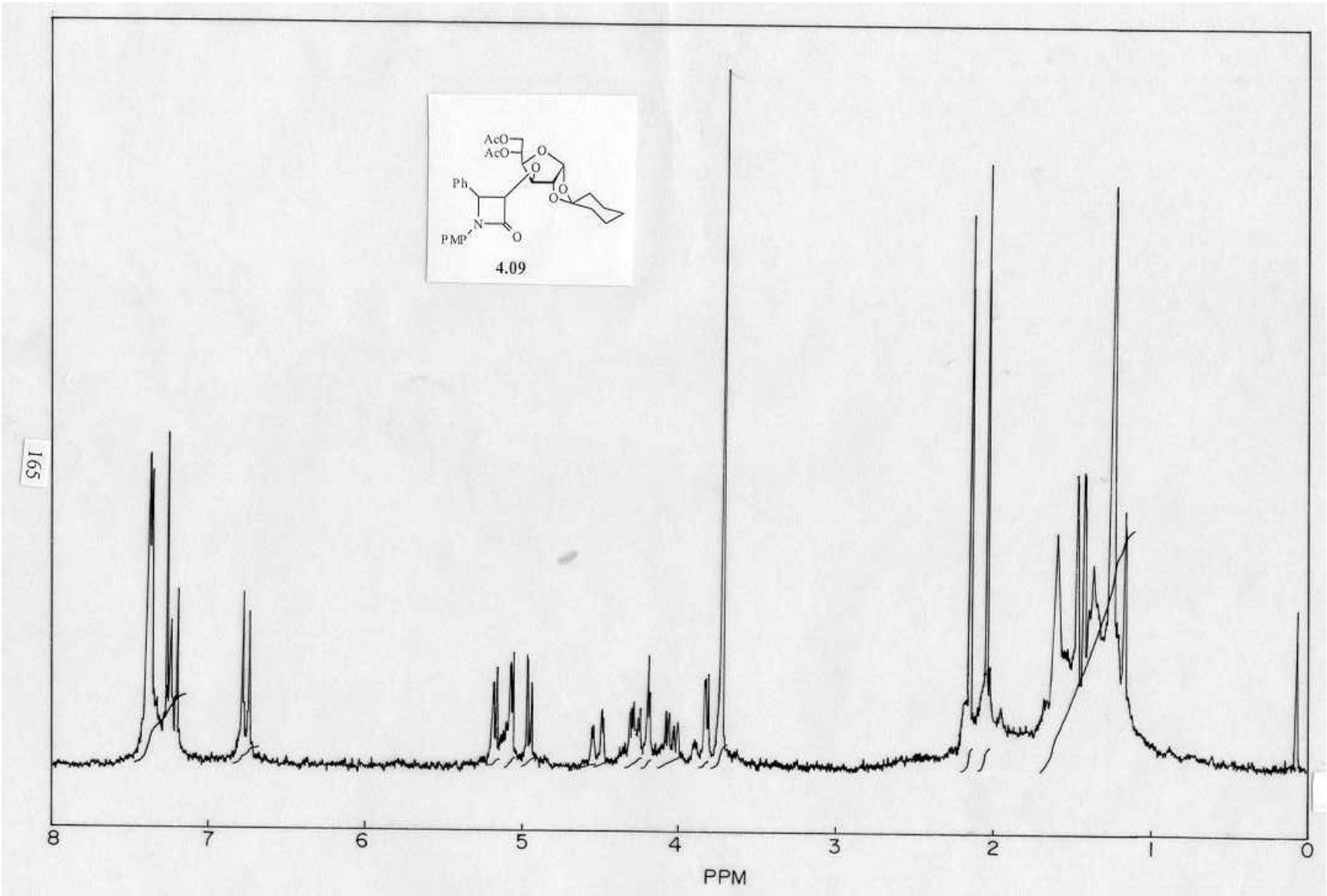
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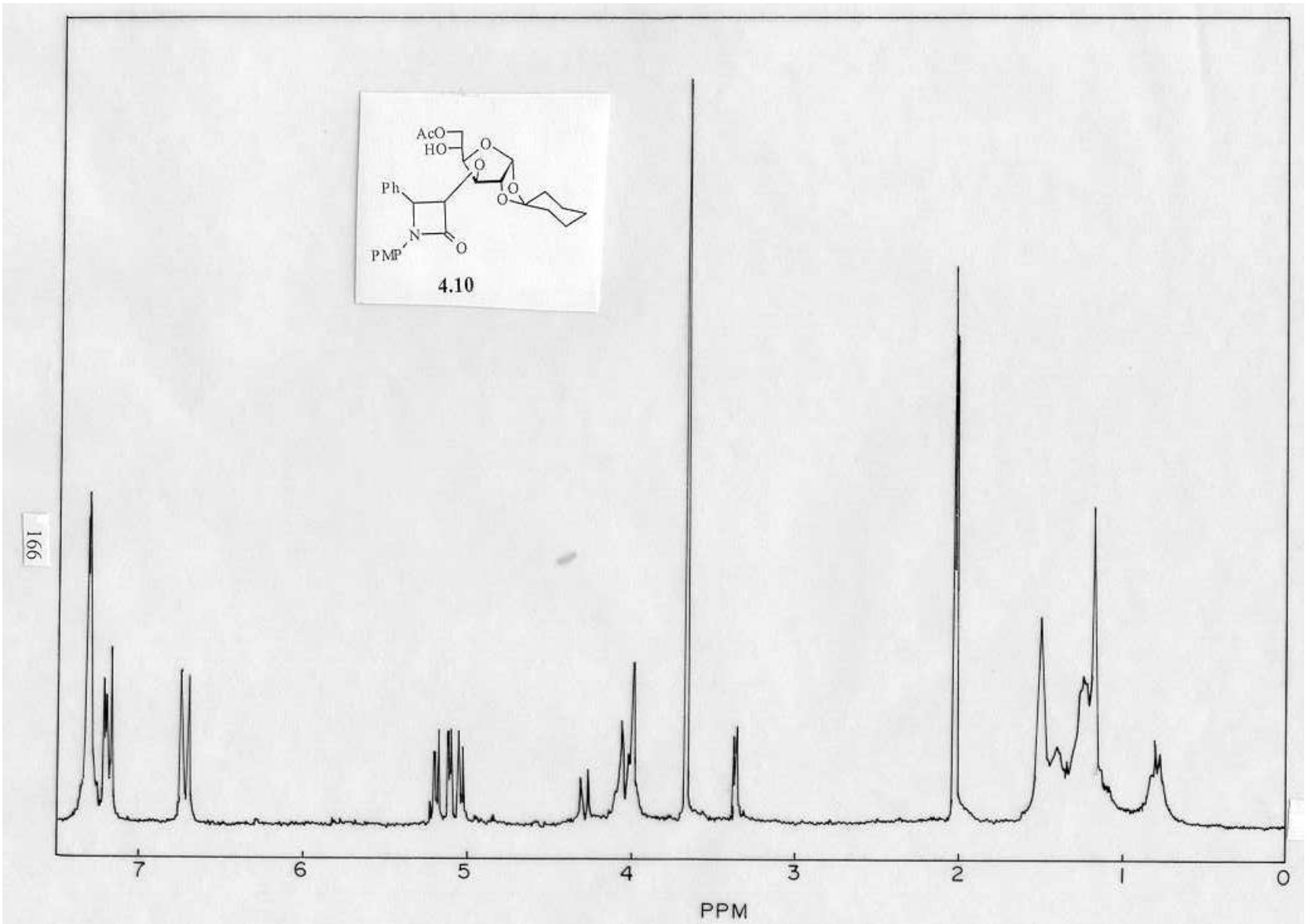
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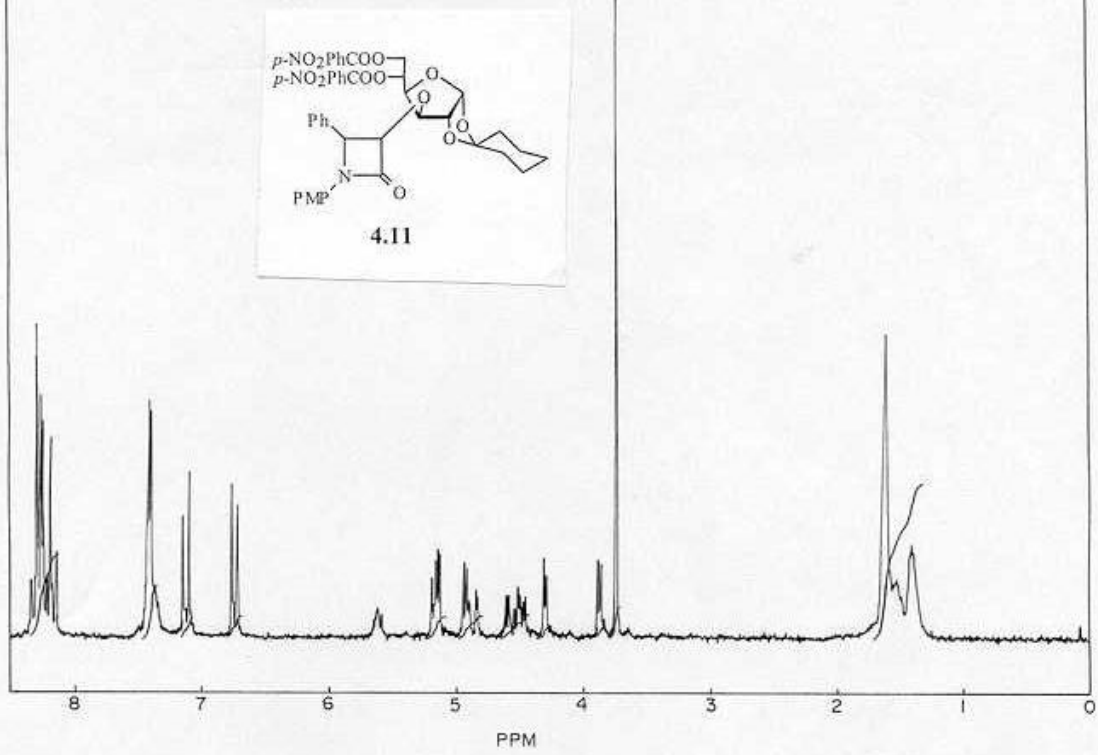
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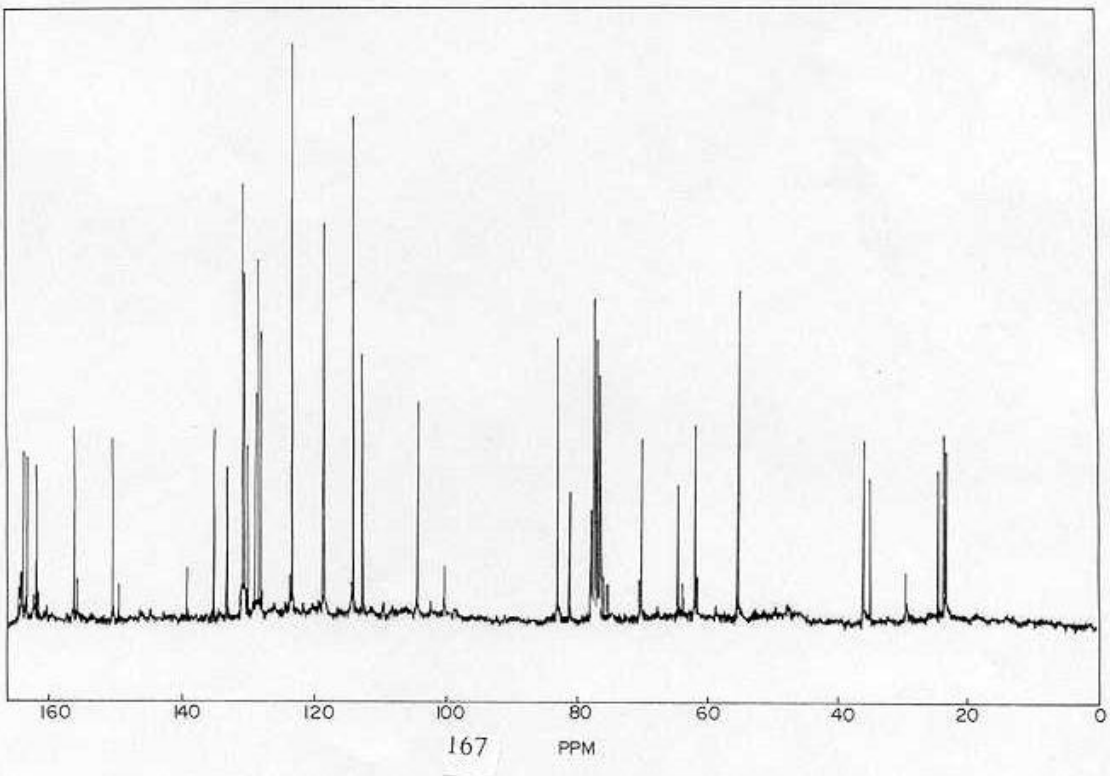
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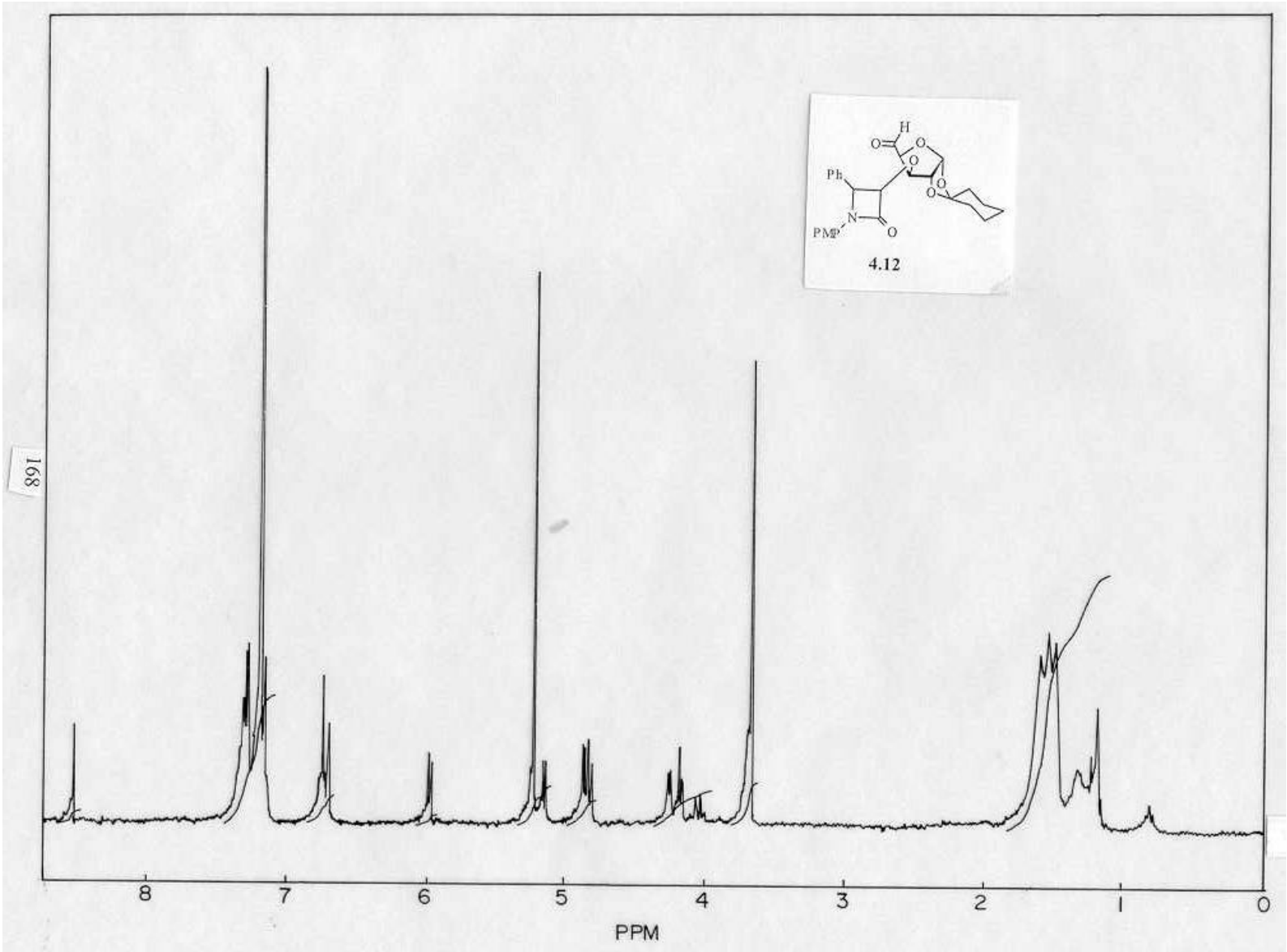
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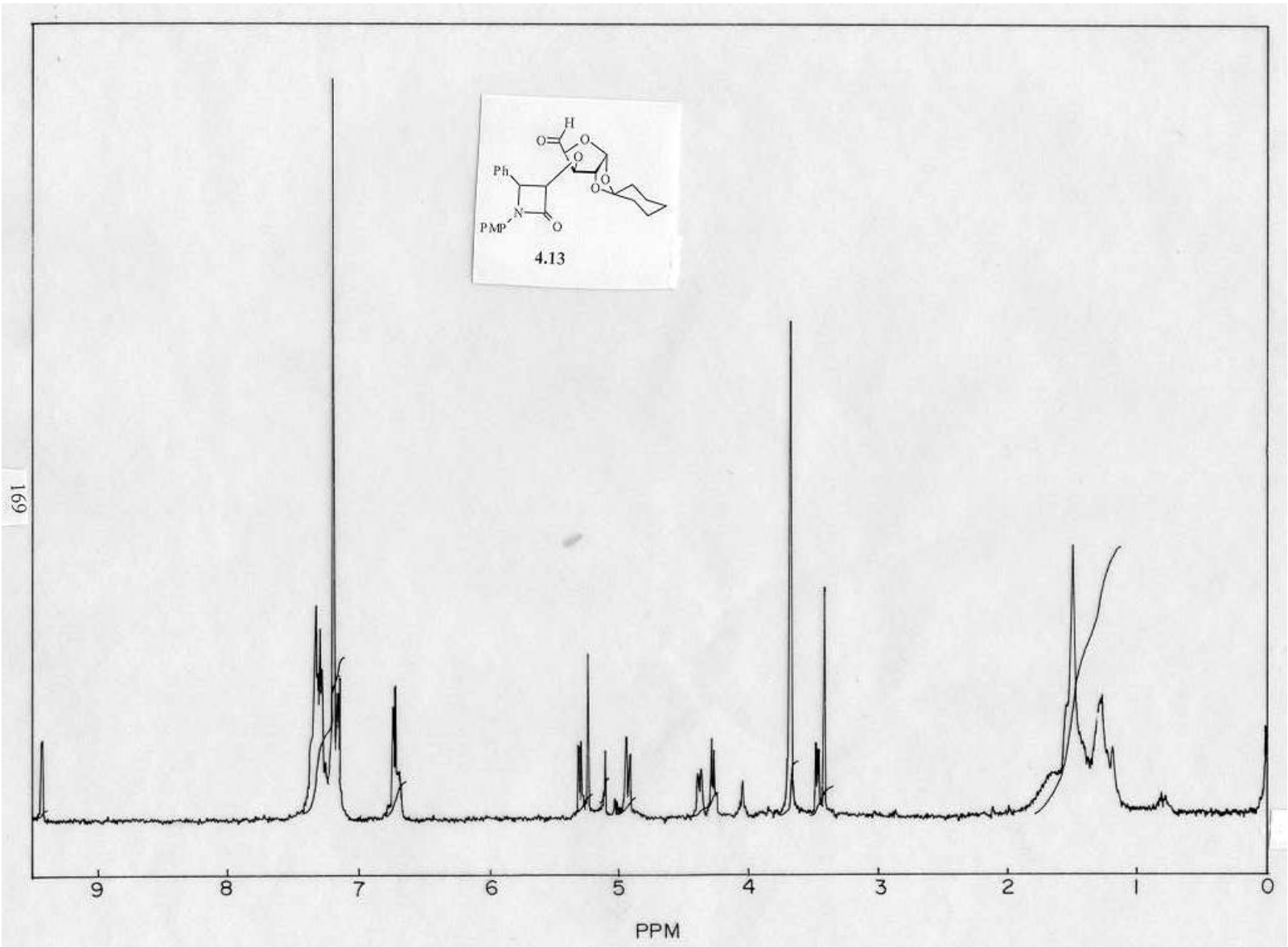
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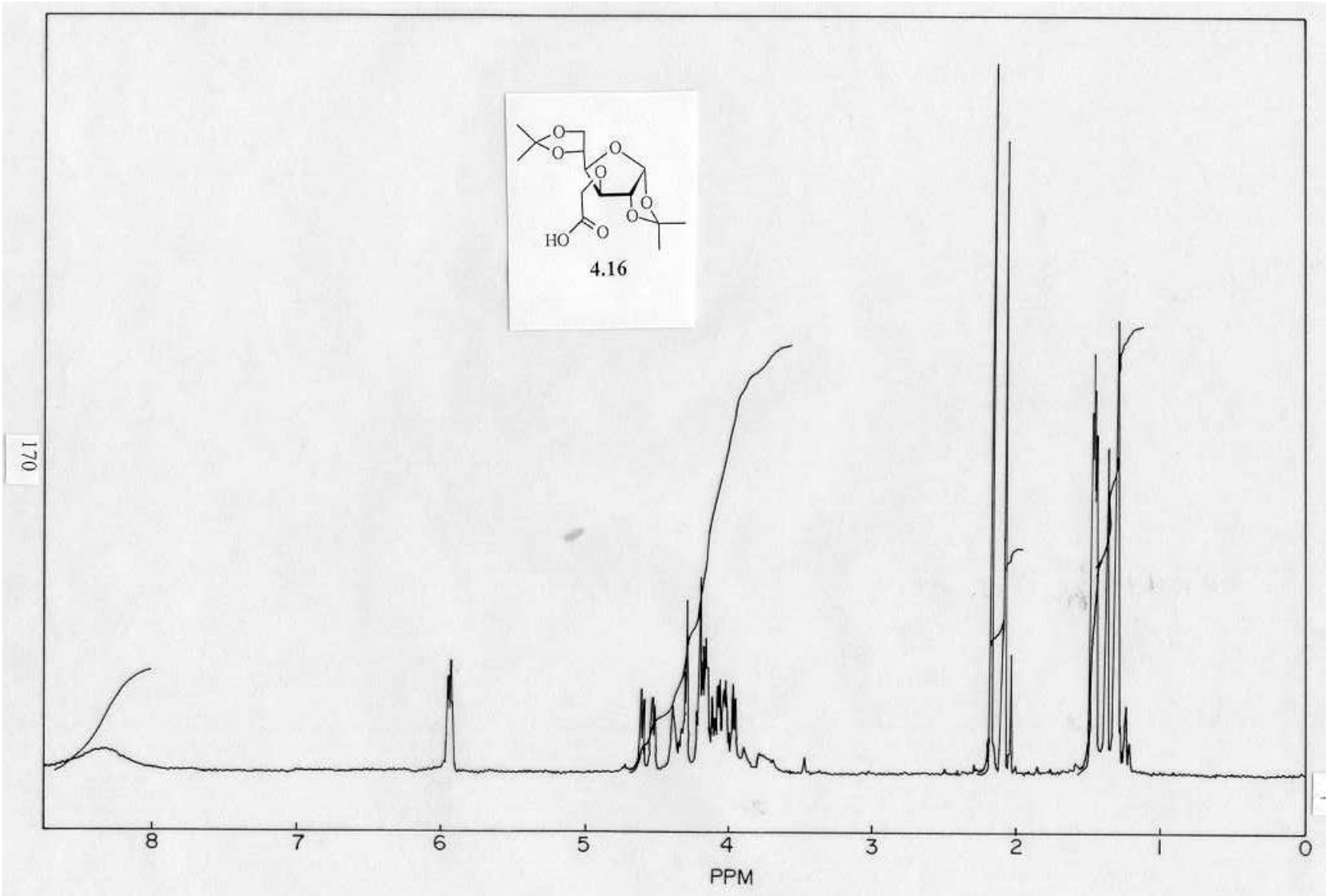
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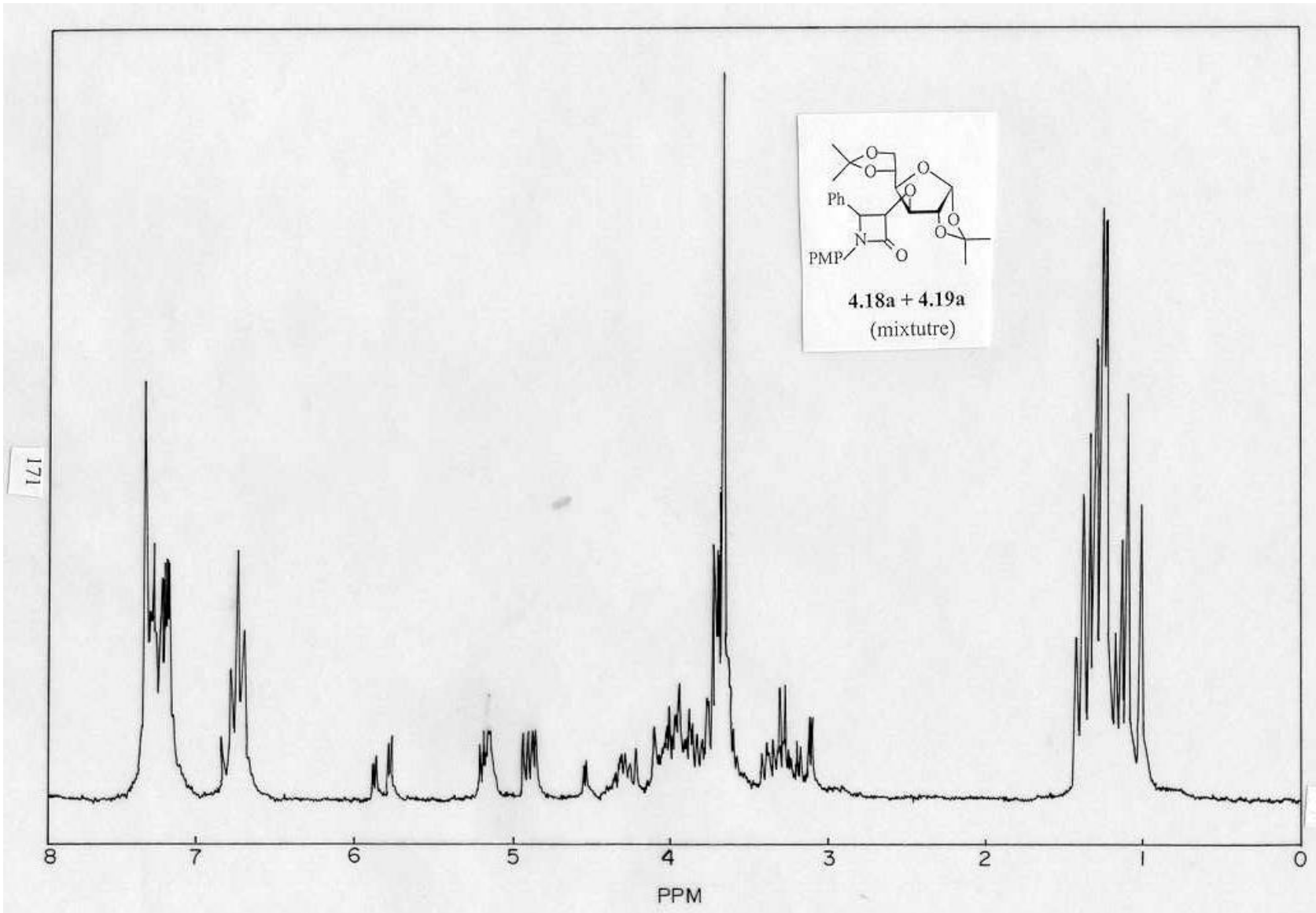
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(mixtutre)
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5
4
3
2
1
0
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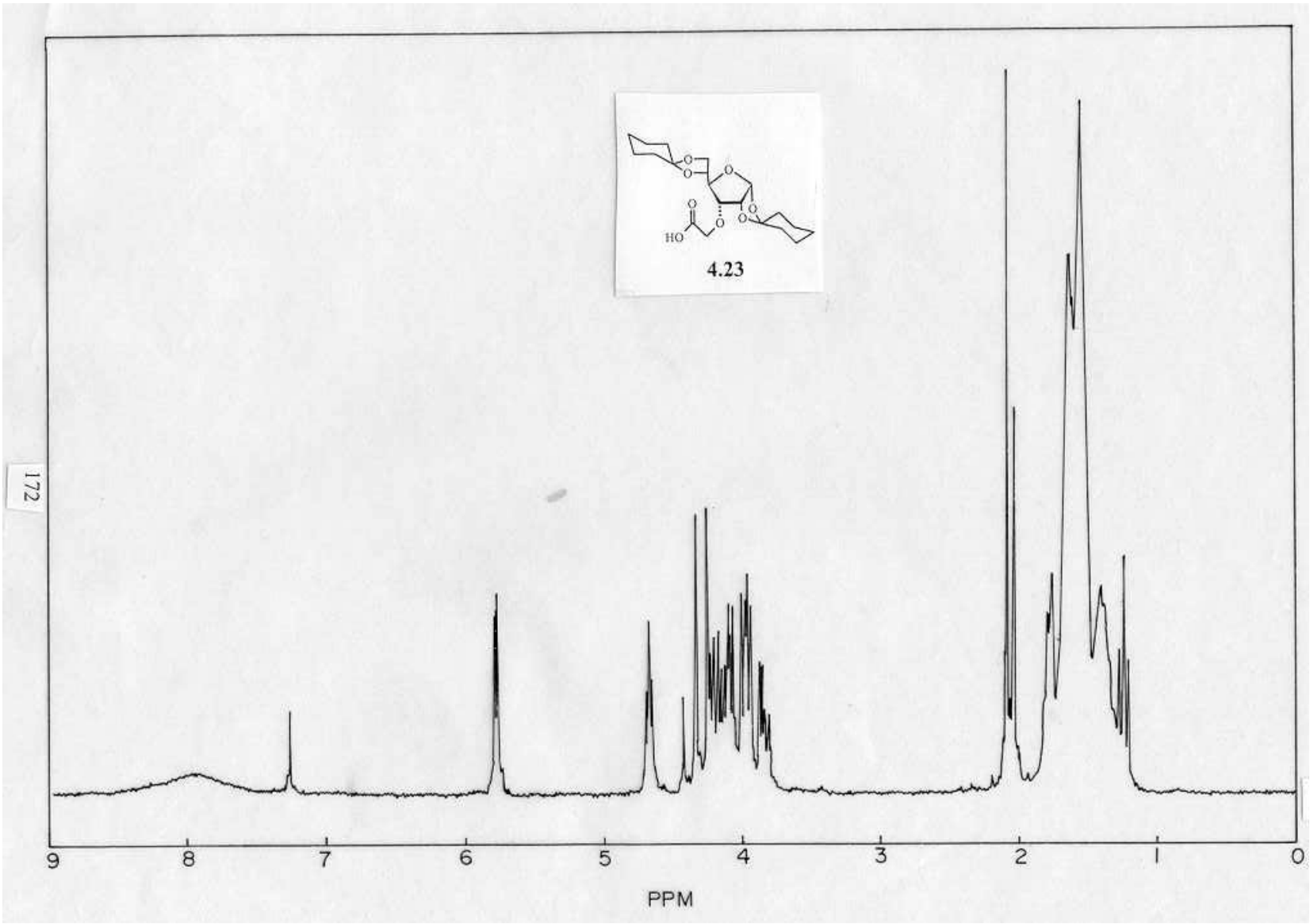
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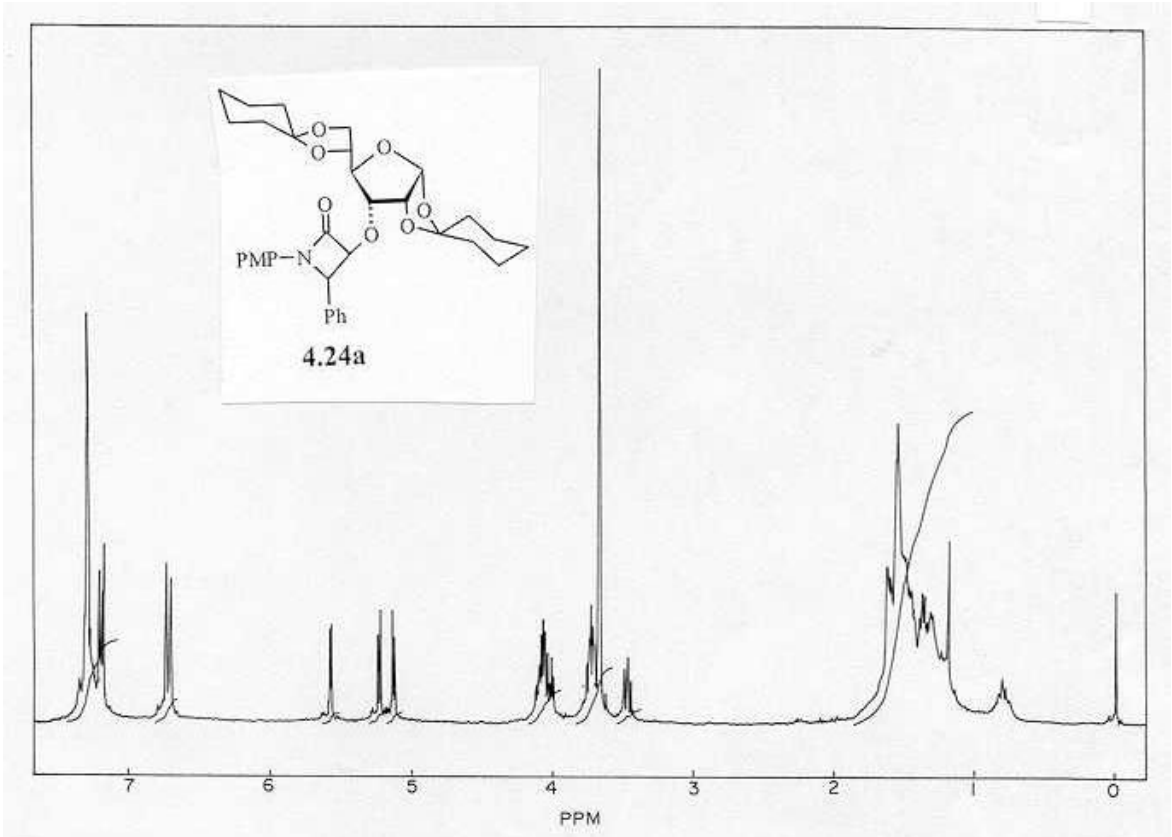
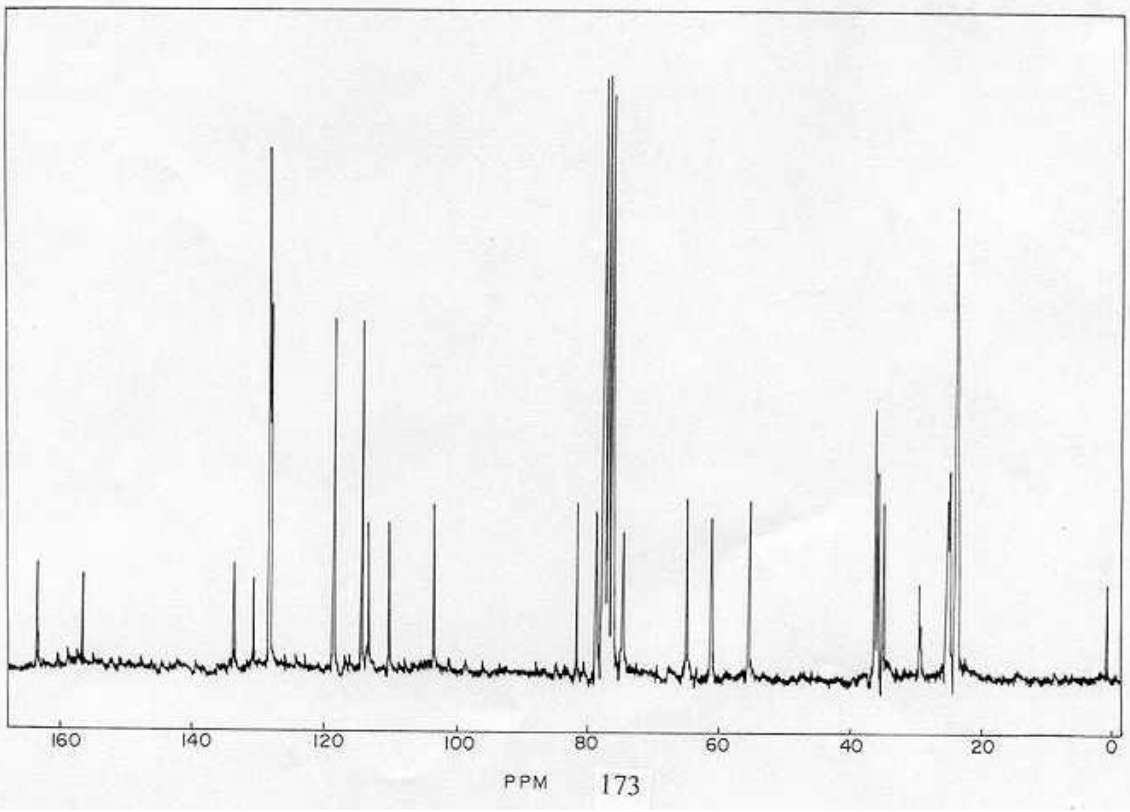
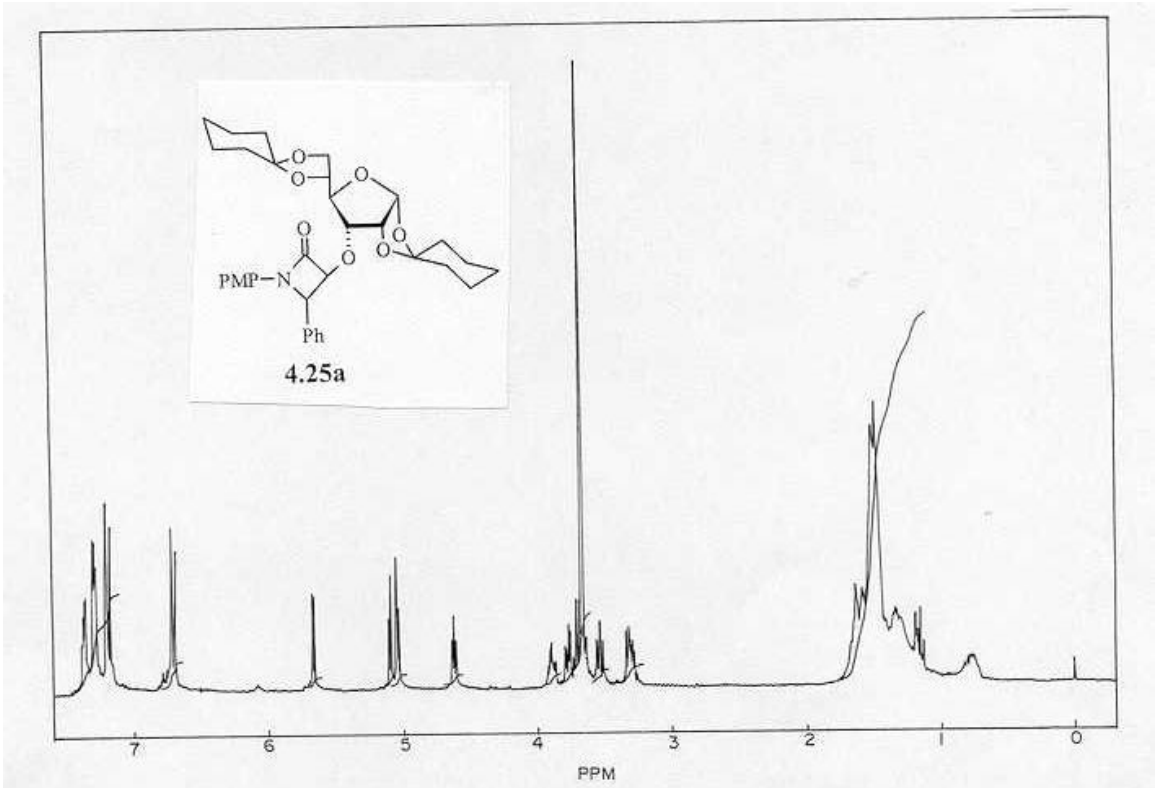


4.24a

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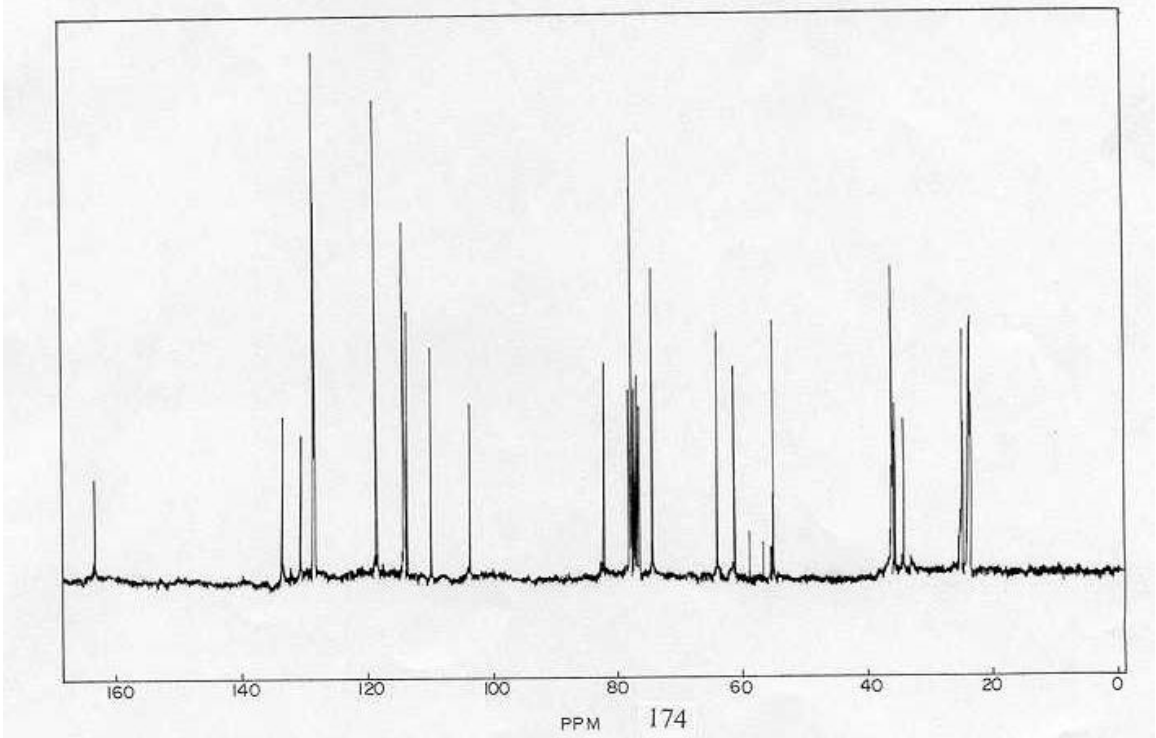
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Reprint of the Papers published

Pergamon

Tetrahedron Letters, Vol. 38, No. 24, pp. 4281-4284, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00879-4

Synthesis of N^1-unsubstituted β-lactams : Introducing N^1-(1′-thiophenyl)benzyl as an N-protecting group

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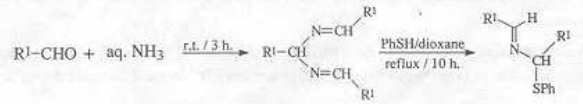
Division of Organic Chemistry (Synthesis)
National Chemical Laboratory, Pune 411 008, India

Abstract : A diastereoselective synthesis of (±) *cis*-β–lactams (5 & 6) *via* cycloaddition reaction of N^1-(α-thiophenyl)benzyl imines (3) with acid chlorides (4) in the presence of triethyl amine is described. Deprotection of N^1-(α-thiophenyl)-benzyl group was achieved in good yields by oxidation using potassium persulfate.

N-Unsubstituted β-lactams are intermediates in the synthesis of monocyclic and bicyclic β-lactam antibiotics.[1] As a part of our ongoing project on β-lactam synthon method[2] for the synthesis of natural and unnatural products, we were interested in developing methods for the preparation of NH-β-lactams. Generally, the selection of N^1-protective groups in β-lactam synthesis is based on the ease of selective removal of these groups at the appropriate stage. Benzyl,[3] allyl,[4] silyl[5] and *p*-methoxyphenyl[6] groups are often used for N^1-protection and can be removed under various conditions to get N-H β-lactams. In this communication we report the utility of (α-thiophenyl)benzyl as an N^1-protective group and its oxidative removal using potassium persulfate to yield N-unsubstituted β-lactams.

The starting hydrobenzamide[7] [1-phenyl-N,N'-bis(phenylmethylene)methane diamine (**2a**) & 1-*p*-anisyl-N,N'-bis-(*p*-anisylmethylene)methane diamine (**2b**)] were readily obtained in excellent yields by stirring a mixture of aromatic aldehydes (**1a,b**) with a 10 fold excess of aq. ammonia solution (30%) for 3 h. The reaction of **2a,b** with thiophenol in refluxing dioxane afforded imines **3a,b** in good yield[8] (Scheme 1).

Scheme 1

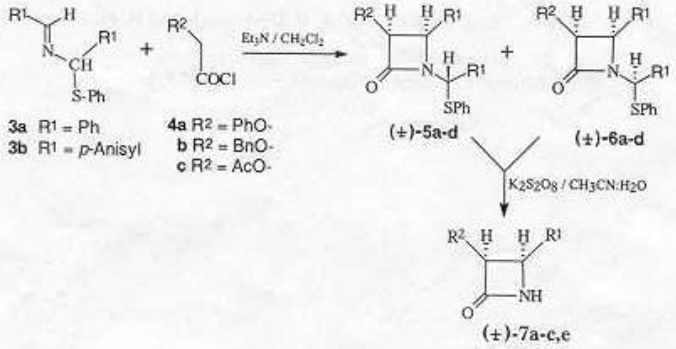


1a,b **2a,b** **3a,b**

1,2,3 a R^1 = Ph
b R^1 = *p*-Anisyl

Cycloaddition reaction of the imines **3a,b** with various acid chlorides (**4a-c**) in presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-β-lactams[9] (**5a-d** & **6a-d**)[10] in 50-79% yield (Table 1, Scheme 2). The diastereomeric ratio was determined by the HPLC[11] and ^{1}H NMR analyses of crude reaction mixtures. The major (5) and minor (6) diastereomers were separated by crystallization.

Sheme 2



The relative stereochemistry of the major diastereomer **5a** was established as 3*S*, 4*R*, 1′*S* by single crystal X-ray analysis[12] (Fig. 1).

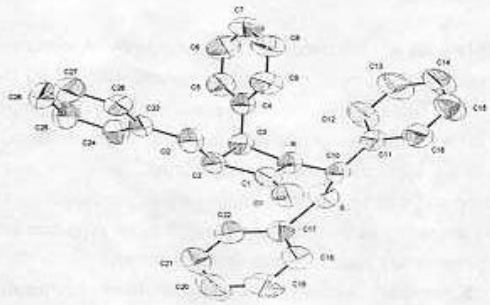


Fig. 1. The ORTEP diagram of the β-lactam **5a**

The chiral acid chloride (**4d**, R^2 = *l*-menthyl), on reaction with imine **3a** under similar reaction conditions gave a diastereomeric mixture of four *cis*-β-lactams in the ratio of 35:35:18:12 (HPLC, ^{1}H NMR). One of the diasteromers was isolated in the pure form by crystallization (acetone-petroleum ether) from the mixture.

Individual diastereomers **5** or **6**, or a mixture of **5** & **6**, reacted with potassium persulfate (aceto-nitrile/water, reflux, 4 h) to give the N-unsubstituted β-lactams (**7**)[13] in good yields (Scheme 2, Table 1).

Table 1. Synthesis of β-lactams **5a-e** & **6a-e** and N^1-unsubstituted β-lactams **7a,b,d,e**.

Compd.	R^1	R^2	Compound 5 & 6			Compound 7	
			Yield[a] (%)	Ratio[b] of 5 & 6	m.p. of 5 (°C)	yield[c] (%)	m.p. (°C)
a	Ph	PhO	74	74:26	214-215	70	159-160
b	Ph	BnO	58	64:36	119-120	64	188-189
c	Ph	AcO	50	74:26	153-154	--	--
d	Anisyl	PhO	79	83:17	157-159	70	165-167
e	Ph		62	35:35:18:12[d]	158-160[e]	65	173-174[f]

[a] Isolated yields of diastereomeric mixture of 5 & 6; [b] Ratio of 5 & 6 from HPLC and ^{1}H NMR spectral data; [c] Isolated yield; [d] Ratio of four diastereomers; [e] M.p. of one of the pure diastereomer isolated from the mixture by crystallization; [f] Prepared from the pure diastereomer obtained by crystallization.

In summary, we have introduced (α-thiophenyl)benzyl as a novel N-protective group in β-lactam molecules, which can be removed *via* mild oxidative conditions tolerated by most common organic functional groups.

Acknowledgment : We thank Dr. A. Sarkar for valuable suggestions and the authors (K.K. & V.S.) thanks CSIR for the financial support.

References and Notes :

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9. The formation of the *cis*- isomer only was observed as confirmed from ^{1}H NMR analysis ($J_{3,4}$ = 4-5 Hz) of the crude reaction mixture.

10. *Typical procedure for β-lactams 5a & 6a* : A solution of the acid chloride (**4a**, 320 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imines (**3a**, 450 mg, 1.5 mmol) and triethylamine (600 mg, 6 mmol) in CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was then allowed to warm to r.t. and stirred further for 13 h. The usual work gave a diastereomeric mixture of β-lactams (**5a** & **6a**) in 74% yields. The major diastereomer **5a** was separated by crystallization from pet. ether - acetone.

    (5a) : M. p. 214-215 °C. ^{1}H NMR : δ 5.0 (d, *J* = 5 Hz, 1H); 5.2 (d, *J* = 5 Hz, 1H); 6.47 (s, 1H); 6.8 (d, *J* = 10 Hz, 2H); 6.83 (t, *J* = 10 Hz, 1H); 6.95 - 7.70 (m, 17H). ^{13}C NMR : 61.20, 62.34, 81.22, 115.64, 122.00, 127.55, 127.85, 128.08, 128.22, 128.57, 128.81, 129.08, 129.42, 132.49, 133.03, 135.07, 156.87, 165.98. IR : 1740 cm^{-1}. Anal. for Cald $C_{28}H_{23}O_2NS$: C, 76.86; H, 5.30; N, 3.20; S, 7.33. Found : C, 76.68; H, 5.37; N, 3.27.

    (6a) : Isolated as an oil. ^{1}H NMR : δ 4.45 (d, *J* = 5 Hz, 1H); 5.2 (d, *J* = 5 Hz, 1H); 6.15 (s, 1H); 6.6 (d, *J* = 10 Hz, 2H); 6.85 (t, *J* = 10 Hz, 1H); 6.95 - 7.60 (m, 17H). ^{13}C NMR : 63.23, 63.93, 80.30, 115.56, 121.95, 127.84, 128.06, 128.64, 128.75, 129.05, 129.44, 132.28, 133.04, 133.54, 135.78, 156.79, 164.91. IR : 1740 cm^{-1}.

11. HPLC : Perkin-Elmer 410-pump. H.P. 1050 MWD at 254 nm connected to H-P 3396 Ser-II integrater. Col. MN-C-18, 8 mm, 4 mm X 100 mm length. Solvent system (v/v): 80 : 20 (MeOH :H_2O) flow rate 1.5 mL/min.

12. For details see : Srirajan, V.; Bhawal, B.M; Puranik, V.G. *Acta. Cryst. C* (in press).

13. *Typical procedure for 3-Phenoxy-4-phenylazetidin-2-one (7a)* : A mixture of **5a** (0.088 g, 0.2 mmol), acetonitrile (8 mL), water (3 mL), and potassium persulfate (0.162 g, 0.6 mmol) was refluxed for 4 h. The solvent was removed by distillation under reduced pressure and the residue on usual work up gave **7a** in 70% yield. M.p. 159-160 °C. ^{1}H NMR : δ 5.05 (d, *J* = 4.8 Hz, 1H,); 5.5 (dd, *J* = 4.8 & 5.5 Hz, 1H,); 6.6 (bs, 1H,); 6.8 (two d, *J* = 9 Hz, 2H,); 6.9 (t, J = 9 Hz, 1H,); 7.10-7.40 (m, 7H,). IR : 2800 - 3500, 1770 cm^{-1}. Anal. Cald for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found : C, 75.51; H, 5.73; N, 5.62.

(*Received in UK* 2 *April* 1997; *revised* 29 *April* 1997; *accepted* 2 *May* 1997)

Pergamon

Tetrahedron 54 (1998) 4375–4386

TETRAHEDRON

Synthesis of N1-unsubstituted β-lactams *via* a facile deprotection of N1-[(α-thiophenyl)benzyl] group

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Received 17 December 1997; revised 9 February 1998; accepted 12 February 1998

Abstract : A diastereoselective synthesis of (±) *cis*-β-lactams (5 & 6) *via* cycloaddition reactions of N1-(α-thiophenyl)benzyl imines (3) with acid chlorides (4) in the presence of triethylamine is described. The deprotection of N1-(α-thiophenyl)benzyl group has been achieved by oxidation using potassium persulfate to give N-unsubstituted β-lactams (7) in good yields.

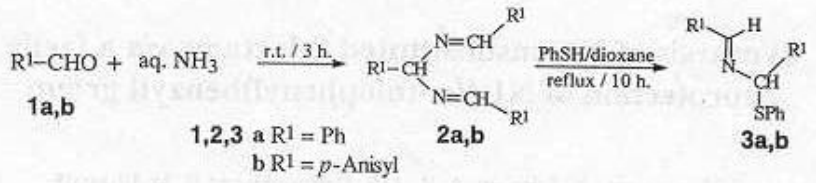
N1-Unsubstituted β-lactams are key intermediates for the synthesis of monocyclic as well as bicyclic β-lactam antibiotics.[1] In most cases, the β-lactam nitrogen is protected during the synthesis. The choice of the protective group is based on the ease of selective removal of these protective groups at an appropriate time. Among the various groups,[2] benzyl,[3] *p*-methoxyphenyl,[4] allyl[5] and silyl[6] groups are more popular owing to their easy accessibility and convenience of removal under mild reaction conditions.

As a part of our project on β-lactam as a synthon[7] for the synthesis of natural and unnatural products, we were interested in developing methods for the preparation of NH-β-lactams. In our recent communication[8] we have reported the use of (α-thiophenyl)benzyl as a novel N-protective group in the synthesis of β-lactams and its oxidative removal using potassium persulfate to yield N-unsubstituted β-lactams. In this paper, we wish to report the detailed account of this work.

The starting 1-phenyl-N,N′-bis(phenylmethylene)methanediamine (**2a**) and 1-*p*-anisyl-N,N′-bis(*p*-anisylmethylene)mehtanediamine (**2b**) were prepared in excellent yields[9] by stirring a mixture of the aromatic aldehydes (**1a,b**) with a 10 fold excess of ammonia solution (30%) for 3 h (Scheme 1). The imines **2a,b** on reaction with the appropriate thiophenol in dioxane under reflux conditions gave the imines **3a,b** in good yields.[10]

0040-4020/98/$19.00
PII: S0040-4020(98)00151-3

Scheme 1



The imines **3a,b** on cycloaddition reaction (Staudinger reaction) with various acid chlorides (**4a-c**) in presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-β-lactams[11] (**5a-e** & **6a-e**) in 50-79% yields (Scheme 2, Table 1). The diastereomeric ratio was determined by the HPLC[12] and ^{1}H NMR analysis of a crude reaction mixture. The major (**5**) and minor (**6**) diastereomers were separated by crystallization.

Scheme 2

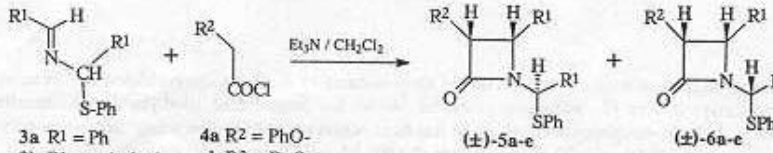


Table 1. Synthesis of β-lactams **5** & **6** and N^1-unsubstituted β-lactams **7**.

Compd	R^1	R^2	Compound **5** & **6**			Compound **7**	
			Yield[a] (%)	Ratio[b] of **5** & **6**	m.p.[c] of **5** (°C)	yield[d] (%)	m.p. (°C)
a	Ph	PhO	74	74:26	214-215	70	159-160
b	Ph	BnO	58	64:36	119-120	64	188-189
c	Ph	AcO	50	74:26	153-154	--	--
d	*p*-Anisyl	PhO	79	83:17	157-159	70	165-167
e	*p*-Anisyl	BnO	57	78:22	149-151	--	--

[a] Isolated yields of diastereomeric mixture of **5** & **6**; [b] Ratio of **5** & **6** from HPLC and ^{1}H NMR spectral data; [c] The diastereomers **5a-e** were obtained by column chromatography in pure form. [d] Isolated yield.

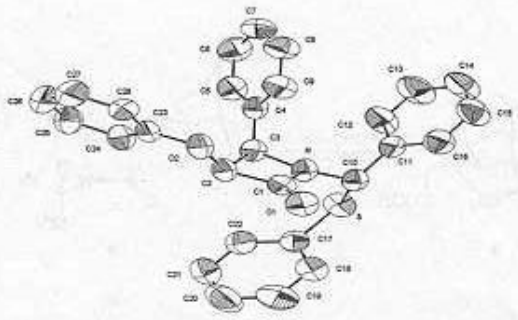
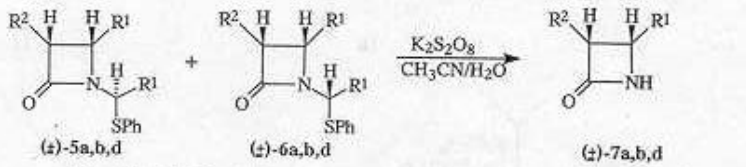


Fig. 1. The ORTEP diagram of the β-lactam **5a**

The relative configuration of the major diastereomer (±)-**5a** was established by single crystal X-ray analysis[13,14] as 1′*S*, 3*S*, 4*R* (Fig. 1).

N-Deprotection of pure major diastereomers **5** was carried out under mild oxidative conditions using potassium persulfate in acetonitrile/water at reflux temperature to give N1-unsubstituted β-lactams **7** in good yields (Scheme 3). The diastereomeric mixture of **5** and **6** on oxidative N-deprotection under similar conditions also gave the same β-lactams **7**. This further establishes that the β-lactams **5** and **6** are diasteromeric at (α-thiophenyl)benzylic position.

Scheme 3



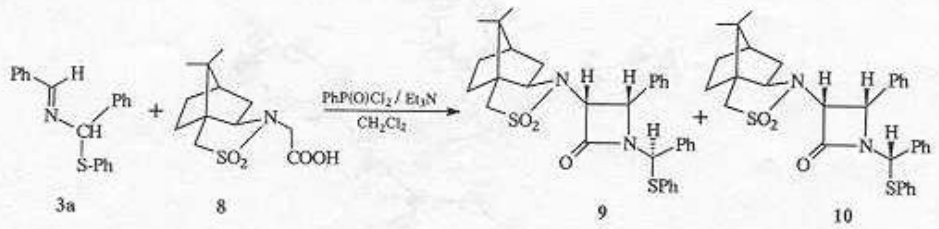
(±)-5a,b,d (±)-6a,b,d (±)-7a,b,d

5, 6 a R^1 = Ph, R^2 = PhO
b R^1 = Ph, R^2 = BnO
d R^1 = *p*-Anisyl, R^2 = PhO

7 a R^1 = Ph, R^2 = PhO
b R^1 = Ph, R^2 = BnO
d R^1 = *p*-Anisyl, R^2 = PhO

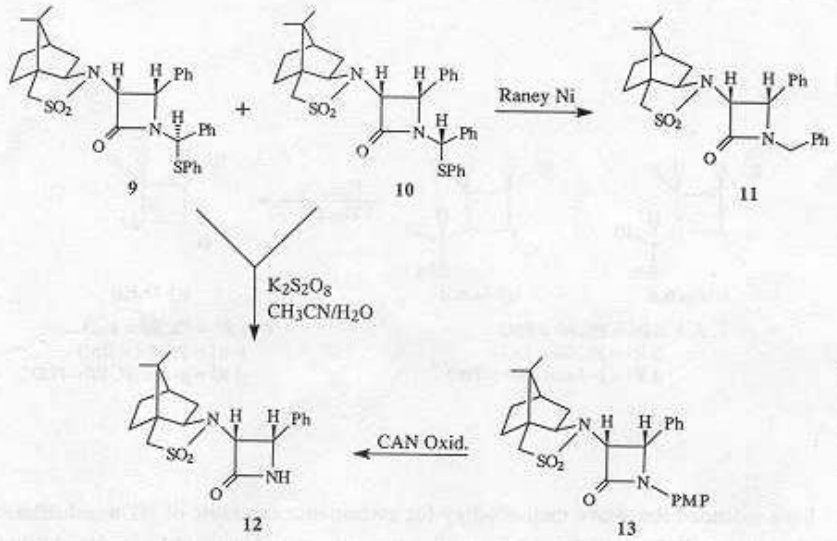
We have extended the above methodology for asymmetric synthesis of N1-unsubstituted β-lactams. To achieve the diastereoselectivity in β-lactam ring formation *via* ketene-imine cycloaddition reaction, a sterically demanding chiral acid **8**, derived from camphorsultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **8** was obtained in overall 70% yield from camphorsultam[15] in two steps using our earlier reported procedure.[16] The cycloaddition reaction of ketene derived from the acid **8** with imine **3a** in presence of triethylamine and phenyldichlorophosphate, an acid activator, offered a diastereomeric mixture of β-lactams **9** and **10** (Scheme 4) in the ratio of 92:8 (HPLC).

Scheme 4



In this reaction diastereospecific *cis*-β-lactam[11]ring formation was observed. The isomers (**9** & **10**) obtained were diastereomeric at N1-(α-thiophenyl)benzylic position, which was confirmed by converting them to N1-benzyl-*cis*-β-lactam via reductive removal of thiophenyl group. Thus, elimination of thiophenyl group of distereomeric mixture of β-lactams **9** and **10** using Raney Ni gave N1-benzyl-*cis*-β-lactam (**11**) as a single diastereomer (^{1}H NMR) in high yield (Scheme 5). The spectral data and rotation of the β-lactam **11** were found to be identical with a compound of known absolute configuration reported earlier.[16] Therefore, the absolute stereochemistry at 3 and 4 positions of β-lactam ring in **9** and **10** was assigned as 3*R*, 4*S*.

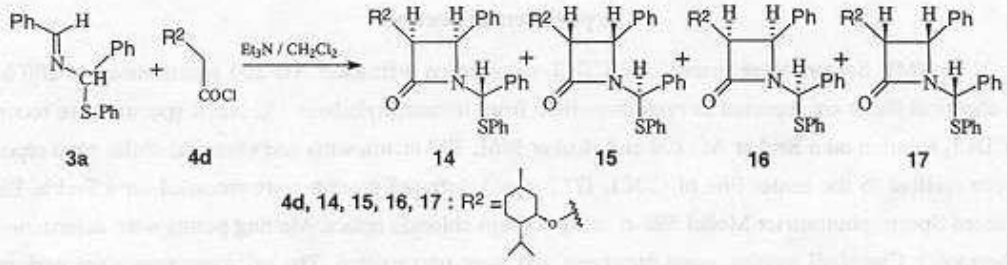
Scheme 5



These assignments were further confirmed by deprotection of the N1-(α-thiophenyl)benzylic group. The oxidative removal of the N1-(α-thiophenyl)benzylic group of the diastereomeric mixture of β-lactams **9** and **10** using potassium persulfate in acetonitrile/water under reflux conditions gave the N1-unsubstituted β-lactam (**12**) as a single diastereomer (^{1}H NMR) in good yield (Scheme 5). This N1-unsubstituted β-lactam (**12**) was also prepared from the N1-(*p*-methoxyphenyl)-β-lactam (**13**) known to have (3*R*, 4*S*) absolute configuration. Thus, **13** on treatment with ceric(IV)ammonium nitrate (CAN) in acetonitrile/water gave the NH-β-lactam **12** in 86.8% yield (Scheme 5) which showed identical spectral (NMR) and analytical (m.p., rotation) data with the NH-compound **12** prepared from the diastereomeric mixture of β-lactams **9** & **10**. From the above chemical transformations the absolute configuration at the 3 and 4 positions of β-lactam ring in **9**, **10** & **12** was unambiguously established as 3*R*, 4*S*.

We have also studied the effect of the chiral ketene derived from menthyloxyacetyl chloride (**4d**) on diastereoselective β-lactam ring formation. The starting chiral menthyloxyacetic acid was obtained in good yield by alkylation[17] of *l*-menthol with chloroacetic acid using sodium metal in dry toluene under refluxing conditions. The menthyloxyacetic acid on treatment with thionyl chloride gave the required chiral acid chloride **4d** in high yield. The acid chloride **4d** on reaction with imine **3a** in presence of triethylamine gave a diastereomeric mixture of *cis*-β-lactams (**14-17**) in good yield (Scheme 6).

Scheme 6

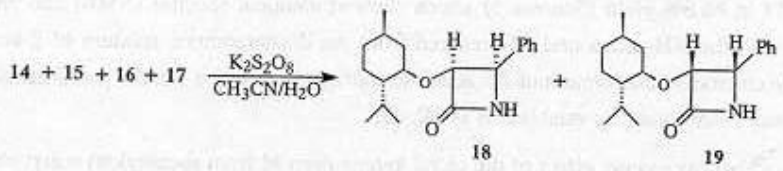


^{1}H NMR analysis of the crude reaction product showed the presence of four *cis*-β-lactams (**14**, **15**, **16** & **17**) in the diastereomeric ratio of 35:35:18:12, the diastereomeric ratio due to N1-(α- thiophenyl)benzyl group being found to be 70:30 (**14** + **15** : **16** + **17**). However, this chiral acid chloride **4d**, did not give appreciable asymmetric induction in β-lactam ring formation and almost equal amounts of two major (**14** & **15**) and two minor (**16** & **17**) diastereomers were formed. Crystallization of diastereomeric mixture from pet. ether : acetone (96:4) gave only one diastereomer, out of the four, in pure form as a white solid, which was found to be one of the minor diastereomers (**16** or **17**) by ^{1}H NMR spectral analysis. The absolute stereochemistry could not be determined as this pure compound failed to give X-ray quality crystals.

The N1-deprotection of the diasteromeric mixture of β-lactams **14**, **15**, **16** & **17** using potassium persulfate in acetonitrile/water under reflux condition gave a mixture two diastereomers **18** & **19** in almost equal amounts (Scheme 7). This further confirms that the diastereomeric ratio of 70:30 is due to the chiral

center of N1-(α-thiophenyl)benzyl group and there is no diastereoselectivity in β-lactam ring formation. Similarly, the potassium persulfate oxidation of pure diastereomer (**16** or **17**) gave one of the N-unsustituted β-lactam **18** or **19** in good yield.

Scheme 7



In conclusion, we have developed a useful method for the synthesis of N1-unsubstituted β-lactams, which can be prepared with high diastereoselectivity in certain set of substrates.

Acknowledgment : We thank Dr. A. Sarkar for valuable suggestions and the authors (KK & VS) thanks CSIR for the financial support.

Experimental Section

^{1}H NMR Spectra were recorded in $CDCl_3$ solution on a Brucker AC 200 spectrometer at 200 MHz and chemical shifts are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 and Bruker MSL 300 instruments and chemical shifts were reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. Methylene chloride was distilled over P_2O_5 under argon. Silica gel (SD's, 60 - 120 mesh) was used for column chromatography.

Preparation of Hydrazamides (2a & 2b) : Freshly distilled aldehyde was added to a ca. 10 fold excess of aq. NH_3 (30%). The reaction mixture was stirred for 3 h. at room temperature. The supernatant liquid was decanted off and the lumps were crushed, treated with water and filtered. The crude solid so obtained was crystallized from ethanol to give pure hydrazamides **2a,b** in very high yield.

1-Phenyl-N,N′-bis(phenylmethylene)methanediamine(2a): Yield : 92%. M.p. 101-102 °C [lit.[9a] m.p. 101-102 °C]. ^{1}H NMR : δ 5.80 (s, 1H); 7.18 (m, 9H); 7.62 (m, 6H); 8.30 (s, 2H). IR : 1630, 754, 693 cm^{-1}.

1-*p*-Anisyl-N,N′-bis(*p*-anisylmethylene)mehtanediamine(2b) : Yield : 89%. M. p. 126-128 °C [lit.[9b] m.p. 128.5-130.5 °C]. ^{1}H NMR : δ 3.68 (s, 3H); 3.75 (s, 6H); 5.73 (s, 1H); 6.73 (d, J = 9 Hz, 6H); 7.27 (d, J = 9 Hz, 2H); 7.62 (d, J = 9 Hz, 4H); 8.28 (s, 2H). IR : 1610, 1030, 760 cm^{-1}.

Synthesis of N-[(α-thiophenyl)benzyl]imine (3a) : A mixture of hydrobenzamide (**1a**, 5.96 g, 0.02 mol), thiophenol (3.34 g, 0.03 mol) and 1,4-dioxane (30 mL) was refluxed for 10 h. The dioxane was removed by distillation under reduced pressure and the residue was treated with pet. ether (10 mL) and kept in refrigerator over night. The precipitated solid was filtered and washed with cold pet. ether (5 mL) to get 9 g (99%) of imine **3a**, which was sufficiently pure so as to be used in next step with out further purification. M. p. 79-80 °C [lit.[10] m.p. 79.5 °C]. ^{1}H NMR : δ 5.93 (s, 1H); 7.30 (m, 11H); 7.48 (d, J = 7.5, 2H); 7.61 (d, J = 7.5, 2H); 8.0 (s, 1H). IR : 1628, 749, 694 cm^{-1}.

N-[(α-Thiophenyl)-*p*-methoxybenzyl]imine (3b) : Using the above procedure the imine **3b** was prepared from **2b** in 98% yield. M. p. 94 - 95 °C. ^{1}H NMR : δ 3.80 (s, 3H); 3.86 (s, 3H); 5.90 (s, 1H); 6.95 (d, J = 8.8 Hz, 4H); 7.25 (m, 3H); 7.43 (m, 2H); 7.52 (d, J = 8.8 Hz, 2H); 7.70 (d, J = 8.8 Hz, 2H); 7.95 (s, 1H). IR : 1605, 836, 736 cm^{-1}.

Typical procedure for the preparation of β-lactams (5a-e & 6a-e) : A solution of the acid chloride (**4a-c**, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imines (**3a,b**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was then allowed to warm-up to r.t. and stirred further for 13 h. It was then washed with water (2x15 mL), satd. $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether:acetone, 9:1) to give diastereomeric mixture of β-lactams (**5a-e** & **6a-e**) in good yields. The major and minor diastereomers were separated by crystallization from pet. ether - acetone.

3-Phenoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5a) : M. p. 214 - 215 °C. ^{1}H NMR : δ 5.0 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.47 (s, 1H); 6.8 (d, J = 10 Hz, 2H); 6.83 (t, J = 10 Hz, 1H); 6.95 - 7.70 (m, 17H). ^{13}C NMR : 61.20, 62.34, 81.22, 115.64, 122.00, 127.55, 127.85, 128.08, 128.22, 128.57, 128.81, 129.08, 129.42, 132.49, 133.03, 135.07, 156.87, 165.98. MS : m/z 328 (M$^+$- SPh), 199, 132 (100%), 109. IR : 1740 cm^{-1}. Anal. Cald for $C_{28}H_{23}O_2NS$: C, 76.86; H, 5.30; N, 3.20. Found : C, 76.68; H, 5.37; N, 3.27.

3-Phenoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (6a) : Isolated as an oil. ^{1}H NMR : δ 4.45 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.15 (s, 1H); 6.6 (d, J = 10 Hz, 2H); 6.85 (t, J = 10 Hz, 1H); 6.95 - 7.60 (m, 17H). ^{13}C NMR : 63.23, 63.93, 80.30, 115.56, 121.95, 127.84, 128.06, 128.64, 128.75, 129.05, 129.44, 132.28, 133.04, 133.54, 135.78, 156.79, 164.91. IR : 1740 cm^{-1}.

3-Benzyloxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5b) : M.p. 119 - 120 °C. ^{1}H NMR : δ 4.0 (d, J = 10.5 Hz, 1H); 4.15 (d, J = 10.5 Hz, 1H); 4.5 (d, J = 4.8 Hz, 1H); 5.05 (d, J = 4.8 Hz, 1H); 6.43 (s, 1H); 6.76 - 6.85 (m, 2H); 7.00 - 7.65 (m, 18H). ^{13}C NMR : 61.00, 62.17, 72.24, 82.83, 127.73, 127.86, 127.99, 128.14, 128.46, 128.75, 129.32, 132.50, 133.02, 133.85, 135.25, 136.25, 167.0. MS : m/z 342 (M$^+$-SPh), 199, 132, 109, 91 (100%). IR : 1740 cm^{-1}. Anal. Cald for $C_{29}H_{25}NO_2S$: C, 77.13; H, 5.58; N, 3.10. Found : C, 77.07; H, 5.77; N, 3.07.

3-Benzyloxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (6b) : Isolated as an oil. ^{1}H NMR : δ 4.05 (d, J = 10.8 Hz, 1H); 4.15 (d, J = 10.8 Hz, 1H); 4.35 (d, J = 4.8 Hz, 1H); 4.65 (d, J = 4.8 Hz, 1H); 6.15

(s, 1H); 6.82 - 7.50 (m, 20H). ^{13}C NMR : 62.91, 63.43, 72.04, 82.67, 127.65, 127.89, 128.44, 128.60, 128.85, 131.91, 133.76, 165.92. IR : 1740 cm^{-1}.

3-Acetoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5c) : M. p. 153 -154 °C. ^{1}H NMR : δ 1.55 (s, 3H); 5.22 (d, J = 5.3 Hz, 1H); 5.40 (d, J = 5.3 Hz, 1H); 6.44 (s, 1H); 6.85 - 7.70 (m, 15H). ^{13}C NMR : 19.57, 60.40, 62.66, 76.12, 127.54, 127.81, 128.05, 128.22, 128.42, 128.63, 128.76, 129.42, 132.59, 133.39, 134.78, 164.89, 168.76. IR : 1750 cm^{-1}. Anal. Cald for $C_{24}H_{21}O_3NS$: C, 71.44; H, 5.25; N, 3.47. Found : C, 71.32; H,5.14; N,3.54.

3-Phenoxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (5d) : M.p. 157 - 159 °C. ^{1}H NMR : δ 3.70 (s, 3H); 3.72 (s, 3H); 4.95 (d, J = 4.8 Hz, 1H); 5.12 (d, J = 4.8 Hz, 1H); 6.4 (s, 1H); 6.50 - 7.65 (m, 18H). ^{13}C NMR : 54.97, 55.05, 60.66, 61.43, 81.05, 113.02, 113.43, 115.50, 121.78, 125.02, 127.31, 128.23, 128.95, 129.19, 129.96, 132.64, 156.82, 159.32, 159.47, 165.71. MS : m/z 388 (M$^+$- SPh), 254, 162 (%), 109. IR : 1740 cm^{-1}. Anal. Cald for $C_{30}H_{27}O_4NS$: C, 72.41; H, 5.47; N, 2.81. Found C, 72.44; H, 5.56; N, 2.87.

3-Benzyloxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (5e) : M. p. 149-151 °C. ^{1}H NMR : δ 3.71 (s, 3H); 3.77 (s, 3H); 4.02 (d, J = 11 Hz, 1H); 4.16 (d, J = 11 Hz, 1H); 4.43 (d, J = 5.4 Hz, 1H); 4.96 (d, J = 5.4 Hz, 1H); 6.35 (s, 1H); 6.53 - 6.72 (m, 4H); 6.83 - 7.45 (m, 12H); 7.53 - 7.64 (m, 2H). ^{13}C NMR : 55.29, 60.59, 61.50, 72.21, 82.74, 113.37, 113.60, 125.98, 127.72, 127.80, 128.03, 128.16, 128.33, 129.17, 129.33, 130.11, 132.85, 159.61, 167.02. IR : 1750 cm^{-1}. Anal. Cald for $C_{31}H_{28}O_4NS$: C, 72.92; H, 5.53; N, 2.74. Found C, 72.24; H, 6.07; N, 2.76.

3-Benzyloxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (6e) : Isolated as an oil .^{1}H NMR : δ 3.80 (s, 3H); 3.83 (s, 3H); 4.07 (d, J = 10.8 Hz, 1H); 4.15 (d, J = 10.8 Hz, 1H); 4.25 (d, J = 5.5 Hz, 1H); 4.63 (d, J = 5.5 Hz, 1H); 6.10 (s, 1H); 6.80 - 7.45 (m, 18H). IR : 1745 cm^{-1}.

Preparation of N1-unsubstituted β-lactams (7a-c) : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of β-lactams 5 (0.2 mmol) in acetonitrile (8 mL) was added and the reaction mixture was refluxed with stirring for 4 h. After completion of the reaction (TLC), the acetonitrile was removed by distillation under reduced pressure and the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was washed with water (15 mL), brine (10 mL) and dried over Na_2SO_4. It was filtered and filtrate on removal of solvent provided the crude product, which was column chromatographed to get of pure unsubstituted β-lactams 7.

3-Phenoxy-4-phenylazetidin-2-one (7a) : Yield 70%. M.p. 160 °C. ^{1}H NMR : δ 5.05 (d, J = 4.8 Hz, 1H, C3H); 5.5 (dd, J = 2.5 & 4.8 Hz, 1H, C4H); 6.6 (bs, 1H, NH); 6.8 (d, J = 9 Hz, 2H, Ar); 6.9 (t, J = 9 Hz, 1H, Ar); 7.10 - 7.40 (m, 7H, Ar). IR : 2800 - 3500, 1770 cm^{-1}. Analysis Cald for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found : C, 75.51; H, 5.73; N, 5.62.

3-Benzyloxy-4-phenylazetidin-2-one (7b) : Yield 64%. M. p. 188-189 °C. ^{1}H NMR : δ 4.25 (d, J = 12 Hz, 1H); 4.35 (d, J = 12 Hz, 1H); 4.85 (d, J = 4.8 Hz, 1H); 4.95 (m, 1H); 6.25 - 6.30 (bs, 1H); 6.9 - 7.8 (m, 10H). IR : 1750, 3195 cm^{-1}. Anal. for Cald $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found : C, 75.48; H, 6.01; N, 5.46.

3-Phenoxy-4-*p*-anisylazetidin-2-one (7c) : Yield 70%. M. p. 165 - 167 °C. ^{1}H NMR : δ 3.80 (s, 3H); 5.03 (d, *J* = 4.5 Hz, 1H); 5.42 (dd, *J* = 2.4 & 4.5 Hz, 1H); 6.50 (s, 1H); 6.75 - 6.97 (m, 5H); 7.11 - 7.23 (m, 2H); 7.30 (d, *J* = 8.2 Hz, 2H). IR : 1720 & 3190 cm^{-1}. Anal. for Cald $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found : C, 71.78; H, 5.27; N, 5.46.

Preparation of diastereomeric mixture of {N1′-[(α-thiophenyl)benzyl]-4′-phenylazetidin-2′-one-3′-yl}-2,10-comphorsultam (9 & 10) : To a stirred mixture of acid **8** (0.4 g, 1.46 mmol), imine **3a** (0.653 g, 2.15 mmol), triethylamine (0.6 mL) and dry CH_2Cl_2 (10 mL), a solution of phenyl dichlorophosphate (0.32 mL, 2.15 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and successively washed with water (15 mL), satd. $NaHCO_3$ solution (15 mL), brine (15 mL) and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to give the crude product, which was column chromatographed (silica gel, 60-120, pet. ether/acetone) to furnish 0.614 g (75.4%) of the diastereomeric mixture of **9** & **10** as a white solid, m. p. 98 - 100 °C. This mixture was used for deprotection without separation. ^{1}H NMR (diastereo-meric mixture **9** & **10**) : δ 0.12 (s, 3H); 0.68 (s, 3H); 0.82-1.03 (m, 1H); 1.1-1.47 (m, 4H); 1.50-1.85 (m, 2H); 2.82 & 3.00 (2xdd, *J* = 4.8 & 13.2 Hz, total 2H, CH_2); 3.39 & 3.54 (2xdd, *J* = 3.9 & 6.8 Hz, total 1H); 4.27 & 4.67 (2xd, *J* = 4.8 Hz, total 1H); 4.78 and 5.23 (2xd, *J* = 4.8 Hz, total 1H); 5.97 and 6.38 (2xs, total 1H); 6.71 - 6.82 (m, total 2H, Ar); 6.92 - 7.84 (m, total 13H, Ar). IR (diastereomeric mixture) : 1755 cm^{-1}. $[\alpha]^{25}_D$ (diastereomeric mixture) : +96.086° (c 1, CH_2Cl_2). Anal. Cald for $C_{32}H_{34}N_2O_3S_2$: C, 68.79; H, 6.13; N, 5.01. Found C, 68.67; H, 6.71; N, 4.50.

Preparation of (2R, 3S, 6R, 3′R, 4′S)-[N1′-benzyl-4′-phenylazetidin-2′-one-3′-yl}-2,10-comphorsultam (11) from diastereomeric mixture of 9 & 10 : To a solution of diastereomeric mixture of β-lactams **9** & **10** (0.050 g , 0.089 mmol) in ethanol (5 mL) was added Raney nickel (0.8 mL suspension in ethanol) and the resultant mixture was stirred for 30 min at room temperature. After completion of the reaction (TLC), it was filtered through celite pad, washed with ethanol. The filtrate on removal of solvent yielded 0.040 g (99.3%) of N1-benzyl-β-lactam (**11**) as a white crystalline solid, m. p. 222 - 223 °C [lit.[16] m.p. 221-222 °C]. ^{1}H NMR : δ 0.20 (s, 3H); 0.75 (s, 3H); 1.30 (m, 2H); 1.7(m, 5H); 2.95 (d, *J* = 14 Hz, 1H); 3.05 (d, *J* = 14 Hz, 1H); 3.55 (t, *J* = 7 Hz, 1H); 4.05 (d, *J* = 16 Hz, 1H); 4.7 (d, *J* = 5.4 Hz, 1H); 5.0 (d, *J* = 16 Hz, 1H); 5.05 (d, *J* = 5.4 Hz, 1H); 7.10 - 7.45 (m, 10H). IR : 1760 cm^{-1}. $[\alpha]^{25}_D$: +62.87° (c 1.1, CH_2Cl_2); {lit.[16] $[\alpha]^{25}_D$: +62.0° (c 1, CH_2Cl_2)}.

Preparation of (2R, 3S, 6R, 3′R, 4′S)-[4′-phenylazetidin-2′-one-3′-yl]-2,10-camphorsultam (12) from diastereomeric mixture of 9 & 10 : To a solution of potassium persulfate (0.850 g, 3.11 mmol) in water (10 mL), a solution of diastereomeric mixture of β-lactams **9** & **10** (0.7 g, 1.25 mmol) in acetonitrile (25 mL) was added and the reaction mixture was refluxed with stirring for 4 h. After completion of the reaction (TLC), the reaction mixture was work-up as described for compound **7**. The crude product obtained was column chromatographed to get 0.341 g (75.8%) of pure NH β-lactam **12** as a white solid, which was crystallized from acetone/pet. ether, m. p. 234 - 236 °C. ^{1}H NMR : δ 0.09 (s, 3H); 0.71 (S, 3H); 0.77 - 0.99 (m, 1H); 1.03 - 1.47 (m, 4H); 1.52 - 1.89 (m, 2H); 2.98 (dd, *J* = 13.66 Hz, and 33.17 Hz, 2H); 3.57 (t, *J* =

5.36 Hz, 1H); 5.00 (d, 4.8 Hz, 1H); 5.21 (bd, 1H); 6.67 (bs, 1H); 7.17 - 7.68 (m, 5H). IR : 1760, 3300 cm^{-1}. $[a]^{25}_{D}$: +43.85° (c 1, CH_2Cl_2).

Preparation of (2R, 3S, 6R, 3'R, 4'S)-[4'-phenylazetidin-2'-one-3'-yl]-2,10-comphorsultam (12) from (2R, 3S, 6R, 3'R, 4'S)-[N1'-(p-Anisyl)-4'-phenylazetidine-2'-one-3'-yl]-2,10-comphorsultam (13) : A solution of β-lactam 13 (0.074 g, 0.16 mmol) in acetonitrile/tetrahyrofuran (3:1mL) was cooled to 0°C and treated with a solution of ceric (IV) ammonium nitrate (0.482 mmol) in water (1.5 mL) over 3 min. The solution was stirred at 0 - 5 °C for 45 min. and diluted with 10 mL of water. The mixture was extracted with ethyl acetate (3x5 mL). The organic extracts were washed with satd. sodium bicarbonate (5 mL) and the aqueous solution back extracted with ethyl acetate (5 mL). The combined organic extracts were washed with sodium sulfite (10%, 2x10 mL), satd. sodium bicarbonate (5 mL), and brine (10 mL), It was then dried over Na_2SO_4) and filtered through celite. The filtrate on removal of solvent furnished crude product, which was purified by column chromatography to give 0.050 g (86.8%) of NH-β-lactam **12** as a white solid, m. p. 233 - 234 °C. $[\alpha]^{25}_{D}$: + 43.6° (c 0.9, CH_2Cl_2). The spectral data for this compound was identical to that of NH-β-lactam **12** prepared from diastereomeric mixture of **9** & **10**.

3-Menthyloxy-N1-[(1'-thiophenyl)benzyl]-4-phenylazetidin-2-one (14-17) : A solution of the menthyl-oxyacetyl chloride (**4d**, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imine (**3a**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was then allowed to warm to r.t. and stirred further for 15 h. It was then washed with water (2x15 mL), satd. $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether:acetone, 9:1) to give 0.77 g (62.2%) of a semi solid mixture of β-lactams (**14-17**) with diastereomeric ratio of 35:35:18:12. ^1H NMR (mixture of **14-17**) : δ 0.02 - 1.01 (m, total 13H); 1.02 - 1.24 (m, 2H); 1.24 - 1.58 (m, 2H); 1.85 - 2.17 (m, 1H); 2.72 - 2.83 and 3.02 - 3.22 (2xm, total 1H); 4.28, 4.31, 4.40 and 4.43 (4xd, J = 4.5 Hz, total 1H); 4.60, 4.67, 4.97 and 4.99 (4xd, J = 4.5 Hz, total 1H); 6.11, 6.16, 6.27 and 6.29 (4xs, total 1H); 6.87 - 7.88 (m, 15). IR : 1745 cm^{-1}.

The diastereomeric mixture of **14 - 17** was crystallized from pet. ether - acetone to give 60 mg of one of the minor diastereomer (**16** or **17**) in pure form. M. p. 158 - 160 °C. ^1H NMR : δ 0.1 (d, J = 8 Hz, 3H); 0.48 (d, J = 8 Hz, 3H); 0.60 - 0.75 (m, 2H); 0.82 (d, J = 8 Hz, 3H); 0.9 - 1.3 (m, 3H); 1.35 - 1.50 (m, 1H); 1.85 - 2.05 (m, 1H); 2.75 (m, 1H); 4.40 (d, J = 5.2 Hz, 1H); 5.00 (d, J = 5.2 Hz, 1H); 6.4 (s, 1H); 6.9 - 7.6 (m, 15H). ^{13}C NMR : 15.61, 20.61, 22.13, 22.86, 24.47, 31.17, 31.41, 34.16, 40.87, 47.53, 61.68, 61.89, 80.77, 82.19, 127.39, 127.59, 127.84, 128.05, 128.18, 128.30, 128.67, 128.88, 128.97, 129.21, 131.94, 132.70, 134.37, 135.50, 168.96. IR : 1740 cm^{-1}. $[a]^{D}_{23}$: +98.58° (c 1, $CHCl_3$). Anal. Cald for $C_{32}H_{37}O_2NS$: C, 76.91; H, 7.46; N, 2.80. Found C, 76.53; H, 7.52; N, 2.92.

Preparation of NH-β-lactams 18 and 19 form diastereomeric mixture of β-lactams 14-17 : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of diastereomeric mixture of β-lactams **14-17** (0.1g, 0.2mmol) in acetonitrile (8 mL) was added and the reaction mixture was refluxed with stirring for 4 h. The usual work-up as described for compound **7** gave crude product, which was purified by column chromatography to give 45 mg (75%) of NH-β-lactams (**18** & **19**) as a mixture of two diastereomers.

^{1}H NMR (mixture of **18** & **19**) : δ 0.21 - 1.08 (m, 13H); 1.12 - 1.32 (m, 2H); 1.42 - 1.68 (m, 2H); 1.92 - 2.18 (m, 1H); 2.98 and 3.29 (2xtd, *J* = 4.5 & 9.9 Hz, total 1H); 4.82 and 4.85 (2xd, *J* = 4.5 Hz, total 1H); 4.90 - 4.93 and 4.95 - 4.99 (2xdd, *J* = 2.2, & 4.8 Hz, total 1H); 6.30 (bs, 1H); 7.20 - 7.49 (m, 5H). IR : 3410, 1750 cm^{-1}.

Preparation of 3-menthyloxy-4-phenylazetidin-2-one (18 or 19) from pure β-lactam 16 or 17 : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of pure β-lactam **16** or **17** (0.1 g, 0.2 mmol) in acetonitrile (8 mL), was added and the reaction mixture was refluxed with stirring for 4 h. The usual work-up as described for compound **7** gave crude product, which was purified by column chromatography to give 39 mg (65%) of pure NH-β-lactam (**18** or **19**) as a white solid. M.p. 173-174 °C. ^{1}H NMR : δ 0.26 (d, *J* = 8 Hz, 3H); 0.55 (d, *J* = 8 Hz, 3H); 0.76 (m, 2H); 0.88 (d, *J* = 8 Hz, 3H); 0.97 (m, 2H); 1.26 (m, 2H); 1.52 (m, 2H); 2.15 (m, 1H); 2.95 (td, *J* = 4. 5 &10.2, IH); 4.81 (d, *J* = 4.8 Hz, 1H); 4.88 (dd, *J* = 2.2, & 4.8 Hz, 1H); 6.30 (bs, 1H); 7.42 (m, 5H). ^{13}C NMR : 15.87, 20.70, 22.21, 23.02, 24.68, 31.55, 34.28, 41.22, 47.61, 58.79, 81.37, 84.56, 127.80, 128.12, 136.48, 169.89. IR : 1759, 3413 cm^{-1}. Anal. for Cald $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found : C, 75.92; H, 9.15; N, 4.64. $[a]^{25}_D$: +25.51° (c 0.97, CH_2Cl_2).

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11. The ^{1}H NMR of the crude reaction mixture indicated the formation of only *cis*-isomers ($J_{3,4}$ = 4 -5 Hz).
12. HPLC : Perkin-elmer 410-pump, H.P. 1050 MWD at 254 nm connected to HP 3396 Ser-II integrater. Col. MN-C-18, 8 mm X 100 mm length. Solvent system (v/v) : 80:20 (MeOH:H_2O) flow rate 1.5 mL/min.
13. Data was measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer[13] with Mo-Kα (λ= 0.7093 A°) radiation at 293 K. Crystal belongs to monoclinic, space group $P2_1$ /c with a = 11.813 (2), b = 6.410 (2), c = 30.552 (4) A°; V = 2312.6 A° 3, Z = 4, dcalc = 1.257 Mgm^{-3}, μ = 0.165 mm^{-1}. The structure was solved by direct methods using MULTAN-80 Least squares refinement of scale factor, positional and anisotroic thermal parameters for non hydrogen atoms converged to R = 0.068. Hydrogen atoms geometrically fixed and confirmed by difference fourier were held fixed during refinement. Structure solution and refinements were carried out using NRCVAX programs.
14. *For details of the X-ray data see* : Srirajan, V.; Bhawal, B. M; Puranik, V. G. *Acta. Cryst. C* **1997**, *C53*, 358.
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Pergamon

Tetrahedron 56 (2000) 8555–8560

TETRAHEDRON

Stereoselective Synthesis of *cis*-Bis-β-lactams Linked with an Ethylene Bridge

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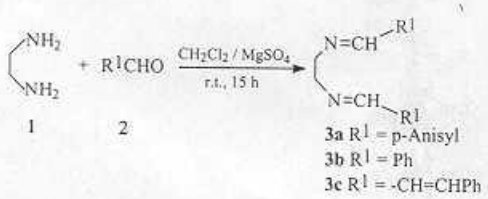
Received 5 June 2000; revised 14 August 2000; accepted 30 August 2000

Abstract—An efficient synthesis of (±)-*cis*-bis-β-lactams (**5** and **6**) via cycloaddition reaction of bisimines (**3a–c**) with acid chlorides (**4**) in the presence of triethylamine in very good yield is described. © 2000 Published by Elsevier Science Ltd.

Although β-lactam derivatives are well known for their antibiotic activities,[1] recently they have also been used as a synthon for the synthesis of various natural and unnatural products.[2] Ojima has shown the utility of bis-β-lactams for the synthesis[3] of peptides. The synthesis of bis-β-lactams, in general, have been reported by step-wise construction of β-lactam rings.[4] In continuation of our work on synthesis of bis-β-lactams,[4d,5] we were interested in building bis-β-lactams with spacer groups. Herein, we report the synthesis of bis-β-lactams in single step from bisimines derived from bis-amines.

The starting *N,N′*-bis-(*p*-anisylmethylene)ethane diamine (**3a**)[6] and *N,N′*-bis-(phenylmethylene)ethane diamine (**3b**)[7] were prepared in excellent yields by stirring a mixture of the aromatic aldehydes (**2a,b**), ethylenediamine and anhydrous $MgSO_4$ in dry dichloromethane (Scheme 1). The bisimine *N,N′*-bis-(styrylmethylene)ethane diamine (**3c**)[8] was prepared in quantitative yield by refluxing ethanolic solution of ethylenediamine and cinnamaldehyde.

The bisimines **3a–c** on cycloaddition reaction (Staudinger reaction) with various acid chlorides (**4a–c**) in the presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-bis-β-lactams[9] (**5a–g** and **6a–g**) in good to excellent yields (Scheme 2, Table 1). The TLC and ^{1}H NMR spectral analysis of the crude reaction mixture showed the presence two diastereomers. These diastereomers were separated by flash column chromatography. The *C*-symmetric structure for bis-β-lactams **5a–g** was assigned from the ^{1}H NMR spectral analysis. The ^{1}H NMR spectra of all these compounds showed two doublets at about δ 2.8 and 3.8 with geminal coupling of 11–12 Hz for the protons of the methylene group joining two β-lactam rings. The *meso* structure was assigned to the other diastereomers **6a–g** as ^{1}H NMR spectra of all compounds in this series showed two multiplets (δ ~3.0 and 3.5) due to non-equivalence of two methylenes joining two β-lactam rings.



Scheme 1.

The structures for both C_2-symmetric and *meso* bis-β-lactams (**5a–g** and **6a–g**) were further confirmed by single crystal X-ray analysis of the representative compounds **5b** and **6c**. The X-ray crystal analysis of isomer (±)-**5b** showed C_2-symmetry in the molecule and the relative stereochemistry of β-lactam ring centres was assigned as 3*S*, 4*R*, 3′*S*, 4′*R* or 3*R*, 4*S*, 3′*R*, 4′*S* (Fig. 1).

The *meso* stereochemistry of the isomer (±)-**6c** was established from its X-ray structure and the relative stereochemistry of β-lactam ring centres was assigned as 3*S*, 4*R*, 3′*R*, 4′*S* or 3*R*, 4*S*, 3′*S*, 4′*R* (Fig. 2).

We have extended the above methodology to the asymmetric synthesis of bis-β-lactams. To achieve the stereoselectivity in β-lactam ring formation via ketene–imine cycloaddition reaction, a sterically demanding chiral acid **7**, derived from camphor sultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **7** was obtained in overall 70% yield from camphor sultam in

Keywords: cycloaddition reaction; azetidinones; Staudinger reaction; bisimines; bis-β-lactams.
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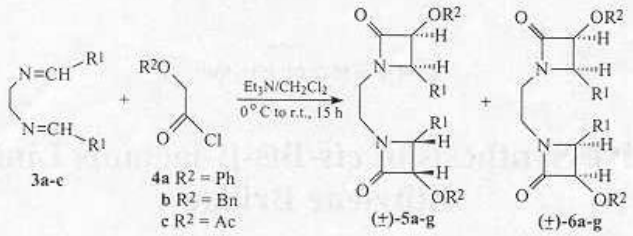
0040–4020/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4020(00)00800-0



Scheme 2.

Table 1. Synthesis of bis-β-lactams **5** and **6**

Compound	R^1	R^2	Compound **5** and **6**			
			Yield[a] (%)	Ratio[b] of **5** and **6**	mp of **5**[c] (°C)	mp of **6**[c] (°C)
a	Anisyl	Ph	80	42:58	204–205	182–183
b	Anisyl	Bn	86	55:45	138–139	227–228
c	Anisyl	Ac	75	51:49	184–185	194–195
d	Ph	Ph	79	38:62	212–213	195–196
e	Ph	Bn	85	30:70	128–129	242–243
f	Styryl	Bn	60	58:42	Semisolid	151–153
g	Styryl	Ph	66	61:39	196–198	195–196

[a] Isolated yields of diastereomeric mix of **5** and **6**.
[b] The diastereomeric ratio of **5** and **6** was determined from ^{1}H NMR spectral data.
[c] The diastereomers **5** and **6** were separated by flash column chromatography.

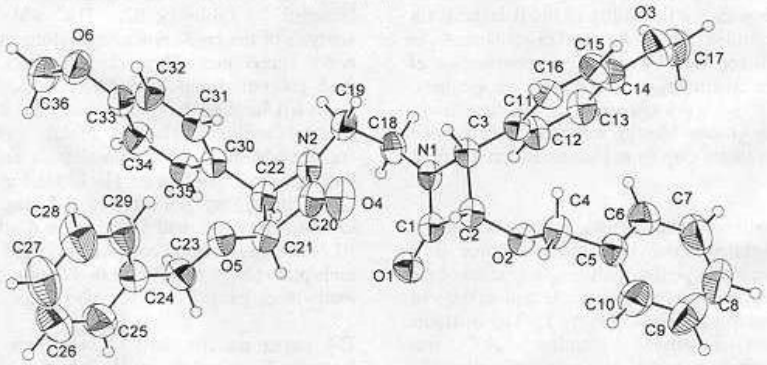


Figure 1. ORTEP diagram of bis-β-lactam **5b** without solvent molecule.

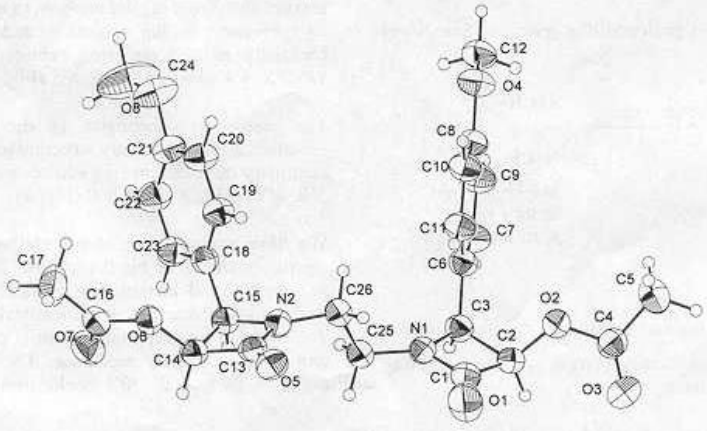
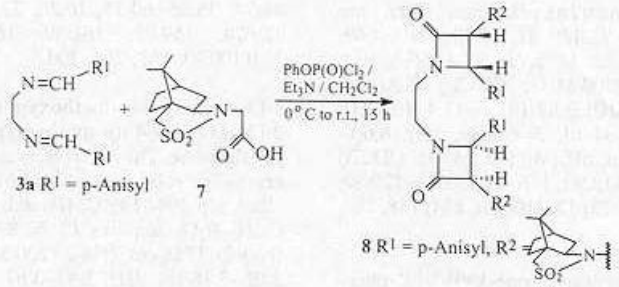


Figure 2. ORTEP diagram of bis-β-lactam **6c**.



Scheme 3.

two steps using our earlier reported procedure.[10] The cycloaddition reaction of ketene derived from the acid **7** with imine **3a** in the presence of triethylamine and phenyldichlorophosphate, as an acid activator, furnished stereospecifically bis-β-lactam **8** in excellent yield (Scheme 3). The formation of a single diastereomer was evident from ^{1}H NMR and HPLC analysis of the crude reaction mixture. The C_2-symmetric structure was assigned to bis-β-lactam **8** based on its ^{1}H NMR spectrum, which compares very well with the ^{1}H NMR spectra of C_2-symmetric bis-β-lactams **5** obtained earlier. The absolute stereochemistry for this bis-β-lactam **8** was assigned as 3*R*, 4*S*, 3′*R*, 4′*S* based on our earlier work on asymmetric synthesis of β-lactams[10] using ketene derived from Oppolzer's sultam and imines.

Experimental

General

^{1}H NMR Spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 spectrometer at 200 MHz and chemical shifts are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 and Bruker MSL 300 instruments and chemical shifts were reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions.

General procedure for imines 3a and 3b

A mixture of freshly distilled aldehyde (0.15 mol), ethylenediamine (0.05 mol), anhydrous $MgSO_4$ (24 g) and dry dichloromethane (200 mL) was stirred for 15 h at room temperature. The reaction mixture was then filtered through a bed of celite and the solvent from the filtrate was removed by distillation under reduced pressure. The residue was then treated with a 10% solution of ethyl acetate in petroleum ether (60–80) to remove unreacted aldehyde and filtered to give required imines **3a**,**b** in excellent yield as a crystalline solid.

***N*,*N*′-Bis(*p*-methoxyphenylmethylene)ethane-1,2-diamine 3a.** It was obtained as a white solid, crystallized from EtOAc:petroleum ether (90:10) as needles, yield 88%; mp 109–110°C [lit. mp[6] 110–111°C]; ν_{max} ($CHCl_3$) 830, 1010, 1450, 1630 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.74 (s, 6H); 3.84 (s, 4H); 6.78 (d, *J*=8 Hz, 4H); 7.50 (d, *J*=8 Hz, 4H); 8.06 (s, 2H).

***N*,*N*′-Bis(phenylmethylene)ethane-1,2-diamine 3b.** It was isolated as a white solid and crystallized from EtOAc: petroleum ether (90:10) to give white needles; yield 84%; mp 52–53°C [lit. mp[7] 51.5–53°C]; ν_{max} ($CHCl_3$) 960, 1000, 1350, 1430, 1610 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.88 (s, 4H); 6.92–7.88 (m, 10H); 8.14 (s, 2H).

Preparation of *N*,*N*′-bis(styrylmethylene)ethane-1,2-diamine 3c

A solution of freshly distilled cinnamaldehyde (14.18 g, 0.107 mol) and ethylenediamine (3 g, 0.05 mol) in ethanol (40 mL) was refluxed for 1 h. The solvent was removed by distillation under reduced pressure and the residue was purified by crystallization from ethyl acetate:petroleum ether (90:10) to yield 14.38 g (100%) of pure bisimine **3c** as a crystalline pale yellow solid, mp 108–109°C [lit. mp[8] 109°C]; ν_{max} ($CHCl_3$) 979, 1164, 1218, 1450, 1635, 2846, 2939 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.80 (s, 4H); 6.70–6.95 (m, 4H); 7.15–7.55 (m, 10H); 7.95 (d, *J*=6.6 Hz, 2H).

Typical procedure for the preparation of β-lactams 5a–g and 6a–g

A solution of the acid chlorides (**4a–c**, 2.53 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of imines (**3a–c**, 3.5 mmol) and triethylamine (10 mmol) in CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. It was then washed with water (2×20 mL), satd $NaHCO_3$ (15 mL), brine (15 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product of a diastereomeric mixture. The diastereomers were separated by flash column chromatography (silica gel, 230–400, petroleum ether:ethyl acetate, 3:1) to give pure diastereomer of β-lactams (**5a–g** and **6a–g**).

1,2-Bis[3′-phenoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]ethane 5a. It was isolated as white solid from diastereomeric mixture by flash column chromatography and

crystallized from dichloromethane:petroleum ether, mp 204–205°C; [Found. C, 72.40; H, 5.49; N, 4.69. $C_{34}H_{32}N_2O_6$ requires C, 72.32; H, 5.71; N, 4.96%]; ν_{max} (Nujol) 1735 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.80 (d, J=11.4 Hz, 2H); 3.75 (s, 6H); 3.82 (d, J=11.4 Hz, 2H); 5.17 (d, J=6.5 Hz, 2H); 5.34 (d, J=6.5 Hz, 2H); 6.60–6.93 (m, 12H); 7.02–7.33 (m, 6H); δ_C (75.2 MHz, $CDCl_3$) 37.36, 55.24, 60.76, 82.55, 113.93, 116.86, 129.16, 129.80, 155.37, 160.14, 166.82; *m/z* (EI) 121(100%), 134, 148, 161, 226.

1-[3-Phenoxy-4-(*p*-anisyl)azetidin-2′-one-1′yl]-2-[3[1]-phenoxy-4[1]-(*p*-methoxy-phenyl)-azetidin-2″-one-1″-yl]ethane 6a. It was obtained as a white solid, which was crystallized from dichloromethane:petroleum ether, mp 182–183°C; [Found: C, 72.50; H, 5.76; N, 4.76. $C_{34}H_{32}N_2O_6$ requires C, 72.32; H, 5.71; N, 4.96]; ν_{max} (Nujol) 1740 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.00–3.24 (m, 2H); 3.50–3.75 (m, 2H); 3.78 (s, 6H); 4.88 (d, J=5.4 Hz, 2H); 5.24 (d, J=5.4 Hz, 2H); 6.57–7.42 (m, 18H); δ_C (75.2 MHz, $CDCl_3$) 38.24, 55.27, 61.68, 82.16, 113.99, 116.80, 129.16, 129.86, 155.37, 160.23, 165.84; *m/z* (EI) 245 (100%), 148, 161, 226, 254.

1,2-Bis[3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]ethane 5b. It was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 138–139°C; [Found: C, 72.69; H, 6.22; N, 4.58. $C_{36}H_{36}N_2O_6$ requires C, 72.95; H, 6.12; N, 4.72]; ν_{max} (Nujol) 1735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.72 (d, J=10.8 Hz, 2H); 3.72 (d, 10.79 Hz, 2H); 3.81 (s, 6H); 4.14 (d, J=8.1 Hz, 2H); 4.30 (d, J=8.1 Hz, 2H); 4.82 (d, J=4.2 Hz, 2H); 5.00 (d, J=4.2 Hz, 2H); 6.73–7.04 (m, 8H); 7.12–7.41 (m, 10H); δ_C (50.3 MHz, $CDCl_3$) 37.34, 55.64, 60.99, 72.65, 84.69, 114.34, 125.77, 128.16, 128.39, 128.52, 130.12, 136.85, 160.32, 168.32; *m/z* (EI) 91(100%), 149, 261, 281, 331, 484, 501(M^+-Bn).

1-[3-Benzyloxy-4-(*p*-methoxyphenyl)azetidin-2′-one-1′yl]-2-[3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2″-one-1″-yl]ethane 6b. The *title compound* **6b** was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 227–228°C; [Found: C, 72.76; H, 6.17; N, 4.85. $C_{36}H_{36}N_2O_6$ requires C, 72.95; H, 6.12; N, 4.72]; ν_{max} (Nujol) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.81–3.02 (m, 2H); 3.41–3.62 (m, 2H); 3.82 (s, 6H); 4.14 (d, J=10.8, Hz, 2H); 4.26 (d, J=10.8 Hz, 2H); 4.58 (d, J=4.2 Hz, 2H); 4.70 (d, J=4.2 Hz, 2H); 6.78–7.02 (m, 8H); 7.12–7.33 (m, 10H); δ_C (75.2 MHz, $CDCl_3$) 37.81, 55.48, 61.59, 72.33, 83.77, 114.17, 125.22, 128.00, 128.24, 128.36, 129.92, 136.54, 160.22, 167.34; *m/z* (EI) 90 (100%), 148, 240, 268, 501 (M^+-Bn).

1,2-Bis[3′-acetoxy-4′-(*p*-methoxyphenyl)azetidin-2′one-1′-yl]ethane 5c. It was obtained as a white solid, crystallized from ethyl acetate:petroleum ether, mp 184–185°C. [Found: C, 62.77; H, 5.72; N, 5.77. $C_{26}H_{28}N_2O_8$ requires C, 62.90; H, 5.68; N, 5.64]; ν_{max} (Nujol) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.72 (s, 6H); 2.88 (d, J=10.3 Hz, 2H); 3.79 (d, J=10.3 Hz, 2H); 3.82 (s, 6H); 5.13 (d, J=4.5 Hz, 2H); 5.74 (d, J=4.5 Hz, 2H); 6.89 (d, J=8.69 Hz, 4H); 7.17–7.32 (m, 4H); δ_C (50.3 MHz, 1:1DMSO:$CDCl_3$) 19.98, 38.23, 38.77, 39.18, 39.59, 40.01, 40.43, 40.85, 41.27, 55.36, 60.13, 76.26, 77.26, 77.62, 113.98, 124,97, 129.74, 159.85, 161.39, 165.40, 168.66; *m/z* (EI) 121(100%), 161, 262, 304.

1-[3-Acetoxy-4-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3′-Acetoxy-4′-(*p*-meth-oxyphenyl)azetidin-2″-one-1″-yl]ethane 6c. The *title compound* **6c** was obtained as a white crystalline solid, crystallized from ethyl acetate: petroleum ether, mp 194–195°C; [Found: C, 62.62; H, 5.69; N, 5.50. $C_{26}H_{28}N_2O_8$ requires C, 62.89; H, 5.68; N, 5.64]; ν_{max} (Nujol) 1758 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.73 (s, 6H); 3.02–3.18 (m, 2H); 3.46–3.67 (m, 2H); 3.83 (s, 6H); 4.85 (d, J=5.4 Hz, 2H); 5.65 (d, J=5.4 Hz, 2H); 6.92 (d, J=9.7 Hz, 4H); 7.14–7.30 (m, 4H); δ_C (75.2 MHz, $CDCl_3$) 19.84, 38.45, 55.24, 61.31, 77.43, 113.93, 123.82, 129.65, 160.14, 165.26, 168.92; *m/z* (EI) 150 (100%), 121, 135.

1,2-Di-[3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]ethane 5d. It was obtained as a white crystalline solid, crystallized from dichloromethane:petroleum ether; mp 212–213°C; [Found: C, 76.05; H, 5.30; N, 5.40. $C_{32}H_{28}N2O_4$ requires C, 76.17; H, 5.59; N, 5.55]; ν_{max} ($CHCl_3$) 1752 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.86 (d, J=11.5 Hz, 2H); 3.88 (d, J=11.5 Hz, 2H); 5.22 (d, J=3.9 Hz, 2H); 5.38 (d, J=3.9 Hz, 2H); 6.58–7.39 (m, 20H). δ_C (75.2 MHz, $CDCl_3$) 37.54, 61.16, 82.62, 115.64, 116.92, 128.49, 129.01, 129.13, 132.45, 155.28, 166.85; *m/z* (EI) 230 (100%), 196, 224.

1-[3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-phenylazetidin 2″-one-1″-yl]ethane 6d. It was isolated as a white solid, crystallized from dichloromethane:petroleum ether, mp 195–196°C; [Found: C, 76.30; H, 5.36; N, 5.31. $C_{32}H_{28}N_2O_4$ requires C, 76.17; H, 5.59; N, 5.55]; ν_{max} ($CHCl_3$) 1729 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.00–3.23 (m, 2H); 3.55–3.79 (m, 2H); 4.87 (d, J=4.2 Hz, 2H); 5.22 (d, J=4.2 Hz, 2H); 6.52–6.73 (m, 4H); 6.97–7.20 (m, 4H); 7.20–7.43 (m, 12H); δ_C (75.2 MHz, $CDCl_3$) 38.30, 62.08, 82.16, 116.80, 128.55, 129.16, 132.27, 155.28, 165.81; *m/z* (EI) 230 (100%), 196.

1,2-Di[3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl]ethane 5e. It was obtained from the diastereomeric mixture by column chromatography (silica gel, 230–400) and crystallized from dichloromethane:petroleum ether, mp 128–129°C; [Found: C, 76.43; H, 6.16; N, 4.98. $C_{34}H_{32}N_2O_4$ requires C, 76.67; H, 6.05; N, 5.26]; ν_{max} (Nujol) 1740 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.75 (d, J=10.9 Hz, 2H); 3.80 (d, J=10.9 Hz, 2H); 4.12 (d, J=10.8 Hz, 2H); 4.29 (d, J=10.8 Hz, 2H); 4.90 (d, J=4.4 Hz, 2H); 5.08 (d, J=4.4 Hz, 2H); 6.94 (m, 4H); 7.18–7.46 (m, 16H); δ_C (50.3 MHz, $CDCl_3$) 37.29, 61.32, 69.19, 72.64, 80.16, 81.13, 82.98, 83.11, 84.73, 86.08, 90.09, 128.03, 128.25, 128.38, 128.72, 133.90, 136.56, 166.11, 168.21, 175.39.

1-[3′-Benzyloxy-4′-phenylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-phenylazetidin-2″-one-1″-yl]ethane 6e. It was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 242–243°C; [Found: C, 76.51; H, 6.31; N, 5.27. $C_{34}H_{32}N_2O_4$ requires C, 76.67; H, 6.05; N, 5.26]; ν_{max} (Nujol) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.90–3.10 (m, 2H); 3.51–3.71 (m, 2H); 4.12 (d,

J=10.3 Hz, 2H); 4.24 (d, J=10.34 Hz, 2H);.59 (d, J=4.3 Hz, 2H); 4.68 (d, J=4.3 Hz, 2H); 6.84–6.97 (m, 4H); 7.14–7.54 (m, 16H); δ_C (75.2 MHz, $CDCl_3$) 37.72, 61.95, 72.24, 83.71, 127.88, 128.21, 128.46, 128.58, 128.79, 133.34, 136.24, 167.09.

1-[3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-styrylazetidin-2″-one-1″-yl]ethane 5f. Isolated as a semisolid material. [Found: C, 78.17; H, 6.13; N, 4.54. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.20; N, 4.79]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.00 (d, J=11.8 Hz, 2H); 3.62 (d, J=11.8 Hz, 2H); 4.52 (dd, J=4.4, 9.2 Hz, 2H); 4.62 (d, J=7.3 Hz, 2H); 4.68 (d, J=7.3 Hz, 2H); 4.83 (d, J=4.4 Hz, 2H); 6.23 (dd, J=9.2, 16.1 Hz, 2H); 6.72 (d, J=16.1 Hz, 2H); 7.15–7.50 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 37.89, 60.53, 72.59, 83.65, 122.69, 126.37, 127.84, 128.02, 128.31, 135.44, 136.40, 167.17. m/z 494 (M^+-90), 236, 91(100%).

1-[3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-styrylazetidin-2″-one-1″-yl]ethane 6f. The *title compound* **6f** was obtained as a white solid, crystallized from dichloromethane/methanol, mp 158–159°C; [Found: C, 77.87; H, 6.41; N, 4.84. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.20; N, 4.79]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.10–3.27 (m, 2H); 3.39–3.50 (m, 2H); 4.37 (dd, J=4.4, 9.5 Hz, 2H); 4.53 (d, J=11.0 Hz, 2H); 4.64 (d, J=10.8 Hz, 2H); 4.76 (d, J=4.4 Hz, 2H); 6.30 (dd, J=9.5, 15.4 Hz, 2H); 6.63 (d, J=15.4 Hz, 2H); 7.15–7.50 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 38.39, 61.31, 72.82, 83.68, 123.54, 126.87, 128.00, 128.21, 128.39, 128.73, 135.93, 136.51, 136.76, 167.31; m/z (EI) 494 (M^+-90), 236, 91 (100%).

1-[3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl]ethane 5g. It was obtained as a white solid, crystallized from dichloromethane/methanol, mp 196–198°C; [Found: C, 77.56; H, 5.71; N, 4.89. $C_{36}H_{32}N_2O_4$ requires C, 77.67; H, 5.79; N, 5.03]; ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.12 (d, J=11.3 Hz, 2H); 3.76 (d, J=11.7 Hz, 2H); 4.80 (dd, J=4.9, 9.3 Hz, 2H); 5.40 (d, J=4.9 Hz, 2H); 6.25 (dd, J=9.3, 15.6 Hz, 2H); 6.80 (d, J=15.6 Hz, 2H); 6.90–7.60 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 37.57, 38.67, 38.94, 39.22, 59.70, 81.15, 114.42, 121.13, 121.34, 125.65,.127.36, 127.60, 128.46, 134.65, 136.12, 156.14, 164.93; m/z (EI) 292, 222, 128 (100%).

1-[3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl]ethane 6g. It was obtained as white solid, crystallized from dichloromethane/methanol, mp 195–196°C. [Found: C, 77.45; H, 5.68; N, 4.81. $C_{36}H_{32}N_2O_4$ requires C, 77.67; H, 5.79; N, 5.03]; ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.27–3.67 (m, 4H); 4.75 (dd, J=4.3, 9.2 Hz, 2H); 5.42 (d, J=4.4 Hz, 2H); 6.37 (dd, J=9.2, 15.6 Hz, 2H); 6.75 (d, J=15.6 Hz, 2H); 6.88–7.55 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 38.33, 39.31, 3958, 39.86, 60.89, 81.61, 114.17, 115.09, 121.68, 122.20, 126.35, 127.94, 128.18, 128.97, 135.32, 136.64, 156.78, 165.63. m/z (EI) 292, 222, 128 (100%).

Preparation of bis-β-lactam 8. To a stirred mixture of bisimine **3a** (0.75 g, 2.53 mmol), acid **7** (2.418 g, 8.86 mmol), triethylamine (0.6 mL) and dry CH_2Cl_2 (10 mL), a solution of phenyl dichlorophosphate (2 mL, 0.013 mol) in dry CH_2Cl_2 (40 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and successively washed with water (30 mL), satd. $NaHCO_3$ solution (30 mL), brine (30 mL) and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to give the crude product, which was column chromatographed (silica gel, 60–120, petroleum ether:ethyl acetate) to furnish 1.9 g (93%) of pure **8** as a white crystalline solid, mp 229–231°C; [Found: C, 62.32; H, 6.54; N, 6.85. $C_{42}H_{54}N_4O_8S_2$ requires C, 62.51; H, 6.74; N, 6.94]; $[\alpha]_D^{25}$=+96.56 (c 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.36 (s, 6H); 0.76 (s, 6H); 1.15–1.52 (m, 4H); 1.60–1.90 (m, 10H); 2.80–3.12 (m, 6H); 3.47–3.62 (m, 2H); 3.78 (s, 6H); 3.84 (d, J=10.8 Hz, 2H); 4.94 (d, J=4.8 Hz, 2H); 5.02 (d, J=4.8 Hz, 2H); 6.88 (d, J=8.7 Hz, 4H); 7.19 (d, J=8.7 Hz, 4H); δ_C (50.3 MHz, $CDCl_3$) 19.97, 20.27, 26.99, 32.94, 38.27, 39.10, 45.41, 47.62, 48.92, 50.30, 55.62, 59.71, 63.60, 66.36, 114.38, 126.53, 129.24, 160.17, 165.15; m/z (EI) 121 (100%), 228, 459.

X-Ray diffraction study

X-Ray structure determination of **5b** [$C_{37}H_{36}N_2O_8$]: Single crystals of compound **5b** were grown by slow evaporation of dichloromrthane:petroleum ether. A crystal of size 0.60×0.47×0.06 mm was used for data collection on an Enaraf Nonius CAD-4 single crystal X-ray diffractometer using CuKα radiation (λ=1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M=636.68, monoclinic, space group $C2/c$, a=23.944 (3), b=10.716(3), c=25.821(3) Å, β=95.47(2)°, V=6595(2) $Å^3$, Z=8, D_c=1.282 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by full-matrix least-squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of scale, positional and anisotropic thermal parameters of non-hydrogen atoms was carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 410, converged to R_1=0.0665, R_w=0.190, $w=1/\sigma^2[(Fo^2)+(0.1513P)^2+1.199P]$ where P=(Fo^2+2Fc^2)/3 from 5977 unique reflections ([$I>2\sigma(I)$]), from a total of 6806 collected. The residual density in the difference map for peak and hole is 0.390 and -0.612 e $Å^{-3}$, respectively.

X-Ray structure determination of **6c** [$C_{26}H_{28}N_2O_8$]: Single crystals of compound **6c** were grown by slow evaporation of methylene chloride/petroleum ether. A crystal of size 0.62×0.5×0.2 mm was used for data collection on Enaraf Nonius CAD-4 single crystal X-ray diffractometer using CuKα radiation (λ=1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M=496.50, Triclinic, space group P-1, a=6.425 (2), b=14.161 (2), c=14.811(3) Å, α=106.45 (2), β=100.58 (2), γ=98.76 (2)°, V=1240.3 (5) $Å^3$, Z=2, D_c=1.330 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by full-matrix least-squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of

scale, positional and anisotropic thermal parameters of non-hydrogen atoms was carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 326, converged to R_1=0.0532, R_w=0.168, $w=1/\sigma^2[(Fo^2)+(0.1075P)^2+0.5243P]$ where $P=(Fo^2+2Fc^2)/3$ from 3934 unique reflections ($[I>2\sigma(I)]$), from a total of 4516 collected. The residual density in the difference map for peak and hole is 0.362 and -0.252 e $\AA^{-3}$, respectively.

Acknowledgements

One of the authors (K. K.) thanks CSIR for financial support.

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