Studies in b-lactams Synthesis

K.THIAGARAJAN

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K.THIAGARAJAN

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE - 411 008

To
my
parents

CERTIFICATE

*This is to certify that the work incorporated in the thesis entitled "***Studies in** *b-***Lactams synthesis***" submitted by Mr K.Thiagarajan was carried out by him under my supervision at the National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

Date:
National Chemical Laboratory
Pune411008.

(Dr. B. M. Bhawal)
Research Guide

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	Spectra	

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or 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. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, Bruker MSL-300, Bruker DRX-500 and Bruker AMX-500. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, dt=doublet of triplet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker MSL-300 and Bruker AC-200 instrument operating at 75.2 MHz and 50.3 MHz respectively.
5. Elemental analyses (C, H, N) were obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Optical rotation was measured on a JASCO-181 digital polarimeter using sodium line (5893 Å). Concentration is expressed in gm/100mL.
7. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck). Purification of the products was carried out by flash column chromatography using silica gel obtained from Merck (230-400 mesh, 9385 grade).
8. ^{1}H NMR & ^{13}C NMR spectra of the compounds are attached at the end of corresponding chapter.
9. Pet. ether refers to the petroleum fraction boiling between 60-80 °C.
10. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.

ABBREVIATIONS

Ac	*Acetyl*
AIBN	*2,2'-Azobisisobutyronitrile*
Bn	*Benzyl*
CAN	*Ceric AmmoniumNitrate*
COSY	*2D-Correlation spectroscopy*
DMAP	*N, N'-Dimethylaminopyridine*
DCC	*Dicyclohexylcarbodiimide*
DCM	*Dichloromethane*
DMF	*N,N'Dimethylformamide*
EtOAc	*Ethylacetate*
LDA	*Lithium diisopropylamide*
Me	*Methyl*
Ms	*Methane sulfonyl*
M.P	*Melting point*
NOESY	*2D-Nuclear overhauser spectroscopy*
Ph	*Phenyl*
PNB	*p-Nitrobenzyl*
PMP	*p-Methoxyphenyl*
Pr	*Propyl*
TPP	*Triphenylphospine*
PTSA	*p-Toluene sulfonic acid*
RT	*Room temperature*
TBDMS	***Tertiarybutyl dimethyl silyl***
TLC	*Thin layer chromatography*
THF	*Tetrahydrofuran*
Ts	*p-Toluene sulfonyl*

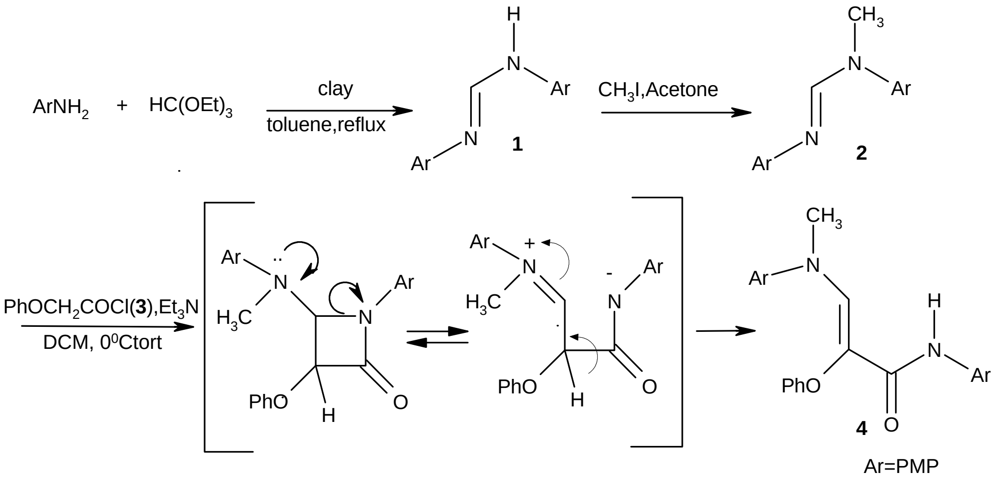
Synopsis of the thesis

The thesis entitled ***“Studies in b-lactams synthesis”*** is divided into four chapters.

CHAPTER 1 Facile Synthesis of 4-Acylamino and4-Sulphonamido b-lactams

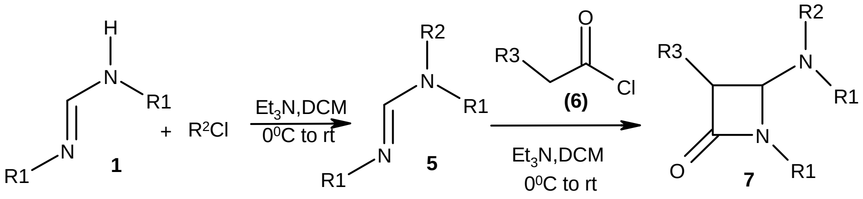
A number of β-lactam derivatives are known with various functional groups such as O, S, P, Si, Se, Sn and halogens directly attached at C4 position. However, there are very few reports on the synthesis of 4-amino substituted β-lactams as these compounds are sensitive towards moisture and undergo ring cleavage. Therefore, we were interested developing suitable method for the synthesis of 4-amino substituted β-lactams. We thought that N,N’-diarylformimidine (**1**), as an imine on 2+2 cycloaddition reaction with ketene derived from acid chloride will lead to the formation of 4-amino substituted β-lactams. The N,N’-diarylformimidine (**1**) was prepared from aromatic amines by the reaction of with triethyl orthoformate in presence of clay catalyst. The free N-H group of imidine (**1**) was alkylated with methyl iodide to get **2**. The imidine **2** on treatment with phenoxyacetyl chloride (**3**) in presence of triethylamine in dichloromethane gave enaminoamide (**4**) instead of expected β-lactam (Scheme1). The formation of enaminoamide (**4**) is presumably by 1,4 cleavage of the initially formed β-lactam assisted by participation of loan pair of 4-amino group of β-lactam.

Scheme1



We envisaged that the stability of the β-lactam ring could be increased by reducing the availability of the lone pair of nitrogen at 4 position. Thus various trisubstituted formimidines (**5**) bearing electron withdrawing substituents on the nitrogen were prepared from imidine **1**. These imidines **5** when reacted with ketenes derived from acid chlorides (**6**) in presence of triethylamine indeed afforded exclusively trans β-lactams (**7**) in very good yields (Scheme2).

Scheme 2



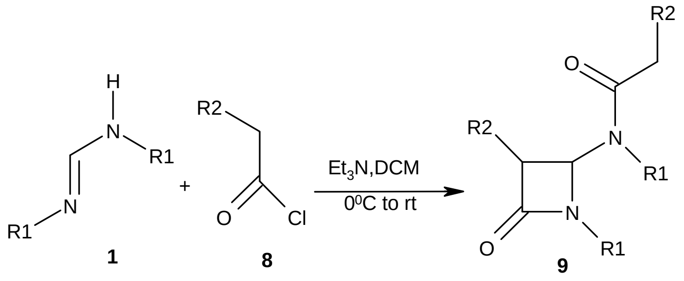
1a R^1=Ph
b R^1=4-ClC6H4
c R^1=4-MeOC6H4
d R^1=4-MeC6H4

5a R^2 =PhCO
b R^2 =4-O2NC6H4CO
c R^2 =Ts

Compd **7**	R^1	R^2	R^3
7a	Ph	PhCO-	PhO-
7b	Ph	4-$NO_2C_6H_4$CO-	PhO-
7c	Ph	Ts-	PhO-
7d	4-ClC_6H_4-	Ts-	PhO-
7e	3-MeC_6H_4-	Ts-	PhO-
7f	4-$MeOC_6H_4$-	Ts-	PhO-
7g	Ph	Ts-	PhthN-
7h	4-$MeOC_6H_4$-	Ts-	PhthN-

We were also successful in synthesizing *trans* β-lactams (**9**) N,N'-diarylformimidine (**1**) by *in situ* generation of trisubstituted imidines like **6** by using two equivalents of acid chloride (**8**) in presence of triethylamine (Scheme3).

Scheme 3

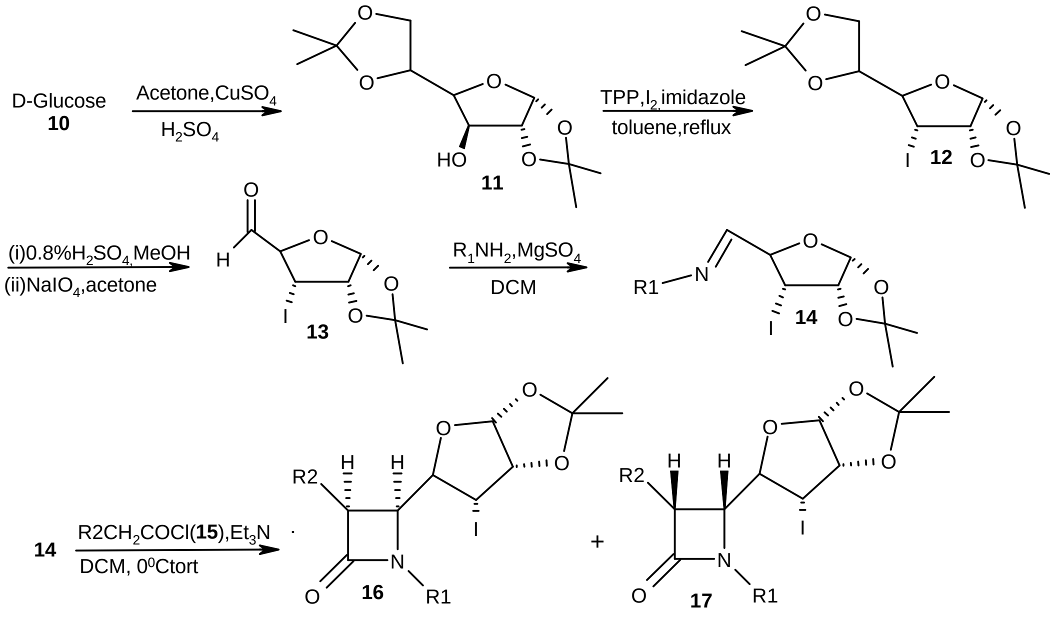


Compd **9**	R^1	R^2	R^3
9a	Ph	PhCO-	PhO-
9b	Ph	4-$NO_2C_6H_4CO$-	PhO-
9c	Ph	Ts-	PhO-
9d	4-ClC_6H_4-	Ts-	PhO-
9e	3-MeC_6H_4-	Ts-	PhO-
9f	4-$MeOC_6H_4$-	Ts-	PhO-
9g	Ph	Ts-	PhthN-
9h	4-$MeOC_6H_4$-	Ts-	PhthN-

CHAPTER 2 Diastereoselective synthesis of b-lactams using Glucose derived chiral aldehydes via asymmetric Staudinger reaction.

In order to probe the effect of the steric disposition on the stereoselectivity in β-lactam ring construction *via* Staudinger reaction, sterically demanding aldimines (**14**) were prepared from D-glucose (**10**) as depicted in Scheme 4. The reaction of various acid chloride (**15**) with the imine (**14**) in presence of triethylamine in DCM gave a diastereomeric mixture of *cis*-β-lactams (**16** & **17**) in good yields (Scheme 4). The diastereomers were separated by either coloumn chromatography or crystallization. The absolute stereochemistry of these β-lactams was established from single crystal X-ray analysis of one of the diastereomer.

Scheme 4


D-Glucose
10
Acetone,CuSO$_4$
H$_2$SO$_4$
HO
11
TPP,I$_2$,imidazole
toluene,reflux
I
12
(i)0.8%H$_2$SO$_4$,MeOH
(ii)NaIO$_4$,acetone
H
13
R$_1$NH$_2$,MgSO$_4$
DCM
R1
N
14
14
R2CH$_2$COCl(15),Et$_3$N
DCM, 0^{0}Ctort
R2
H
H
N
R1
16
+
17
O
I

a R1 – allyl R2 – PhO

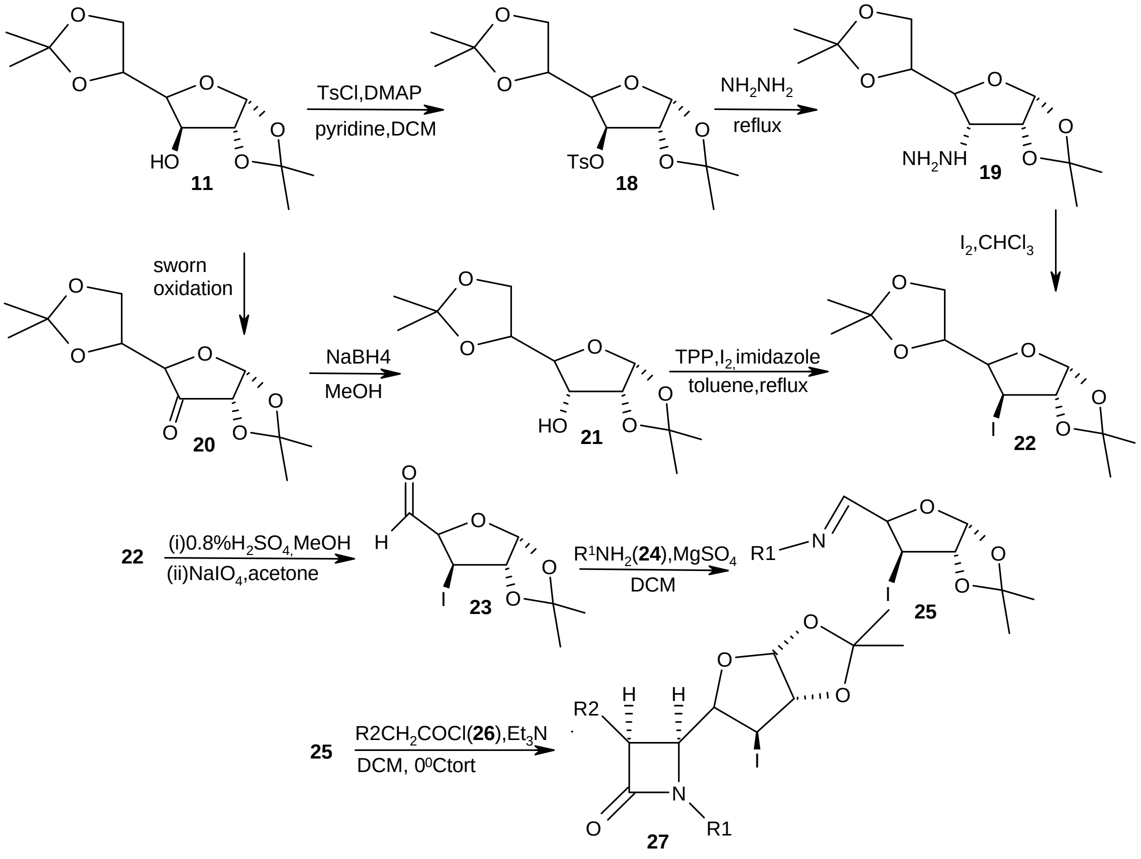
b R1 – allyl R2 - BnO

c R1 – ally R2 – N3

d R1 – pmp R2 - PhO

Since the aldimine (**14**) didn’t give good selectivity in β-lactam ring formation, a chiral aldimine (**25**) epimeric at carbon bearing halogen was prepared and used as a precursor for construction of β-lactam as depicted in Scheme 5. The reaction of this imine (**25**) with acid chloride (**26**) in the presence of triethylamine resulted in the diastereospecific formation of *cis*-β-lactams (**27**) in good yields. In all the cases a single diastereomer was isolated and NMR could detect no trace of other isomer.

Scheme 5


TsCl,DMAP
pyridine,DCM
NH_2NH_2
reflux
HO
11
TsO
18
NH_2NH
19
I_2,$CHCl_3$
sworn oxidation
20
NaBH4
MeOH
HO
21
TPP,I_2,imidazole
toluene,reflux
I
22
22
(i)0.8%H_2SO_4,MeOH
(ii)$NaIO_4$,acetone
H
I
23
R^1NH_2(**24**),$MgSO_4$
DCM
R1
N
I
25
25
R2CH_2COCl(**26**),Et_3N
DCM, 0^0Ctort
R2
H
H
N
R1
I
27

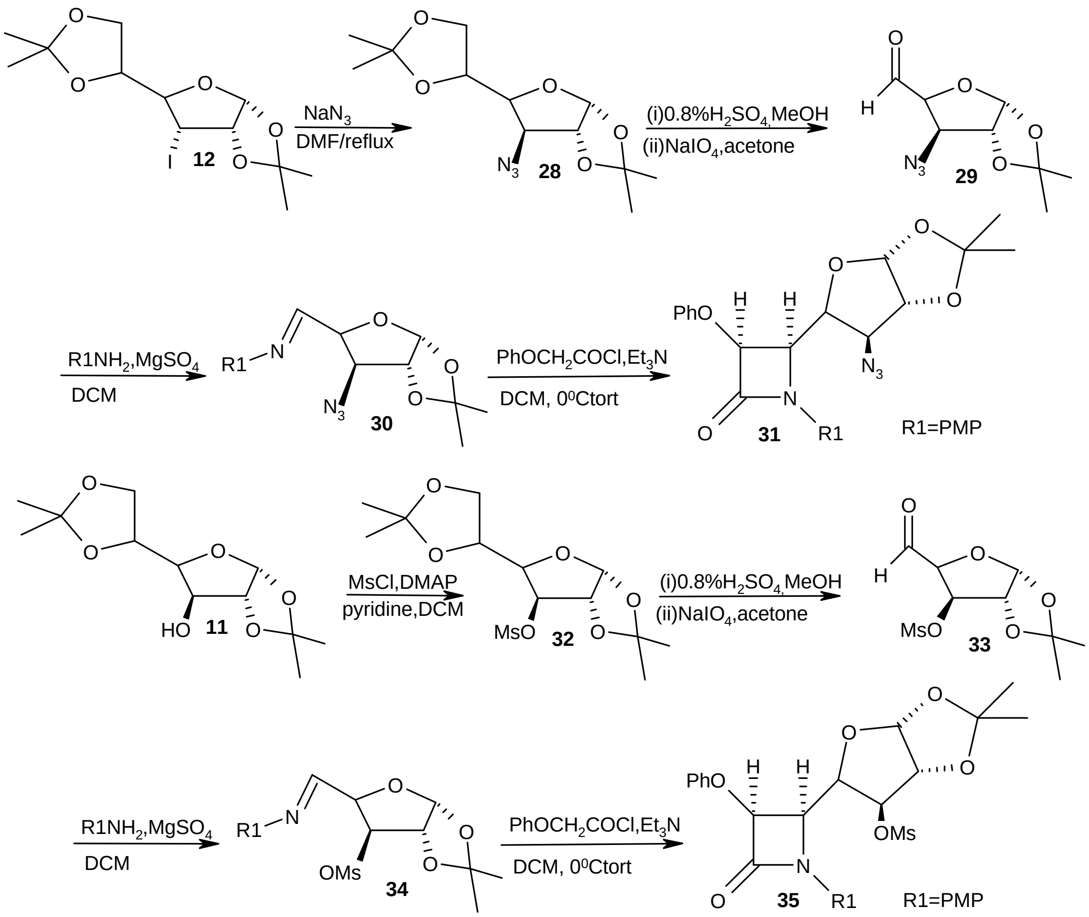
a R1 – pmp R2 – PhO

b R1 – allyl R2 – PhO

CHAPTER 3 Diastereoselective synthesis of b-lactams from chiral aldehyde derived from 3-Deoxy-3–azido and 3-O-Methane-sulfony-1,2;5,6-di-O-isopropylidene-a-D-glucofuranose

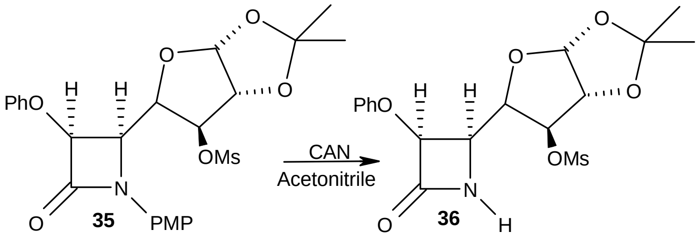
In order to study the effect of stereoselectivity in β-lactam ring construction *via* Staudinger reaction, other sterically demanding aldimines (**30** & **34**) were prepared as depicted in Scheme 6. These imines on cycloaddition reaction with the ketene derived from phenoxyacetyl chloride in presence of triethylamine in dichloromethane gave *cis* β-lactams **31** & **35** with complete diastereoselectivity in good yields and NMR could detect no trace of other isomer.

Sheme 6


12
NaN$_3$
DMF/reflux
28
(i)0.8%H$_2$SO$_4$,MeOH
(ii)NaIO$_4$,acetone
29
R1NH$_2$,MgSO$_4$
DCM
30
PhOCH$_2$COCl,Et$_3$N
DCM, 0^{0}Ctort
31
R1=PMP
11
MsCl,DMAP
pyridine,DCM
32
(i)0.8%H$_2$SO$_4$,MeOH
(ii)NaIO$_4$,acetone
33
R1NH$_2$,MgSO$_4$
DCM
34
PhOCH$_2$COCl,Et$_3$N
DCM, 0^{0}Ctort
35
R1=PMP

The oxidative cleavage of the N-PMP substituted β-lactam **35** with ceric ammonium nitrate yielded N-unsubstituted β-lactam **36** in good yield (Scheme 7).

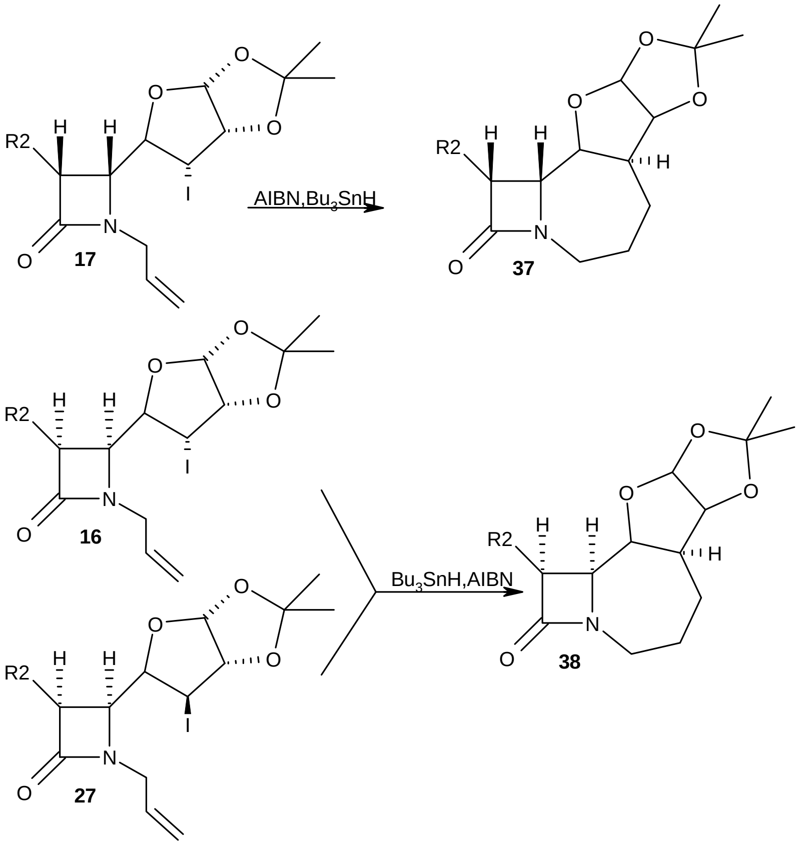
Scheme 7


35
CAN
Acetonitrile
36

CHAPTER 4 *Diastereoselective synthesis of novel tetracyclic b-lactams via intramolecular radical addition to alkene bond.*

The haloseries of β-lactams **16**, **17** and **27** with N1-allyl substituents were prepared in good yields. These β-lactams on treatment with Bu_3SnH underwent 7-*endo-trig* radical cyclization with complete diastereoselectivity to furnish novel tetracyclic β-lactams (**37**, **38**) (Scheme 8). The absolute stereochemistry was established from the single crystal X-ray analysis.

Scheme 8



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

Chapter I

Facile Synthesis of 4-Acylamino and 4-Sulphonamido-β-lactams

1.1 : Abstract

This chapter deals with the synthesis of synthesis of 4-amino-β-lactams from trisubstituted imidines (**1.4a-f**). The trisubstituted imidines (**1.4a-f**) underwent [2+2] stereospecific cycloaddition reaction with ketenes to give 4-acylamino and 4-sulphonamido-*trans*-β-lactams (**1.6a-h**). Similarly N,N′-diarylimidines (**1.1a-d**) on reaction with two equivalents of acid chlorides (**1.5a,b**) gave 4-acylamino-*trans*-β-lactams (**1.7a-e**) *via in situ* generated acylimidines followed by cycloaddition reaction.

1.2 : Introduction

History

In 1928 Alexander Fleming made serendipitous observation[1] that the growth of staphylococcus colonies was inhibited in the vicinity of *Penicillinium notatum*. The antibiotic causing this phenomenon was given name penicillin. In early 1940s the therauptic potentialities of penicillin[2] were recognized. After the discovery of this magic drug, Fleming used it as an antiseptic and observed reasonably good results. He used penicillin, mainly as a method of differential culture & believed that discovery of lysosomes was his major contribution to the field of bacteriology. That's how, 12 years later he wrote[3], "*The trouble of making it seemed not worth while*". Interestingly, latter on it was proved beyond doubt that penicillin and its derivatives were the most important class of antibiotics.

The structure of penicillin was debated until 1940. Sir Robert Robinson proposed thiazolidine-oxazolone structure while Prof. R. B. Woodward strongly supported structure based on a 4 membered amide framework. Finally, in 1949 Dorothy Hodgkins[4] and Barbara Low completed a three dimensional X-ray crystallographic analysis of benzyl penicillin. With this discovery it was established for the first time the presence of a 4 membered amide in the form of *b*-lactam, which was responsible for the effective biological activity of antibiotics.

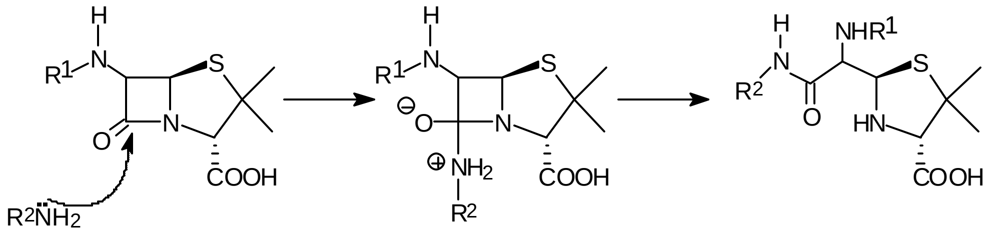
Among the naturally occurring bicyclic antibiotics, penicillin and cephalosporin are the most important ones. The detailed structure activity relationship (SAR) studies of these antibiotics has led to innumerable number of derivatives some of them are used in clinical trials routinely.

Mode of Action:

The biological activity of these antibiotics is mainly due to the presence of *b*-lactam ring. The SAR studies[5] have shown that the essential requirement for an antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in an active form to the target site. Penicillin binds to the so-called 'penicillin-binding proteins' (PCBs), which are specific molecules on the inner membrane of the cell wall. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[6] The schematic representation of this phenomenon in the case of penicillin *(Scheme 1)* and cephalosporin *(Scheme 2)* is shown below.

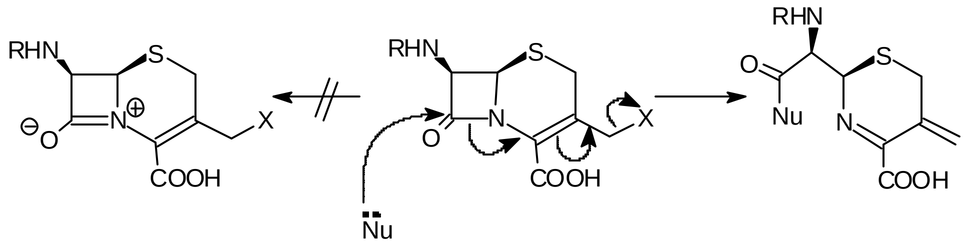
Biological Activity of Penicillin.[7]

Scheme 1



Biological Activity of Cephalosporin:[8]

Scheme 2



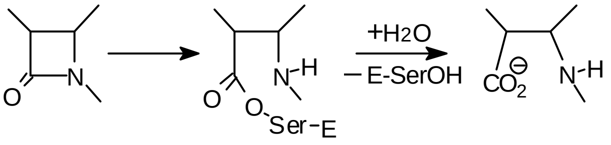
b-Lactamases, b-Lactamase Inhibitors and the Resistance to Antibiotics:

b-Lactamases[9] are the enzymes that bacteria produce to defend themselves against *b*-lactam antibiotics. There are mainly two classes of *b*-lactamases:

1) Serine enzyme lactamases
2) Zinc enzyme lactamases.

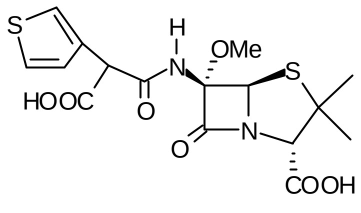
The serine type enzyme lactamases act by covalent acyl enzyme mechanism *(scheme 3)*.[10] These are further classified into class A, class C and class D. The zinc enzyme lactamases are class B type lactamases and they act by non-covalent intermediate method.

Scheme 3

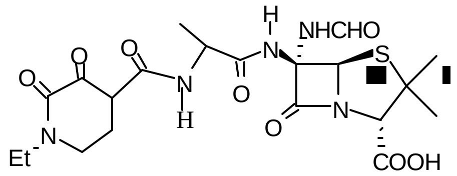


The *b*-lactamases affects the action of *b*-lactam antibiotics making it inactive against the bacteria. This drastically limits the therauptic use of *b*-lactam antibiotics and the bacteria are said to have developed resistance against the drug derivative. The phenomenon of bacterial resistance led to a serious research in this field and paved the way for development of novel *b*-lactams called as the *b*-lactamase inhibitors[11]. Inhibitor, as the name suggests, inhibits the action of lactamases. Basically *b*-lactamase inhibitors are compounds, which are structural variants of the classical *b*-lactams with modified skeleton. They may not have antibiotic activity of their own but they are used in the combination with biologically active antibiotics. Specifically, they associate themselves with the lactamases thereby preventing prior interaction of *b*-lactamase with the β-lactam antibiotics. The antibiotic activity of the *b*-lactams is thereby safeguarded and it can penetrate through the bacterial cell wall.

Temocillin and Formidacillin[11] are the examples of *b*-lactamase inhibitors, which are the result of extensive SAR studies of penicillin.



Temocillin



Formidacillin

With the extensive SAR studies and the discovery of novel, biologically active molecules the earlier conceptions regarding the comparison of chemical and biological activity have started becoming somewhat irrelevant. Earlier it was suggested that the antibacterial activity was mainly due to inherent strain in the 4-membered ring or due to the reduced amide resonance. But both, kinetic and ground state effects do not indicate a significant degree of inhibition of amide resonance in penicillin and cephalosporin. The bicyclic *b*-lactams also does not show exceptional reactivity. Monocyclic *b*-lactams with suitable electron withdrawing substituents may be as reactive as bicyclic *b*-lactams. Strained *b*-lactams are not necessarily better antibiotics and so the biological reactivity is not directly correlated with the chemical reactivity.

Until 1970 most of the *b*-lactam antibiotic chemistry was revolving around either penicillin or cephalosporin. The isolation of 7-α-methoxycephalosporins[12] from *Streptomyces* in 1971 stimulated the search for novel *b*-lactam antibiotics from microbes. This extensive quest for novel *b*-lactam skeleton has led to the isolation of active antibiotics not only from eukaryotic fungi, actinomycetes but also from bacteria. This has led to the expansion of *b*-lactam antibiotic family to an ever-increasing number. Currently, following classes of *b*-lactam antibiotics are known (Fig 1).

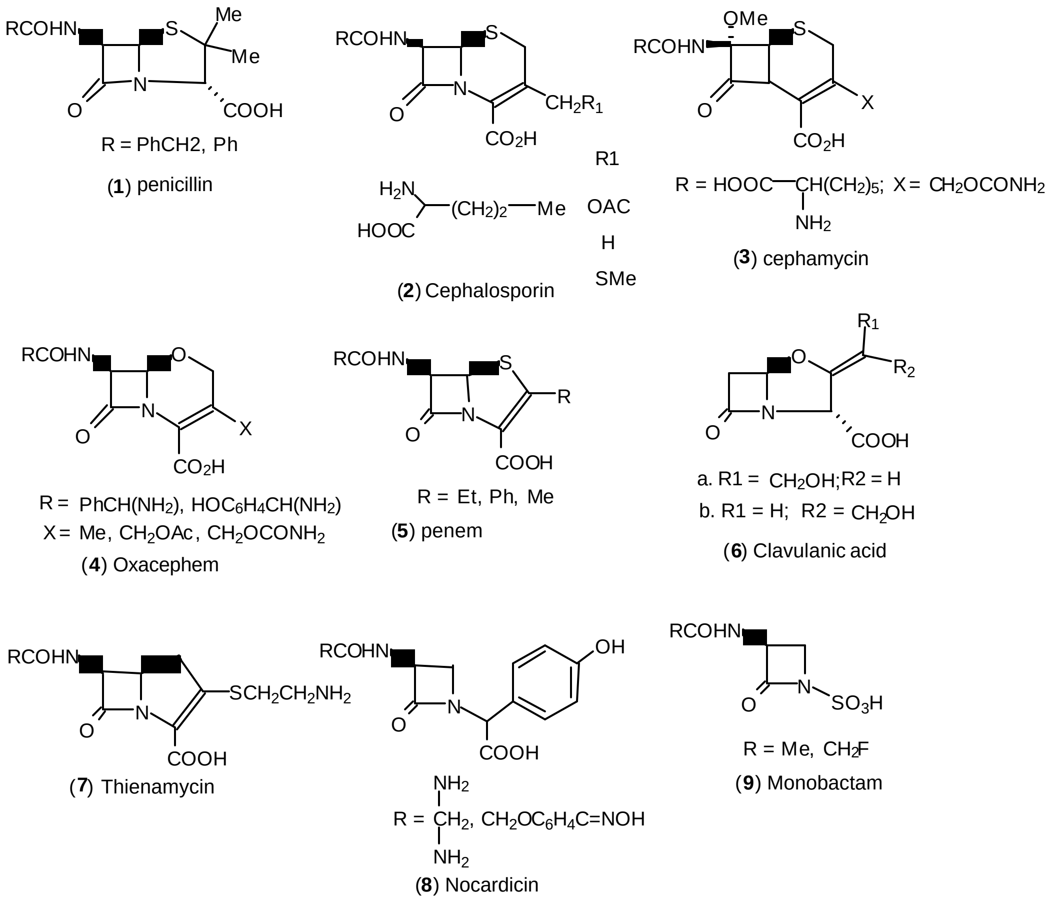
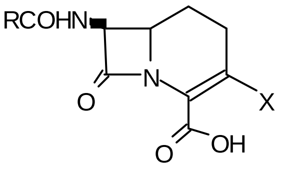

RCOHN
S
Me
Me
N
O
COOH
R = PhCH2, Ph
(1) penicillin
RCOHN
S
N
O
CH2R1
CO2H
R1
H2N
(CH2)2—Me
HOOC
OAC
H
SMe
(2) Cephalosporin
OMe
RCOHN
S
O
X
CO2H
R = HOOC—CH(CH2)5; X = CH2OCONH2
NH2
(3) cephamycin
RCOHN
O
N
O
X
CO2H
R = PhCH(NH2), HOC6H4CH(NH2)
X = Me, CH2OAc, CH2OCONH2
(4) Oxacephem
RCOHN
S
N
R
O
COOH
R = Et, Ph, Me
(5) penem
R1
O
R2
N
O
COOH
a. R1 = CH2OH; R2 = H
b. R1 = H; R2 = CH2OH
(6) Clavulanic acid
RCOHN
SCH2CH2NH2
N
O
COOH
(7) Thienamycin
RCOHN
OH
N
O
COOH
NH2
R = CH2, CH2OC6H4C=NOH
NH2
(8) Nocardicin
RCOHN
N
O
SO3H
R = Me, CH2F
(9) Monobactam

Fig 1. Different classes of *b*-lactam antibiotics.

Recent Developments in the Field of b-Lactam Antibiotics:

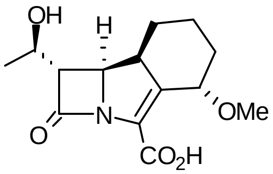
Carbacephems,[13] which are the carbon analogues of cephalosporins, are sensational new antibiotics. Superior stability of this antibiotic over cephalosporin and the ease with which it can be derivatised at 3-position, is synthetically attractive. With the approval of first carbacephem, loracarbef (lorabid) for clinical use, the interest is continued further.



Lorarbid

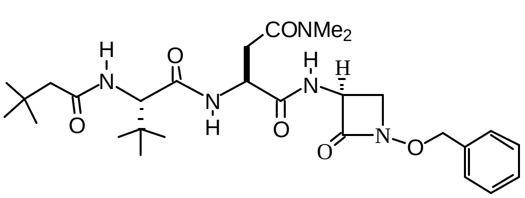
(X = Cl, R = $PhCH_2NH_2$)

The tricyclic *b*-lactam antibiotics called trienems[14] are also new class of tricyclic carbapenems. GV 104326, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria has attracted the synthetic as well as biological community.

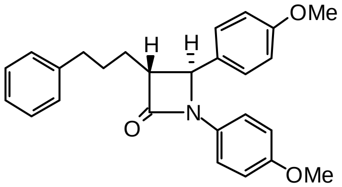


GV 104326 (tribactam)

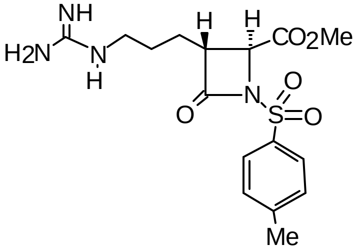
Discovery of new active *b*-lactam compounds such as thrombin,[15] prostate specific antigen,[16] human cytomegalovirus protease[17] or the new cholesterol absorption inhibitor[18] has renewed interest in the field.



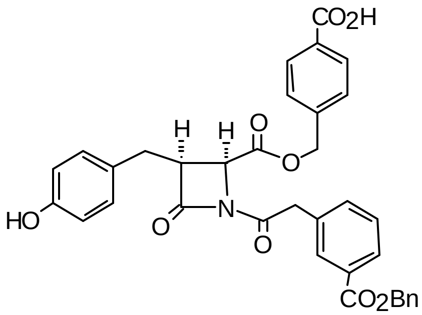
Human Cytomegalovirus Protease Inhibitor



Cholesterol absorption Inhibitor


NH
H2N
N
H
H
H
CO2Me
O
N
S
O
O
Me

Thrombin Inhibitor


CO2H
H
H
O
O
HO
O
N
O
CO2Bn

Prostate Specific Antigen Inhibitor

General Methods of b-Lactam Synthesis:

The traditional methods in the *b*-lactam field involve formation of 4-membered amide ring by the general methodologies as shown in the fig. 2.

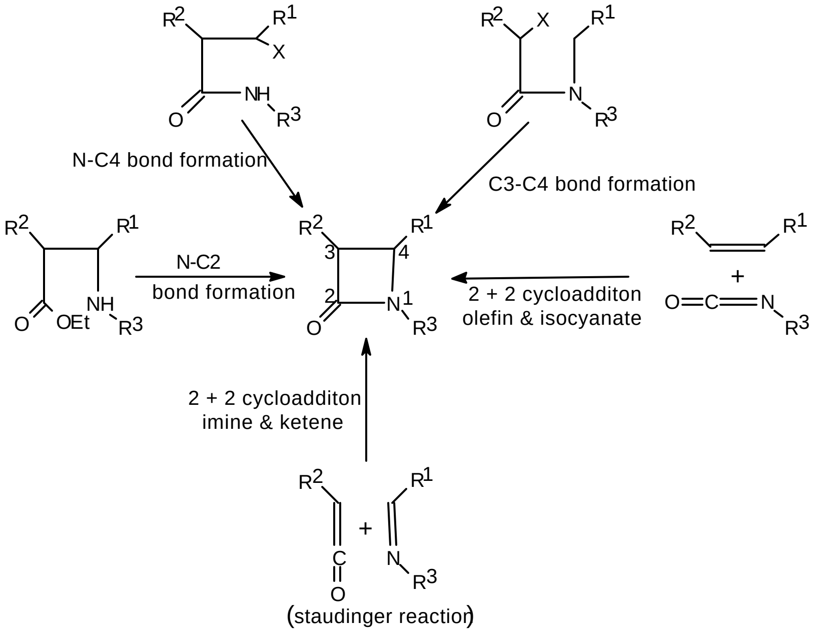
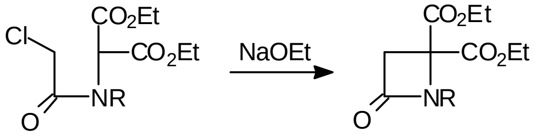

N-C4 bond formation
C3-C4 bond formation
N-C2
bond formation
2 + 2 cycloadditon
olefin & isocyanate
2 + 2 cycloadditon
imine & ketene
(staudinger reaction)
R2
R1
R3
X
NH
N
O
OEt
3
4
2
1
O=C=N

Fig. 2: Schematic representation of conventional methods of *b*-lactam synthesis.

_C_3 – C_4 Bond Formation_:[19]

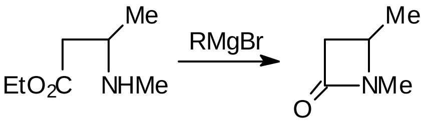
Scheme 4


Cl
CO2Et
CO2Et
NR
O
NaOEt
CO2Et
CO2Et
NR
O

R = aryl, cyclohexyl

***N – C2 Ring Closure*:**[20]

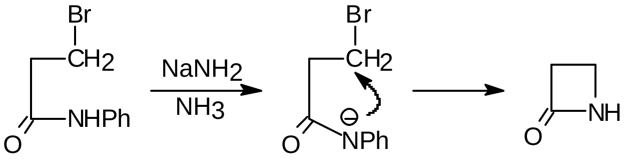
Scheme 5



Me
EtO2C
NHMe
RMgBr
Me
O
NMe

***N – C4 Bond Formation*:**[21]

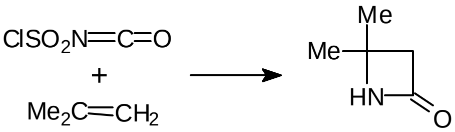
Scheme 6



Br
CH2
O
NHPh
NaNH2
NH3
Br
CH2
O
NPh
O
NH

***Cycloaddition Reactions*:**[22]

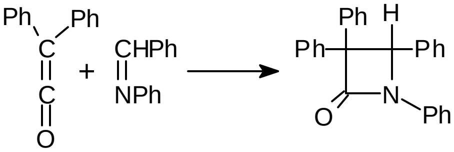
Scheme 7



ClSO2N=C=O
+
Me2C=CH2
Me
Me
HN
O

***Staudinger Reaction*:**[23]

Scheme 8

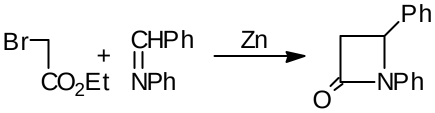


Ph
Ph
C
C
O
+
CHPh
NPh
Ph
H
Ph
Ph
O
N
Ph

***Reformatsky Type Reaction Approach*:**

***Gilman-Speeter Approach*:** This reaction is mainly used for the synthesis of 3-unsubstitued *b*-lactams. The yield of *b*-lactam is generally dependent on the activation and type of zinc used. Gilman and Speeter first described this type of synthesis (*Scheme 9*).[24]

Scheme 9

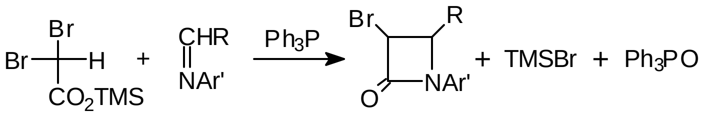


Br
CO2Et
+
CHPh
NPh
Zn
Ph
O
NPh

Manhas's a -Bromo-b -Lactam Approach :

Manhas et. al. have developed this approach wherein they condensed halo ester with imines in presence of triphenylphosphine *(Scheme 10).*[25]

Scheme 10


Br
Br
H
CO2TMS
+
CHR
NAr'
Ph3P
Br
R
O
NAr'
+ TMSBr + Ph3PO

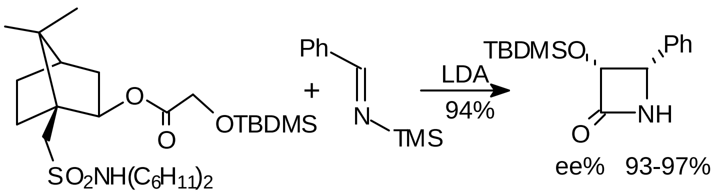
Asymmetric Synthesis of b-Lactams:

Asymmetric synthesis of β-lactams[26] has become an important area, as biological activity of these antibiotics is closely related with the stereochemistry. Among the various methods of β-lactam construction, metallo ester enolate-imine cyclocondensation, isocyanate-olefin cycloaddition and ketene-imine cycloaddition are the most widely used.

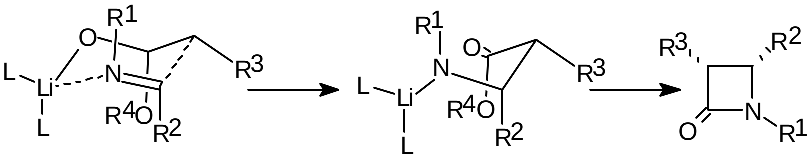
Ester Enolate-Imine Condensation:[27]

Cyclocondensation of imine with ester is emerging as a powerful method in the asymmetric synthesis of β-lactams. Georg et. al. have used silyl protected chiral ester effectively for the synthesis of NH β-lactams with very high enantioselectivity *(Scheme 11).*[28]

Scheme 11


O
O
OTBDMS
SO2NH(C6H11)2
+
Ph
N
TMS
LDA
94%
TBDMSO
Ph
O
NH
ee% 93-97%

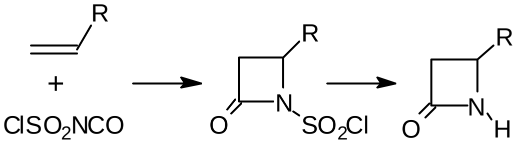
The proposed transition State for the ester enolate-imine cycloaddition reaction involved a six membered transition state[29,30] similar to aldol condensation.


R1
O
L
Li
L
N
R4O
R2
R3
R1
N
O
L
Li
L
R4O
R2
R3
R3
R2
O
N
R1

Isocyanate-Olefin Cycloaddition:[31]

In 1963, Graf[22] reported a method of *b*-lactam formation suitable for large-scale preparation, which involved cycloaddition between N-chlorosulfonyl isocyanate (CSI) and alkenes. Since then this strategy has become an important method in *b*-lactam chemistry *(Scheme 12).*

Scheme 12



Ketene-Imine Cycloaddition Reaction (*Staudinger Reaction*):[32]

Staudinger reaction (ketene-imine cycloaddition reaction) is still the most attractive and widely used method in *b*-lactam ring construction. This has been mainly due to the operational simplicity, versatility and far-reaching applicability. Cycloaddition of ketene, usually generated *in situ* from an acid chloride and an imine typically proceeds with very high *cis* stereoselectivity. The asymmetric version of this reaction involves the use of,

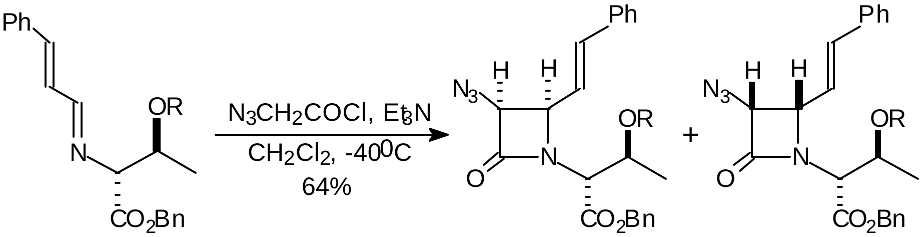
1) Chiral imine and achiral acid chloride
1) Achiral imine and chiral acid chloride
2) Double stereodifferentiation in which both components i. e. acid chloride and imine are chiral.

Asymmetric Induction Using Chiral Imines

Among the chiral imines, the possible combination can be chiral aldehyde and achiral amine or chiral amine and achiral aldehyde. The use of chiral aldehydes derived from sugar derivatives have been reported. The diastereoselectivity in β-lactam ring formation is also exceptionally high by using these aldehydes derived from carbohydrate (This will be discussed in details in the Chapter 2).

The use of chiral imines derived from chiral amines and achiral aldehydes is not among the efficient ways of introducing chirality in the cycloaddition reaction.[32b,32c] Since the newly formed chiral center in the β-lactam ring is away from the chiral center on the amine, the effect of the stereodirecting groups in facial differentiation is drastically reduced. Therefore, poor to moderate diastereoselectivity was observed by using chiral amines. However, there are few reports on efficient use of chiral amines in the asymmetric Staudinger reaction, which uses bulkier silyl protecting groups for effective stereodifferentiation *(Scheme 13).*[33]

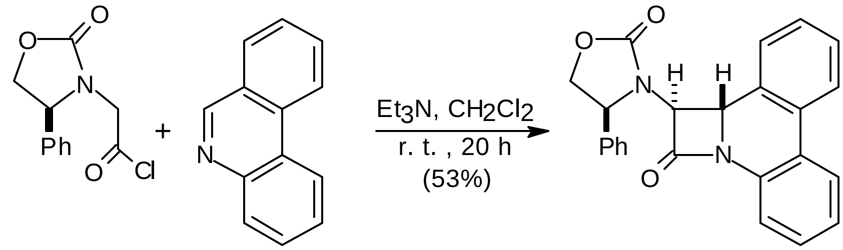
Scheme 13


Ph
OR
N
CO2Bn
N3CH2COCl, Et3N
CH2Cl2, -40⁰C
64%
Ph
H H
N3
OR
N
O
CO2Bn
+
Ph
H H
N3
OR
N
O
CO2Bn

R: TPS ($SiPh_3$) 95:5
R: TBS ($SiMe_2{}^tBu$) 90:10

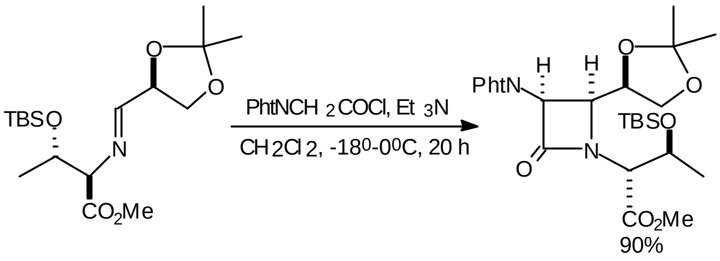
The use of chiral ketene and achiral imine is also well exploited method in β-lactam ring construction. Generally, the use of hydroxy protected chiral acids as ketene precursors does not involve significant chiral induction. But the Evans-Sjogren derived ketenes are used successfully in the asymmetric synthesis of β-lactams. Recently, phenantridine has been reported to give exclusively trans β-lactam with Evans-Sjoren chiral ketene *(Scheme 14).*[34]

Scheme 14


O
O
N
Ph
O
Cl
+
N
Et3N, CH2Cl2
r. t. , 20 h
(53%)
O
O
N
H H
Ph
O
N

The concept of double stereodifferentiation is applied with variable success to the [2 + 2] cycloaddition reaction. High levels of double asymmetric induction is observed when Evans-Sjögrens ketenes and imines derived from (R) & (S)-α-amino acid esters were used *(Scheme 15).*[35]

Scheme 15


O
O
TBSO
N
CO2Me
PhtNCH2COCl, Et3N
CH2Cl2, -18⁰-0⁰C, 20 h
PhtN
H H
O
O
TBSO
O
N
CO2Me
90%

Mechanism (Acid Chloride-Imine Cycloaddtion):

According to the accepted model, the reaction between acyl chlorides and imines is assumed to proceed thorough *in situ* formation of ketene,[36] followed by interaction with the imine to form a zwitterionic intermediate, which undergoes an electrocyclic conrotatory ring closure to give the β-lactam ring. In general, (E) imines lead preferentially to the more hindered *cis-b*-lactams, while (Z) imines give predominantly the corresponding trans isomers.[32c,37]

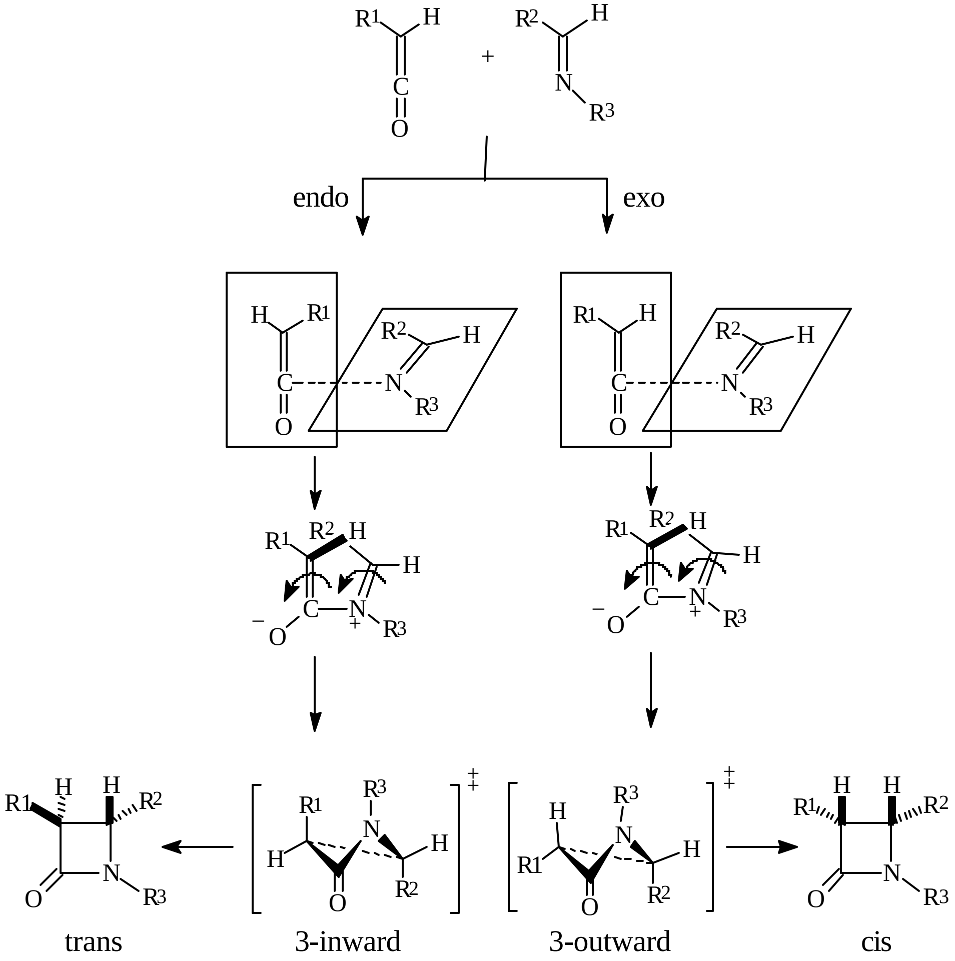


Fig. 2.

Theoretical studies undertaken to establish the origin of the *cis*/*trans* stereoselection revealed that the relative energies of the rate-determining transition states, leading from zwitterions to β-lactams, are dictated not necessarily by steric effects, but by electronic torquo-selectivity.[38] For instance, it has been calculated[38b] at the RHF/6-31G* level that the zwitterionic intermediate having an electron-donating group in the ketene fragment (R^1 = OH, CH_3) has a barrier for conrotatory closure to the *b*-lactam that is 8-12 Kcal/mol lower when it adopts an "outward " rotation. Since the imine (*E*) attack on the ketene is preferably from the side opposite (*exo*) to the R^1 group, which leads to the formation of *cis-b*-lactams. The situation is exactly reversed when R^1 is electron-withdrawing group. In this case the "inward" rotation is energetically favorable (for instance in case of $R^1= BH_2$ the rotation is favorable by about 12-15 kcal / mol).

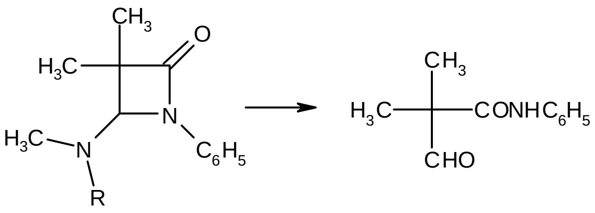
This concept of torquoselectivity, though, permits the rationalization of a substantial amount of the known experimental data concerning the Staudinger reaction; it is evident that further investigation in this area is required.

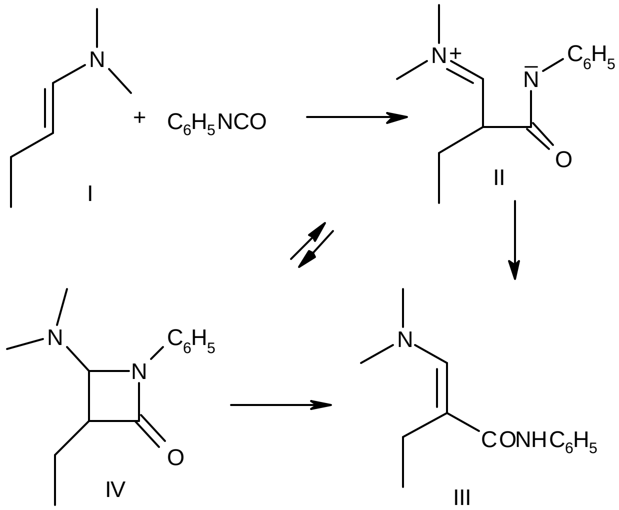
1.3 : Background

A number of β-lactam derivatives are known with various functional groups such as O, S, P, Si, Se, Sn and halogens directly attached at C4 position. However, there are very few reports on the synthesis of 4-amino substituted β-lactams as these compounds are sensitive towards moisture and undergo ring cleavage.

Mel Perelman et al[39] have treated the β,β′-disubstituted enamines with aryl isocyanates. The mode of decomposition of the β-lactam with formation of the transient diethylimine cation of II, suggests that delocalization of the free electron pair on the amino nitrogen would stabilize the ring system. The reaction product is rapidly decomposes to III by abstraction of the Cβ-H *(Scheme 16)*.

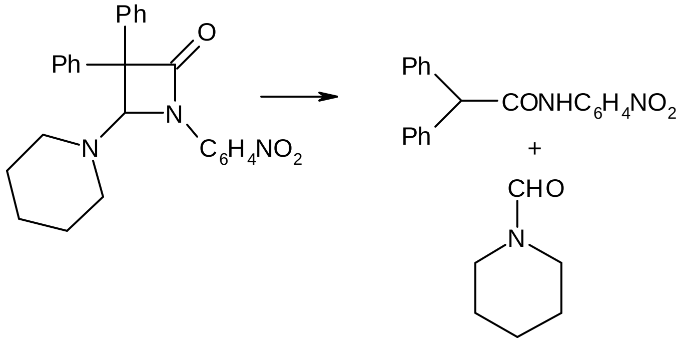
Scheme 16




N
+
C_6H_5NCO
I
N+
N
C_6H_5
O
II
N
C_6H_5
N
O
IV
N
$CONHC_6H_5$
III

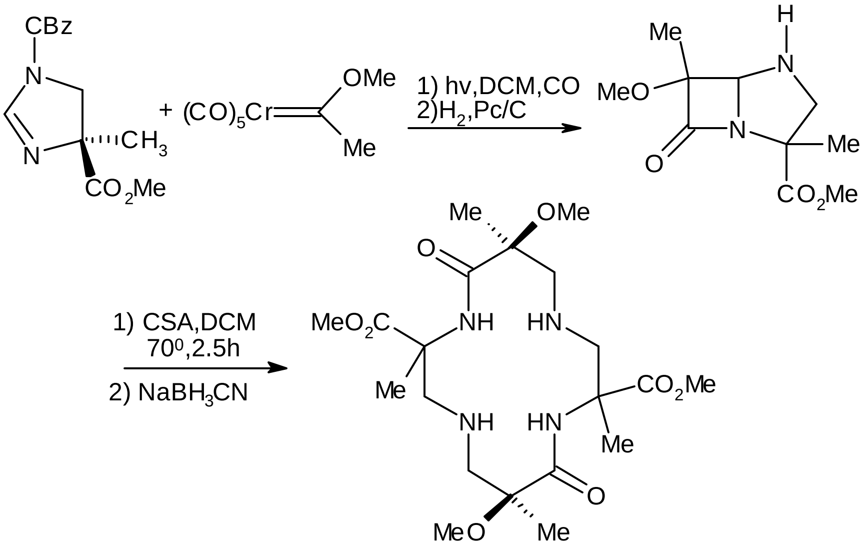
A.K. Bose et al[40] have reported the synthesis β-amino-β-lactams by cyclo-addition of diphenylketene and N,N,N'-trisubstituted amidines. The mode of decomposition of the β-lactam is by rupture of the bond between carbon-3 and carbon-4 to form the decomposition product (S*cheme 17).*

Scheme 17


Ph
Ph
O
N
N
$C_6H_4NO_2$
Ph
Ph
$CONHC_6H_4NO_2$
+
CHO
N

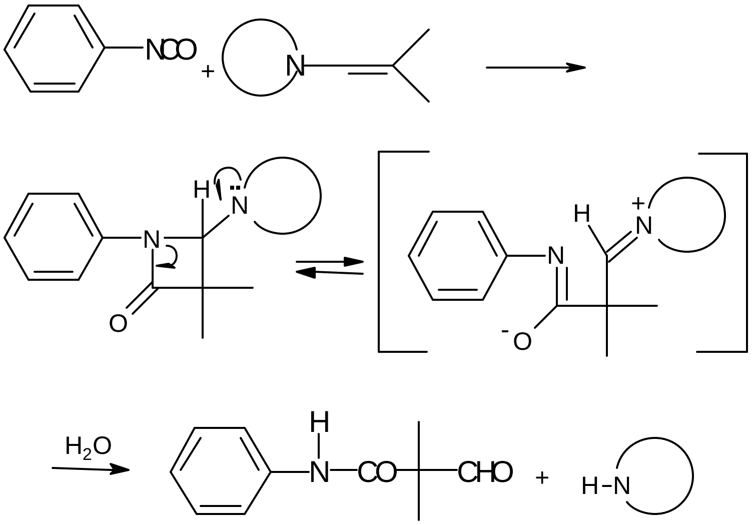
Hegedus et al[41] have reported that photolysis of imidazoline with the (methoxymethyl carbene)chromium complex yields the desired azapenem. The acid-catalyzed dimerization of azapenem produced, after reduction of the imine moieties, dioxocyclam in excellent yield as a single diastereoisomer (S*cheme 18).*

Scheme 18


CBz
N
N
CH3
CO2Me
+ (CO)5Cr
OMe
Me
1) hv,DCM,CO
2)H2,Pc/C
Me
H
N
MeO
N
O
Me
CO2Me
1) CSA,DCM
70⁰,2.5h
2) NaBH3CN
Me
OMe
O
MeO2C
NH
HN
Me
CO2Me
NH
HN
Me
O
MeO
Me

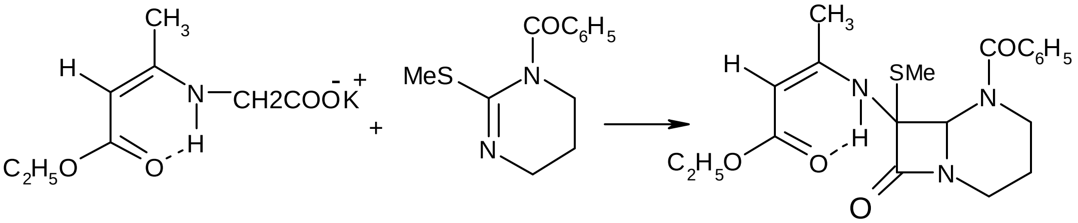
Abdulla et al[42] have reported that 2 + 2 cycloaddition of β,β′-disubstituted enamines with aryl isocyanates to give β-amino-β-lactams. It undergoes β-lactam ring fission between aminal carbon atom C4 and the lactam nitrogen N1 to give formylacetanilide (S*cheme 19)*.

Scheme 19


NCO
+
N
H
N
N
O
H
+
N
N
-O
H2O
H
N
CO
CHO
+
H-N

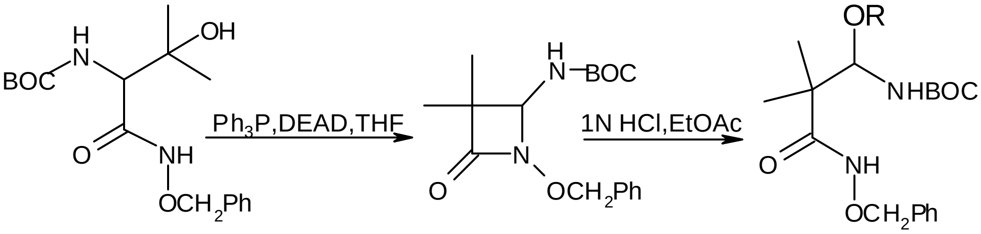
Sharma et al[43] have reported that potassium carbethoxyacetonyl glycinates on treatment with the schiff base gives enamino-β-lactam (S*cheme 20)*.

Scheme 20



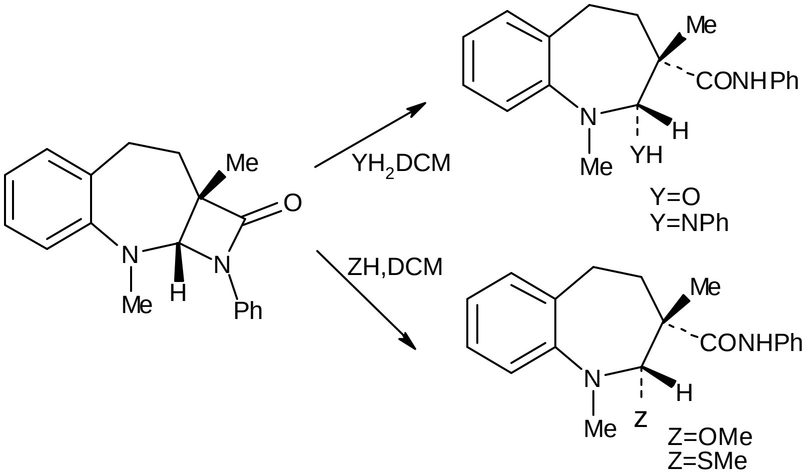
Slusarchyk et al[44] have reported that cyclization using Mitsunobu conditions afforded the desired β-lactam, which on mild acid hydrolysis gave hemiaminal (S*cheme 21)*.

Scheme 21



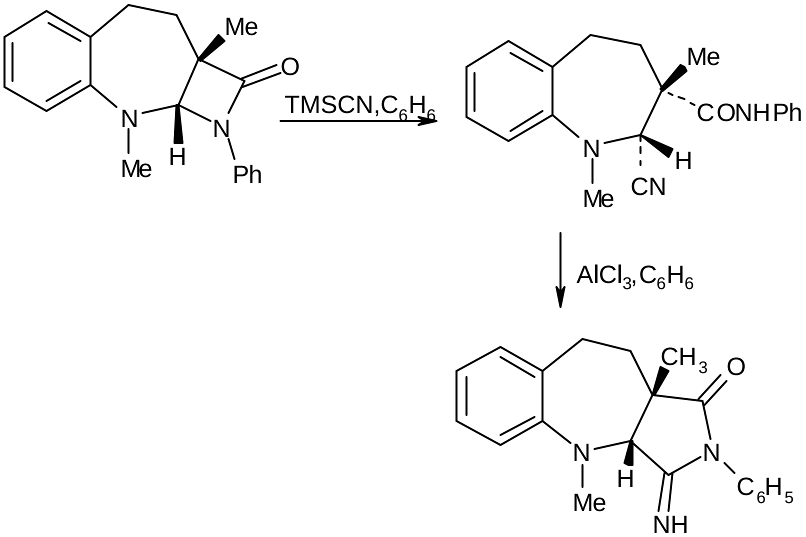
Philippe Uriac et al[45] have reported the reactivity of 4-aminoazetidin-2-ones with various protic reagents which undergo amide hydrolysis by cleavage of the N-1-C-2 bond (S*cheme 22).*

Scheme 22



Philippe Uriac et al[46] have reported that ring opening of 4-aminoazetidin-2-ones using trimethylsilyl cyanide to give stereospecifically β-cyanoamides, which could cyclize into 4-amino-5-iminopyrrolidin-2-ones in the presence of $AlCl_3$ (S*cheme 23)*.

Scheme 23


Me
O
N
N
Me
H
Ph
TMSCN,C6H6
Me
CONHPh
N
H
Me
CN
AlCl3,C6H6
CH3
O
N
N
H
Me
C6H5
NH

1.4 : Present Work.

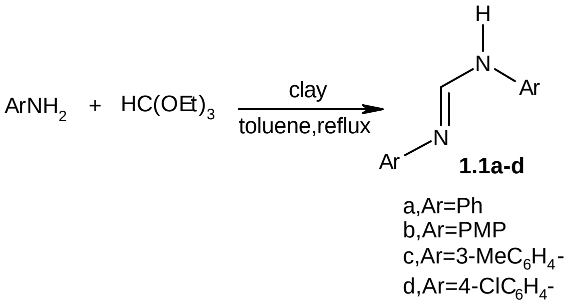
The synthesis of substituted β-lactams and their utility as a synthon for the synthesis of various biologically important compounds, we were interested in synthesis of 4-amino-β-lactams. Therefore, we were interested in developing suitable method for the synthesis of 4-amino substituted β-lactams. We thought that N,N'-diarylformimidine (**1.1a-d**), as an imine on 2+2 cycloaddition reaction with ketene derived from acid chloride will lead to the formation of 4-amino substituted β-lactams.

1.5 : Results & Discussion

Preparation of N,N'-diarylformimidine 1.1a-d

The N,N'-diarylformimidines (**1.1a-d**) was prepared from aromatic amines by the reaction of with triethyl orthoformate in presence of clay catalyst (S*cheme 24)*.

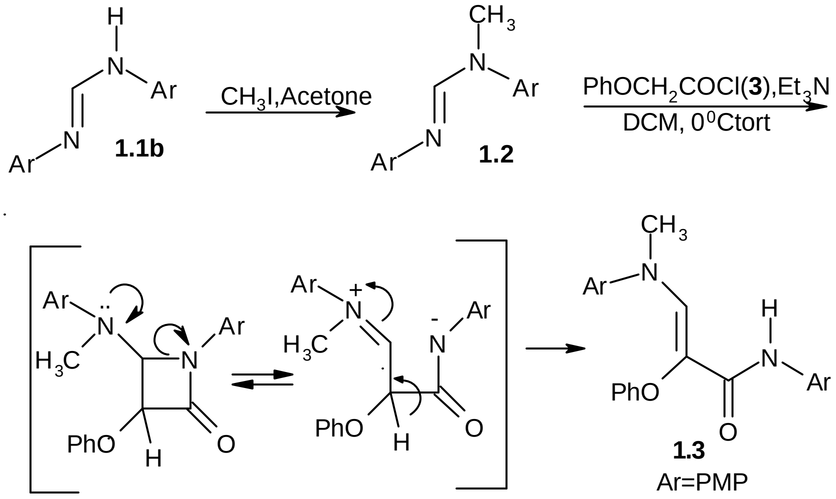
Scheme 24



Preparation of Enamino amide 1.3

The free N-H group of imidine (**1.1b**) was alkylated with methyl iodide to get imidine **1.2**. The imidine **1.2** on treatment with phenoxyacetyl chloride in presence of triethylamine in dichloromethane gave enaminoamide (**1.3**) instead of expected β-lactam (S*cheme 25)*. The formation of enaminoamide (**1.3**) is presumably by 1,4 cleavage of the initially formed β-lactam assisted by participation of loan pair of 4-amino group of β-lactam.

Scheme 25



The enamino amide was isolated as a pale yellow solid with mp 138^{0} C. The IR spectrum of this compound showed strong bands at 1650, 1580 cm^{-1} indicating the presence of the amide carbonyl group and the double bond of the enamine.

The ^{1}H NMR spectrum showed N-methyl protons as a singlet at 3.3. The two methoxy group of the PMP appeared as two singlet at 3.75 and 3.80. The amide N-H proton as well as the alkene proton of the enamine moiety and aromatic protons appeared in the region 6.75-7.65.

The mass spectral analysis of this compound showed the molecular ion peak at 404 (100%), which is also the base peak.

Preparation of N¢-benzoyl and p-toluenesulphonyl-N,N¢-diarylimidines 1.4a-f.

It was thought that the stability of the 4-amino-β-lactam ring could be increased by reducing the availability of the lone pair of nitrogen at 4 position. The trisubstituted formimidines haveing electron withdrawing substituents on the nitrogen would be ideal starting material for the synthesis of 4-amino-β-lactam. Therefore, trisubstituted imidines, N′-benzoyl-N,N′-diarylimidines (**1.4a-b**) and N′-sulphonyl-N,N′-diarylimidines (**1.4c-f**) were prepared by reacting N,N′-diarylimidines (**1.1a-d**) with aryloyl chloride or *p*-toluenesulphonyl chloride in presence of triethylamine (S*cheme 26)*.

Scheme 26

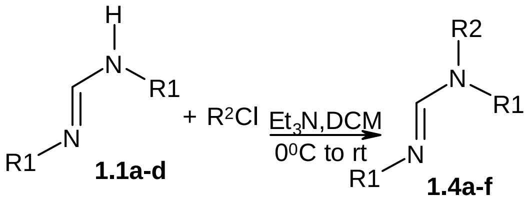


Table 1. Synthesis of imidines **1.4a-f**

Sr.No.	Imidines **1.4a-f**	R^1	R^2	Yield (%)	M.p. (°C)
1.	**1.4a**	Ph	PhCO-	91	129-30
2.	**1.4b**	Ph	4-$NO_2C_6H_4CO$-	84	77-78
3.	**1.4c**	Ph	Ts	98	198-199
4.	**1.4d**	4-ClC_6H_4-	Ts	93	99-100
5.	**1.4e**	3-MeC_6H_4-	Ts	81	118-119
6.	**1.4f**	4-$MeOC_6H_4$-	Ts	93	244-245

The N,N′-Diphenyl-N′-(p-toluenesulphonyl)imidine **1.4c** was chosen as representative example for the discussion.

Preparation of N,N¢-Diphenyl-N¢-(p- toluenesulphonyl)imidine 1.4c

The N,N′-diphenylformimidines on reaction with *p*-toluenesulphonyl chloride in the presence of triethylamine in dry DCM gave N’-sulphonyl-N,N′-diphenyl-formimidine (**1.4c**) in 98% yield.

The sulphonated imidine **1.4c** was isolated as a white solid, mp 198-199 ^{o} C. The IR spectrum of this compound showed strong bands at 1620, 1580, and 1440 cm^{-1} indicating the presence of the imine double bond and the sulphonyl group.

The ^{1}H NMR spectrum showed the tosyl methyl protons as a singlet at 2.45. The imine protons appeared as a singlet at 8.72. The aromatic protons appeared in the region 6.90-7.70.

The mass spectral analysis of this compound showed the molecular ion peak at 350 (100%), which is also the base peak.

Preparation of b-lactams 1.6a-h from N¢-benzoyl and p-toluenesulphony-N,N¢-diarylimidines.

The trisubstituted imidines **1.4a-f** on cycloaddition reaction with ketenes derived from acid chlorides (phenoxyacetyl chloride, phthalimidoacetyl chloride) in presence of triethylamine afforded exclusively *trans*-β-lactams (**1.6a-h**) in very good yields (S*cheme 27).* The assignment of *trans* stereochemistry for β-lactam protons is based on observed low vicinal coupling constant (~1-1.5 Hz) for β-lactam ring protons (H-3 & H-4). As anticipated these β-lactams (**1.6a-h**) were found to be stable to aqueous work-up and did not undergo any decomposition even after keeping for several months at room temperature.

Scheme 27

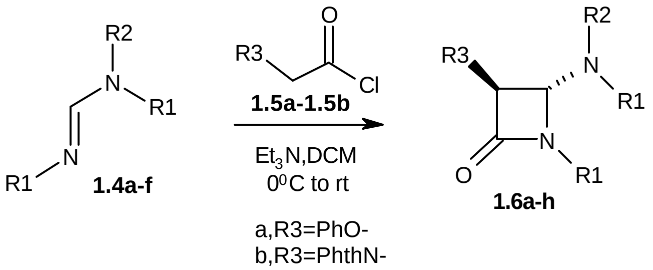


Table 2. Synthesis of β-lactams **1.6a-h**.

Sr.No.	Compd **1.6a-h**	R^1	R^2	R^3	Yield (%)	M.p. (°C)
1	**1.6a**	Ph	PhCO-	PhO-	72	140-141
2	**1.6b**	Ph	$4\text{-}NO_2C_6H_4CO\text{-}$	PhO-	68	96-97
4	**1.6c**	Ph	Ts-	PhO-	80	179-180
5	**1.6d**	$4\text{-}ClC_6H_4\text{-}$	Ts-	PhO-	87	199-200
6	**1.6e**	$3\text{-}MeC_6H_4\text{-}$	Ts-	PhO-	86	161-162
7	**1.6f**	$4\text{-}MeOC_6H_4\text{-}$	Ts-	PhO-	82	191-192
8	**1.6g**	Ph	Ts-	PhthN-	82	239-240
9	**1.6h**	$4\text{-}MeOC_6H_4\text{-}$	Ts-	PhthN-	89	248-249

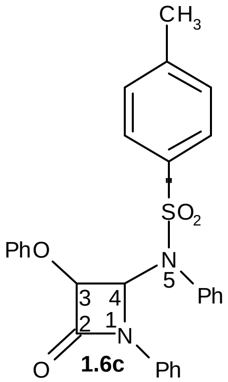
The β-lactam 1.6c was choosen as representative example for the discussion.

Preparation of b-lactam 1.6c

The sulphonated imidine on reaction with the acid chloride in the presence of triethylamine, underwent cycloaddition reaction to give exclusively *trans*-β-lactams in 98% yield.

The β-lactam was isolated as a white solid with mp 179-180 ^{o}C. The IR spectrum of this compound showed strong bands at 1750, 1580, 1480 cm^{-1} indicating the presence of the carbonyl group of β-lactam ring and the sulphonamide group.

The ^{1}H NMR spectrum showed methyl protons of the tosyl group at 2.45. The H-3 proton of the *b*-lactam ring shows doublet at 4.95 with J=1.1 Hz. The H-4 proton of the *b*-lactam ring appeared at 6.65 as a doublet with J=1.1 Hz. The aromatic protons appeared in the region 6.70-7.80.



1.6c

In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 160.79. The methyl carbon of the tosyl group appeared at 21.73. The β-lactam carbons, C-4 and C-3 appeared at 71.61 and 84.73. The aromatic carbons appeared in the region 116.41 to 157.29.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 484 (100%), which is also the base peak.

*Preparation of b-lactam (**1.7a-e**) form N,N'-diarylformimidine 1.1a-d.*

A one pot acylation and cycloaddition reactions were carried by using two equivalent of phenoxyacetyl chloride and N,N′-diphenylimidine (**1.1a-d**) in presence of triethylamine, which gave *trans*-β-lactam (**1.7a-d**) in very good yield. Similarly, other *trans*-β-lactams

(**1.7e**) were also prepared by the reaction of N,N′-diarylimidines **1.1a** with two equivalents phthalimidoacetyl chloride in presence of triethylamine (*Scheme 28*). The *trans* stereochemistry of β-lactam ring protons was further confirmed from single crystal X-ray analysis of compound **1.7a** (Fig. 1).

Scheme 28

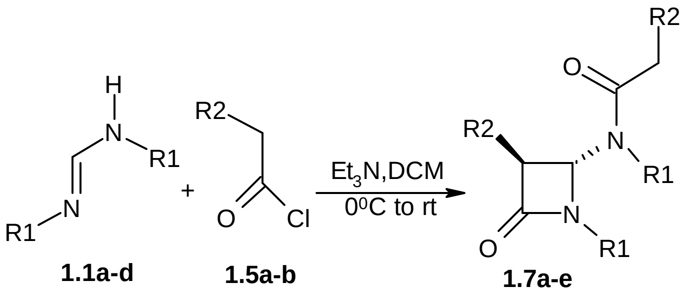


Table 3. Synthesis of *trans*-β-lactam (**1.7a-e**) using two equivalents of acid chlorides

Sr. No.	Compd **1.7a-1.7e**	R^1	R^2	Yield (%)	M.p. (^{o}C)
1	**1.7a**	Ph	PhO-	77	146-147
2	**1.7b**	4-ClC$_6$H$_4$-	PhO-	82	144-145
3	**1.7c**	3-MeC$_6$H$_4$-	PhO-	81	131-132
4	**1.7d**	4-MeOC$_6$H$_4$-	PhO-	73	142-143
5	**1.7e**	Ph	PhthN-	79	279-280

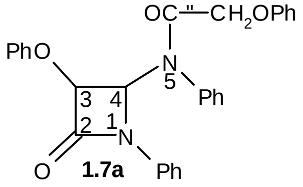
The β-lactam **1.7a** was chosen as representative example for the discussion.

Preparation of b-lactam 1.7a.

The N,N′-diphenylimidine on reaction with two equivalent of the acid chloride in the presence of triethylamine, underwent cycloaddition reaction to give exclusively *trans*-β-lactams **1.7a** in 77% yield.

The β-lactam **1.7a** was isolated as a white solid with mp 146 ^{o}C. The IR spectrum of this compound showed strong bands at 1766, 1693 cm^{-1} indicating the presence of the carbonyl group of β-lactam ring and the amide group.

The ^{1}H NMR spectrum showed methylene protons attached with the amide carbonyl at 4.25 and 4.50 with J = 17.5 Hz. The H-3 proton of the *b*-lactam ring shows doublet at 4.95 with J=1.2 Hz. The H-4 proton of the *b*-lactam ring was merged with the aromatic protons, which were seen in the region of 6.70-7.20.



1.7a

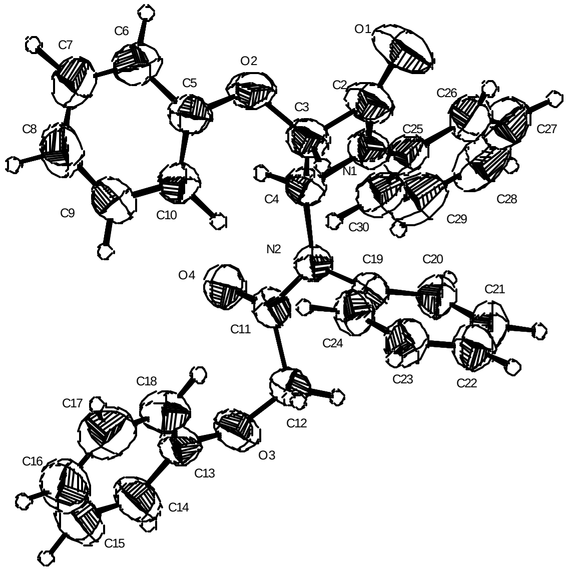
In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 169.30. The methylene carbon appeared at 66.25. The β-lactam carbon C-3 appeared at 82.80. The β-lactam carbon C-4 and the aromatic carbons appeared in the region 114.40 to 160.80.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 479 (100%), which is also the base peak.

The *trans* stereochemistry of β-lactam ring protons in **1.7** was further confirmed from the single crystal X-ray analysis of **1.7a**.

X-Ray diffraction study of 1.7a.

X-Ray Structure determination of ***1.7a*** $[C_{29}H_{24}N_2O_4.0.5(H_2O)]$: Colorless needles (0.74X0.2X0.12 mm grown from methanol). M = 473.51, monoclinic, space group $P2_1/C$, a = 8.720(5) Å, b = 16.606(7) Å, c = 17.424(1) Å, β = 16.606(1)°, V=2518.8(18) Å^3, Z=4, D=1.249 g cm^{-3}, μ=0.689 mm^{-1}, F(000)= 996, T = 293 K. Data were collected 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°. The structure was solved by direct methods using MULTAN-80 (NRCVAX- program).[10] Least squares refinement of scale, positional and anisotropic thermal parameters for non hydrogen atom converged to R = 0.0776. Rw = 0.192 for 3340 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference fourier was held fixed during the refinement. The refinements were carried out using SHELXL-97[47].


C6
C7
O1
C5
O2
C2
C26
C3
C25
C27
C8
N1
C4
C28
C9
C10
C30
C29
N2
C19
C20
O4
C21
C11
C24
C23
C22
C18
C17
C12
O3
C16
C13
C14
C15

ORTEP diagram of **1.7a**

1.6 : Summary

It has also been shown that 4-(N-alky)-β-lactam with hydrogen on C3 (3-mono substituted β-lactams) under go rapid ring opening *via* N1-C4 bond cleavage to give enamino amide. The formation of enamino amide (**1.3**) is presumably due to the N1,C4 cleavage of initially formed β-lactam assisted by the participation of nitrogen lone pair of 4-amino group. We envisaged that this problem could be addressed by arresting the availability of lone pair with electron withdrawing group on amino nitrogen. The cycloaddition reaction of ketenes with trisubstituted imidines bearing electron-withdrawing substituent on enamino nitrogen such as N′-benzoyl and N′-sulphonyl-N,N′-diarylimidines (**1.4a-f**) afforded stable 4-substituted amino-β-lactams (**1.6a-h**). Similarly N,N′-diarylimidines (**1.1a-d**) on reaction with two equivalents of acid chlorides (**1.5a,b**) gave 4-acylamino-*trans*-β-lactams (**1.7a-e**) in very good yield.

1.7 : Experimental

All dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Dichloromethane was dried over anhydrous P_2O_5, stored over 4A molecular sieves. Acetone was purified by distilling over $KMnO_4$, and dried over anhydrous $CaSO_4$, and stored over K_2CO_3.

Preparation of N,N′-di-(p-anisyl)-N′-methylimidine 1.2.

To a stirred mixture of N,N′-di-(*p*-anisyl)imidine **1.1b** (1.28 g, 5 mmol), K_2CO_3 (1.38 g) and acetone (25 ml), iodomethane (1.06 g, 0.0074 mol) was added at room temperature and stirred further for 12 h. The reaction mixture was filtered and filtrate was distilled to remove acetone. The residue so obtained was crystallized from chloroform:pet. ether to give 1.24 g (91.8%) of pure methylated imidine **1.2**.

MP : 114-116 ^{o}C

IR ($CHCl_3$) : 1620, 1500 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.45 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 6.70-7.15 (m, 8H), 7.95 (s, 1H).

MS (*m/z*) : 270 (M^+).

Analysis **$C_{16}H_{18}N_2O_2$** : Calculated: C: 71.09, H: 6.71, N: 10.01
Found: C: 70.61, H: 6.86, N: 10.01

Preparation of ***Enamino amide 1.3.***

To a mixture of N,N′-di-(*p*-anisyl)-N′-methylimidine **1.2** (1.35 g, 5 mmol), triethylamine (2.3 g, 22 mmol), CH_2Cl_2 (20 mL), a solution of phenoxyacetyl chloride (1.3 g, 7.5 mmol) in CH_2Cl_2 (20 mL) was added over a period of 30 min at 0 ^{o}C with stirring. The reaction mixture was allowed to warm-up to room temperature and stirred further for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with water (15 mL), $NaHCO_3$ (20 mL), brine (10 mL) and dried over Na_2SO_4. The solution was passed through short column (silica gel, 60-120). The removal of solvent by distillation under reduced pressure gave crude product, which was purified by crystallization from methanol to give 1.25 g (61.8%) of pure enamino amide (**1.3**) as white crystalline solid.

MP : 137-139 °C

IR ($CHCl_3$) : 1650, 1580 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.30 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 6.75-6.85 (m, 4 H), 6.90-7.10 (m, 5 H), 7.25-7.45 (m, 4 H), 7.65 (s, 2H).

MS (*m/z*) : 404 (M^+).

Analysis **($C_{26}H_{29}NO_7$)** : Calculated: C: 71.27, H: 5.98, N: 6.93

Found: C: 70.95, H: 6.18, N: 6.96

Typical procedure for N,N′-diaryl-N′-benzoylimidine 1.4a,b.

To a mixture of N,N′-diarylimidine (**1.1a,b** 6 mol), triethylamine (2 ml, 15 mmol), CH_2Cl_2 (20 mL), a solution of benzoyl chloride (0.93 g, 6.6 mmol) in CH_2Cl_2 (20 mL) was added over a period of 10 min at 0 °C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 4 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed successively with water (15 mL), $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. It was then filtered and filtrate on distillation under reduced pressure gave crude product (**1.4a,b**), which was purified by crystallization from chloroform:pet. ether.

Preparation of N,N′-Diphenyl-N′-benzoylimidine 1.4a.

The N,N′-Diphenylformimidine **1.1a** (1.96 g, 10 mmol) on treatment with benzoyl chloride (2.1 g, 15 mmol), in the presence of triethylamine (4.6 g, 45 mmol) provided the N′-benzoylimidine **1.4a** (2.73 g, 91%), which was purified by crystallization from chloroform:pet. ether.

MP : 129-130 °C

Yield 91%.

IR ($CHCl_3$) : 1630, 1570 cm^{-1}.

^{1}H NMR ($CDCl_3$) : 6.90-7.50 (m, 15H), 9.00 (s, 1H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : 25.54, 26.09, 54.69, 57.96, 70.05, 78.54, 80.71, 81.19, 82.18, 104.16, 11.04, 113.24, 114.97, 116.81, 119.09, 121.77, 128.94, 130.048, 133.09, 155.88, 156.76, 162.72
MS (*m/z*) : 300 (M^+).
Analysis : Calculated: C: 79.96, H: 5.37, N: 9.33
($C_{20}H_{16}N_2O$) Found: C: 79.28, H: 5.46, N: 8.91

Preparation of N,N¢-Diphenyl-N¢-(p-nitrobenzoyl)imidine 1.4b.

The N,N′-Diphenylformimidine **1.1a** (1.96 g, 10 mmol) on treatment with *p*-nitrobenzoyl chloride (2.71 g, 15 mmol), in the presence of triethylamine (4.6 g, 45 mmol) provided the N′- *p*-nitrobenzoyl imidine **1.4b** (2.89 g, 84%), which was purified by crystallization from chloroform:pet. ether.

MP : 77-78 °C
Yield 84%.
IR ($CHCl_3$) : 1630, 1510 cm^{-1}.
^{1}H NMR ($CDCl_3$) : 7.00-7.45 (m, 10H), 7.54 (d, *J* = 9 Hz, 2H), 8.06 (d, *J* = 9 Hz, 2H), 9.85 (s, 1H).
(200 MHz)

MS (*m/z*) : 345 (M^+).
Analysis : Calculated: C: 69.55, H: 4.37, N: 12.16
($C_{20}H_{15}N_3O_3$) Found: C: 69.38, H: 4.23, N: 12.05.

Typical procedure for N,N¢-diaryl-N¢-(p-toluenesulphonyl)imidine (1.4c-f).

To a mixture of N,N′-diarylimidine (**1.1**, 5 mol), triethylamine (2 ml, 15 mmol), CH_2Cl_2 (20 mL), a solution of *p*-toluenesulphonyl chloride (1.045 g, 5.5 mmol) in CH_2Cl_2 (20 mL) was added over a period of 10 min. at 0 °C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 4 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed successively with water (10 mL), $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. It was then filtered and filtrate on distillation under reduced pressure gave crude product (**1.4c-f**), which was purified by crystallization from chloroform:pet. ether.

Preparation of N,N¢-Diphenyl-N¢-(p-toluenesulphonyl)imidine 1.4c.

The N,N′-Diphenylformimidine **1.1a** (1.96 g, 10 mmol) on treatment with *p*-toluenesulphonyl chloride (2.85 g, 15 mmol), in the presence of triethylamine (4.6 g, 45 mmol) provided the N′-tosylimidine **1.4c** (3.43 g, 98%), which was purified by crystallization from chloroform:pet. ether.

MP : 197-198 °C.
Yield 98%.
IR ($CHCl_3$) : 1620, 1580, 1440 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : 2.45 (s, 3H), 6.90-7.70 (m, 14 H), 8.72 (s, 1H).
MS (*m/z*) : 350 (M^+).

Analysis : Calculated: C: 68.55, H: 5.18, N: 7.99, S: 9.15
($C_{20}H_{15}N_3O_3$) Found: C: 69.39, H: 5.36, N: 8.13, S: 9.26

Preparation of N,N¢-Di(4-chlorophenyl)-N¢-(p-toluenesulphonyl)imidine 1.4d.

The N,N′-Di(4-chlorophenyl)formimidine **1.1d** (1.32 g, 5 mmol) on treatment with *p*-toluenesulphonyl chloride (1.42 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the N′-tosylimidine **1.4d** (2.23 g, 93%), which was purified by crystallization from chloroform:pet. ether.

MP : 164-165 °C
Yield 93 %.
IR ($CHCl_3$) : 1620, 1550, 1440 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : 2.45 (s, 3H), 6.90-7.80 (m, 12 H), 8.65 (s, 1H).

MS (*m/z*) : 419 (M^+).

Analysis : Calculated: C: 57.29, H: 3.85, N: 6.68, S: 7.65

($C_{20}H_{15}N_3O_3$) Found: C: 57.39, H: 4.02, N: 6.53, S: 7.88

Preparation of N,N′-Di(3-methylphenyl)-N′-(p-toluenesulphonyl)imidine 1.4e.

The N,N′-Di(3-methylphenyl)formimidine **1.1c** (1.12 g, 5 mmol) on treatment with *p*-toluenesulphonyl chloride (1.42 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the N′-tosylimidine **1.4e** (1.53 g, 81%), which was purified by crystallization from chloroform:pet. ether.

MP : 118-119 °C.

Yield 81 %.

IR ($CHCl_3$) : 1620, 1450 cm^{-1}

^{1}H NMR ($CDCl_3$) : 2.3 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 6.80-7.70 (m, 12

(200 MHz) H), 8.70 (s, 1H).

MS (*m/z*) : 378 (M^+).

Analysis Calcd for : Calculated: C: 69.81, H: 5.86, N: 7.40, S: 8.47

($C_{20}H_{15}N_3O_3$) Found: C: 69.67, H: 5.99, N: 7.26, S: 8.31

Preparation of N,N′-Di(4-methoxyphenyl)-N′-(p-toluenesulphonyl)imidine 1.4f.

The N,N′-Di(4-methoxylphenyl)formimidine **1.1b** (1.28 g, 5 mmol) on treatment with *p*-toluenesulphonyl chloride (1.42 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the N′-tosylimidine **1.4f** (1.9 g, 93%), which was purified by crystallization from chloroform:pet. ether.

MP : 244-245 °C.

Yield 93 %.

IR ($CHCl_3$) : 1620, 1450, 1390 cm^{-1}.

^{1}H NMR ($CDCl_3$) : 2.5 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 6.80-7.80 (m, 12

(200 MHz) H), 8.70 (s, 1H).

MS (*m/z*) : 410 (M^+).
Analysis : Calculated: C: 64.37, H: 5.40, N: 6.82, S: 7.81
($C_{20}H_{15}N_3O_3$) Found: C: 64.62, H: 5.53, N: 7.02, S: 7.57

General procedure for the preparation of b-lactams 1.6a-h.

To a mixture of trisubstituted imidine (**1.4a-f**, 3 mmol), triethylamine (1.7 mL, 12 mmol), CH_2Cl_2 (20 mL), a solution of acid chloride (4.5 mmol) in CH_2Cl_2 (20 mL) was added over a period of 20 min at 0 °C with stirring. The reaction mixture was allowed to warm-up to room temperature and stirred further for 14 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with water (15 mL), $NaHCO_3$ (20 mL), brine (10 mL) and dried over Na_2SO_4. The solution was passed through short column (silica gel, 60-120). The removal of solvent by distillation under reduced pressure gave crude product, which was purified by crystallization from methanol to give pure β-lactams (**1.6a-h**) as white crystalline solids.

Preparation of 1-Phenyl-3-phenoxy-4-(N-phenyl-N-benzoylamino)azetidin-2-one 1.6a.

The trisubstituted imidine **1.4a** (1.5 g, 5 mmol) on treatment with phenoxyacetyl chloride (1.27 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6a** (1.56 g, 72%), which was purified by crystallization from methanol to give pure β-lactam **1.6a** as a white solid.

MP : 140-141 °C.
Yield 72%.
IR ($CHCl_3$) : 1750, 1630, 1510 cm^{-1}.
^{1}H NMR ($CDCl_3$) : 5.05 (d, *J* = 1.2 Hz, 1H), 6.80-8.00 (m, 21H).
(200 MHz)

^{13}C NMR ($CDCl_3$) : 68.12, 83.73, 116.41, 118.43, 123.15, 125.83, 128.26, 128.66, 129.10, 129.84, 130.09, 130.62, 135.38, 136.25, 137.93, 157.60, 161.50, 172.04.
MS (*m/z*) : 341 (M^+– 93).
Analysis : Calculated: C: 77.37, H: 5.10, N: 6.44.

$(C_{28}H_{22}N_2O_3)$ Found: C: 77.13, H: 5.21, N: 6.45.

Preparation of 1-Phenyl-3-phenoxy-4-[N-phenyl-N-(2-nitrobenzoyl)amino]-azetidin-2-one 1.6b.

The trisubstituted imidine **1.4b** (1.72 g, 5 mmol) on treatment with phenoxyacetyl chloride (1.27 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6b** (1.62 g, 68%), which was purified by crystallization from methanol to give yellow solid.

MP : 96-97 °C.
Yield 68%.
IR ($CHCl_3$) : 1760, 1640, 1580 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : 4.95 (d, J = 1.1 Hz, 1H), 6.80-7.90 (m, 20H).
^{13}C NMR ($CDCl_3$) : 67.15, 82.90, 115.70, 117.70, 122.60, 122.80, 125.40, 128.80, 129.20, 129.40, 129.60, 129.80, 135.30, 136.10, 140.60, 148.00, 156.80, 160.60, 169.40.
MS (m/z) : 479 (M^+).
Analysis : Calculated: C: 70.14, H: 4.41, N: 8.76.
$(C_{28}H_{22}N_2O_3)$ Found: C: 69.93, H: 4.34, N: 8.55.

Preparation of 1-phenyl-3-phenoxy-4-[N-phenyl-N-(p-toluenesulphonyl)amino]-azetidin-2-one 1.6c.

The trisubstituted imidine **1.4c** (3.5 g, 10 mmol) on treatment with phenoxyacetyl chloride (2.5 g, 15 mmol), in the presence of triethylamine (4.6 g, 45 mmol) provided the β-lactam **1.6c** (3.87 g, 80%) which was purified by crystallization from methanol to give white solid.

MP : 179-180 °C.
Yield 80%.

IR ($CHCl_3$) : 1750, 1580, 1480 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.45 (s, 3H), 4.95 (d, J = 1.1 Hz, 1H), 6.65 (d, J = 1.1 Hz, 1H), 6.70-6.85 (m, 2H), 6.90-7.80 (m, 17H).

^{13}C NMR ($CDCl_3$) : 21.73, 71.61, 84.73, 116.41, 119.96, 123.31, 127.84, 129.90, 130.10, 130.29, 131.81, 133.21, 134.30, 136.67, 144.95, 157.29, 160.79.

MS : 484 (M$^+$).

Analysis ($C_{28}H_{24}N_2O_4S$) : Calculated: C: 69.40, H: 4.99, N: 5.78, S: 7.22.
Found: C: 68.95, H: 4.84, N: 5.97, S: 7.47.

Preparation of 1-(4-Chlorophenyl)-3-phenoxy-4-[N-(4-chlorophenyl)-N-(p-toluenesulphonyl)amino]-azetidin-2-one 1.6d.

The trisubstituted imidine **1.4d** (2.41 g, 5 mmol) on treatment with phenoxyacetyl chloride (1.27 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6d** (2.4 g, 87%), which was purified by crystallization from methanol to give white solid.

MP : 199-200 °C.

Yield 87%.

IR ($CHCl_3$) : 1750, 1580, 1475 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.45 (s, 3H), 4.95 (d, J = 1.2 Hz, 1H), 6.50 (d, J = 1.2 Hz, 1H), 6.60-7.70 (m, 17H).

^{13}C NMR ($CDCl_3$) : 21.73, 71.62, 84.73, 116.41, 119.96, 123.31, 127.89, 129.91, 130.05, 130.29, 131.81, 133.26, 134.30, 136.68, 144.95, 157.34, 160.81.

MS (*m/z*) : 399 (M$^+$– 153).

Analysis ($C_{28}H_{22}N_2O_4Cl_2S$) : Calculated: C: 60.76, H: 4.00, N: 5.06.
Found: C: 60.50, H: 3.87, N: 4.91.

Preparation of 1-(3-Methylphenyl)-3-phenoxy-4-[N-(3-methylphenyl)-N-(p-toluenesulphonyl)-amino]-azetidin-2-one 1.6e.

The trisubstituted imidine **1.4e** (1.89 g, 5 mmol) on treatment with phenoxyacetyl chloride (1.3 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6e** (2.2 g, 86%), which was purified by crystallization from methanol to give white solid.

MP : 161-162 °C.
Yield 86%.
IR ($CHCl_3$) : 1750, 1580 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : 2.20 (s, 3H), 2.40 (s, 3H), 4.95 (d, *J* = 1.2 Hz, 1H), 6.60 (d, *J* = 1.2 Hz, 1H), 6.90-7.60 (m, 17H).
^{13}C NMR ($CDCl_3$) : 71.50, 84.34, 116.25, 120.00, 123.00, 126.80, 127.80, 128.20, 129.50, 130.00, 130.80, 132.50, 133.00, 135.50, 136.80, 139.00, 144.80, 157.20, 161.00.
MS (*m/z*) : 379 (M$^+$– 133).
Analysis ($C_{28}H_{22}N_2O_4Cl_2S$) : Calculated: C: 70.29, H: 5.51, N: 5.46, S: 6.25
Found: C: 70.04, H: 5.38, N: 5.33, S: 5.99

Preparation of 1-(4-Methoxylphenyl)-3-phenoxy-4-[N-(4-methoxylphenyl)-N-(p-toluene-sulphonyl)amino]-azetidin-2-one 1.6f.

The trisubstituted imidine **1.4f** (2.05 g, 5 mmol) on treatment with phenoxyacetyl chloride (1.3 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6f** (2.23 g, 82%), which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 192 °C.
Yield 82%.
IR ($CHCl_3$) : 1740, 1580, 1500 cm^{-1}.
^{1}H NMR ($CDCl_3$) (200 MHz) : 2.40 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.95 (d, *J* = 1.2 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 6.90-7.80 (m, 17H).
^{13}C NMR ($CDCl_3$) : 21.76, 55.66, 71.50, 84.30, 116.20, 120.40, 123.01, 125.10, 127.80, 128.90, 129.90, 132.90, 136.70, 144.40,

157.40, 157.50, 160.70.

MS (*m/z*) : 545 (M^+).

Analysis : Calculated: C: 66.04, H: 5.36, N: 5.13.

($C_{30}H_{29}N_2O_6S$) Found: C: 65.92, H: 5.27, N: 5.17.

Preparation of 1-Phenyl-3-phthalimido-4-[N-phenyl-N-(p-toluenesulphonyl)-amino]azetidin-2-one 1.6g.

The trisubstituted imidine **1.4c** (1.75 g, 5 mmol) on treatment with phthalimidoacetyl chloride (1.67 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6g** (2.2 g, 82%), which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 239-240 °C.

Yield 82%.

IR ($CHCl_3$) : 1750, 1680, 1480 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.30 (s, 3H), 5.20 (d, *J* = 1.2 Hz, 1H), 6.75 (d, *J* = 1.2 Hz, 1H), 6.90-8.20 (m, 18H).

^{13}C NMR ($CDCl_3$) : 21.47, 40.00, 57.70, 68.80, 78.70, 79.20, 79.60, 117.90, 123.60, 124.02, 125.80, 127.60, 128.90, 130.00, 130.40, 130.80, 131.30, 131.60, 135.00, 135.40, 144.70, 145.60, 166.30, 166.60, 167.09.

MS (*m/z*) : 537 (M^+).

Analysis : Calculated: C: 67.03, H: 4.31, N: 7.82, S: 5.96

($C_{30}H_{23}N_3O_5S$) Found: C: 66.82, H: 4.46, N: 7.63, S: 6.23

Preparation of 1-(4-Methoxylphenyl)-3-phthalimido-4-[N-(4-methoxylphenyl)-N-(p-toluene-sulphonyl)-amino]azetidin-2-one 1.6h.

The trisubstituted imidine **1.4f** (2.05 g, 5 mmol), on treatment with phthalimidoacetyl chloride (1.67 g, 7.5 mmol), in the presence of triethylamine (2.3 g, 22 mmol) provided the β-lactam **1.6h** (2.65 g, 89%), which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 248-249 °C

Yield 89%.

IR ($CHCl_3$) : 1750, 1580, 1480 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.35 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 5.15 (d, *J* = 1.2 Hz, 1H), 6.65 (d, *J* = 1.2 Hz, 1H), 6.80-8.00 (m, 16H).

^{13}C NMR ($CDCl_3$) : 21.27, 55.35, 55.44, 57.70, 69.00, 114.60, 114.80, 120.10, 123.60, 124.60, 127.30, 129.50, 131.50, 132.80, 134.60, 136.80, 144.00, 157.30, 159.20, 160.50, 166.30.

MS (*m/z*) : 448 (M^+– 149).

Analysis ($C_{32}H_{27}N_3O_7S$) : Calculated: C: 64.31, H: 4.55, N: 7.03, S: 5.36.
Found: C: 64.47, H: 4.58, N: 6.93, S: 5.01.

General procedure for the preparation of b-lactams 1.7a-e from imidine 1.1.

To a mixture of diarylimidine (**1.1**, 3 mmol), triethylamine (1.7 mL, 12 mmol), CH_2Cl_2 (20 mL), a solution of acid chloride (6 mmol) in CH_2Cl_2 (20 mL) was added over a period of 30 min at 0 °C with stirring. The reaction mixture was allowed to warm-up to room temperature and stirred further for 14 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed successively with water (15 mL), $NaHCO_3$ (20 mL), brine (10 mL) and dried over Na_2SO_4. The solution was passed through short column (silica gel, 60-120). The removal of solvent by distillation under reduced pressure gave crude product, which was purified by crystallization from methanol to give pure β-lactams (**1.7a-e**) as white crystalline solids.

Preparation of 1-Phenyl-3-phenoxy-4-[N-phenyl-N-(2-phenoxyacetyl)amino]-azetidin-2-one 1.7a.

The N,N′-Diphenylformimidine imidine **1.1a** (1.96 g, 10 mmol) on treatment with phenoxyacetyl chloride (5.1 g, 30 mmol) in the presence of triethylamine (9.18 g, 90 mmol) provided the β-lactam **1.7a** (3.57 g, 77%), which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 146-147 °C.

Yield 77%.

IR ($CHCl_3$) : 1766, 1693 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 4.25 (d, *J* = 17.5 Hz, 1H), 4.50 (d, *J* = 17.5 Hz, 1H), 4.95
(200 MHz) (d, *J* = 1.2 Hz, 1H), 6.70-7.20 (m, 21H).

^{13}C NMR (CDCl$_3$) : 66.25, 82.80, 114.40, 114.70, 115.90, 118.00, 121.10, 121.60, 122.80, 125.50, 128.70, 128.90, 129.40, 129.70, 130.40, 130.50, 134.00, 135.30, 157.00, 157.60, 160.80, 169.30.

MS (*m/z*) : 464 (M$^+$).

Analysis : Calculated: C: 74.98, H: 5.21, N: 6.03.
($C_{29}H_{24}N_2O_4$) Found: C: 74.82, H: 5.45, N: 5.78.

Preparation of 1-(4-Chlorophenyl)-3-phenoxy-4-[N-(4-chlorophenyl)-N-(2-phenoxyacetyl)-amino]azetidin-2-one 1.7b.

The N,N′-Di(4-chlorophenyl)formimidine **1.1d** (1.325 g, 5 mmol) on treatment with phenoxyacetyl chloride (2.5 g, 15 mmol), in the presence of triethylamine (4.5 g, 45 mmol) provided the β-lactam **1.7b** (2.18 g, 82%) which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 144-145 ^{o}C.
Yield 82%.
IR (CHCl$_3$) : 1760, 1680 cm^{-1}.
^{1}H NMR (CDCl$_3$) : 4.30 (d, *J* = 16.6 Hz, 1H), 4.50 (d, *J* = 16.6 Hz, 1H), 4.95
(200 MHz) (d, *J* = 1.2 Hz, 1H), 6.70-7.70 (m, 19H).

^{13}C NMR (CDCl$_3$) : 66.25, 82.80, 114.40, 115.90, 118.00, 121.10, 121.60, 122.80, 125.50, 128.70, 128.90, 129.40, 129.70, 130.40, 130.50, 134.00, 135.30, 157.00, 157.60, 160.80, 169.30.

MS (*m/z*) : 286 (M$^+$– 246).

Analysis : Calculated: C: 65.30, H: 4.16, N: 5.25.
($C_{32}H_{27}N_3O_7S$) Found: C: 65.21, H: 3.98, N: 4.98.

Preparation of 1-(3-Methylphenyl)-3-phenoxy-4-[N-(3-methylphenyl)-N-(2-phenoxyacetyl)-amino]azetidin-2-one 1.7c.

The N,N′-Di(3-methylphenyl)formimidine **1.1c** (1.12 g, 5 mmol) on treatment with phenoxyacetyl chloride (2.5 g, 15 mmol), in the presence of triethylamine (4.5 g, 45 mmol) provided the β-lactam **1.7c** (2 g, 81%) which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 131-132 ^{o}C.

Yield 81%.

IR ($CHCl_3$) : 1750, 1670 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.2 (s, 3H), 2.4 (s, 3H), 4.25 (d, *J* = 16.6 Hz, 1H), 4.55 (d, *J* = 16.6 Hz, 1H), 4.95 (d, *J* = 1.2 Hz, 1H), 6.75-7.50 (m, 19H).

^{13}C NMR ($CDCl_3$) : 20.70, 21.10, 82.40, 114.00, 114.70, 115.50, 118.50, 121.10, 122.30, 125.90, 129.00, 129.30, 129.60, 130.60, 133.70, 134.90, 139.30, 140.20, 156.70, 157.30, 160.40, 168.90.

MS (*m/z*) : 399 (M^+– 93).

Analysis ($C_{31}H_{28}N_2O_4$) : Calculated: C: 75.59, H: 5.73, N: 5.69.
Found: C: 75.33, H: 5.49, N: 5.54.

Preparation of 1-(4-Methoxyphenyl)-3-phenoxy-4-[N-(4-methoxyphenyl)-N-(2-phenoxyacetyl)-amino]-azetidin-2-one 1.7d.

The N,N′-Di(4-methoxylphenyl)formimidine **1.1b** (1.28 g, 5 mmol) on treatment with phenoxyacetyl chloride (2.5 g, 15 mmol), in the presence of triethylamine (4.5 g, 45 mmol) provided the β-lactam **1.7d** (1.9 g, 73%) which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : 142-143 ^{o}C.

Yield 73%.

IR ($CHCl_3$) : 1768, 1685 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 3.85 (s, 3H), 3.88 (s, 3H), 4.25 (d, *J* = 16 Hz, 1H), 4.50
(200 MHz) (d, *J* = 16 Hz, 1H), 5.00 (d, *J* = 1.2 Hz, 1H), 6.60-7.50 (m, 19H).

^{13}C NMR (CDCl$_3$) : 55.50, 55.58, 66.30, 66.47, 82.80, 114.50, 115.00, 115.70, 115.90, 119.00, 121.60, 122.80, 126.20, 128.70, 129.50, 129.80, 130.60, 133.90, 157.20, 157.70, 160.40, 160.70, 169.80.

MS (*m/z*) : 524 (M$^+$).

Analysis : Calculated: C: 70.98, H: 5.38, N: 5.34.
($C_{32}H_{27}N_3O_7S$) Found: C: 70.79, H: 5.28, N: 5.13.

Preparation of 1-Phenyl-3-phthalimido-4-[N-phenyl-N-(2-phthalimidoacetyl)-amino]azetidin-2-one 1.7e.

The N,N′-Diphenylformimidine **1.1a** (1.96 g, 10 mmol) on treatment with phthalimidoacetyl chloride (6.69 g, 30 mmol), in the presence of triethylamine (9.18 g, 90 mmol) provided the β-lactam **1.7e** (4.5 g, 79%) which was purified by crystallization from methanol to give pure β-lactam as a white solid.

MP : .279-280 ^{o}C.

Yield 79%

IR (CHCl$_3$) : 1764, 1724, 1693 cm^{-1}.

^{1}H NMR (CDCl$_3$) : 3.95 (d, *J* = 16 Hz, 1H), 4.20 (d, *J* = 16 Hz, 1H), 5.25 (d, *J*
(200 MHz) = 1.2 Hz, 1H), 7.10 (d, *J* = 1.2 Hz, 1H), 7.2-8.00 (m, 18H).

^{13}C NMR (CDCl$_3$) : 66.65, 117.97, 123.15, 123.65, 125.21, 129.75, 130.00, 130.50, 130.60, 131.00, 131.70, 132.00, 133.80, 134.10, 134.50, 134.79, 159.90, 166.80, 167.50, 168.00.

MS (*m/z*) : 451 (M$^+$– 119).

Analysis : Calculated: C: 69.47, H: 3.89, N: 9.82.
($C_{33}H_{22}N_4O_6$) Found: C: 69.22, H: 3.67, N: 9.58.

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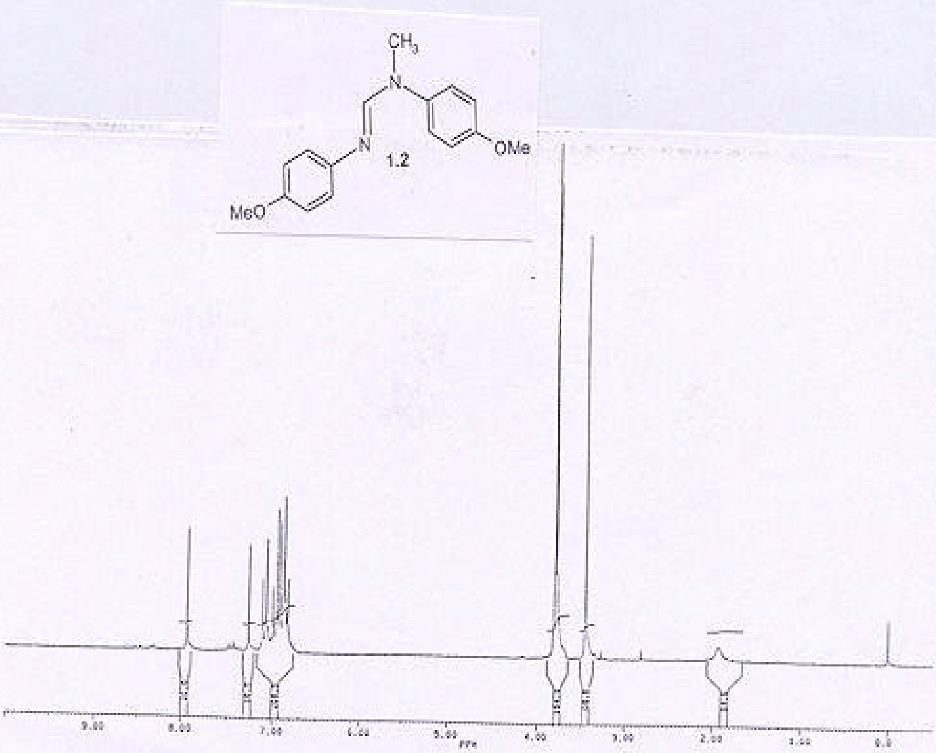
Spectra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N
OMe
MeO
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7.00
6.00
5.00
PPM
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3.00
2.00
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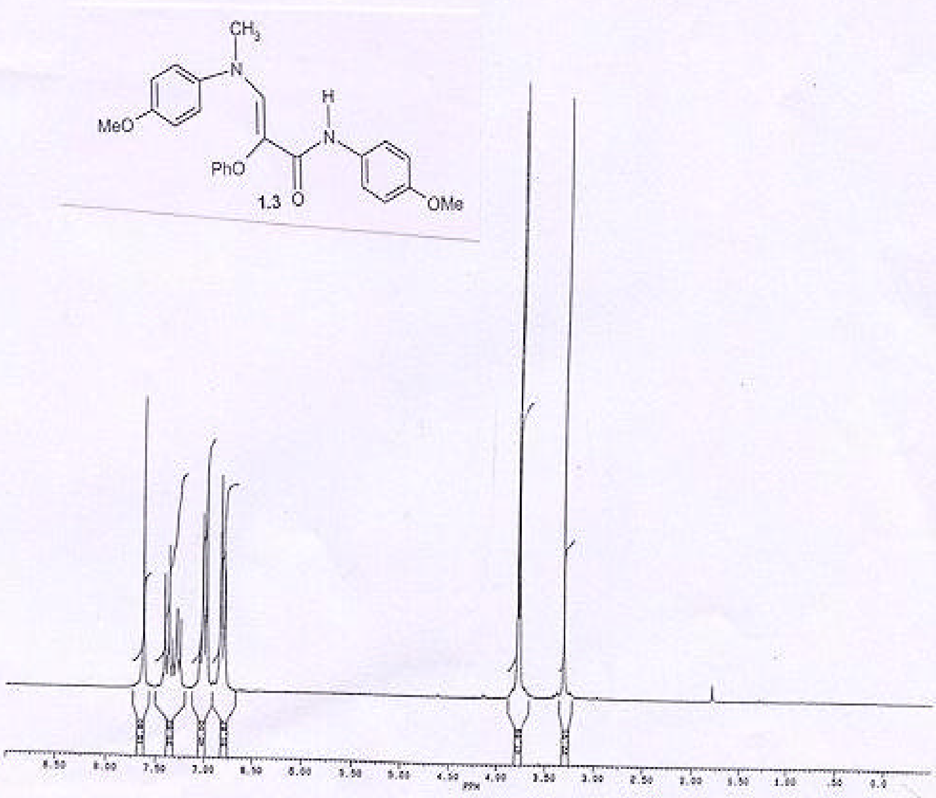
0.0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MeO
H
N
PhO
O
OMe
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7.00
6.50
6.00
5.50
5.00
4.50
PPM
4.00
3.50
3.00
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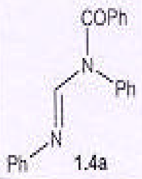
2.00
1.50
1.00
.50
0.0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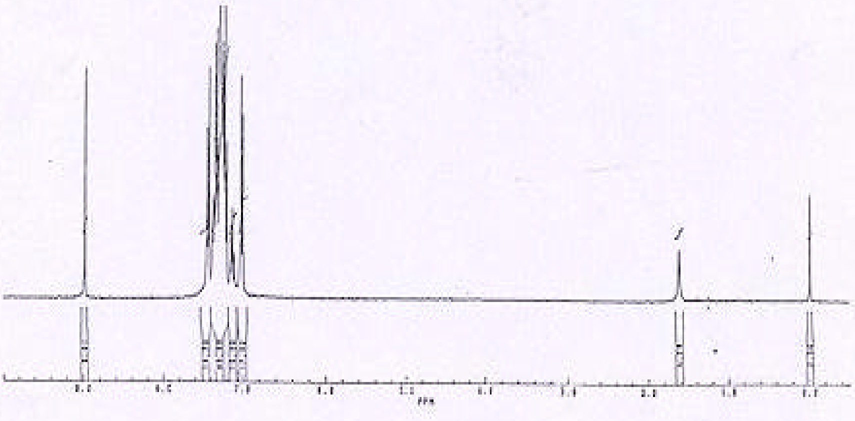
Ph
N
Ph

1.4a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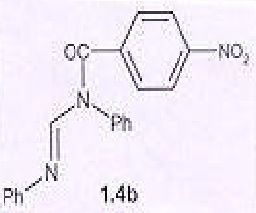
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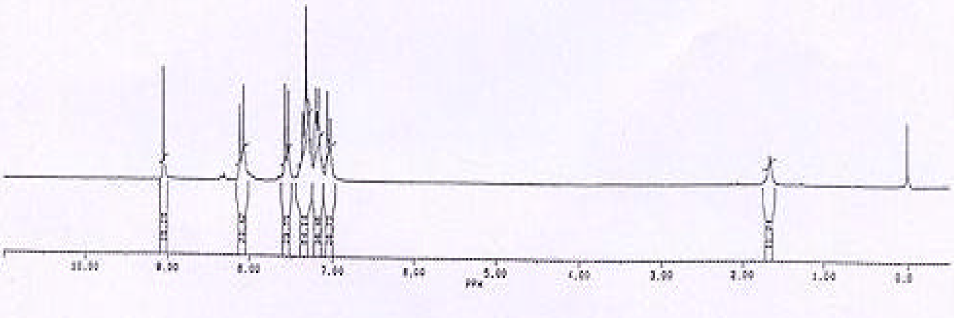
N
Ph
N
Ph

1.4b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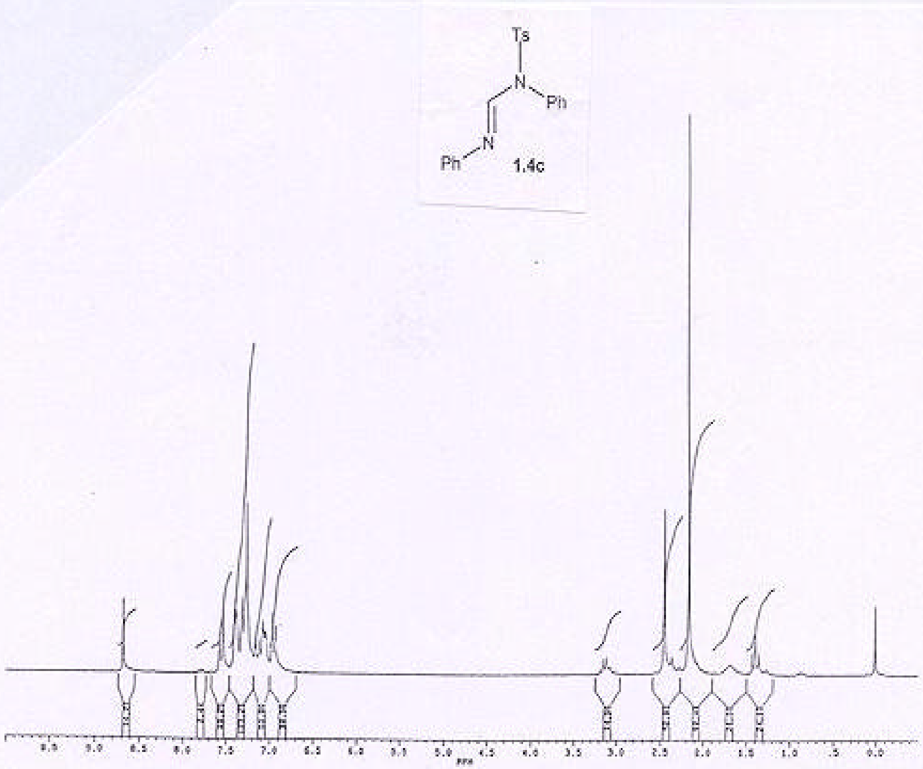
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Ph
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Ph
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7.0
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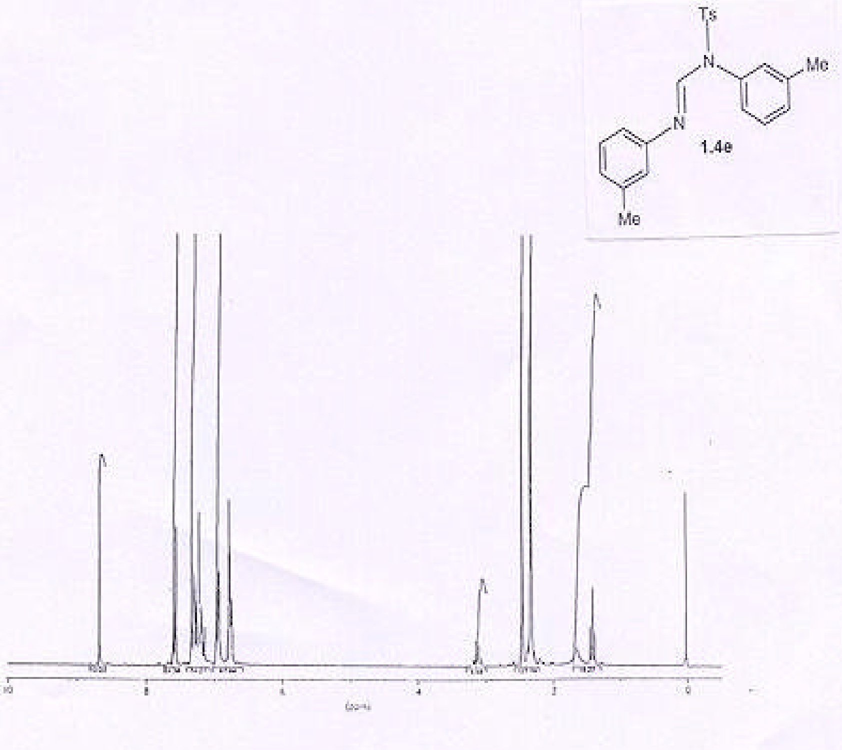
PPM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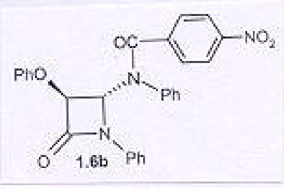
1.4e
Me
10
8
6
4
2
0
(ppm)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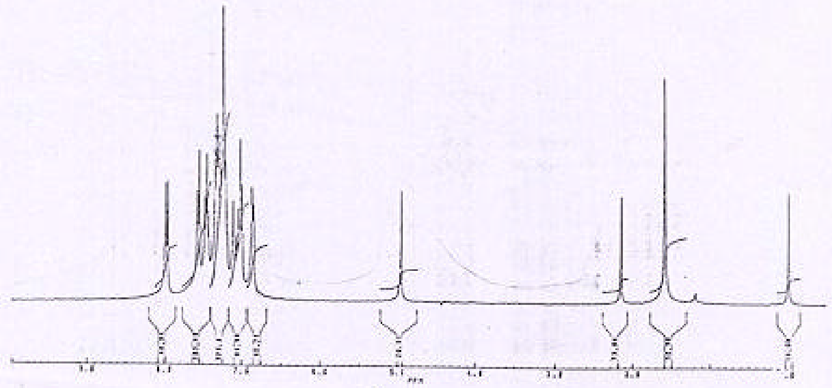
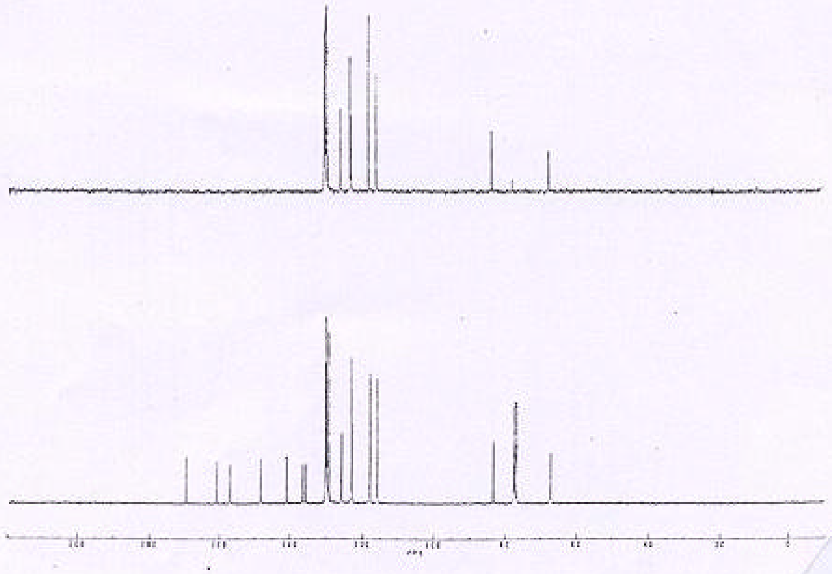
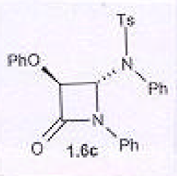
OC
NO2
N
Ph
O
N
Ph

1.6b



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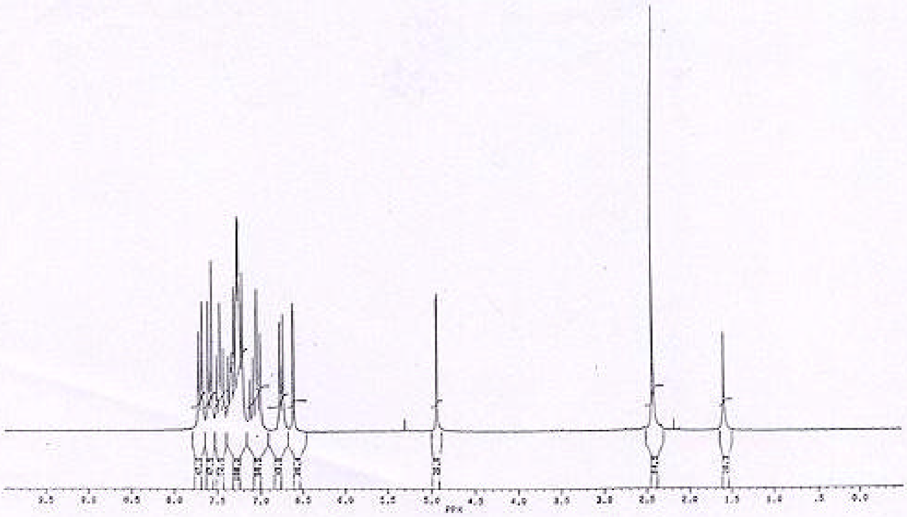
N
Ph
O
N
Ph

1.6c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7.0
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6.0
5.5
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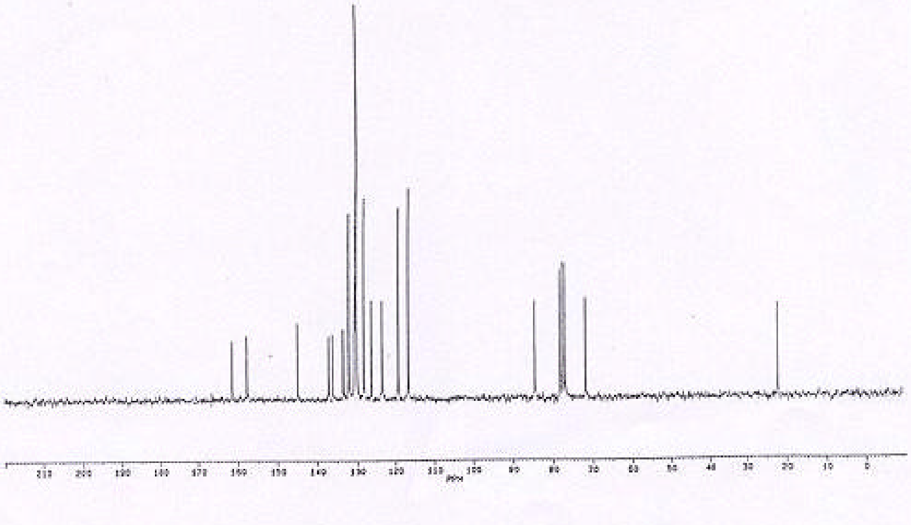
1.5
1.0
.5
0.0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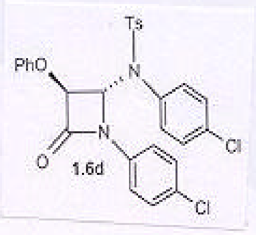
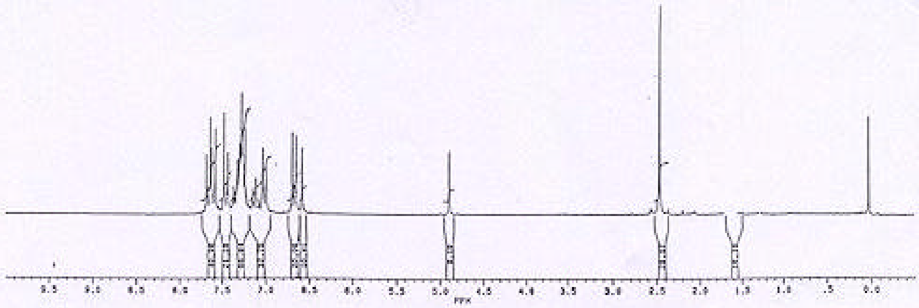
130
120
110
100
PPM
90
80
70
60
50
40
30
20
10
0



Ts
PhO
N
N
O
Cl
Cl

1.6d



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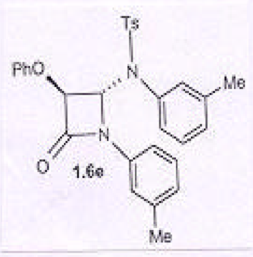
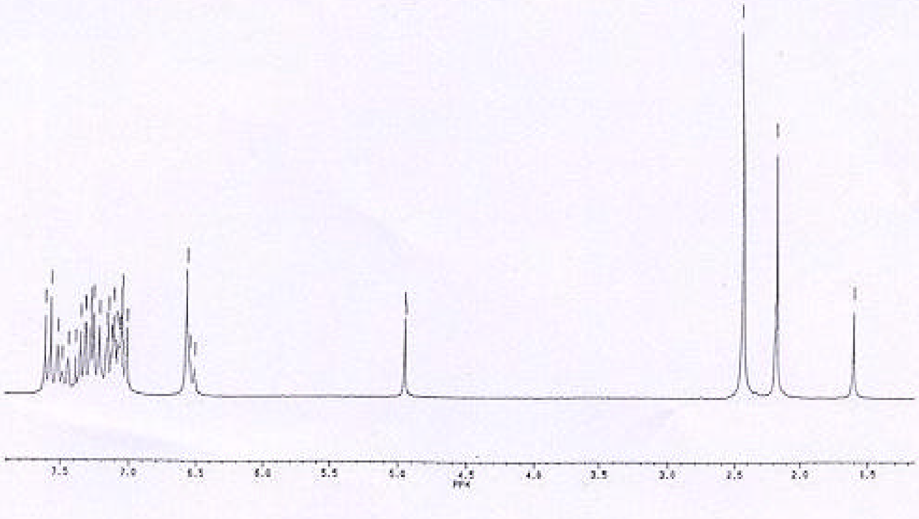
1.5
1.0
.5
0.0
PPM



Ts
PhO
N
Me
N
O
Me

1.6e



7.5
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4.5
4.0
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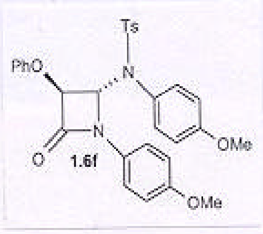
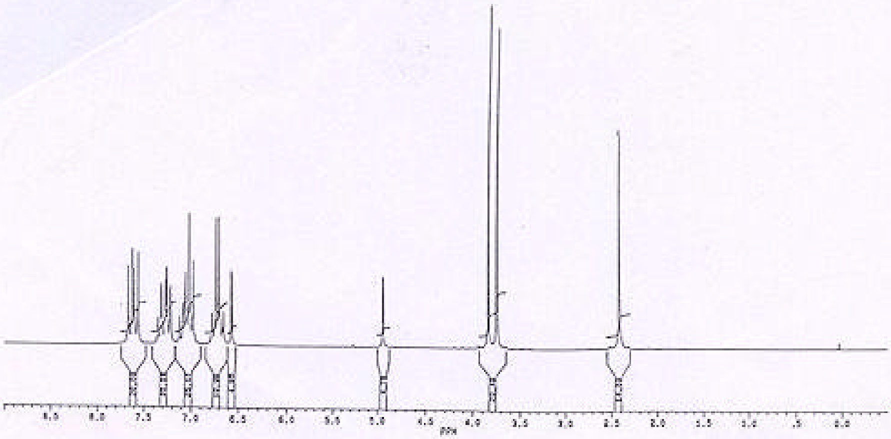
2.0
1.5
PPM


Ts
PhO
N
N
O
OMe
OMe

1.6f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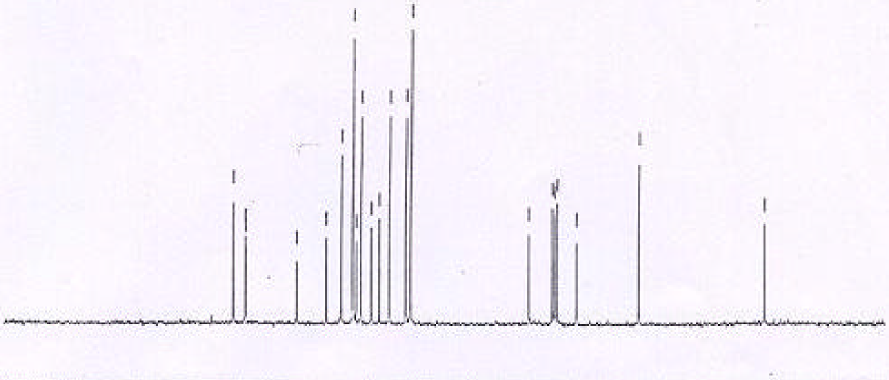
PPM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80
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60
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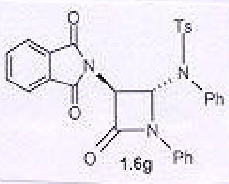
30
20
10
0
PPM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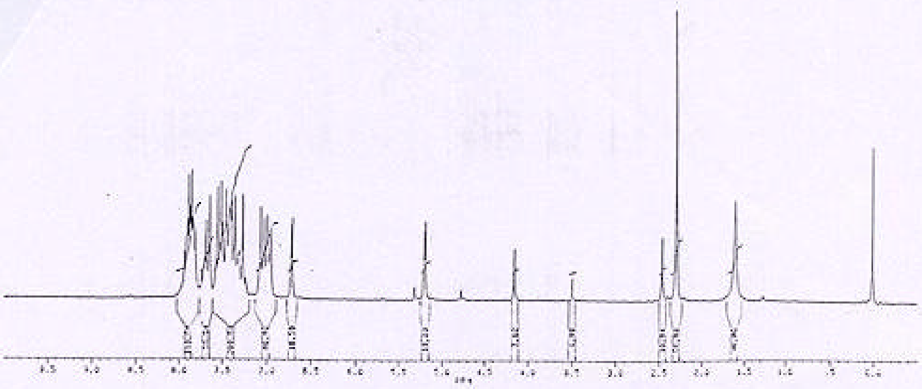
N
Ph
O
O
O
N
Ph

1.6g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6.0
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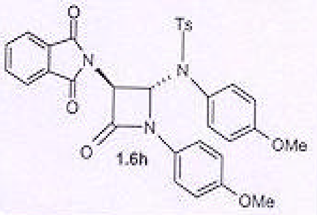
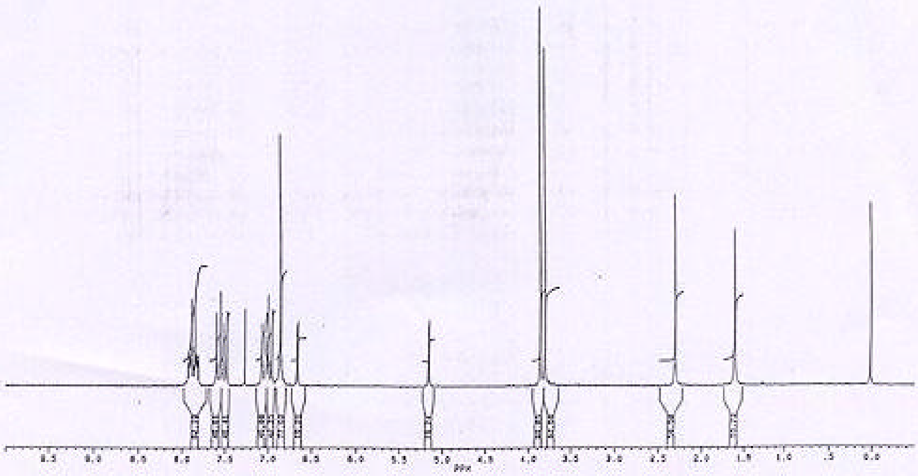
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
ppm


Ts
N
O
O
O
N
OMe
OMe

1.6h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1.5
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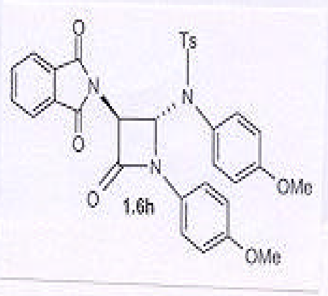
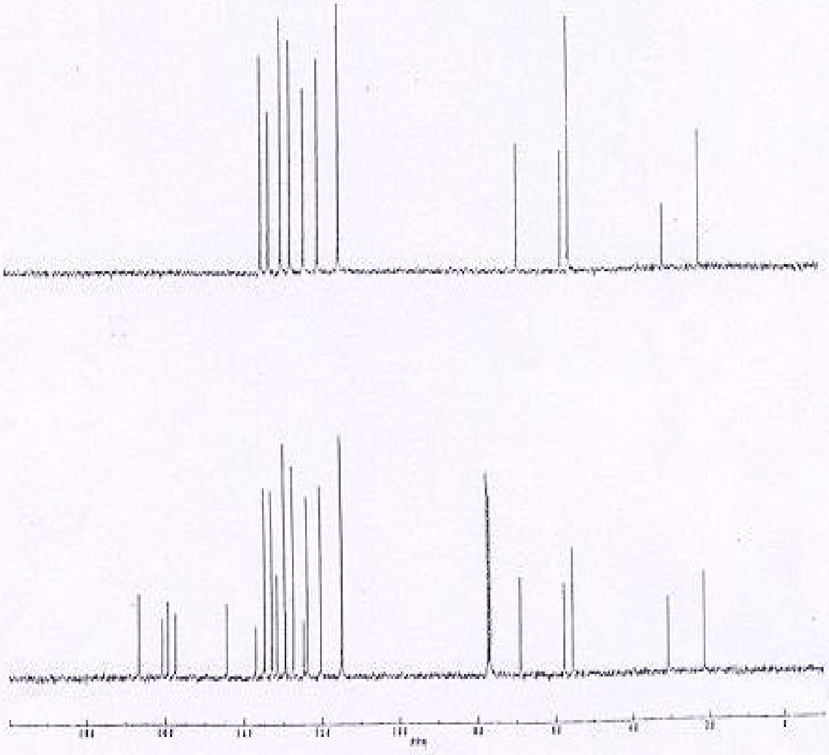
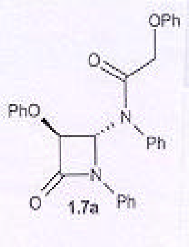
0.0
ppm

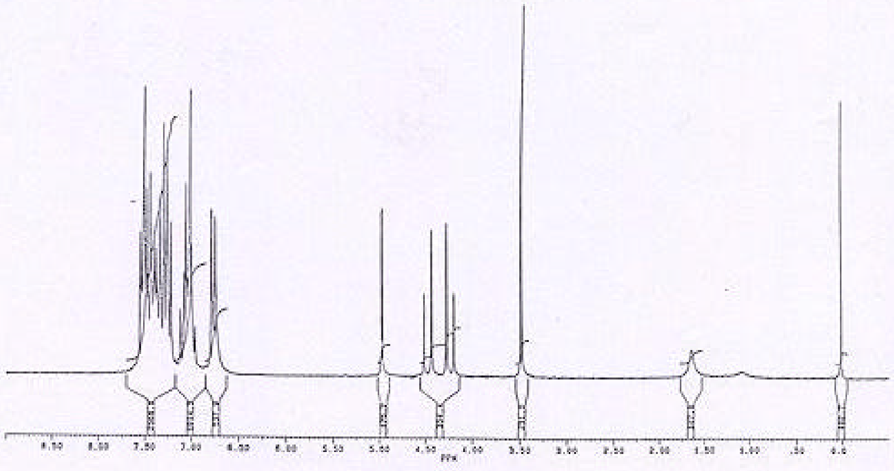

O
Ts
N
N
O
O
N
OMe
OMe

1.6h




OPh
O
N
PhO
Ph
O
N
Ph

1.7a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2.50
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1.50
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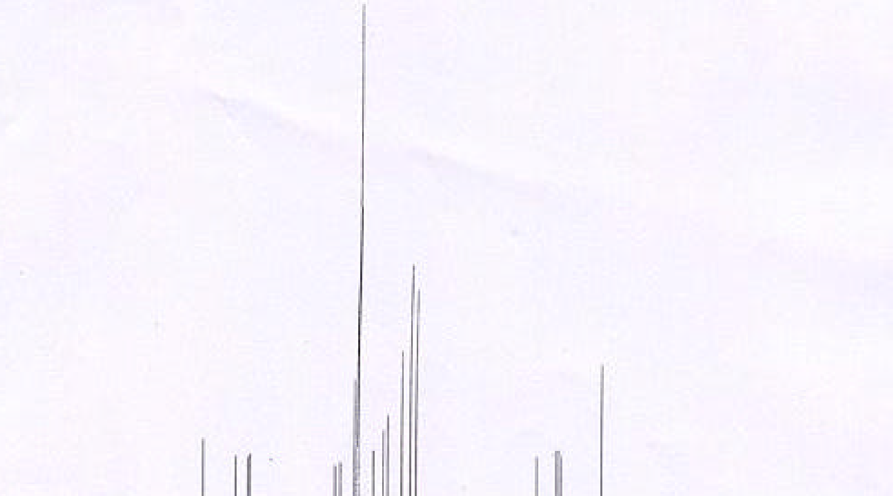
.50
0.0
PPM


210
200
190
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140
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120
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100
90
80
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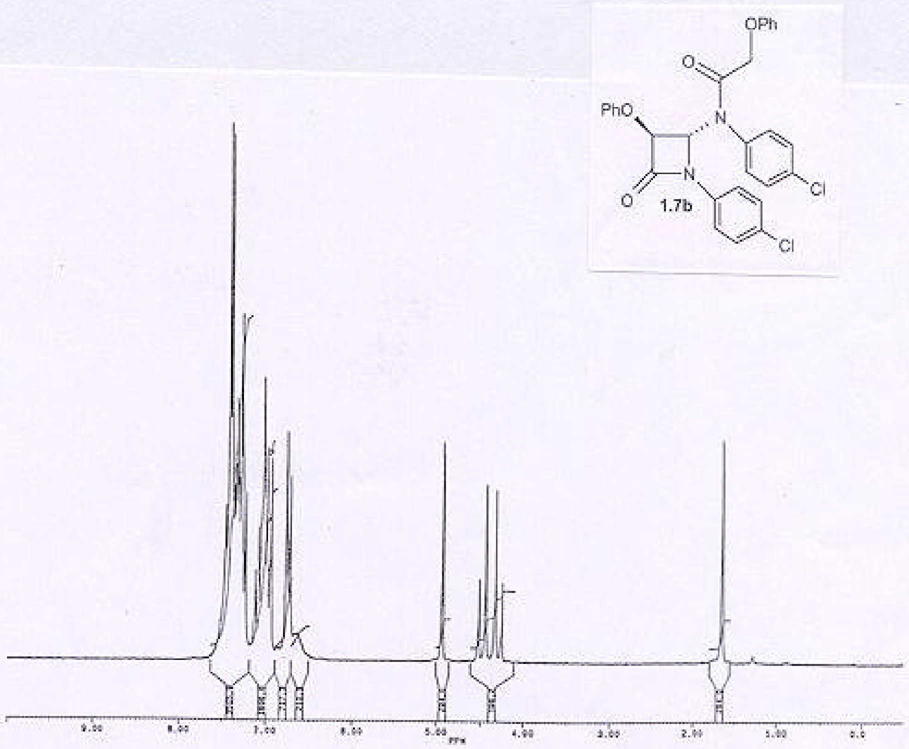
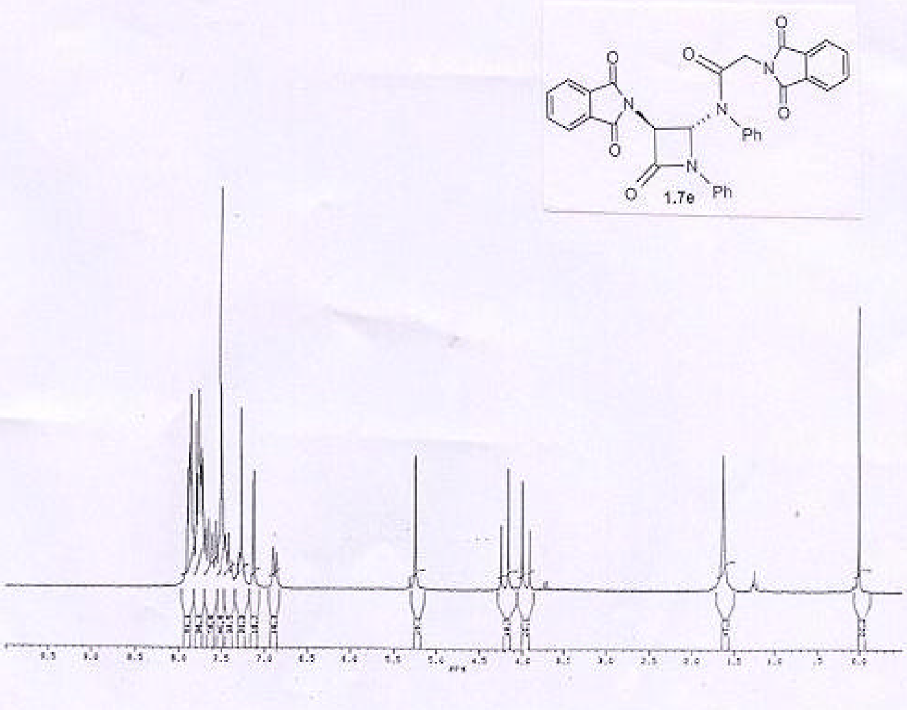
60
50
40
30
20
10
0
PPM


1.7b
OPh
PhO
N
O
Cl
Cl
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


1.7e
O
N
Ph
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8.5
8.0
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6.5
6.0
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.5
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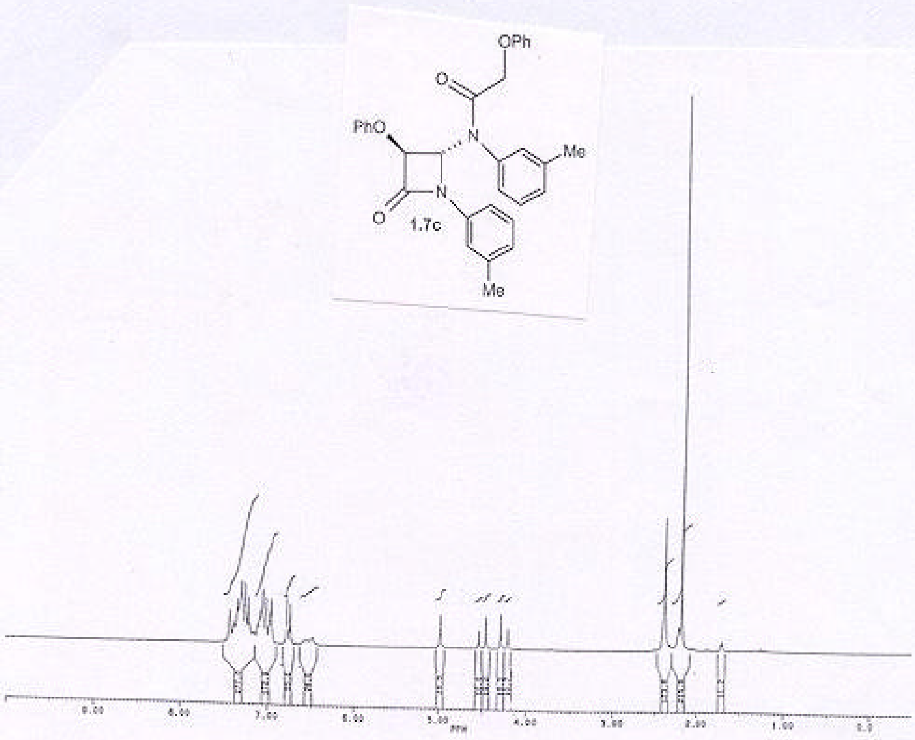
PPM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PhO
N
Me
O
N
Me
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7.00
6.00
5.00
PPM
4.00
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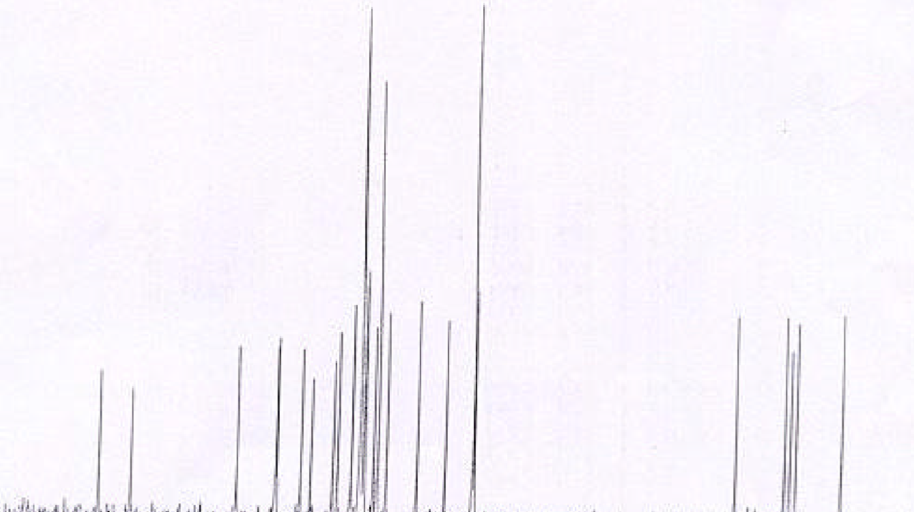
2.00
1.00
0.0

1.7c


170
165
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PPM
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105
100
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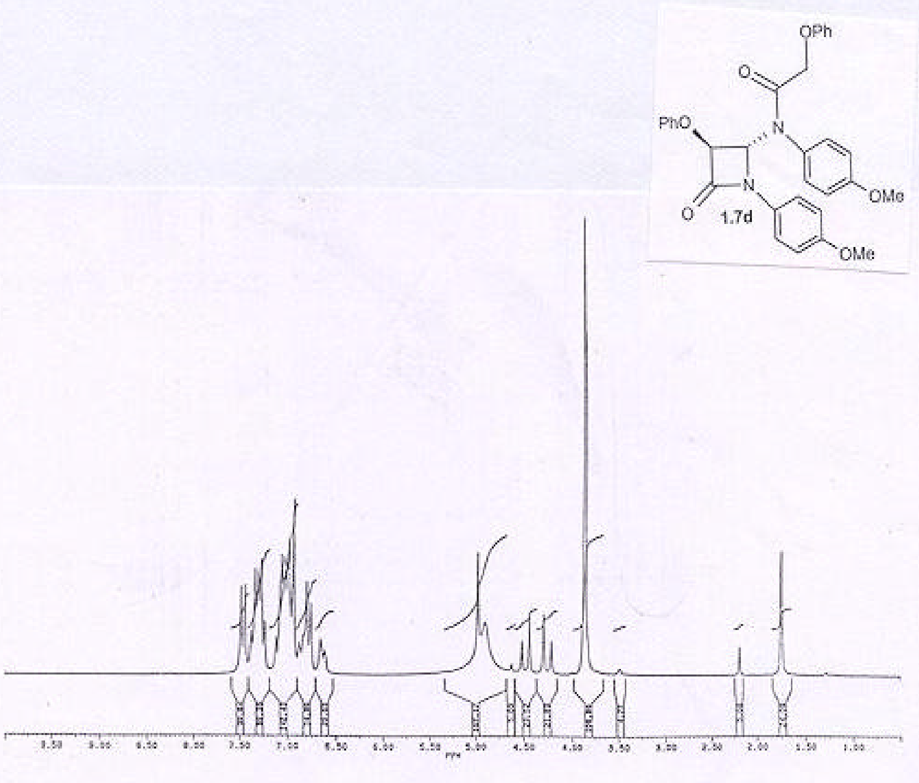
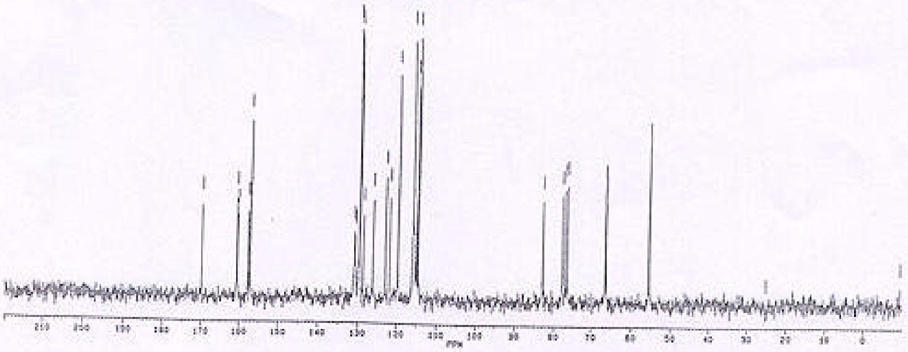
85
80
75
70
65


OPh
O
PhO
N
N
O
OMe
OMe
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
PPM

1.7d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190
180
170
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120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

Chapter II

Diastereoselective synthesis of b-Lactams using Glucose derived chiral aldehydes via asymmetric Staudinger reaction.

2.1 : Abstract

This chapter deals with the diastereospecific synthesis of β-lactams from chiral aldimines **2.5a-b** and **2.10** derived from D-(+)-glucose. The sterically demanding aldimines **2.5a-b** underwent [2+2] cycloaddition reaction with ketenes to provide a diastereomeric mixture of *cis* β-lactams. The other sterically demanding aldimine **2.10** underwent stereospecific [2+2] cycloaddition reaction with ketenes to provide exclusively single diastereomer of *cis* β-lactams. The *cis* stereochemistry was ascertained from the coupling constants of the C-3 and C-4 ring protons (5-6 Hz). The X-ray crystallographic studies of the β-lactam (**2.7a**) were determined and the relative configuration at C-3 and C-4 positions of the β-lactam were established from the known absolute configuration of the sugar moiety and was found to be 3S and 4R.

2.2 : Introduction

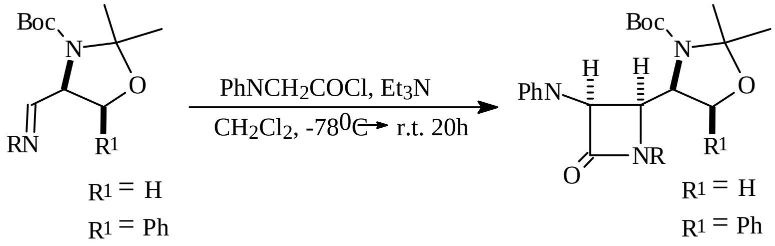
Carbohydrates, a cheap and naturally occurring *chiral pool*, have been extensively used as a chiral auxiliary for the synthesis of various optically active natural products.[2] The carbohydrate derived chiral auxiliaries have also been used for the synthesis of unnatural amino acids *via* opening of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

Staudinger reaction (ketene-imine cycloaddition reaction) is the most attractive and widely used method in *b*-lactam ring construction. The asymmetric version of this reaction involves the use of either chiral imines or chiral ketenes as chiral components in introducing asymmetry in the *b*-lactam ring construction (for detail discussion see Chapter 1). Among the chiral imines, the possible combination can be chiral aldehyde and achiral amine or chiral amine and achiral aldehyde.

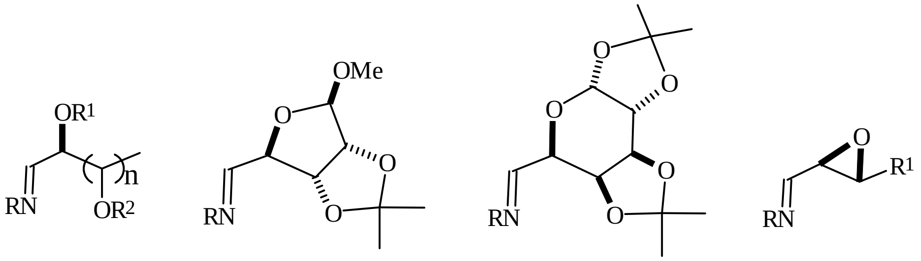
The chiral imines, derived from chiral aldehydes and achiral amines are the most effective for introducing asymmetry in the asymmetric Staudinger reaction. Generally, these imines give very high level of diastereoselectivity in the cycloaddition reaction. Among the useful chiral imines, the N,O- protected aldimines are the most efficient ones (*Scheme 1*).[3]

Scheme 1


Boc
N
O
RN
R1
R1 = H
R1 = Ph
PhNCH2COCl, Et3N
CH2Cl2, -78°C → r.t. 20h
PhN
H
H
Boc
N
O
NR
O
R1
R1 = H
R1 = Ph

The most common approaches in the Staudinger reaction involve the use of α-oxyaldehydes derived imines, sugar derived imines and α,β-epoxyimines (*Chart 1*).[4]

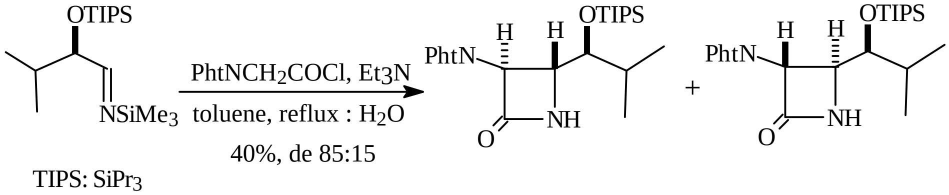
Chart 1


OR1
RN
n
OR2
OMe
O
O
RN
O
O
O
O
RN
O
O
O
R1
RN

In all these cases generally the formation of *cis*-*b*-lactams was observed and *cis*-diastereomers are usually obtained in ratios higher than 90:10.

Recently, Panunzio and co-workers have reported a case of *trans*-stereoselectivity preference in cycloaddition reaction. The method involves the reaction of phthalimidoacetyl chloride with N-trimethylsilyl imines and trimethylamine under toluene reflux conditions (*Scheme 2*).[5]

Scheme 2


OTIPS
NSiMe3
TIPS: SiPr3
PhtNCH2COCl, Et3N
toluene, reflux : H2O
40%, de 85:15
PhtN
H
H
OTIPS
O
NH
+
PhtN
H
H
OTIPS
O
NH

According to the proposed mechanism the cycloaddition step involves intermediate as shown in Fig. 1.

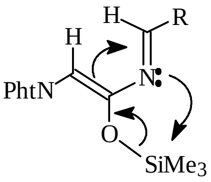


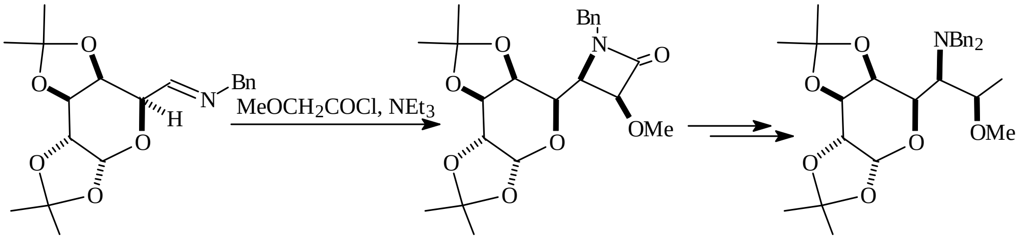
Fig. 1

Carbohydrate derived chiral auxiliaries:

Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as a chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[6] Though carbohydrates contain up to five stereogenic centers with lots of stereochemical information, they are at the same time “over functionalized” for them to be successfully applicable as stereodifferentiating groups.

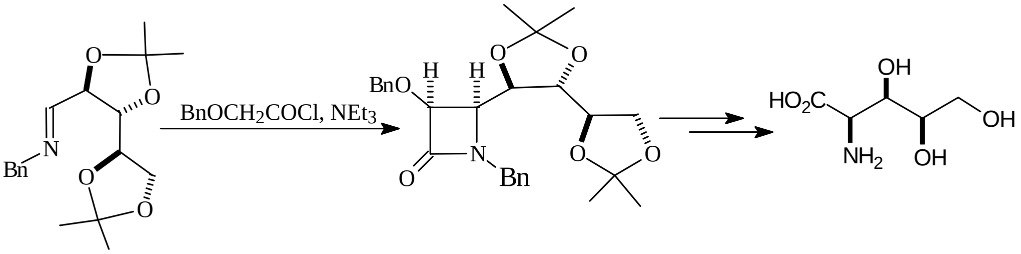
The use of carbohydrates in the asymmetric synthesis of β-lactams is now well known. Bose & Manhas[7] have reported successful utilization of chiral imines derived from carbohydrates in the asymmetric Staudinger reaction. They synthesized different chiral auxiliaries derived from sugars and successfully employed them as chiral imine components. These chiral imines proved to be extremely efficient and always a very high level of diastereoselectivity (de >90%) was obtained. They mainly use these β-lactams as a chiral synthons rather than chiral pool, and utilized the carbohydrate skeleton for the synthesis of important natural products. A single *cis*-diastereomer was obtained from the reaction of carbohydrate derived chiral imine and methoxy-ketene (*Scheme 3*). On further synthetic transformation this isomer was converted into 6-*epi*-lincosamine.[8]

Scheme 3



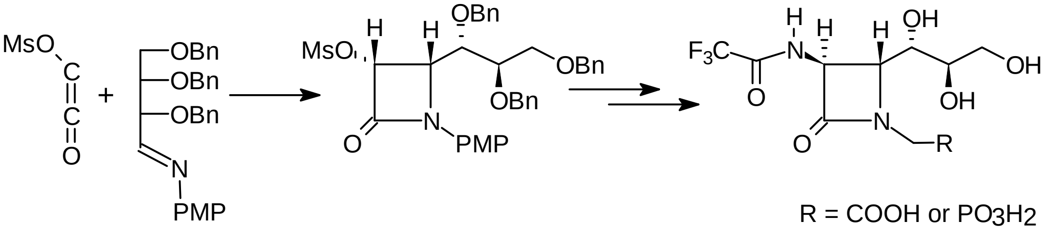
Similarly, the cycloaddition reaction of benzyloxyketene with the imine proceeded *cis*-*b*-lactam with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, a enantiomer of the component of the antifungal polyoxin antibiotic (*Scheme 4*).[9]

Scheme 4


BnOCH2COCl, NEt3
Bn
N
O
O
O
O
BnO
H
H
N
Bn
O
HO2C
OH
OH
NH2
OH

Recently Stortz et. al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-manonoic acid derivatives (*Scheme 5*).[10]

Scheme 5


MsO
C
C
O
+
OBn
OBn
OBn
N
PMP
MsO
H
H
OBn
OBn
OBn
N
PMP
O
F3C
O
H
N
H
H
OH
OH
OH
N
R
O
R = COOH or PO3H2

Mechanism:

The extremely high diastereoselectivity obtained with the chiral aldehydes is intriguing. Attempts are made to rationalize the origin of such a high level of asymmetric induction using theory of molecular mechanics. In the similar studies, Palomo and coworkers have examined the aspects of highly stereoselective cycloaddition of N-protected aldehyde to the ketene components at the molecular mechanics level (*fig 2*). The AM1 calculated transition states in the formation of *cis*-(3*R*, 4*S*) and *cis*-(3*S*, 4*R*)-4-[(*S*)-1-aminoethyl]-3-methoxyazetidin-2-ones are quite decisive.

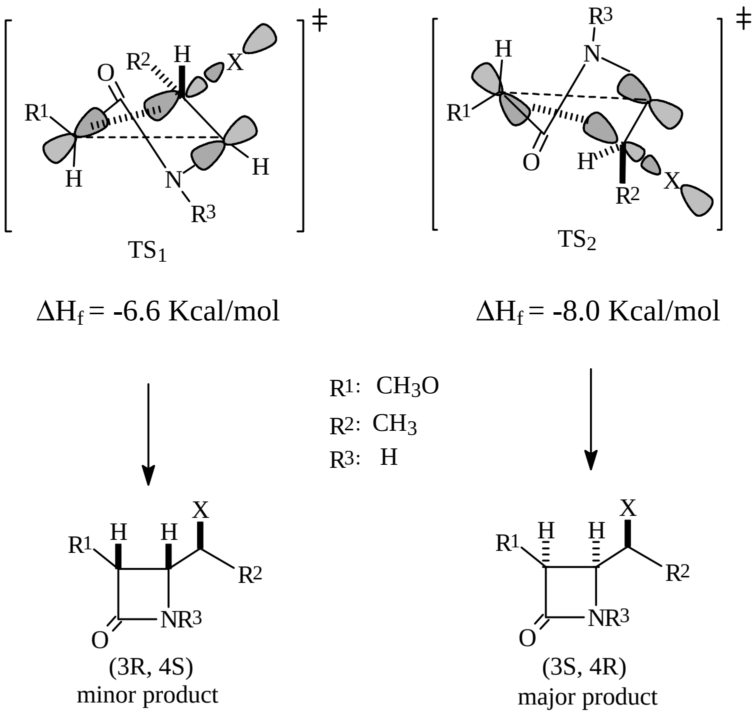
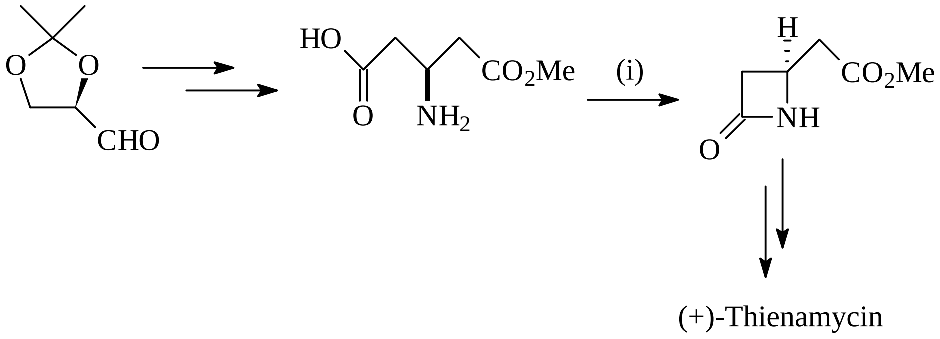

TS1
ΔHf = -6.6 Kcal/mol
TS2
ΔHf = -8.0 Kcal/mol
R1: CH3O
R2: CH3
R3: H
(3R, 4S)
minor product
(3S, 4R)
major product

Fig. 2

In case of TS$_1$, there is angular arrangement between C3 and the exocyclic C-X bond, while linear arrangement exists between the same atoms in TS$_2$. So there is a steric interaction between the methyl group (R$_2$) and the *b*-lactam ring. Such kind of interaction is absent in the case of TS$_2$. As a result, there is effective HOMO-σ* stabilization and the product obtained is major one.

The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into β-amino ester, which on cyclization[11] with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubtituted β-lactam (*Scheme 6*). This β-lactam has been converted into (+)-thienamycin in several steps.

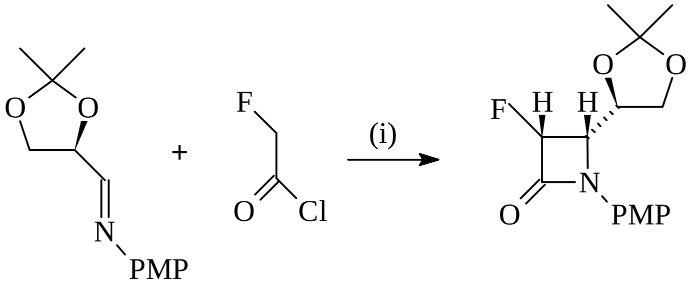
Scheme 6


CHO
HO
O
NH2
CO2Me
(i)
H
NH
O
CO2Me
(+)-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[12] (Staudinger reaction) reaction with the ketene obtained from flouroacetyl chloride in presence of triethylamine to give diastereospecifically only one β-lactam in 68% yield *(Scheme 7).*

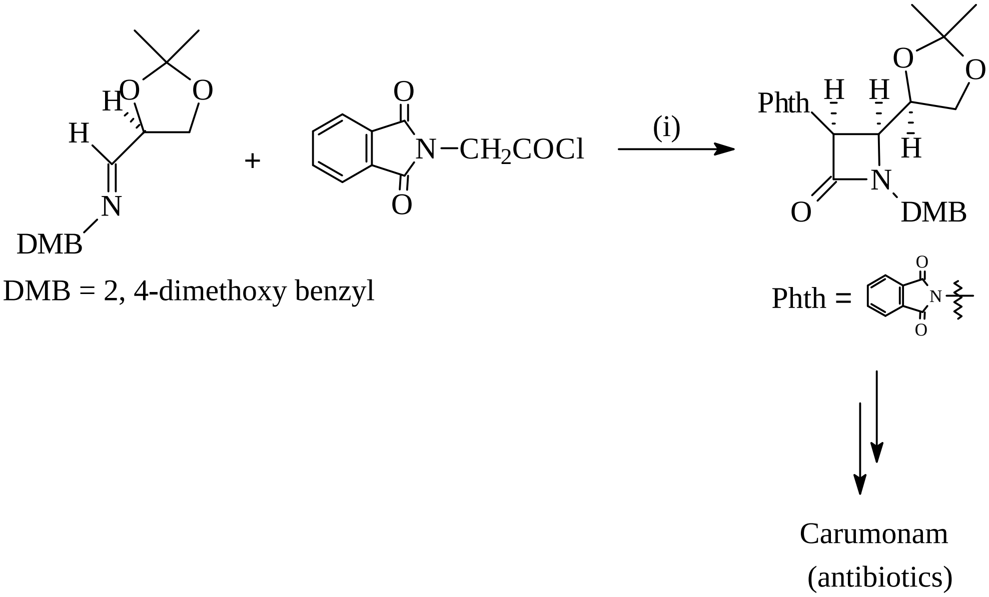
Scheme 7


O
O
N
PMP
+
F
O
Cl
(i)
F
H
H
O
O
O
N
PMP

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

The imine derived from L-(S)-glyceraldehyde and 2,4-dimethoxybenzyl-amine, and phthalimidoaetyl chloride underwent Staudinger reaction[13] to give β-lactam, which is a key intermediate for the synthesis carumonam antibiotics *(Scheme 8).*

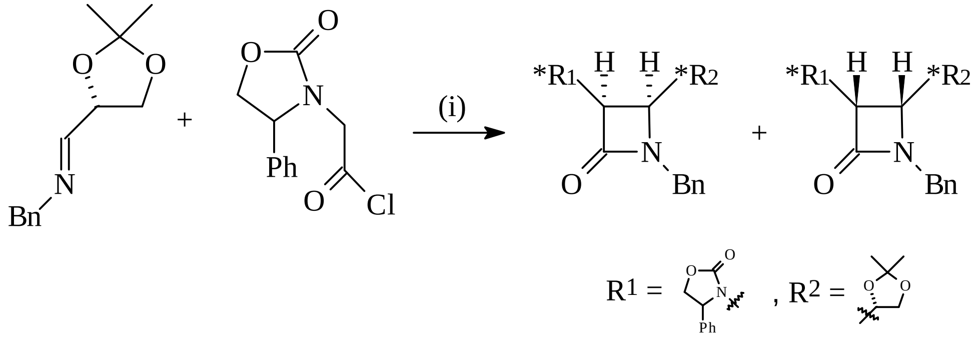
Scheme 8


H
O
O
H
N
DMB
DMB = 2, 4-dimethoxy benzyl
+
O
N−CH2COCl
O
(i)
Phth
H
H
O
O
H
O
N
DMB
Phth =
O
N
O
Carumonam
(antibiotics)

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

J. Palomo et al[14] 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 9).*

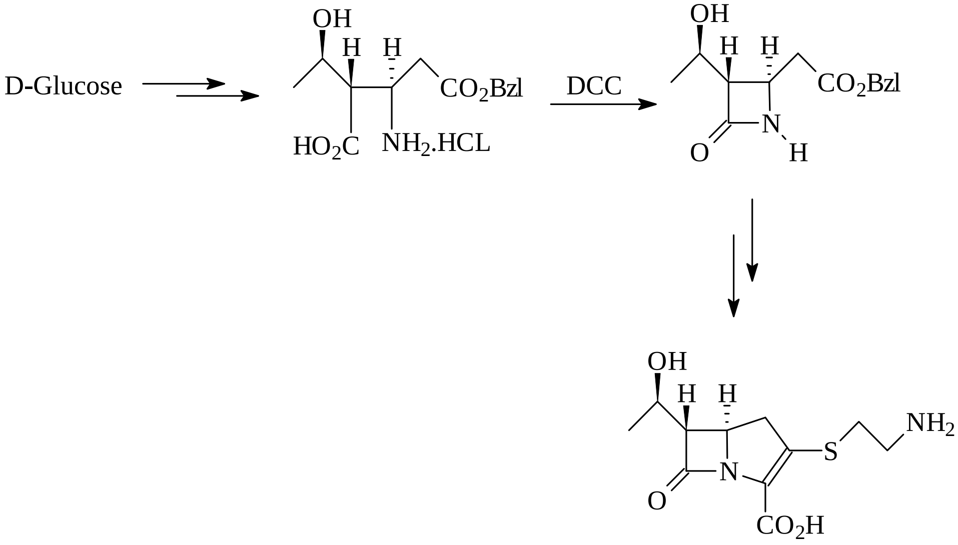
Scheme 9


O
O
N
Bn
+
O
O
N
Ph
O
Cl
(i)
*R1
H
H
*R2
O
N
Bn
+
*R1
H
H
*R2
O
N
Bn
R1 =
O
O
N
Ph
, R2 =
O
O

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

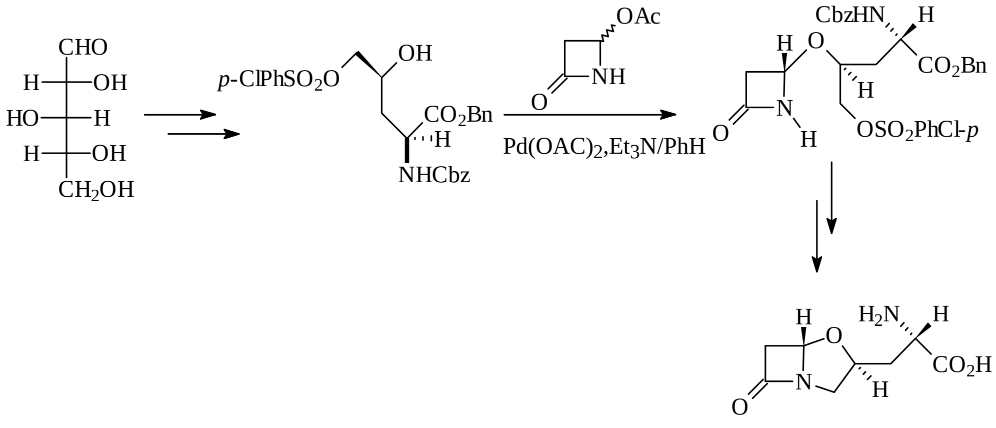
The β-amino acid, derived from D-glucose on cyclization[15] in presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotics in several steps *(Scheme 10).*

Scheme 10


D-Glucose
OH
H
H
CO2Bzl
HO2C
NH2.HCL
DCC
OH
H
H
CO2Bzl
O
N
H
OH
H
H
O
N
S
NH2
CO2H

A chiral amino alcohol derived[16] 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 11).*

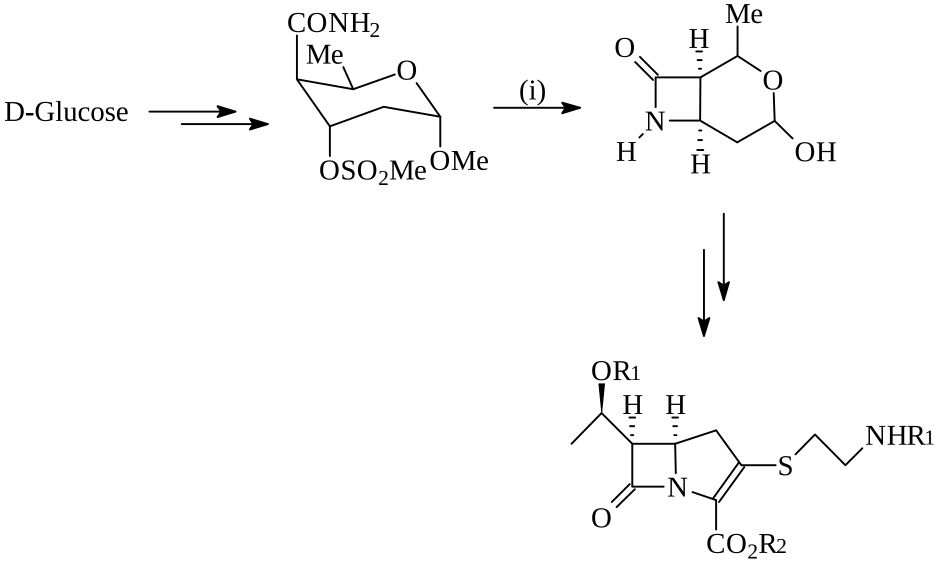
Scheme 11


CHO
H OH
HO H
H OH
CH2OH
p-ClPhSO2O
OH
CO2Bn
H
NHCbz
OAc
NH
O
Pd(OAC)2,Et3N/PhH
CbzHN
H
O
CO2Bn
N
OSO2PhCl-p
H2N
CO2H

Ro 22-5417

The amide derived from D-glucose has been cyclised[17] in presence of potassium *tert*-butoxide, to give bicyclic β-lactam in 45% yield. This bicyclic β-lactam has been transformed into 6-epithienamycin in a multi steps process *(Scheme 12).*

Scheme 12

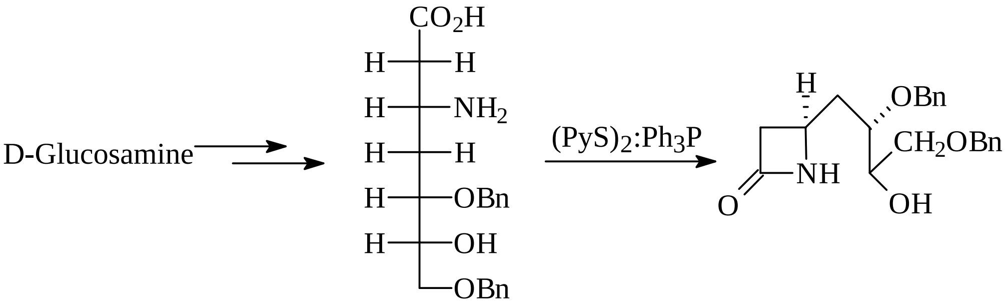

D-Glucose
CONH2
Me
O
OSO2Me
OMe
(i)
Me
O
H
N
OH
OR1
S
NHR1
CO2R2

6-Epithienamycin

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

The β-amino acid derived[18] from D-glucosamine has been cyclised to N-unsubstituted β-lactam in presence of 2,2'-dipyridyl disulfide and Ph_3P. This N-unsubstituted β-lactam serves as an intermediate for the synthesis of (+)- thienamycin *(Scheme 13)*

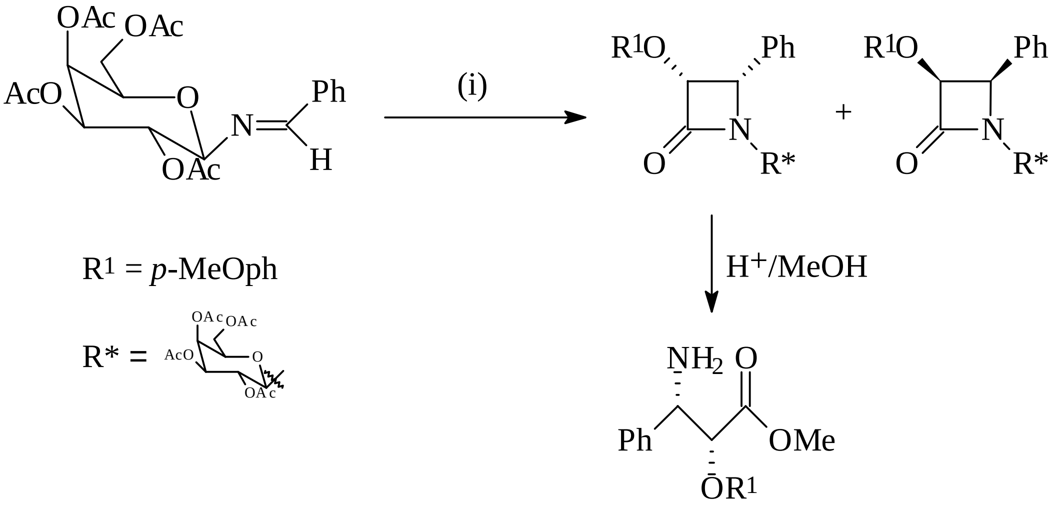
Scheme 13



D-Glucosamine
CO_2H
H
H
NH_2
H
OBn
OH
OBn
$(PyS)_2$:Ph_3P
H
OBn
CH_2OBn
NH
O
OH

Georg. G. I et al[19] 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 14)*.

Scheme 14

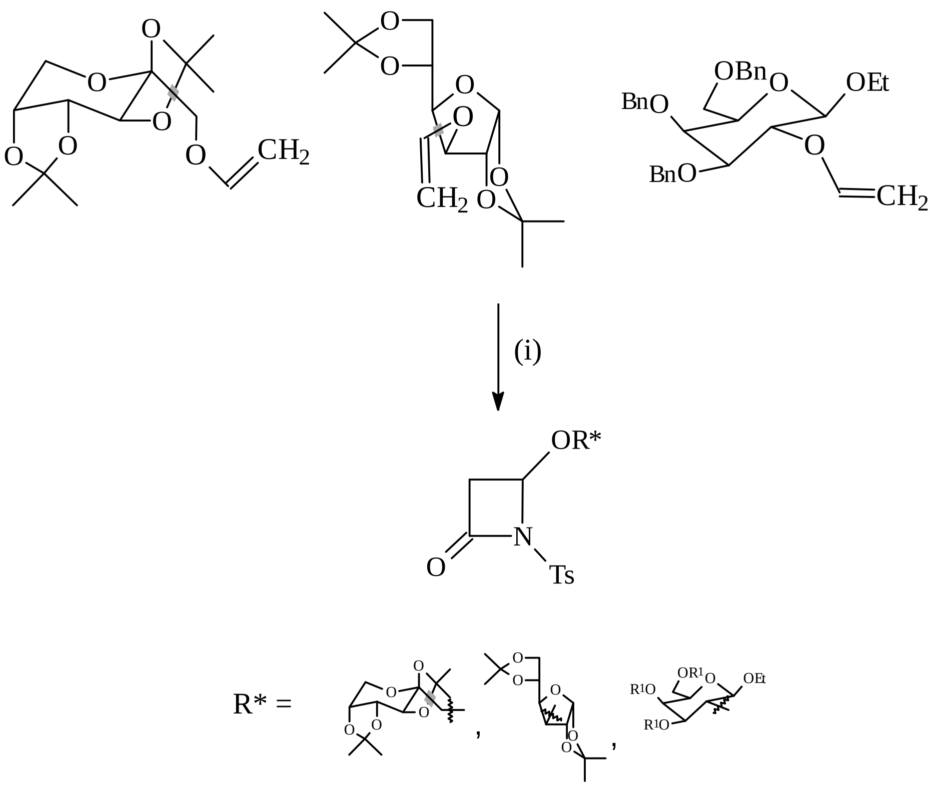


OAc
OAc
AcO
O
OAc
N
Ph
H
(i)
R^1O
Ph
N
O
R*
+
R^1O
Ph
N
O
R*
H^+/MeOH
R^1 = *p*-MeOph
R* =
OAc
OAc
AcO
O
OAc
NH_2
O
Ph
OMe
OR^1

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

The vinyl ethers derived[20a] 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 15)*.

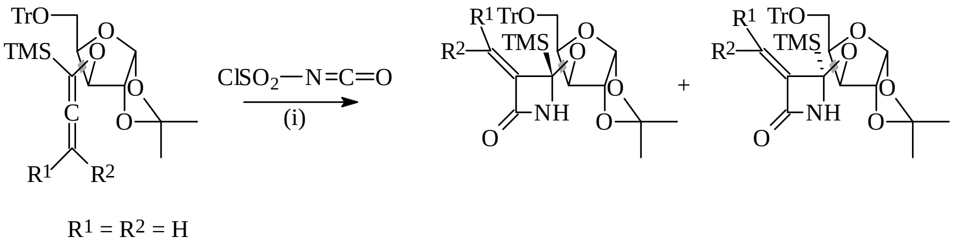
Scheme 15



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[20b] *(Scheme 16).*

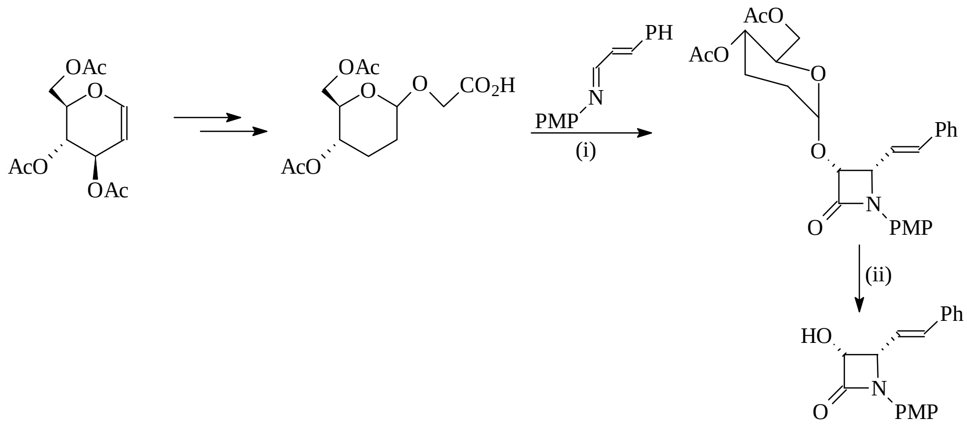
Scheme 16



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

B. C. Borer et al[21] have used tri-O-acetyl-D-glucal derived chiral acid as ketene precursor for diastereoselective synthesis of β-lactams *(Scheme 17).* 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 17


OAc
O
AcO
OAc
OAc
O
O
CO2H
AcO
PH
N
PMP
(i)
AcO
AcO
O
O
Ph
N
O
PMP
(ii)
HO
Ph
N
O
PMP

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

2.3 : Present Work

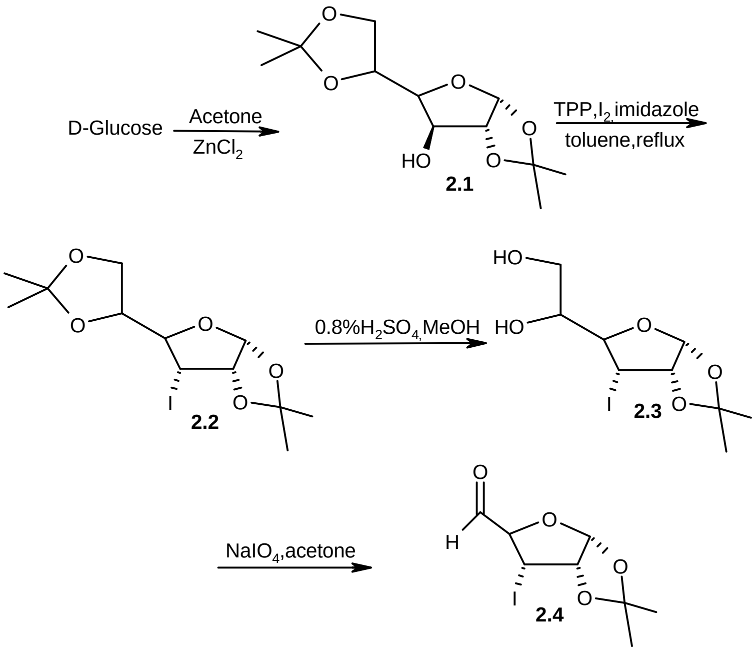
Earlier reports have clearly indicated that the use of homochiral aldehydes in most of the cases resulted in the complete stereo control in the *Staudinger reaction*. It has also been postulated that in the asymmetric *Staudinger reaction* a high level of diastereoselectivity is attained only when a chiral center is α to the imino-group, particularly if it is attached to a heteroatom such as oxygen or nitrogen. Hence we decided to use sterically hindered aldehydes derived from D-glucose, to study the diastereoselectivity in the asymmetric *Staudinger reaction*.

2.4 : Results & Discussion

Preparation of the aldehyde 2.4

The aldehyde **2.4** was prepared from D-glucose in good yields following reported[22-24] procedures *(Scheme 18).*

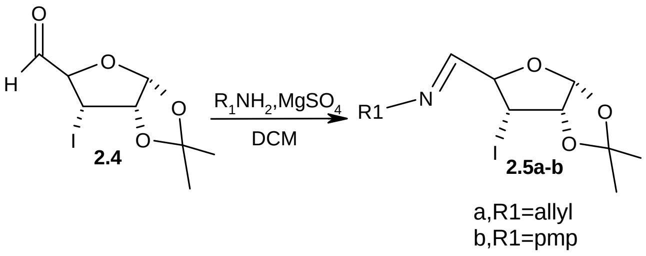
Scheme 18


D-Glucose
Acetone
ZnCl2
HO
2.1
TPP,I2,imidazole
toluene,reflux
I
2.2
0.8%H2SO4,MeOH
HO
HO
2.3
NaIO4,acetone
H
2.4

Preparation of the imines 2.5a,b

The imines **2.5a,b** were prepared by treating the aldehyde **2.4** with various amines (p-anisidine, ally amine) in CH_2Cl_2 at room temperature in presence of $MgSO_4$ *(Scheme 19).* After completion of the reaction (TLC), the reaction mixture was filtered and the filtrate on concentration provided imines in quantitative yields. These imines were used as such for the next step.

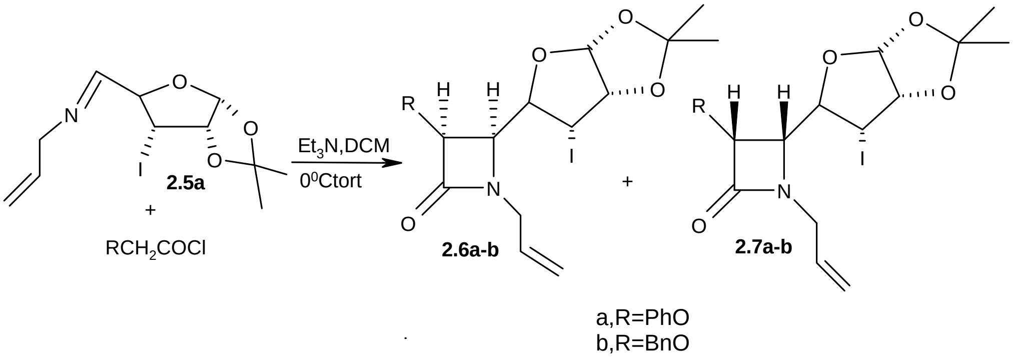
Scheme 19


O
H
O
O
I
O
2.4
R1NH2,MgSO4
DCM
R1
N
O
O
I
O
2.5a-b
a,R1=allyl
b,R1=pmp

Preparation of b-lactam 2.6a-b & 2.7a-b

A solution of various acid chlorides (phenoxy and benzyoxy) in anhydrous methylene chloride was added to a solution of the imine **2.5a** and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere. The resulting mixture was allowed to warm up to room temperature and stirred for 15 hrs. After the usual workup the resulting compound gave a diastereomeric mixture of *cis*-β-lactams (**2.6a-b** & **2.7a-b**) in the ratio of 50:50, in good yields *(Scheme 20).* The diastereomers were separated by column chromatography.

(Scheme 20)


N
O
O
I
O
2.5a
+
RCH2COCl
Et3N,DCM
0⁰Ctort
R
H
H
O
N
O
O
O
I
2.6a-b
+
R
H
H
O
N
O
O
O
I
2.7a-b
a,R=PhO
b,R=BnO

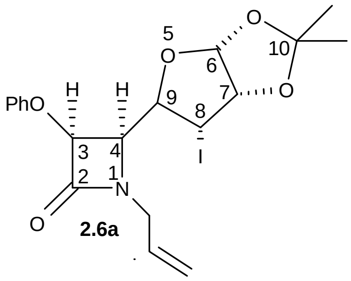
The *b*-lactam **2.6a** was selected for detailed discussion of preparation and structural assignment, which is presented below:

Synthesis of 2.6a

The imine **2.5a** on treatment with phenoxyacetyl chloride in presence of triethylamine underwent ketene-imine cycloaddition reaction to give diastereomeric mixture of *cis*-β-lactams (**2.6a** & **2.7a**) in the ratio of 50:50 in 70% yield. The diastereomers were separated by flash column chromatography.

The β-lactam **2.6a** was isolated as white solid with mp 89 °C. The IR spectrum of this compound showed a strong band at 1766.67 cm^{-1} indicating the presence of the carbonyl group of β-lactam ring.

The ^1H NMR spectrum showed two singlets at 1.35 and 1.45 for methyl protons of acetonide group of sugar. The anomeric proton H-6 shows a doublet at 5.77 with J=3.6 Hz. The proton H-7 adjacent to the anomeric proton appeared at 4.6 as a triplet with J=3.6 Hz. The proton H-8 shows dd at 3.9 with J=3.6 and 4.4 Hz. The proton H-9 shows dd at 4.46 with J=3.1 and J=3.6 Hz.



2.6a

The β-lactam ring proton H-4 appeared as a dd at 4.24 with J=3.1 and 4.7 Hz. One of the methylene proton of the allyl group appeared as a multiplet at 4.19-4.23. The H-3 proton of the β-lactam ring showed doublet at 5.36 with J=4.7 Hz. Other methylene proton of the allyl group appeared as dd at 3.81 with J=6.8 and 7.2 Hz. The terminal olefinic protons of the allyl group appeared as multiplets between 5.26-5.33 and the other olefinic proton resonated as a multiplet, slightly downfield, in the region of 5.78-5.87. The aromatic protons appeared in the region 7.0-7.4.

Decoupling Experiments were carried out to establish the connectivity among adjacent protons. When the proton H-7 was decoupled at 4.6, the doublet due to the anomeric proton H-6 at 5.77 collapsed into a singlet and the dd due to the proton H-8 at 3.9 collapsed into a doublet. When the β-lactam proton H-4 at 4.24 was decoupled, the dd due to the proton H-9 at 4.46 collapsed into a doublet and the doublet due to the β-lactam proton H-3 at 5.36 collapsed into a singlet. These experiments supported above ^1H NMR spectral assignments to β-lactam **2.6a**.

The structure for β-lactam **2.6a** was further confirmed from its two dimensional COSY NMR spectral analysis (Fig. 1, Table 1).

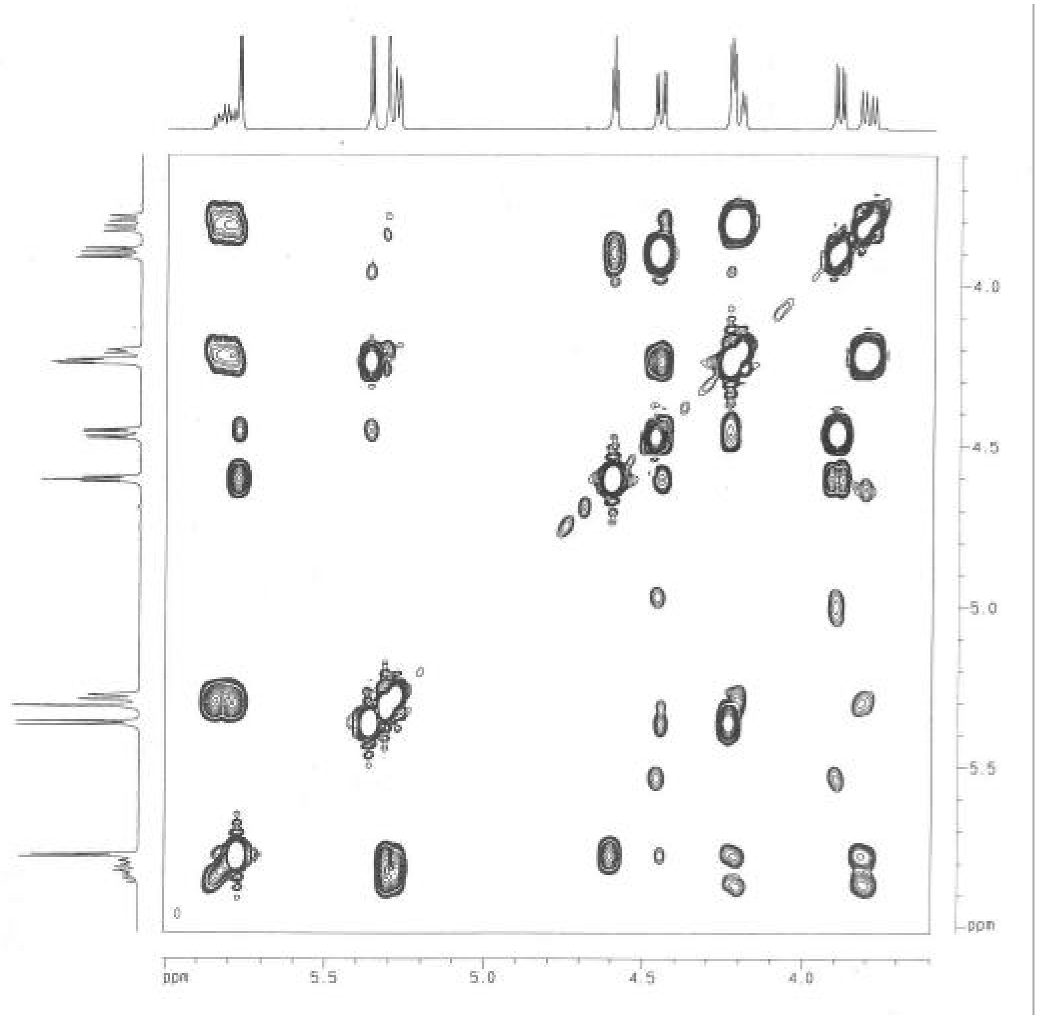
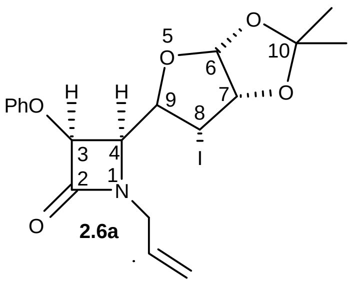


Fig 1. COSY NMR spectrum of **2.6a** (selected region shown)

Table 1. Important connectivities in the COSY NMR of **2.6a**.

Proton	δ (ppm)	*J (Hz)*	*^1H-^1H connectivity*
H-6	5.77 (d)	3.6	H-7
H-7	4.6 (t)	3.6	H-6, H-8
H-8	3.9 (dd)	3.6, 4.4	H-7, H-9
H-9	4.46 (dd)	3.1,3.6	H-8, H-4
H-4	4.24 (dd)	3.1, 4.7	H-9, H-3
H-3	5.36 (d)	4.7	H-4



2.6a

In the COSY NMR spectrum (Table 1), the anomeric proton H-6 shows a strong coupling with H-7. The proton H-7 was further connected with the proton H-8. The H-8 further showed connectivity with H-9. The H-9 showed strong interaction with the β-lactam proton H-4. The H-4 further showed connectivity with the *b*-lactam proton H-3.

The spatial arrangement among different protons was confirmed from the NOESY spectrum of **2.6a** (Fig 2). The NOESY spectrum of **2.6a** showed spatial interaction of H-6 with H-8, indicates protons, H-6, H-7 and H-8 are on the same side of the molecule.

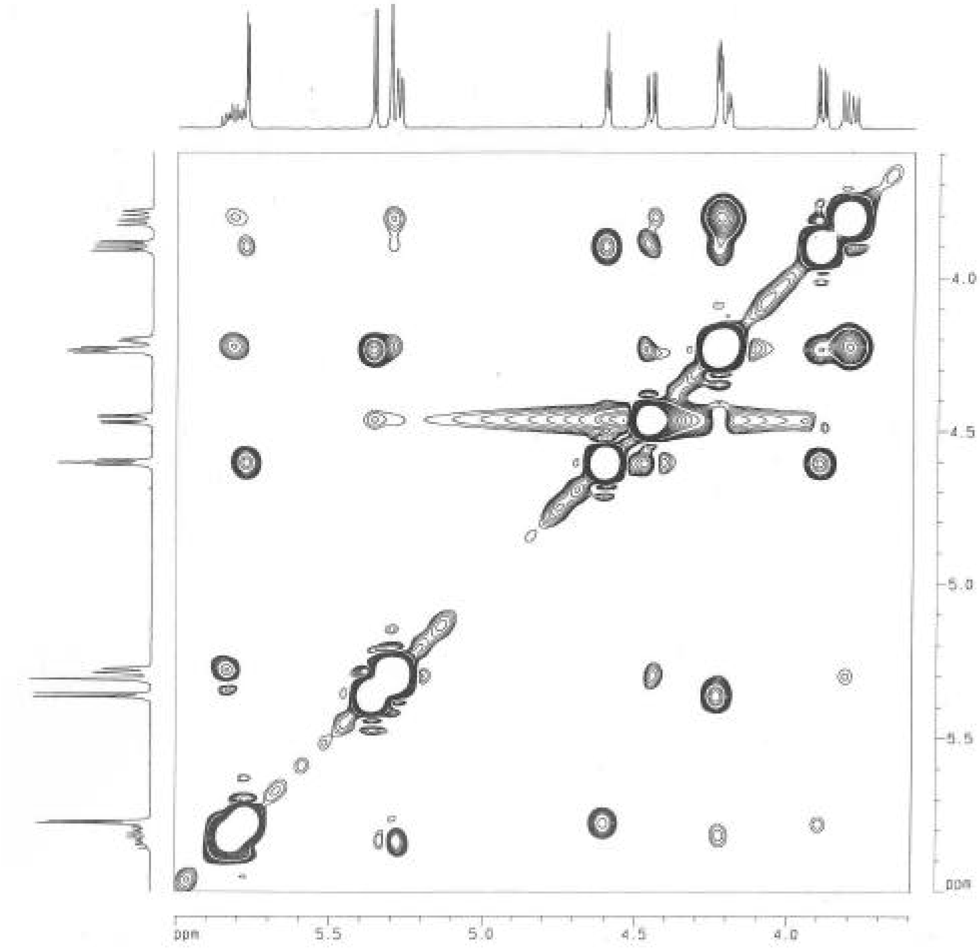


Fig 2. NOESY spectrum of **2.6a** showing spatial connectivities.

In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 165.32. The methine carbon bearing the iodo group appeared at 21.94. The two methyls of the acetonide group attached to the C-10 carbon appeared at 26.22 and 26.55. The methylene carbon from the allyl group appeared at 44.37. The β-lactam carbons, C-4 appeared at 56.37. The β-lactam carbons C-3 and the chiral backbone C-7, C-9 appeared at 78.71, 79.81, and 80.51. The anomeric carbon C-6 appeared at 103.09. The quaternary C-10 carbon of the acetonide group appeared at 111.79. The terminal olefin carbon of the allyl group appeared at 118.93.The aromatic carbons appeared in the region 115.52 to 157.08.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 471 (100%), which is also the base peak.

The β-lactam **2.7a** was isolated as white solid, mp 113 °C. The IR spectrum of this compound showed a strong band at 1770.53 cm^{-1}, which was assigned to the carbonyl group of β-lactam ring. The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.35 and 1.45. The other protons appeared in their usual regions and were consistent with the structure of the compound. In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 165.74. The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 471 (100%), as a base peak.

The 3*R*, 4*S* absolute stereochemistry was established for β-lactam ring protons of **2.7** based on the known absolute stereochemistry of carbohydrate residue by the single crystal X-ray analysis of **2.7a** (Fig. 3).

X-ray Crystallographic Data of 2.7a

X-Ray diffraction study. X-Ray Structure determination of $C_{19}H_{22}INO_5$: Colorless needles (0.40 x 0.16 x 0.13 mm grown from isopropanol). M = 471.28, orthorhombic, space group $P2_12_12_1$, *a* = 8.7798(5) Å, *b* = 17.7493(10) Å, *c* = 38.745(2) Å, , *V*=6037.9(6) Å^3, Z=12, *D*=1.555 g cm^{-3}, μ=1.619 mm^{-1}, *F*(000)= 2832, *T* = 293 K. Data were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 28.25°. The structure was solved by direct methods using SHELXTL. There are three molecules in the asymmetric unit. Least squares refinement of scale, positional and anisotropic thermal parameters for non hydrogen atom converged to R = 0.0572. Rw = 0.1130 for 35906 unique observed reflections out of 13169 reflections measured. Hydrogen atoms were geometrically fixed The refinements were carried out using SHELXL-97. Largest diff. peak and hole 1.145 and -0.386 e. Å $^{-3}$. ORTEP diagram of one the molecule with 50 % probability.

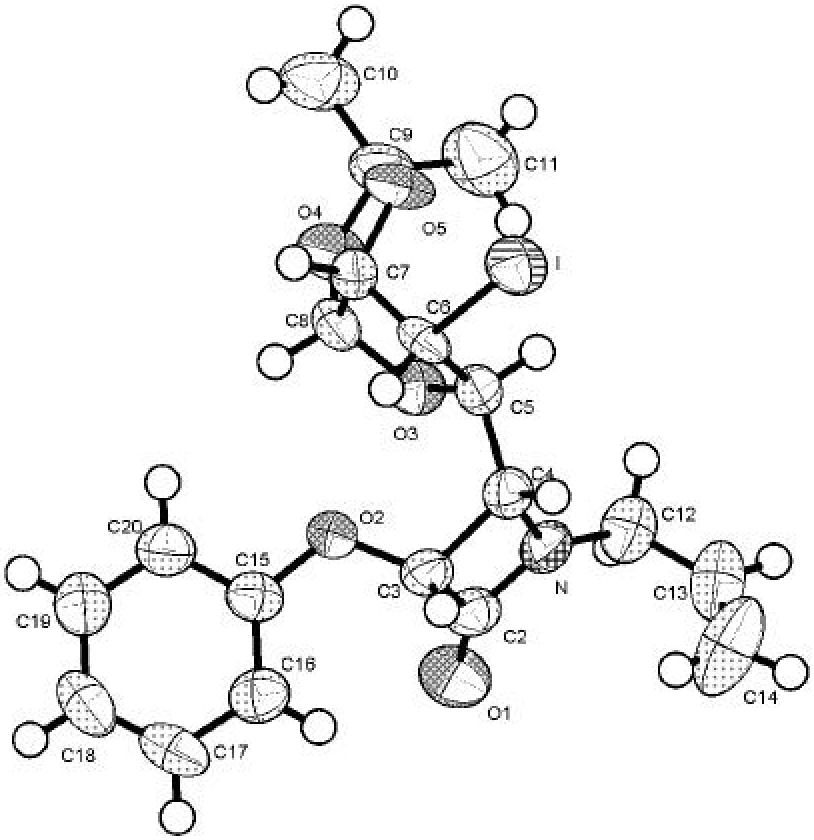
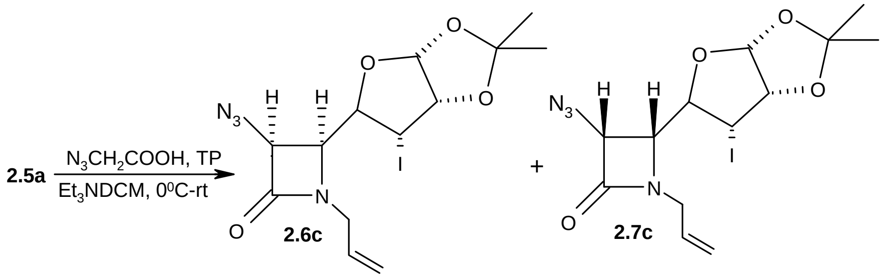

C10
C9
C11
O4
O5
I
C7
C6
C8
C5
O3
C4
O2
C20
C15
C12
C3
N
C13
C19
C2
C16
O1
C14
C18
C17

Fig. 3. ORTEP diagram of **2.7a**

Preparation of b-lactam 2.6c & 2.7c

A solution of triphosgene in anhydrous methylene chloride was added to a solution of the imine **2.5a**, azidoacetic acid, and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere. The resulting mixture was allowed to warm up to RT and stirred for 15 hrs. After the usual workup, the resulting crude product gave a diastereomeric mixture of *cis*-β-lactams (**2.6c** & **2.7c**) in the ratio of 50:50 in good yields (*Scheme 21*). The diastereomers were separated by column chromatography.

Scheme 21



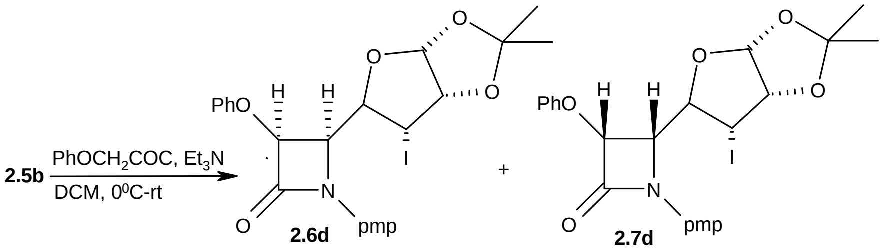
The IR spectrum of the compound **2.6c** showed bands at 1753.17, 2113.84 corresponding to the β-lactam carbonyl and the azido group respectively. The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.3 and 1.55. The other protons appeared in their usual regions and were consistent with the structure of the compound. In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 163.86. The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 420 (100%) as a base peak.

The IR spectrum of the compound **2.7c** showed bands at 1762.82, 2113.84 corresponding to the β-lactam carbonyl and the azido group respectively. The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.35 and 1.55. The other protons appeared in their usual regions and were consistent with the structure of the compound. In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 163.20. The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 420 (100%) as a base peak.

Preparation of b-lactam 2.6d & 2.7d

A solution of phenoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine **2.5b** and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere. The resulting mixture was allowed to warm up to room temperature and stirred for 15 hrs. After the usual workup the resulting compound gave a diastereomeric mixture of *cis*-β-lactams (**2.6d** & **2.7d**) in the ratio of 50:50 in good yields (*Scheme 22*). One of the diastereomer (**2.6d**) was separated by fractional crystallization from methanol.

Scheme 22



The β-lactam **2.6d** was isolated as white solid, mp 124 ^{o}C. The IR spectrum of this compound showed a strong band at 1743.53 indicating the presence of the carbonyl group of β-lactam ring.

The ^{1}H NMR spectrum showed methyl protons of the sugar ring as two singlets at 1.3 and 1.4. The anomeric proton H-6 showed a doublet at 5.85 with J=3.5 Hz. The proton H-7 adjacent to the anomeric proton appeared at 4.6 as a triplet with J=3.5 Hz. The proton H-8 shows dd at 3.9 with J=4.4 and 4.8 Hz. The H-4 proton of the β-lactam ring merged with the proton H-9 at 4.7-4.9. The H-3 proton of the β-lactam ring was seen as a doublet at 5.45 with J=5.4 Hz. The singlet at 3.8 could be assigned to the methyl protons of the PMP group. The aromatic protons appeared in the region 6.8-7.6.

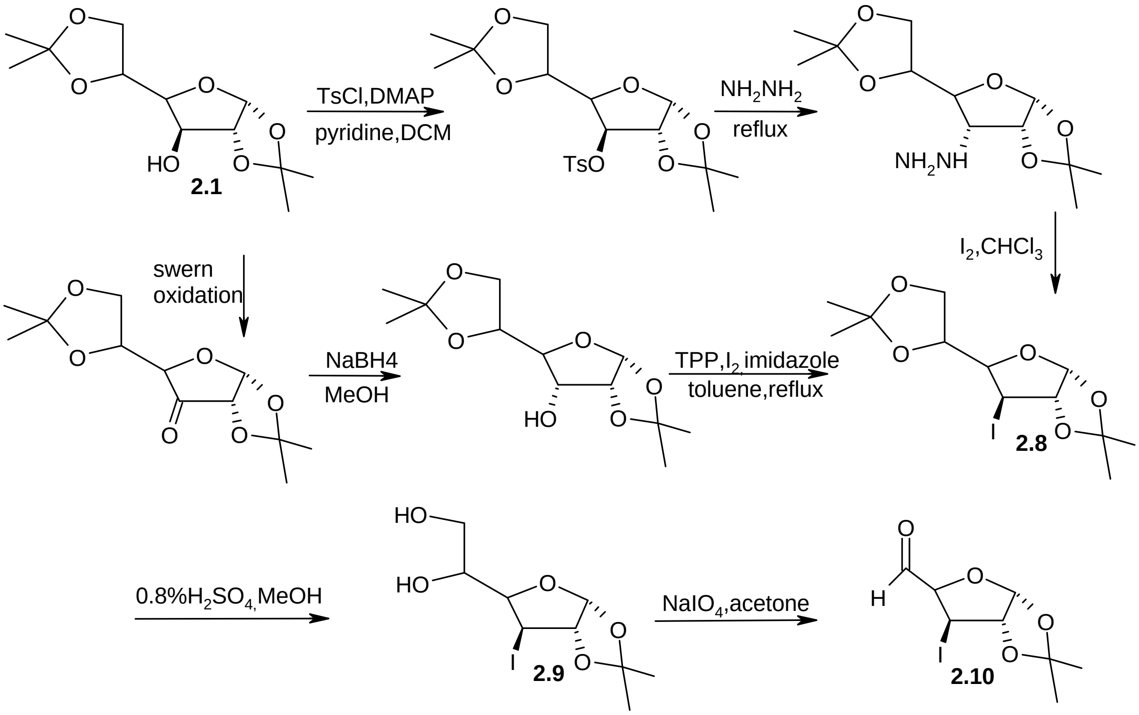
In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 162.83. The two methyls of the acetonide group attached to the C-10 carbon appeared at 26.57. The methine carbon bearing the iodo group appeared at 18.44. The signals for the methoxy group of PMP moiety as well as the *b*-lactam carbon C-4 resonated as 2 peaks at 55.39, and 56.78. The β-lactam carbons C-3 and the chiral backbone C-7, C-9 appeared at 79.1 and 81.52. The anomeric carbon C-6 appeared at 102.95. The C-10 carbon of the acetonide group appeared at 112.03. The aromatic carbons appeared in the region 114.53 to 157.06.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 537 (100%), which is also the base peak.

Preparation of the aldehyde 2.10

The aldehyde **2.10** was prepared from D-glucose in good yields (**Scheme-1.16**) following reported[23-26] procedures *(Scheme 23).*

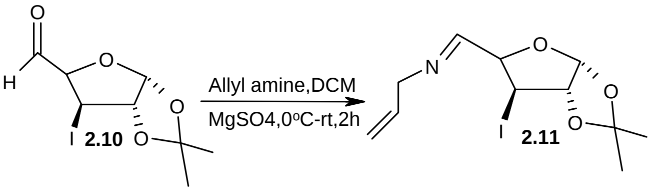
Scheme 23


TsCl,DMAP
pyridine,DCM
NH_2NH_2
reflux
HO
2.1
TsO
NH_2NH
I_2,$CHCl_3$
swern
oxidation
NaBH4
MeOH
HO
TPP,I_2,imidazole
toluene,reflux
I
2.8
0.8%H_2SO_4,MeOH
HO
HO
I
2.9
$NaIO_4$,acetone
H
I
2.10

Preparation of the imine 2.11

The imine **2.11** was prepared by treating the aldehyde **2.10** with ally amine, in CH_2Cl_2 at RT in presence of $MgSO_4$. After completion of the reaction (TLC), the reaction mixture was filtered and the filtrate on concentration provided imines in quantitative yields. The imine was used as such without purification *(Scheme 24).*

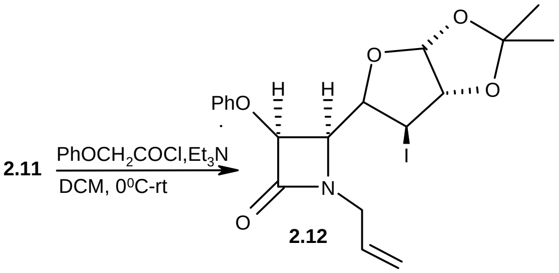
Scheme 24


H
I
2.10
Allyl amine,DCM
MgSO4,0^{o}C-rt,2h
N
I
2.11

Preparation of b-lactam2.12

The imine **2.11** on treatment with phenoxyacetyl chloride in presence of triethylamine underwent cycloaddition reaction to give cis-***b***-lactam **2.12** in 93% yield *(Scheme 25).* The ^{1}H NMR of the crude reaction mixture showed presence of peaks corresponding to only one diastereomer. The crude product was purified by column chromatography.

Scheme 25



The β-lactam **2.12** was isolated as oil. The IR spectrum of this compound showed a strong band at 1743.53 indicating the presence of the carbonyl group of β-lactam ring.

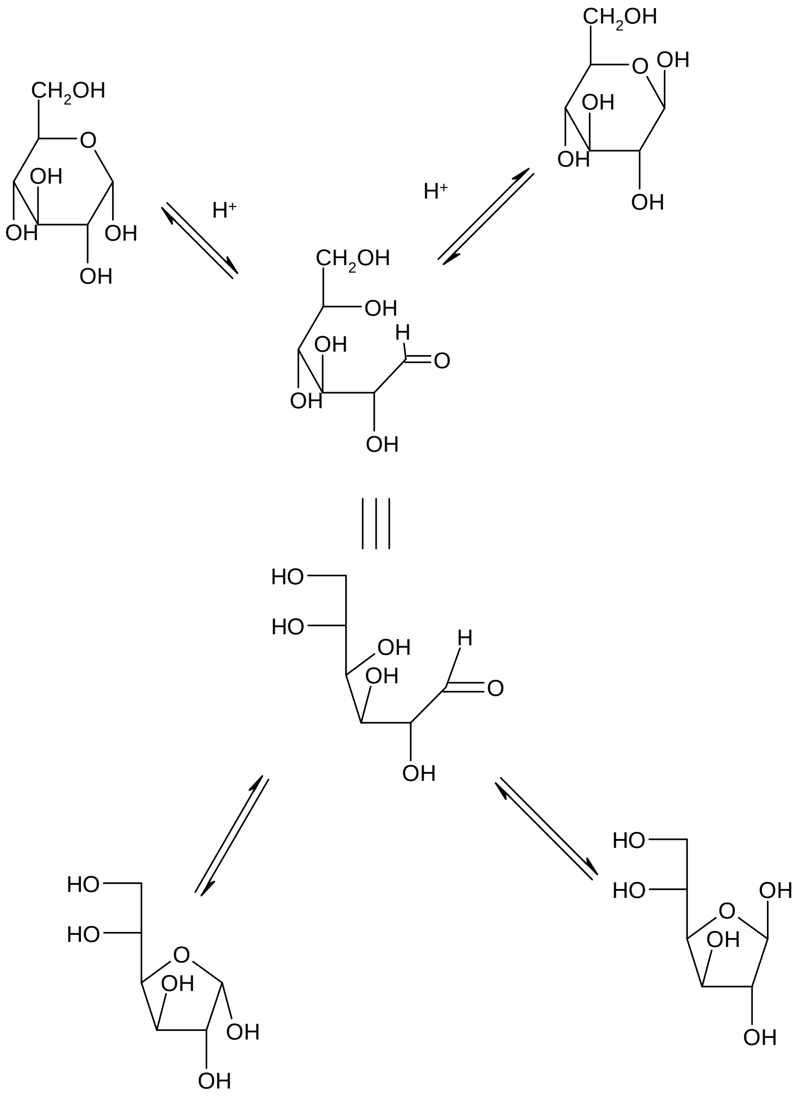
The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.45. The anomeric proton H-6 shows a doublet at 5.98 with J=5.4 Hz. The aromatic protons appeared in the region 6.9-7.4. The other protons appeared in their usual regions and were consistent with the structure of the compound.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 471 (100%), which is also the base peak.

2.5 : Summary

D-Glucose when treated with acetone in presence of ZnCl$_2$ and ortho-phosporic acid afforded the glucose diacetonide **2.1** in good yield. The diacetonide formation could in principle lead to the formation of two products, the five-membered furanose and the six-membered pyranose. Formation of the former is favored because in the furanoid form, glucose offers two suitable vicinal diols for the condensation and fusion of a five membered acetal to a furanoid ring with less strain than similar fusion to a pyranoid ring *(Scheme 26).* The β-forms can be eliminated due to the anti conformation of the two-hydroxyl groups. The acetonide formation is known to preferentially lead to the formation of the furanose form, with the anomeric hydroxyl in the α conformation, the pyranose form being the less favored product under the given reaction conditions. The required furanose form is recrystallized from cyclohexane to get a white crystalline solid melting at 109 ^{0}C. The diacetonide was characterized by ^{1}H NMR and showed the characteristic peaks, 4 singlets in the region δ 1.32 to 1.51 integrating for 12 protons of the diacetonide. The other characteristic peaks are the two doublets at 4.60 (J = 3.7 Hz) and 5.91 (J = 3.7 Hz) corresponding to H-2 and H-1 (anomeric protons) respectively.

Scheme 26


CH2OH
O
OH
OH
OH
OH
H+
H+
CH2OH
O
OH
OH
OH
OH
CH2OH
OH
H
O
OH
OH
OH
HO
HO
OH
OH
H
O
OH
HO
HO
O
OH
OH
OH
HO
HO
O
OH
OH
OH

The free hydroxyl was converted to halo derivative **2.2** using triphenylphosphine, imidazole and Iodine. The selective deprotection at C-5 and C-6 position provided the pure glycol **2.3** as the other acetonide group was more stable to the reaction conditions. The $NaIO_4$ cleavage of the glycol **2.3** provided the pure aldehydes **2.4** in quantative yields. The aldehydes **2.4** underwent imine formation with amines in methylene chloride in presence of $MgSO_4$. The imines **2.5a-b** were characterized by ^1H NMR spectroscopy. The ^1H NMR displayed a doublet at around 7.8 (J = 4.9 Hz) indicating the presence of the imine.

The cycloaddition of various ketenes with the imines **2.5a-b** provided diastereomeric mixture of β-lactams (**2.6a-d** & **2.7a-d**) in the ratio of 50:50, in good yields with exclusively *cis* stereochemistry as ascertained from the coupling constants (4.7-6 Hz) of the C-3 and C-4 protons in ^1H NMR spectra of these compounds. The absolute stereochemistry of these β-lactams was established from single crystal X-ray analysis of **2.7a**.

To improve the selectivity the chiral aldimine **2.11** was synthesized from 3-Deoxy-3-iodo3-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **2.8** as a chiral source. A highly diastereospecific synthesis of *b*-lactams was carried out *via* Staudinger reaction, using the imine. A single diastereomer with exclusively *cis* stereochemistry was obtained.

2.6 : Experimental

All dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Dichloromethane was dried over anhydrous P_2O_5, stored over 4A molecular sieves. Acetone was purified by distilling over $KMnO_4$, and dried over anhydrous $CaSO_4$, and stored over K_2CO_3.

Preparation of diacetone-D-glucose 2.1

A suspension of 75 g (0.0415 mol) of dry D-glucose, 60 g (0.415 mol) of freshly fused zinc chloride and 3.75 g of phosphoric acid (88% v/v) in 500 mL of dry acetone was stirred at ambient temperature for 30 hrs. Unchanged glucose is removed by filtration and the inorganic salts were precipitated by the addition of a solution of 42.5 g of NaOH in 42.5 mL of water. The resulting suspension was filtered; the residue washed with acetone and the acetone is evaporated. The mass, which remains, was dissolved in 100 mL water and extracted with (5x 50 mL) portions of methylene chloride. The organic phase was dried over sodium sulphate and concentrated on a rotary evaporator to give a white solid. Recrystallization from hexane gave 35 g of pure diacetonide **1.2** as a white solid, mp 110 ^{0}C (lit 109-110 ^{0}C); $[\alpha]_D^{20}$-18.5^0 (c=5 in water).

Synthesis of 3-deoxy-3-iodo-1,2:5,6-di-O-isopropylidene-α-D-allofuranose 2.2

A mixture of glucose-diacetonide **2.1** (5 g, 19.23 mmol), triphenylphospine (15.1 g, 57.69 mmol), imidazole (3.9 g, 57.35 mmol), iodine (9.7 g, 38.15 mmol), and toluene (375 mL) was refluxed for 18 hrs. The reaction mixture was then cooled and successively washed with sat. $NaHCO_3$ (25 mL), sat. $Na_2S_2O_3$ (25 mL), and water, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford the crude material, containing triphenyl phosphine oxide. Column chromatography of the crude provided the pure iodide **2.2** (4.98 g, 70%)as oil.

^{1}H NMR ($CDCl_3$) (200 MHz)	1.38 (s, 6H), 1.50 (s, 3H), 1.56 (s, 3H), 3.73 (dd, 1H, J = 4.9 Hz and 4.4 Hz), 4.06 (m, 2H), 4.23 (m, 2H), 4.59 (t, 1H, J = 3.4 Hz), 5.81 (d, 1H, J = 3.4 Hz).

Synthesis of 3-Deoxy-3-iodo-1, 2-O-isopropylidene a-D- allofuranose 2.3

3-Deoxy-3-iodo-1,2:5,6-di-O-isopropylideneα-D-allofuranose **2.2** (3.7 g**,** 10 mmol) was dissolved in 30 mL of MeOH. To this solution 3 mL of 0.8% H_2SO_4 was added and allowed to stir at rt till the disappearance of the starting material (TLC, ca. 24 hrs). The reaction mixture was quenched with triethylamine (3 mL). The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated solution of brine, dried over sodium sulphate, and concentrated under reduced pressure to afford diol **2.3** as a white solid, mp 118 ^{0}C (3 g, 90%). The diol **2.3** was pure enough and used for the next reaction without further purification.

Synthesis of aldehyde 2.4

To a solution of the diol **2.3** (3.3 g, 10 mmol) in a mixture of MeOH (25 mL) and water (25 mL) was added $NaIO_4$ (4.2 g, 20 mmol) in small portions. The white suspension was stirred for an additional 30 min, filtered through a pad of celite and solvent was removed under vacuum. The white residue so obtained was then extracted with EtOAc (3x20 mL) and the combined organic extracts were dried and filtered. Evaporation of the solvent under reduced pressure afforded the pure aldehyde **2.4** (2.8 g, 93%) as oil, which was used as such for imine formation.

Synthesis of imines 2.5a,b

To a solution of the amine (5 mmol of p-anisidine, ally amine) in CH_2Cl_2 (20 ml) and anhydrous $MgSO_4$, was added a solution of the aldehyde **2.4** (1.5 g, 5 mmol)in CH_2Cl_2. The mixture was stirred for 6-8 hrs (TLC). The mixture was filtered through a pad of celite in a sintered glass crucible. The filtrate was concentrated to get the imines **2.5a,b**, which were used as such for the β-lactam formation.

General procedure for the synthesis of b-lactams

A solution of the acid chlorides (phenoxyacetyl chloride and benzyloxyacetyl chloride) (1.5 mmol) in methylene chloride (30 mL) were added to a solution of the imines **2.5a,b** (1 mmol) and triethylamine (4.5 mmol) in CH_2Cl_2 (20 mL) at 0 ^{0}C. It was then allowed to warm up to room temperature and stirred for 15 hrs. The reaction mixture was then washed with water, saturated sodium bicarbonate solution, saturated brine solution. The organic layer was then dried over anhydrous Na_2SO_4, and concentrated to give diastereomeric mixture of β-lactams **2.5 & 2.6** in the ratio of 50:50. The diastereomers were separated by column chromatography using silica gel (60-120 mesh).

Preparation of b-lactams2.6a & 2.7a

The imine **2.5a** (0.67 g, 2 mmol) on treatment with phenoxyacetyl chloride (0.5 g, 3 mmol), in the presence of triethylamine (0.92 g, 9 mmol) provided a diastereomeric mixture of *cis-b*-lactams **2.6a** & **2.7a**, 0.85 g (90%) in the ratio 50:50. The diastereomers were separated by column chromatography.

Compound 2.6a

Isolated as a white solid.

M.P. : 89°C

[a]$_D^{25}$: -25.46 (c = 1, $CHCl_3$)

IR (cm^{-1}) : 1766.67

^{1}H NMR : 1.35 (s, 3H), 1.45 (S, 3H), 3.81 (dd, J=6.8 and 7.2 Hz, 1H), 3.9 (dd, J=3.6 and 4.4 Hz, 1H), 4.19-4.23 (m, 1H), 4.24 (dd, J=3.1 and 4.7, 1H) 4.46 (dd, J=3.1 and 3.6 Hz, 1H), 4.6 (t, J=3.6 Hz, 1H), 5.26-5.33 (m, 2H), 5.36 (d, J=4.7 Hz, 1H), 5.77 (d, J=3.6 Hz, 1H), 5.78-5.87 (m, 1H), 7.0-7.4 (m, 5H).

^{13}C NMR : 21.94, 26.22, 26.55, 44.37, 56.37, 78.71, 79.81, 80.51, 103.09, 111.79, 115.52, 118.93, 122.02, 129.28, 131.54, 157.08, 165.32

MS (*m/z*) : 471(M+)

Microanalysis :

$C_{19}H_{22}INO_5$	Calculated	C: 48.42	H: 4.71	N: 2.97
	Obtained	C: C: 48.32	H: 4.62	N: 2.84

Compound 2.7a

Isolated as a white solid.

M.P. : 113 ^{o}C

$[a]_D^{25}$: +155.8 (c = 1, $CHCl_3$)

IR (cm^{-1}) : 1770.53

^{1}H NMR : 1.35 (s, 3H), 1.45 (s, 3H), 3.8 (dd, J=3.6 and 4.4 Hz, 1H), 3.9-4.2 (m, 3H), 4.5-4.7 (m, 2H), 5.1-5.4 (m, 3H), 5.7-5.9 (m, 2H), 6.9-7.4 (m, 5H).

^{13}C NMR : 19.01, 26.65, 43.41, 55.69, 79.69, 80.36, 81.27, 103.11, 112.00, 115.46, 118.99, 122.33, 129.46, 131.27, 157.33, 165.74.

MS : 471(M+)

Microanalysis :

$C_{19}H_{22}INO_5$	Calculated	C : 48.42	H: 4.71	N: 2.97
	Obtained	C : 48.34	H: 4.91	N: 3.19

Synthesis of b-lactams 2.6b & 2.7b

The imine **2.5a** (0.337 g, 1 mmol) on treatment with benzyloxyacetyl chloride (0.276 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided a diastereomeric mixture of *cis*-β-lactams **2.6b** & **2.7b**, 0.45 g (92%) in the ratio 50:50. The diastereomers were separated by column chromatography.

Compound 2.6b

Isolated as oil.

M.P. : *Oil*

$[a]_D^{25}$: +7.89

IR (cm^{-1}) : 1755.10

^{1}H NMR : 1.35 (s, 3H), 1.5 (s, 3H), 3.7 (dd, 7.3 and 7.5 Hz, 1H), 3.85-4.25 (m, 4H), 4.4 (dd, 2.9 and 3.4 Hz, 1H), 4.5-5 (m, 3H), 5.15-5.35 (m, 2H), 5.6-5.95 (m, 2H), 7.1-7.5 (m, 5H).

^{13}C NMR **:** 21.9, 26.46, 44.18, 56.16, 72.88, 79.06, 80.57, 81.23, 103.21, 111.74, 116.29, 118.83, 127.62, 128.20, 128.46, 131.66, 136.95, 167.09.

Mass **:** 485(M+)

Microanalysis **:**

$C_{20}H_{24}INO_5$	Calculated	C: 49.50	H: 4.98	N: 2.89
	Obtained	C: 49.67	H: 4.79	N: 2.97

Compound 2.7b

Isolated as oil.

M.P. **:** *Oil*

$[a]_D^{25}$ **:** +20.15

IR (cm^{-1}) **:** 1758.96

^{1}H NMR **:** 1.35 (s, 3H), 1.5 (s, 3H), 3.8 (dd, 6.9 and 6.8 Hz, 1H), 3.9-4.2 (m, 3H), 4.45-4.95 (m, 5H), 5.15-5.35 (m, 2H), 5.65-5.9 (m, 2H).

^{13}C NMR **:** 19.4, 26.86, 43.66, 56.12, 73.18, 80.23, 81.59, 103.36, 112.18, 119.01, 127.76, 127.98, 128.46, 131.59, 137.06, 167.57

MS **:** 485 (M+)

Microanalysis **:**

$C_{20}H_{24}INO_5$	Calculated	C: 49.50	H: 4.98	N: 2.89
	Obtained	C : 49.48	H: 5.12	N: 2.94

Synthesis of b-lactams 2.6c & 2.7c

To a stirred solution of imine **2.5a** (0.337 g, 1 mmol) and Et_3N (0.61 g, 6 mmol) in dry dichloromethane (15 mL) and azidoacetic acid (0.202 g, 2 mmol), a solution of triphosgene (0.296 g, 1 mmol) in dry dichloromethane (5 mL) was added drop-wise at 0 °C over a period of 1 h. The reaction mixture was allowed to warm up to room temperature and stirred overnight to give a diastereomeric mixture of *cis*-β-lactams **2.6c** & **2.7c**, 0.301 g

(65%) in the ratio 50:50. The diastereomers **2.6c** & **2.7c** were separated by column chromatography.

Compound 2.6c

Isolated as a white solid.

M.P. : 139^{o}C

$[a]_D^{25}$: -28.08 (c = 1.85, CH_2Cl_2)

IR (cm^{-1}) : 1753.17, 2113.84

^{1}H NMR : 1.3 (s, 3H), 1.55 (s, 3H), 3.6-3.8 (m, 2H), 4-4.2 (m, 2H), 4.3 (dd, J=3.9 and 3.4 Hz, 1H), 4.6 (t, J=3.9 Hz, 1H), 4.7 (d, J=4.9 Hz, 1H), 5.15-5.35 (m, 2H), 5.6-5.8 (m, 1H), 5.85 (d, J=3.4 Hz, 1H).

^{13}C NMR : 21.64, 26.53, 44.80, 56.27, 65.64, 79.17, 80.49, 103.36, 112.14, 119.27, 131.48, 163.86

MS (*m/z*) : 420(M+)

Microanalysis :

$C_{13}H_{17}IN_4O_4$	Calculated	C: 37.16	H: 4.08	N: 13.33
	Obtained	C: 37.27	H: 4.34	N: 13.56

Compound 2.7c

Isolated as a white solid.

M.P. : 164^{o}C

$[a]_D^{25}$: +39.79 (c = 1.85, CH_2Cl_2)

IR (cm^{-1}) : 1762.82, 2113.84.

^{1}H NMR : 1.35 (s, 3H), 1.5 (s, 3H), 3.85 (dd, J=6.4 and 6.3 Hz, 1H), 3.96-4.05 (m, 2H), 4.12 (dd, J=3.9 and 4.4 Hz, 1H), 4.5 (dd, J=2.9 and 3.2 Hz, 1H), 4.57 (d, J=4.9 Hz, 1H), 4.69 (t, J=3.5 Hz, 1H), 5.2-5.4 (m, 2H), 5.7-5.9 (m, 1H), 5.93 (d, J=3.5 Hz, 1H).

^{13}C NMR : 18.96, 26.57, 43.77, 55.31, 64.76, 79.24, 81.15, 103.21, 112.29, 119.38, 131.14, 163.20

MS (*m/z*) : 420(M+)

Microanalysis :

	Calculated	C: 37.16	H: 4.08	N: 13.33
$C_{13}H_{17}IN_4O_4$				
	Obtained	C: 37.32	H: 4.14	N: 13.27

Synthesis of b-lactams 2.6d & 2.7d

The imine **2.5b** (0.4 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.25 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided a 0.46 g (86%) of diastereomeric mixture of *cis-b*-lactams **2.6d** & **2.7d** in the ratio 50:50. One of the diastereomer **2.6d** was separated by crystallization from methanol.

Compound 2.6d

Isolated as a white solid.

M.P. : 124 ^{o}C

[a]$_D$^{25} : +35.15 (c = 1.85, CH_2Cl_2)

IR (cm^{-1}) : 1743.53

^{1}H NMR : 1.3 (s, 3H), 1.4 (s, 3H), 3.8 (s, 3H), 3.9 (dd, J=4.4 and 4.8, 1H), 4.6 (t, J=3.5 Hz, 1H), 4.7-4.9 (m, 2H), 5.45 (d, J=5.4 Hz, 1H), 5.85 (d, J=3.5 Hz, 1H), 6.8-7.6 (m, 9H).

^{13}C NMR : 18.44, 26.57, 55.39, 56.78, 79.1, 81.52, 102.95, 112.03, 114.53, 115.56, 118.72, 122.51, 129.67, 130.45, 156.65, 157.06, 162.83.

MS (*m/z*) : 537(M+)

Microanalysis :

	Calculated	C: 51.41	H: 4.50	N: 2.61
$C_{20}H_{24}INO_5$				
	Obtained	C: 51.36	H: 4.74	N: 2.78

Synthesis of 3-Deoxy-3-iodo-1, 2-O-isopropylidene a-D- glucofuranose 2.9

3-Deoxy-3-iodo-1,2:5,6-di-O-isopropylideneα-D-glucofuranose **2.8** (3.7 g, 10 mmol) was dissolved in 30 mL of MeOH and 3 mL of 0.8% H_2SO_4 was added to it and allowed to stir at room temperature till the disappearance of the starting material (TLC, ca. 24 hrs). The reaction mixture was quenched with triethylamine (3 mL). The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated solution of brine, dried over sodium sulphate, and concentrated under reduced pressure to afford diol **2.9** as oil (3.1g, 94%) which was pure enough to be used for the next reaction without further purification.

Synthesis of aldehyde 2.10

To a solution of the diol **2.9** (1.65 g, 5 mmol) in a mixture of MeOH (25 mL) and water (25 mL) was added $NaIO_4$ (2.14 g, 10 mmol) in small portions. The white suspension was stirred for an additional 30 min, filtered through a pad of celite and solvent was removed under vacuum. The white residue thus obtained was then extracted with EtOAc (3x20 mL) and the combined organic extracts were dried (Na_2SO_4) and filtered. THe filtrate on removal of the solvent under reduced pressure afforded the pure aldehyde **2.10** as oil (1.3 g, 87%).

Synthesis of imine 2.11

To a solution of the allyl amine (0.28 g, 5 mmol) in 30 ml CH_2Cl_2, and anhydrous $MgSO_4$, (2.4 g, 20 mmol) was added a solution of the aldehyde **2.10** (1.5 g, 5 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 6-8 hrs (TLC). The mixture was filtered through a pad of celite in a sintered glass crucible. The filtrate was concentrated to get the imine **2.11** (1.5 g, 88%) which were used as such for the β-lactam reaction.

Synthesis of b-lactam 2.12

The imine **2.11** (0.337 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.255 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided a single diastereomer, which was purified by column chromatography so as to give *cis*-*b*-lactams **2.12** as an oil (0.44 g, 93%).

$[a]_D^{25}$: +41.97

IR (cm^{-1}) : 1743.53

^{1}H NMR : 1.45 (s, 6H), 3.55 (dd, J=7.3 and 7.8 Hz, 1H), 4.2-4.4 (m, 2H), 4.75 (d, J=4.4 Hz, 1H), 4.95 (d, J=5.4 Hz, 1H), 5.15-5.35 (m, 3H), 5.4 (d, J=4.4 Hz, 1H), 5.65-5.9 (m, 1H), 5.98 (d, 1H, J=5.4 Hz), 6.9-7.4 (m, 5H).

MS (*m/z*) : 471(M+)

Microanalysis :

$C_{20}H_{24}INO_5$	Calculated	C: 48.42	H: 4.71	N: 2.97
	Obtained	C: 48.66	H: 4.88	N: 2.85

2.7 : References

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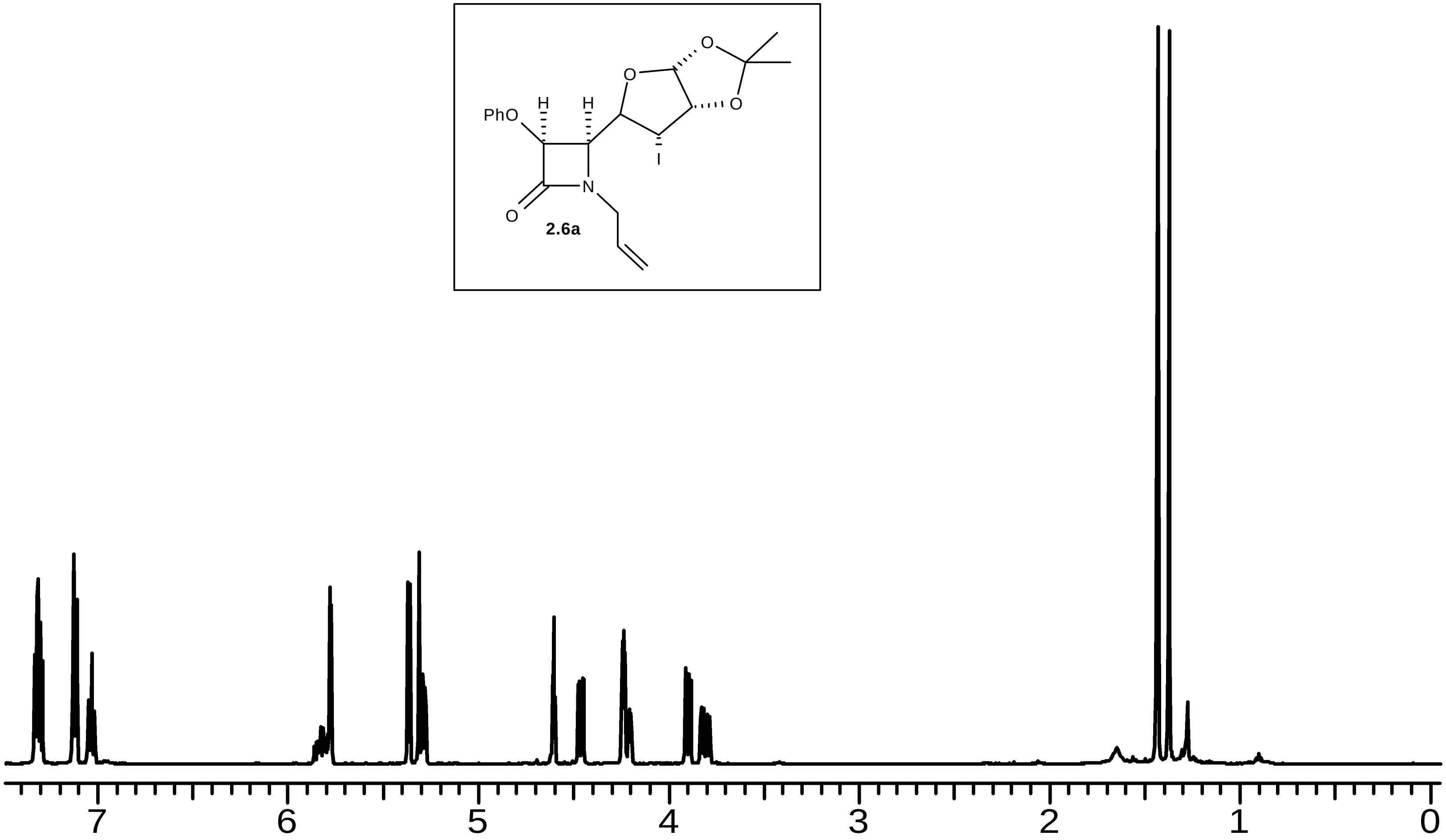

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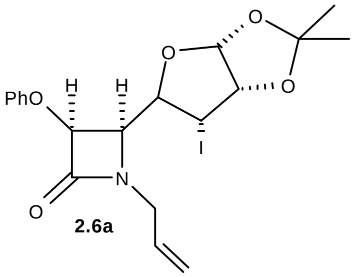
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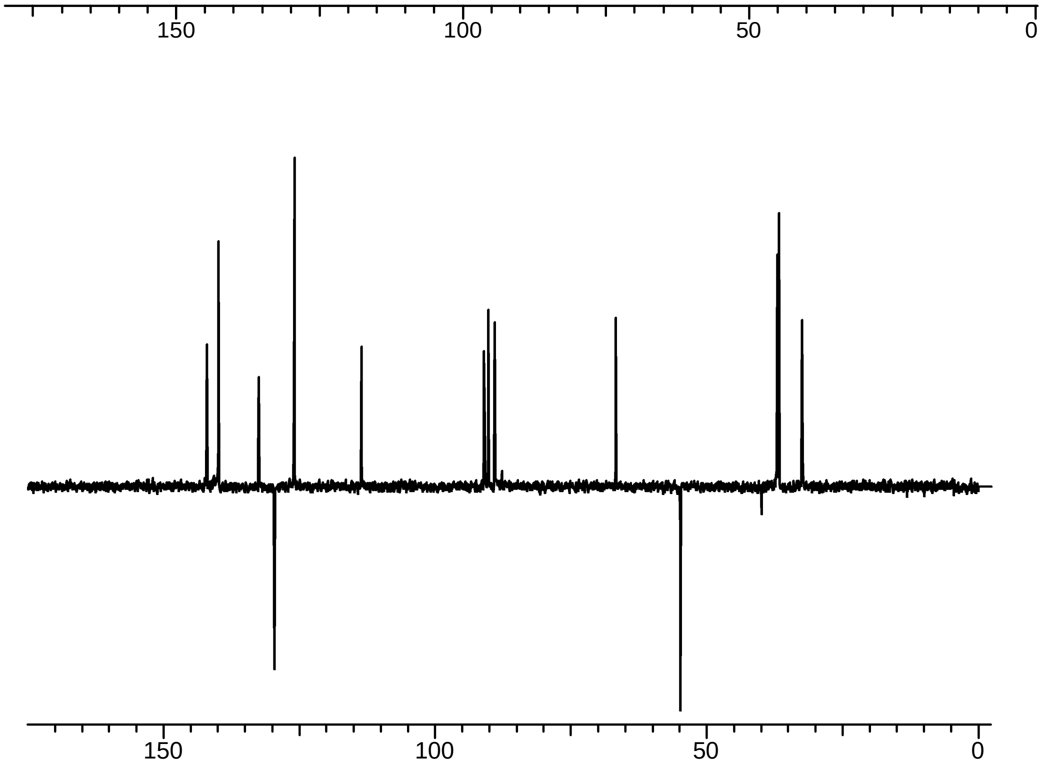

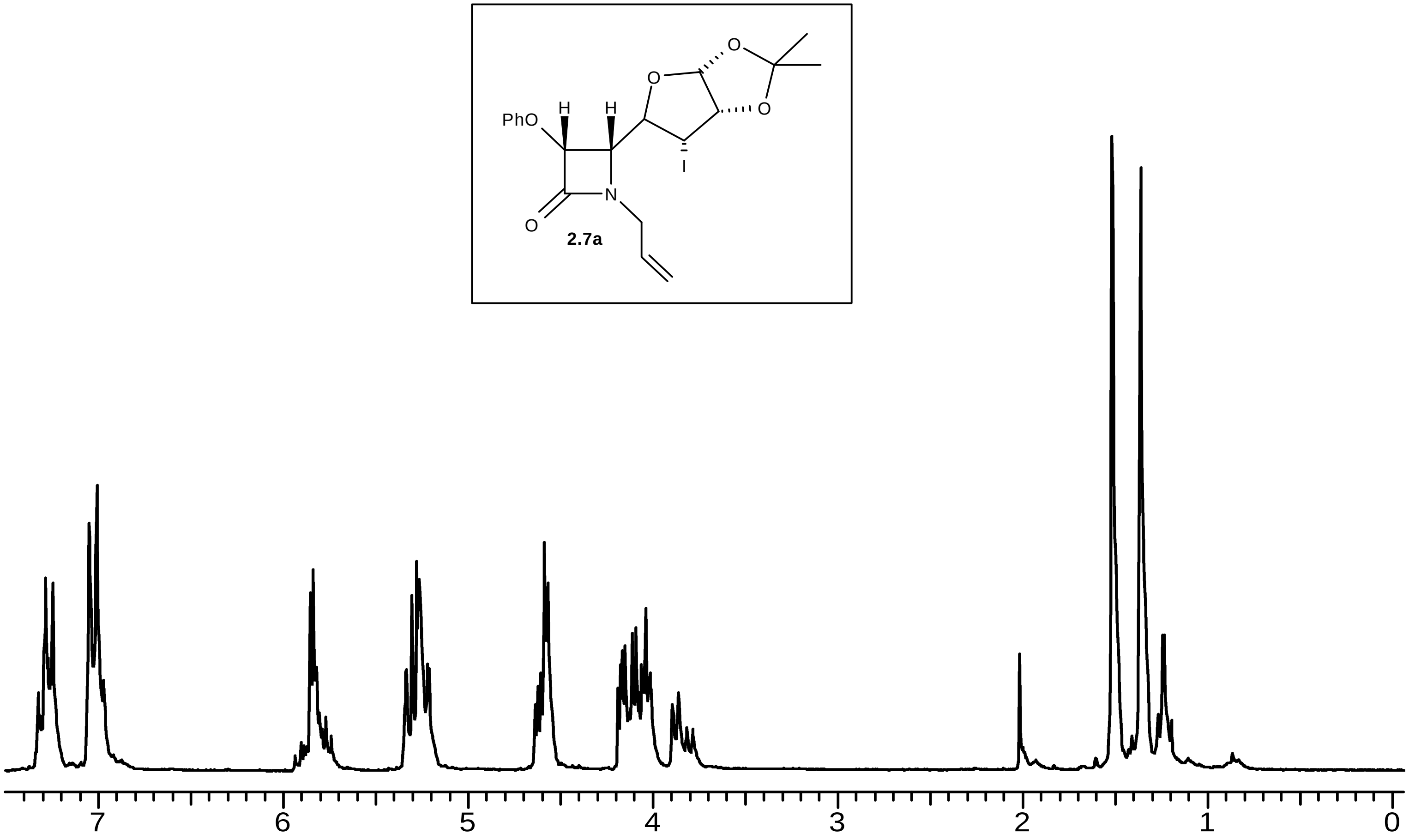
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5
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3
2
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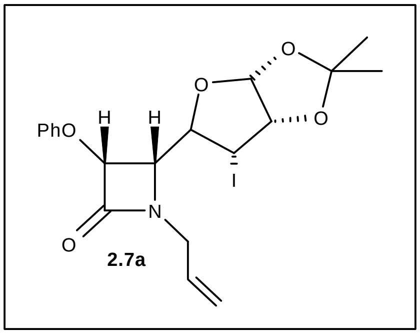
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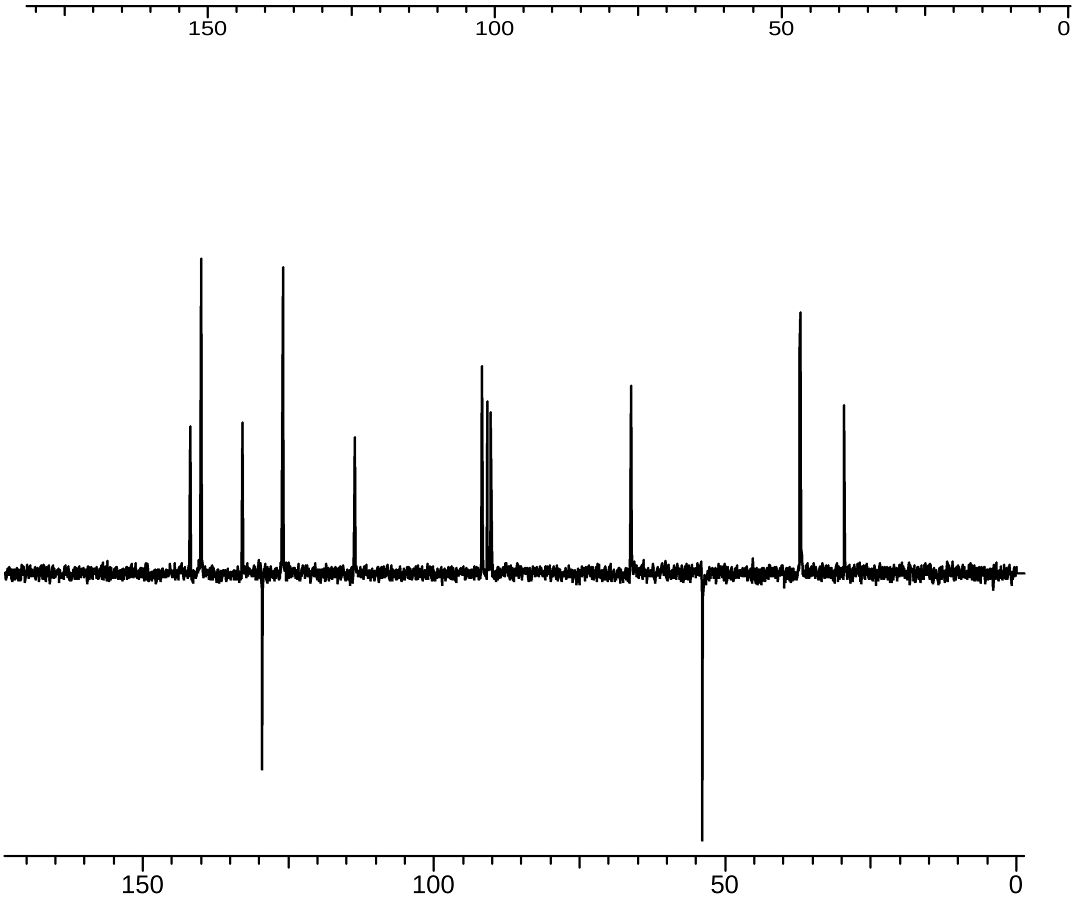
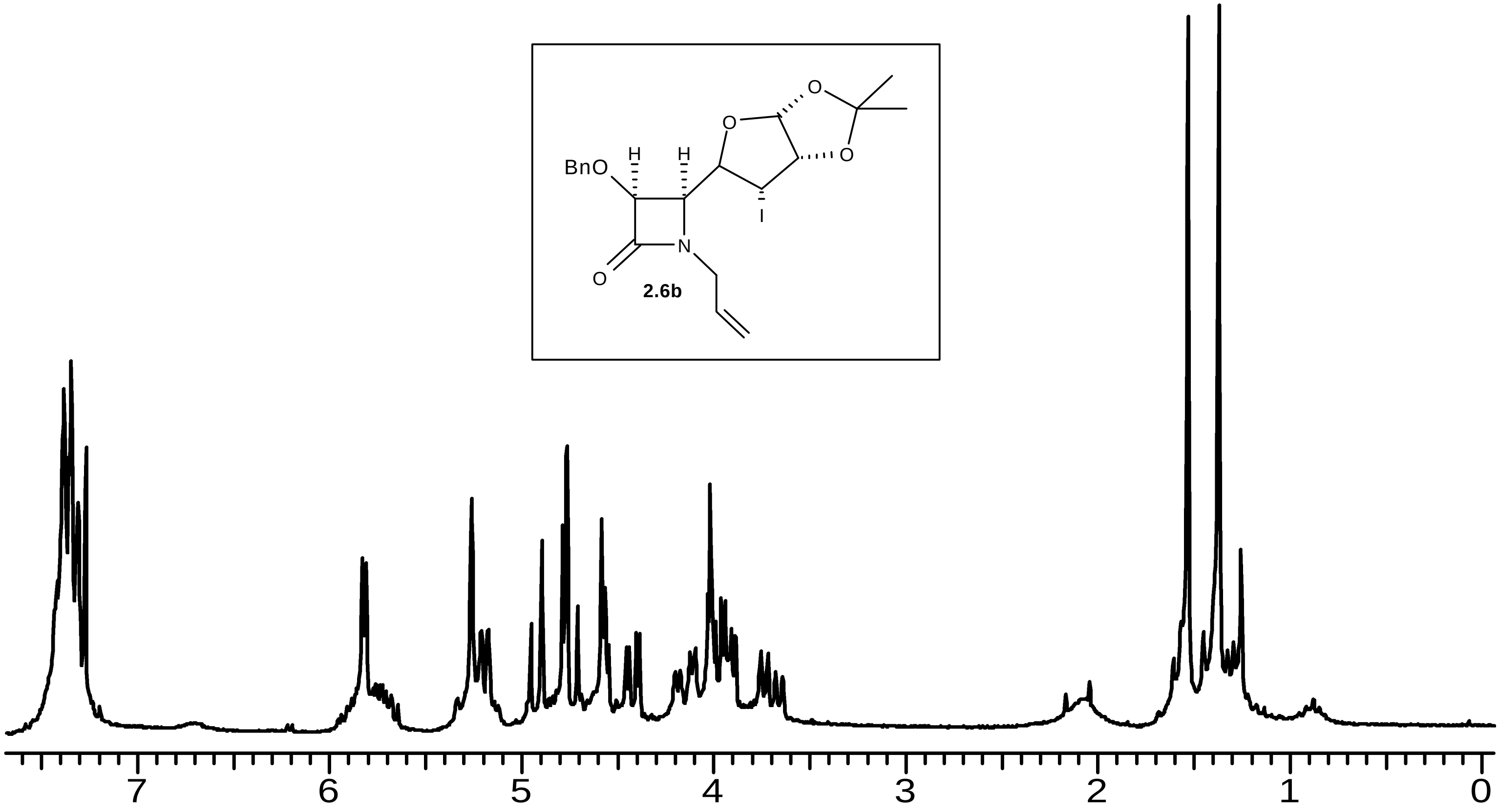
O
I

2.7a

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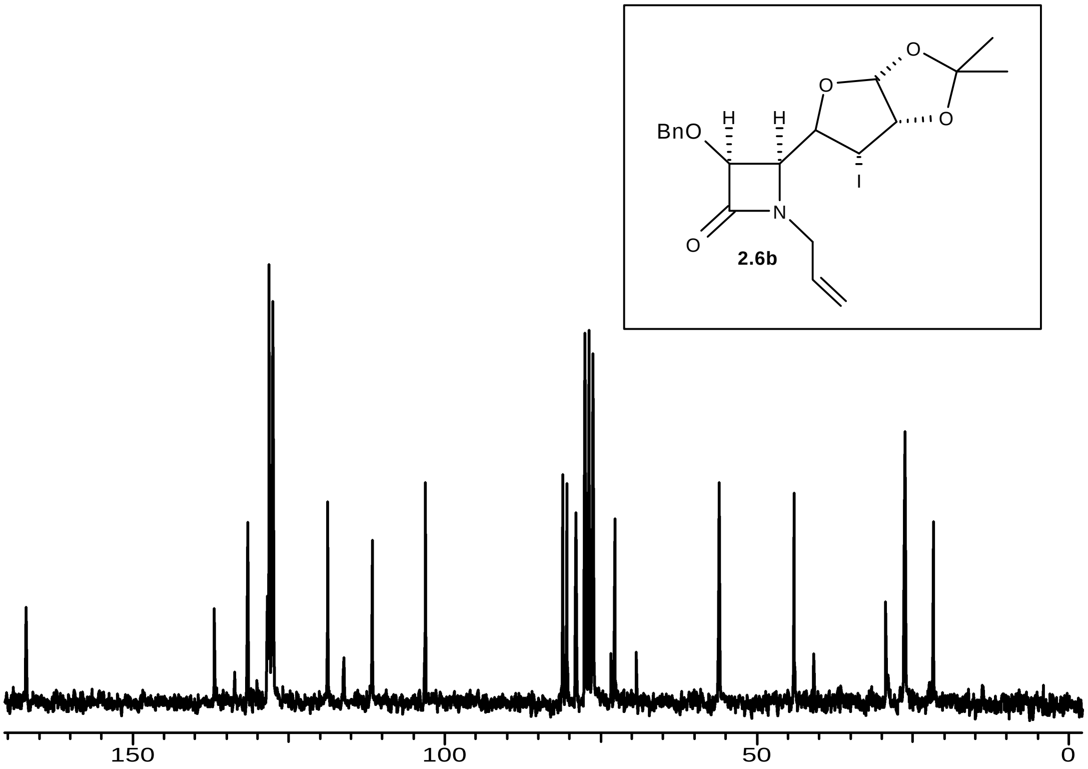
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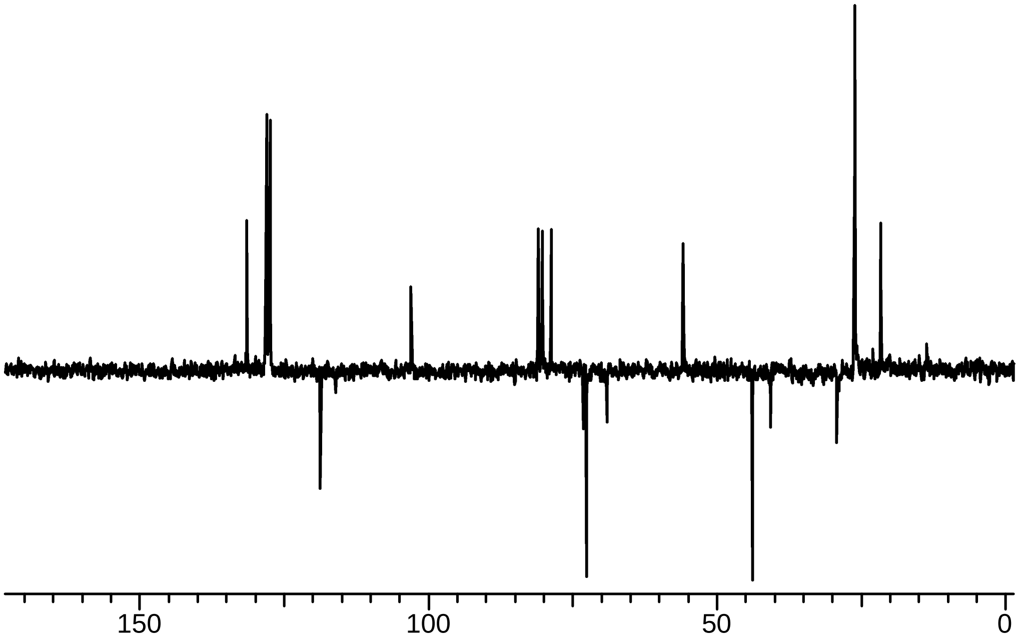

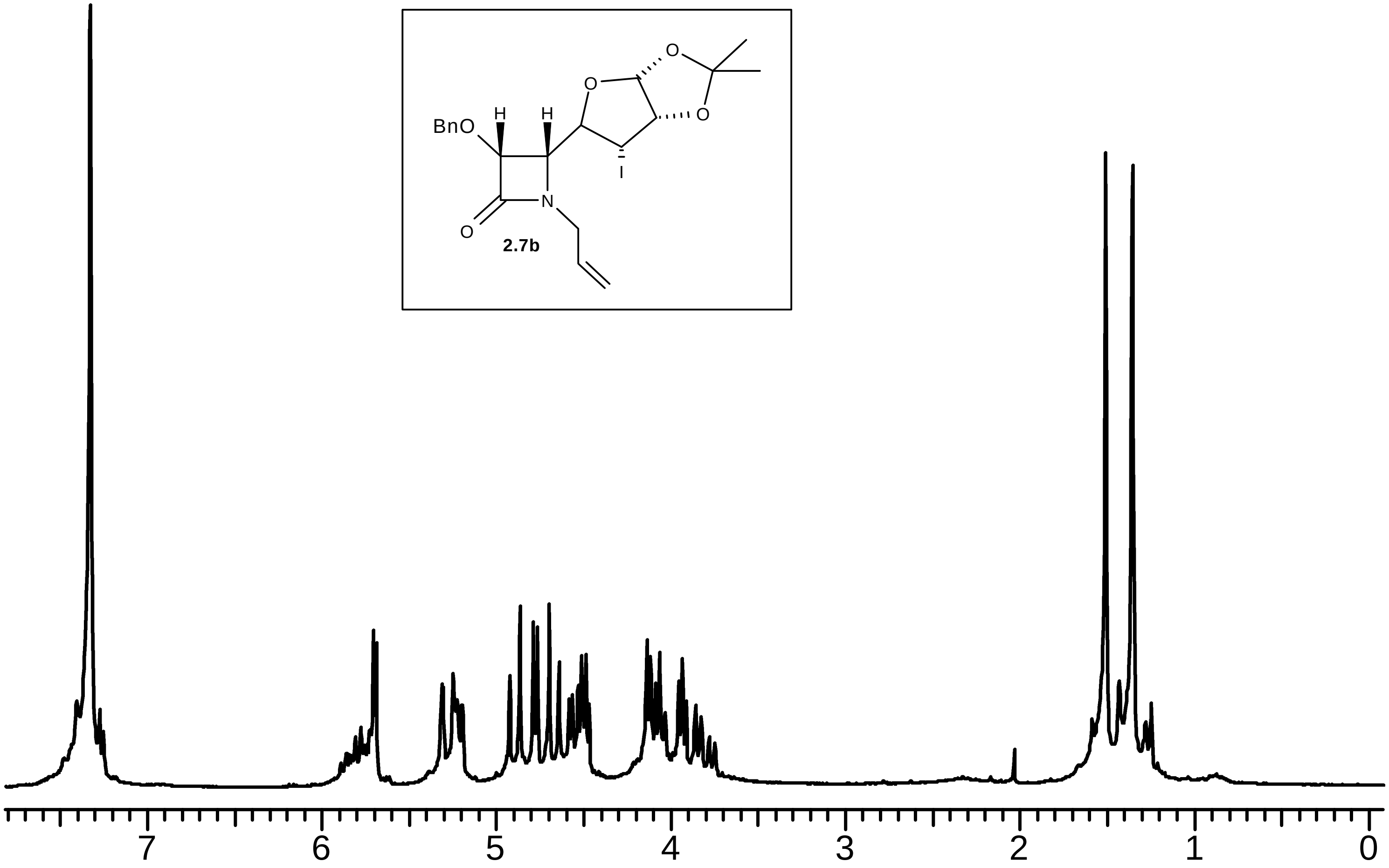
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4
3
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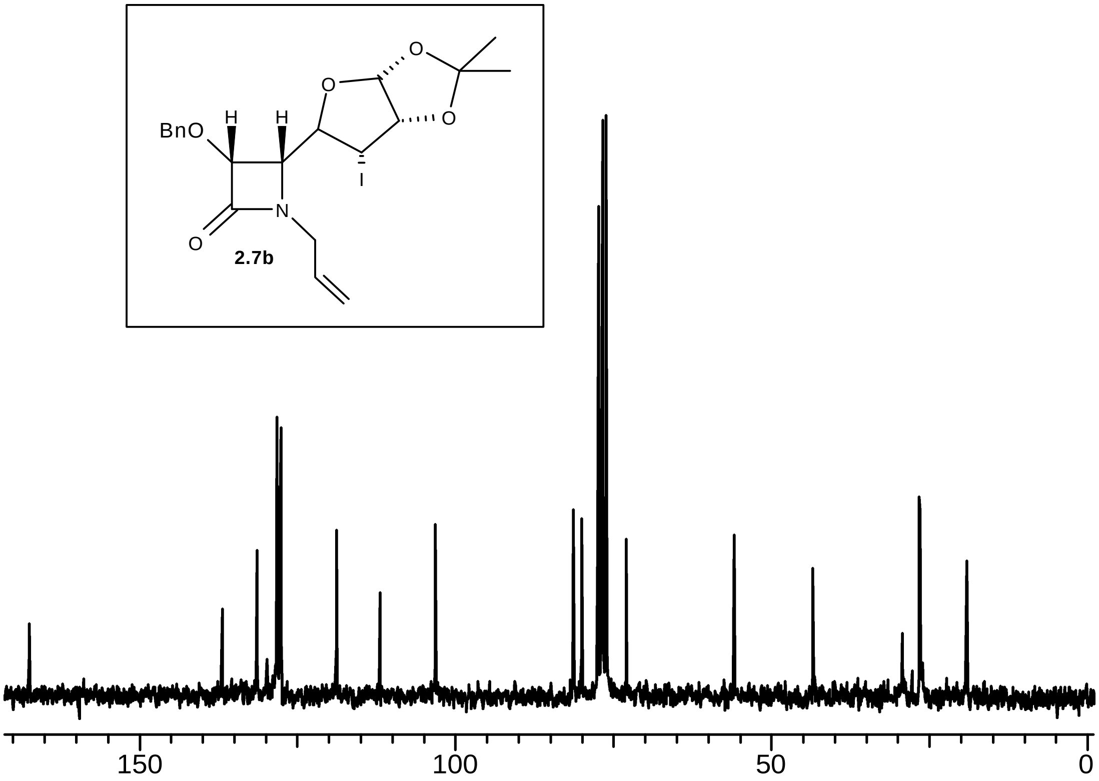
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100
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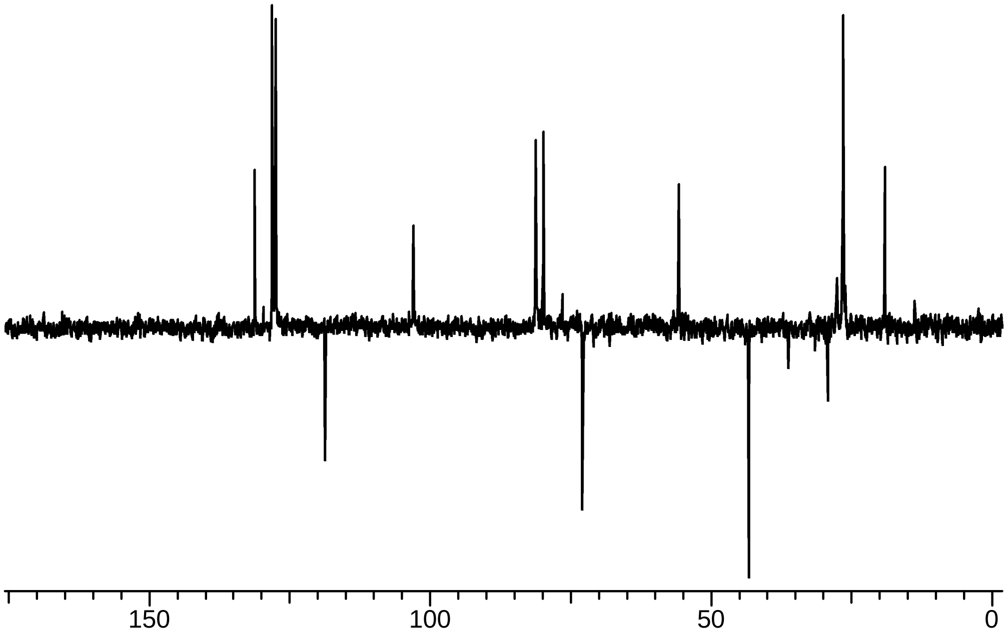
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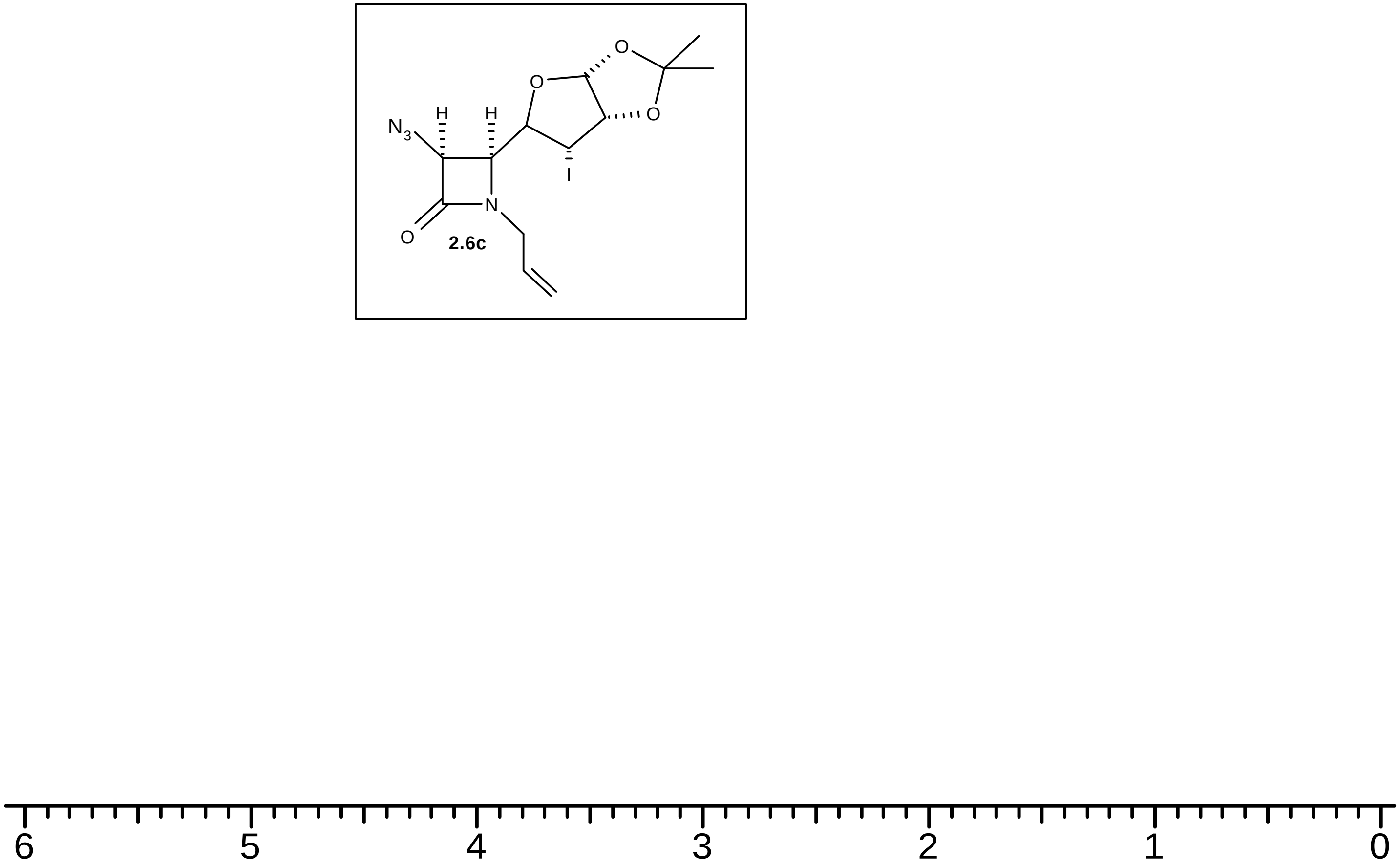

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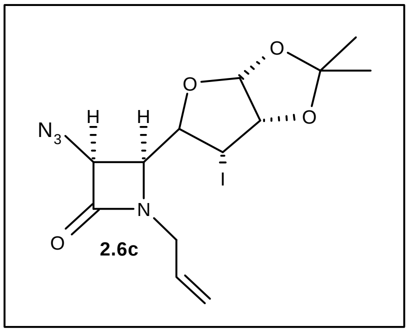
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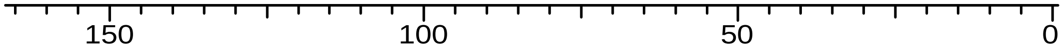
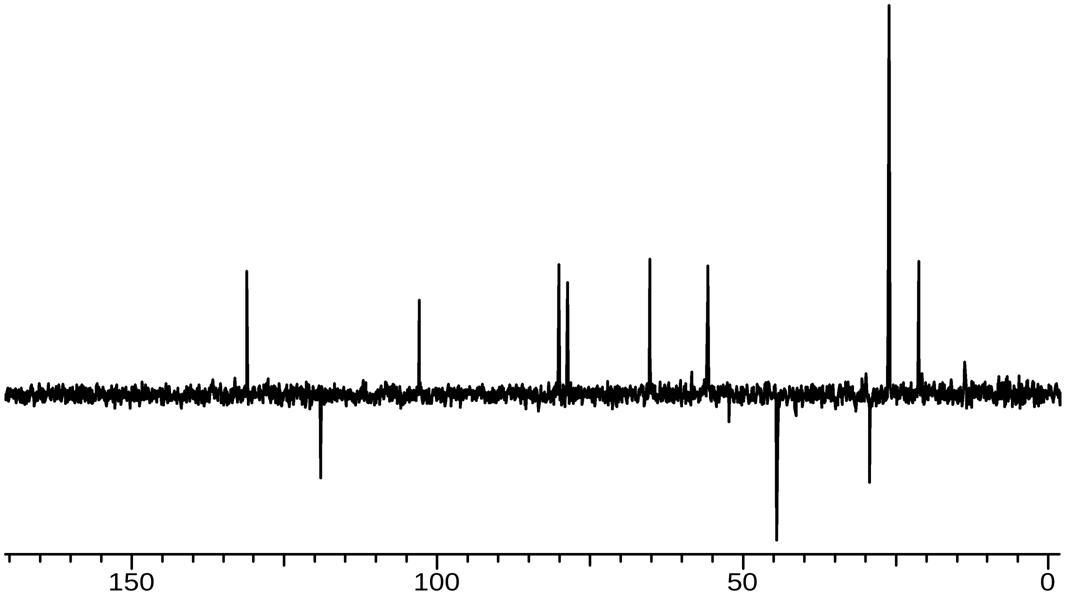
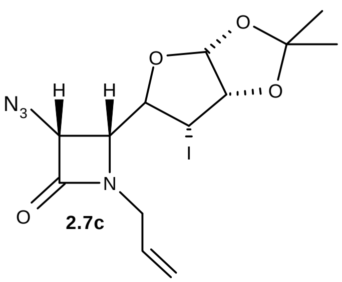
2.6c







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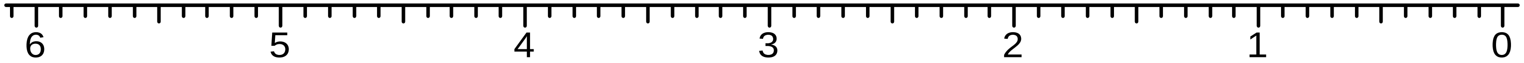
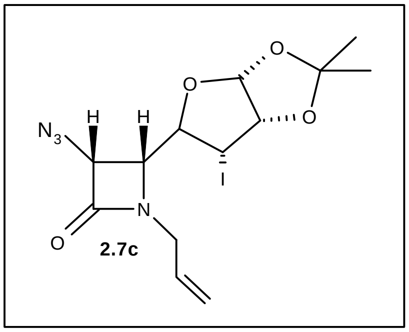
N
O

2.7c

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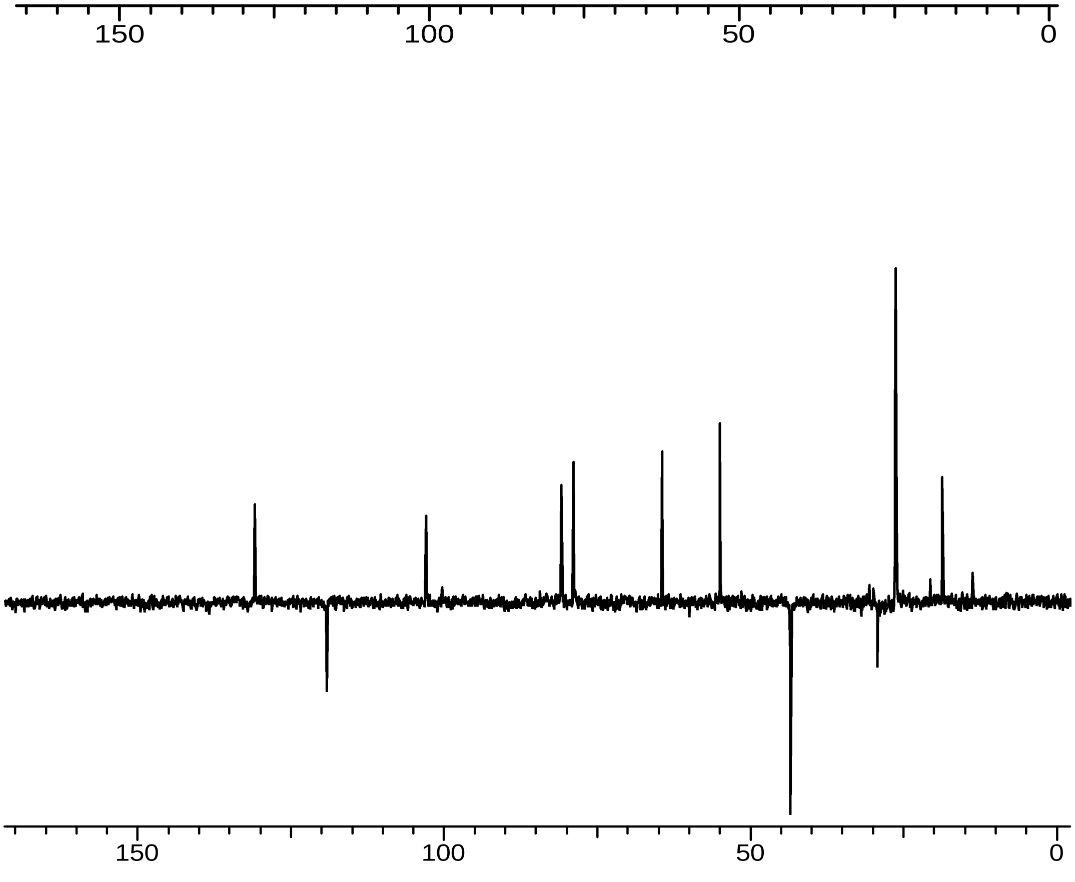

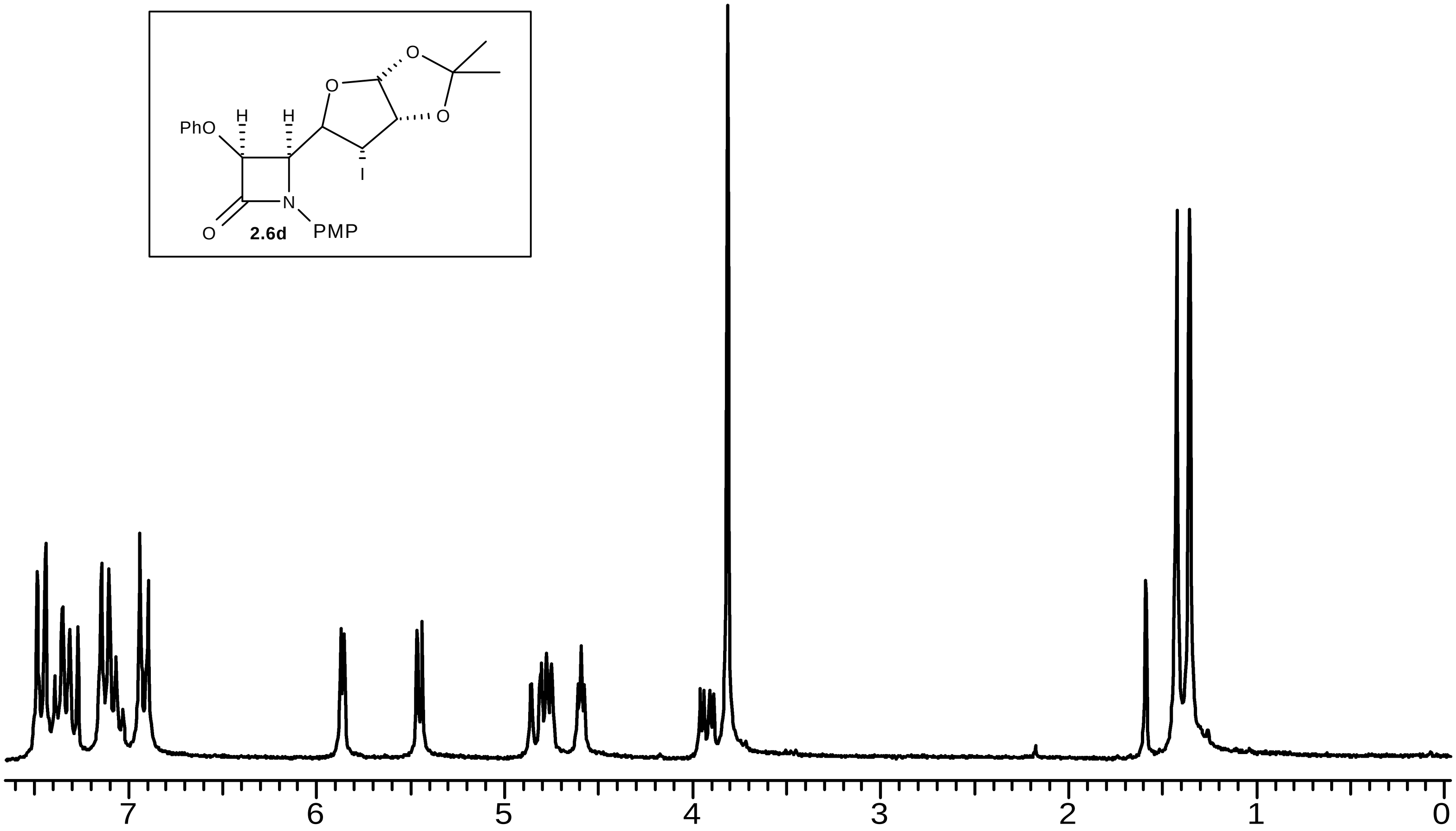
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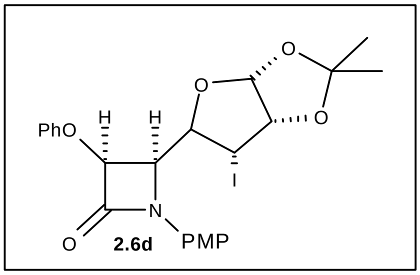
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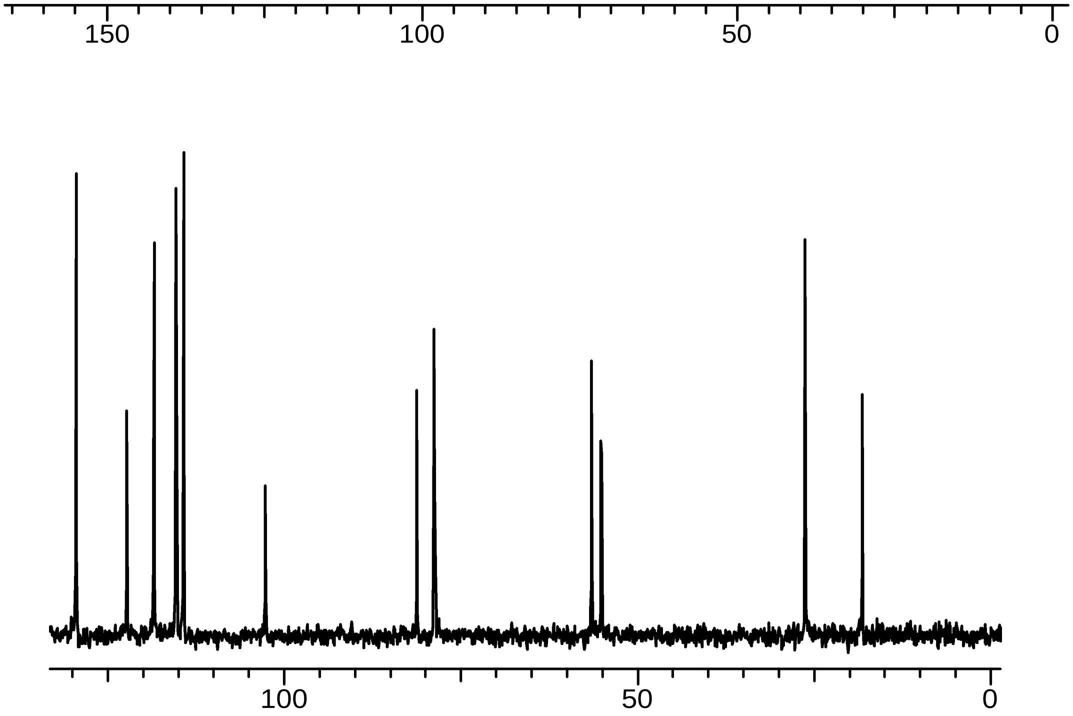
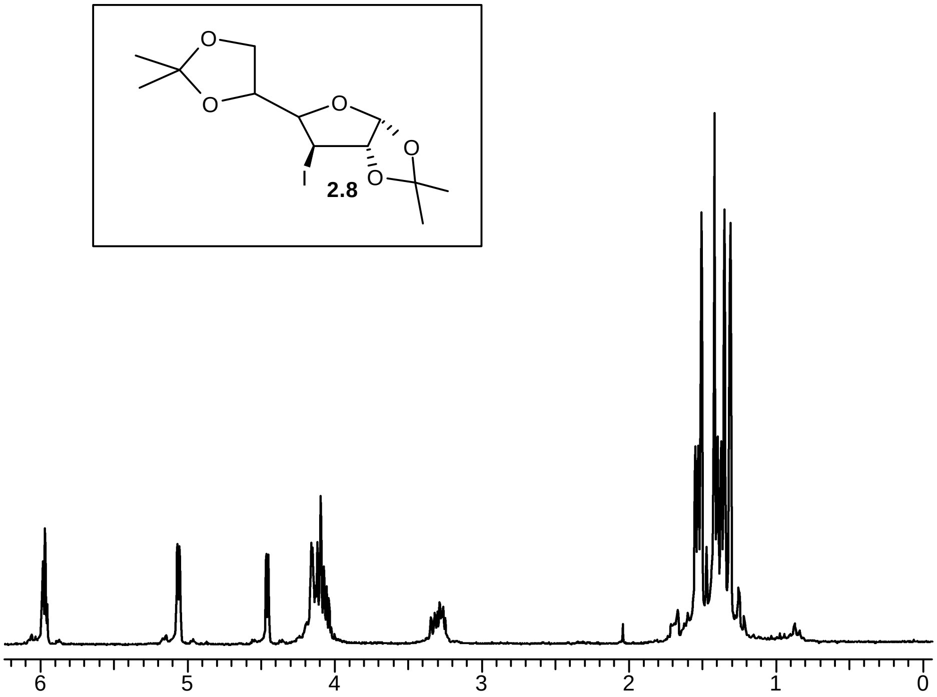
2.6d

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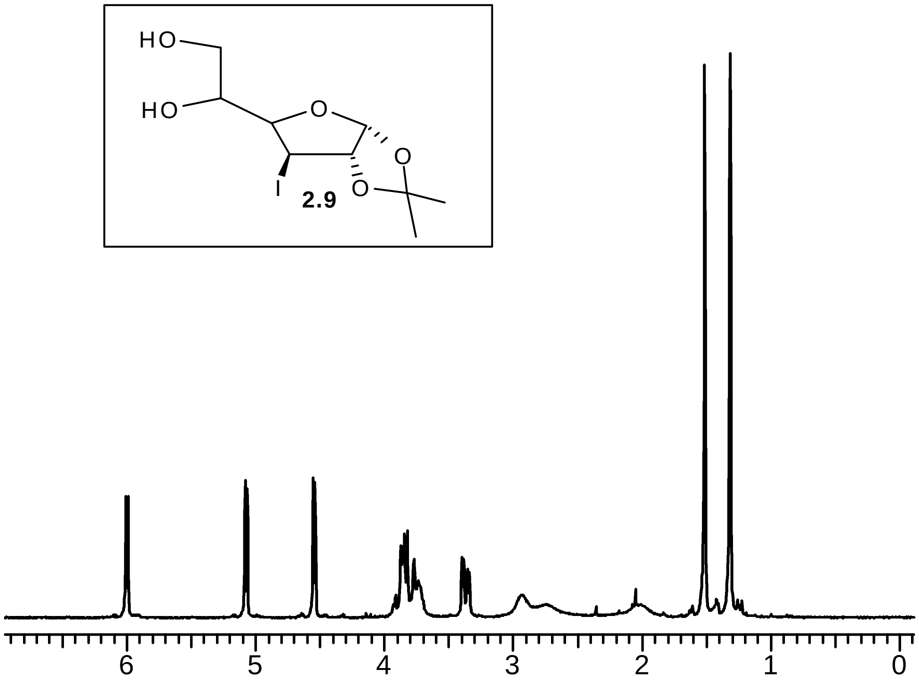
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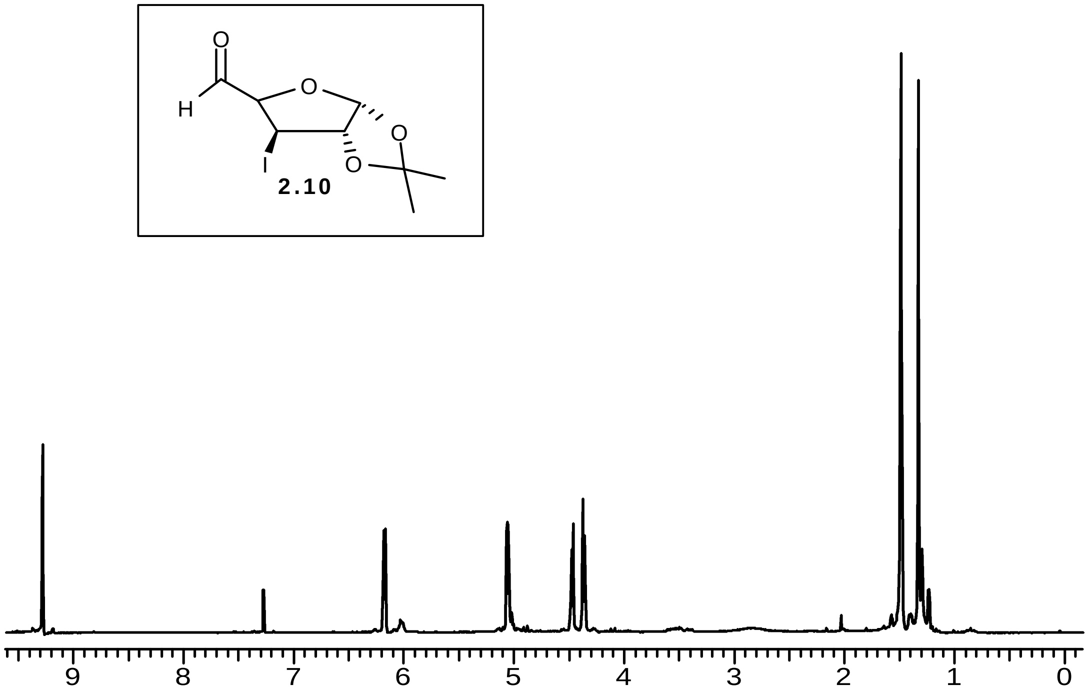

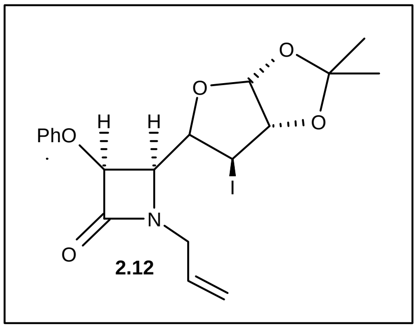
O
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PhO
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N
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I

2.12

Chapter III

Diastereoselective synthesis of b-lactams from chiral aldehyde derived from 3-Deoxy-3–azido and 3-O-Methane-sulfony-1,2;5,6-di-O-isopropylidene-a-D-glucofuranose

3.1 : Abstract

This chapter deals with the asymmetric synthesis of β-lactams from chiral aldimines **3.4** and **3.9** derived from 3-Azido-3-deoxy-1,2:5,6-di-O-isopropylidene α-D-glucofuranose and 3-deoxy-3-methanesulphonyl-1,2:5,6-di-O-isopropylidene α-D-glucofuranose. The sterically demanding aldimine **3.4** was prepared from glucose diacetonide **2.1** in 5 steps and **3.9** in 4 steps. These imines underwent a highly stereospecific Staudinger reaction with ketenes to provide a single diastereomer of β-lactams **3.5** and **3.10**, with exclusively *cis* configuration. The *cis* stereochemistry of these β-lactams was ascertained from the coupling constants of the C-3 and C-4 ring protons (5-6 Hz).

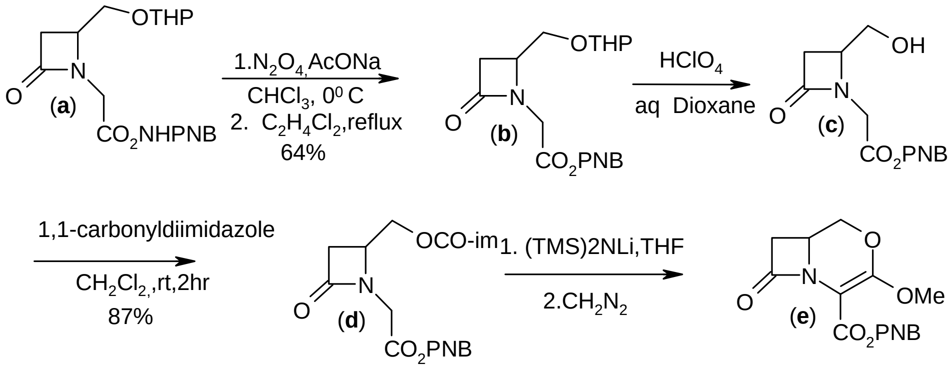
The oxidative cleavage of the β-lactam **3.10** using Ceric Ammonium Nitrate (CAN) afforded the N-unsubstituted β-lactam **3.11** in high yields.

3.2 : Introduction

The unique structural and chemotherapeutic properties of the β-lactam antibiotics continue to attract the attention of the synthetic community as they present a variety of synthetic challenges. During the last few decades much of the efforts were directed towards developing new strategies for the stereoselective synthesis of β-lactam antibiotics. The synthesis usually relied on the prior construction of a monocyclic β-lactams leaving an appropriate tether for ring closure. As a result of their impressive biological activity, polycyclic β-lactams has become interesting targets for synthesis.

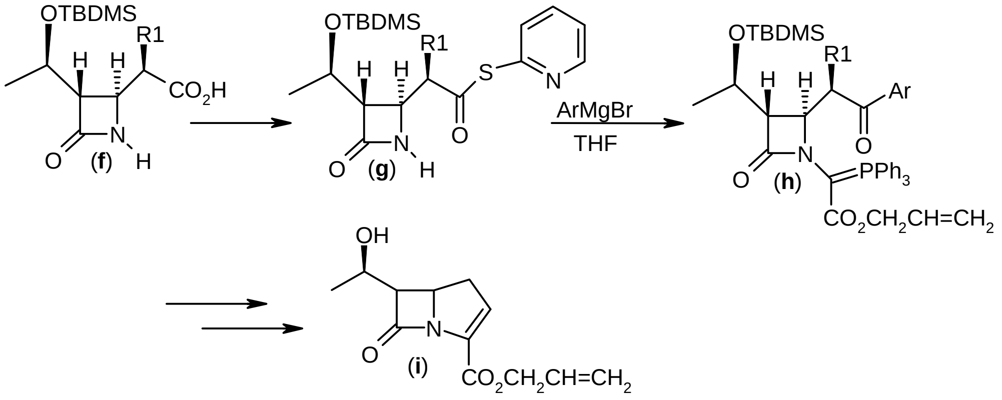
Hatanaka and coworkers[1] reported the synthesis of the O-2,3-methoxy isocephem (**e**) *via* an intermolecular acylation reaction. The key azetidinone (**a**) synthesized using an Ugi condensation reaction, was converted to the PNB ester (**b**) Deprotection to the alcohol (**c**) followed by the treatment with 1,1^1-carbonyldiimidazole afforded the carbamate (**d**) which was cyclised on treatment with 2 equivalents of base (*Scheme 1*). The crude ester was then directly converted to the carbapenem (**e**) on reaction with diazomethane.

Scheme 1


OTHP
O
N
(a)
CO2NHPNB
1.N2O4,AcONa
CHCl3, 0⁰ C
2. C2H4Cl2,reflux
64%
OTHP
O
N
(b)
CO2PNB
HClO4
aq Dioxane
OH
O
N
(c)
CO2PNB
1,1-carbonyldiimidazole
CH2Cl2,,rt,2hr
87%
OCO-im
O
N
(d)
CO2PNB
1. (TMS)2NLi,THF
2.CH2N2
O
O
N
OMe
(e)
CO2PNB

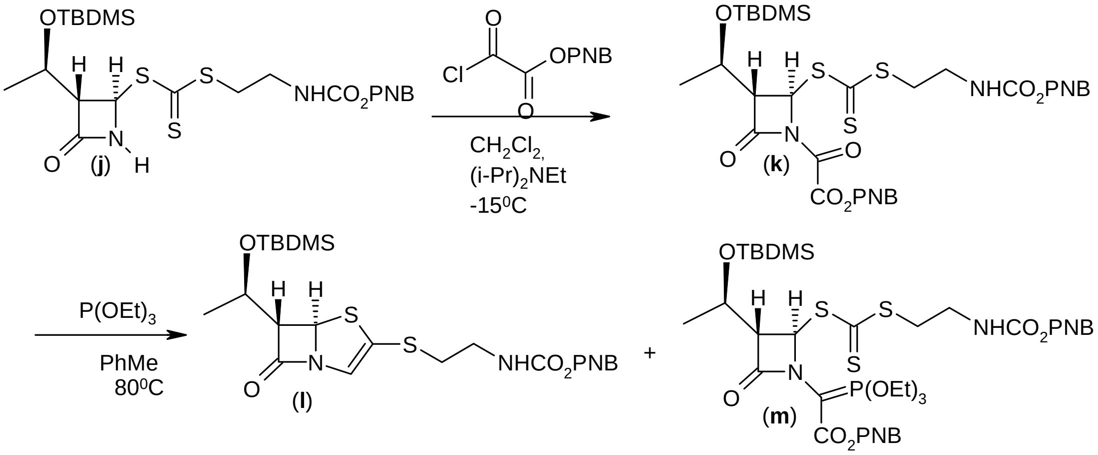
Merck researchers[2] have reported the syntheses and antibacterial activities of a number of C-2 aryl substituted carbapenems (*Scheme 2*). Intramolecular Wittig strategy was employed which provided the carbapenems (**i**) in 58-90% yields.

Scheme 2


OTBDMS
R1
H H
CO2H
O
N
(f)
H
OTBDMS
R1
H H
S
N
O
O
N
(g)
H
ArMgBr
THF
OTBDMS
R1
H H
Ar
O
O
N
(h)
PPh3
CO2CH2CH=CH2
OH
O
N
(i)
CO2CH2CH=CH2

Yoshida and coworkers reported a second preparation of the intermediate (**l**), a material previously converted to 1-thiathienamycin (**m**)[4]. Acylation of azetidinone (**j**) with 2 equivalents each of p-nitro benzyl oxalyl chloride and $(i\text{-}Pr)_2NEt$ in CH_2Cl_2 at –15 ^{0}C gave (**k**) in 77% yield *(Scheme 3)*. Reductive cyclization in toluene at 80 ^{0}C for 1 hr with 5 equivalents of P $(OEt)_3$ afforded the penem (**i**) and the phosporane (**m**).

Scheme 3



3.3 : Present work

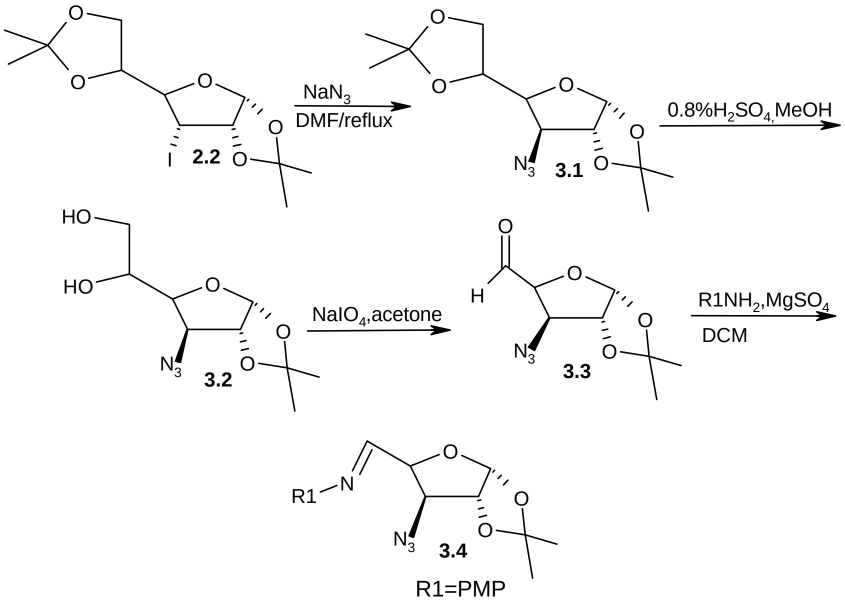
Earlier reports have clearly indicated that the use of homochiral aldehydes in most of the cases resulted in the complete stereo control in the Staudinger reaction. Hence we decided to use sterically hindered aldehydes derived from 3-azido-3-deoxy-1,2:5,6-di-O-isopropylidene α-D-glucofuranose and 3-deoxy-3-methanesulphonyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose to study the diastereoselectivity in the asymmetric Staudinger reaction.

3.4 : Results & Discussion

Preparation of the imine 3.4

The aldehyde was prepared from diacetonide-D-glucose in 3 steps following a reported[5-6] procedure. This aldehyde was converted into the imine on treatment with p-anisidine in methylene chloride at RT in presence of $MgSO_4$ (*Scheme 4*). After the completion of the reaction (TLC), the filtration and concentration of the filtrate provided the imine **3.4**, which was used as such for the [2+2] cycloaddition reaction step without further purification *(Scheme 4).*

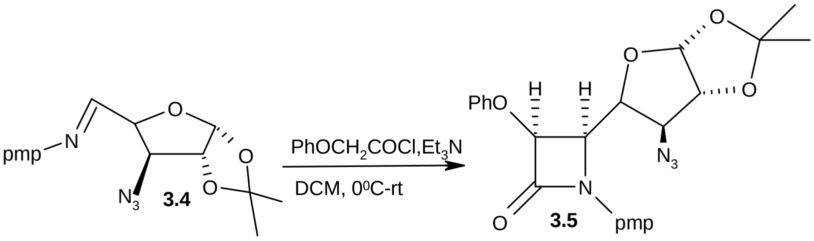
Scheme 4


NaN$_3$
DMF/reflux
2.2
3.1
0.8%H$_2$SO$_4$,MeOH
3.2
NaIO$_4$,acetone
3.3
R1NH$_2$,MgSO$_4$
DCM
R1
N$_3$
3.4
R1=PMP

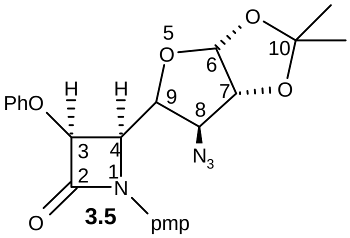
Preparation of* b*-lactam 3.5

A solution of phenoxyacetyl chloride in methylene chloride was added to a solution of the imine (**3.4**), triethylamine at 0 ^{0}C under argon. The resulting mixture was allowed to warm up to room temperature and stirred overnight, after the usual workup and column chromatography, the product was isolated as a single *cis* diastereomer **3.5** in good yield (92%) (*Scheme 5*).

Scheme 5


pmp
N$_3$
3.4
PhOCH$_2$COCl,Et$_3$N
DCM, 0^{0}C-rt
PhO
H
H
N$_3$
O
3.5
pmp

The β-lactam **3.5** was isolated as colourless oil. The IR spectrum of this compound showed a strong band at 1761.97, indicating the presence of the carbonyl group of β-lactam ring and a band at 2113.84 corresponding to the azido group.



3.5

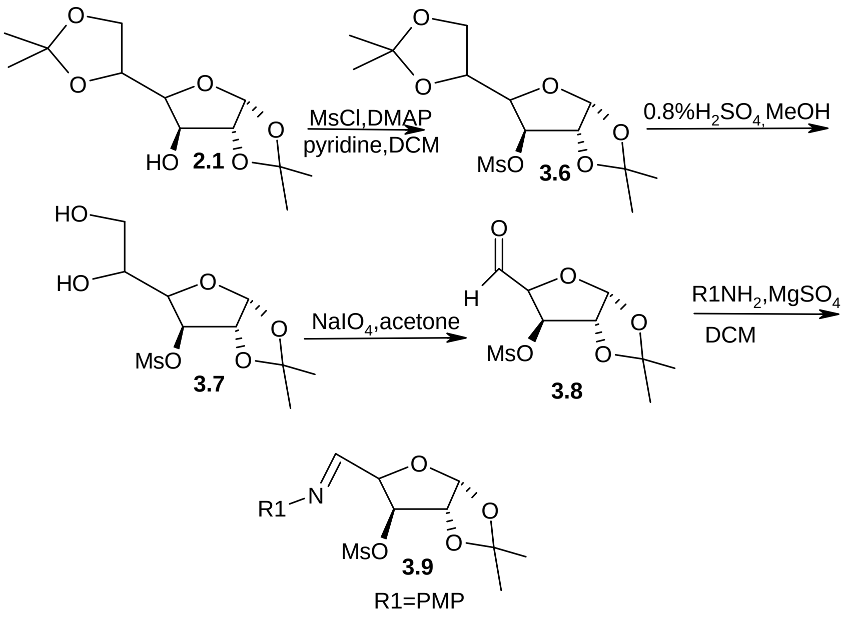
The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.33 and 1.5. The anomeric proton H-6 shows a doublet at 6.03 with J=3.5 Hz. The proton H-7 adjacent to the anomeric proton appeared at 4.73 as a doublet with J=3.5 Hz. The proton H-8 shows singlet at 4.45. The H-4 proton of the *b*-lactam ring was merged with the proton H-9 and appeared as a multiplet to at 4.55-4.65 the. The H-3 proton of the*b*-lactam ring shows doublet at 5.5 with J=4.7 Hz. The methoxy protons of the PMP appeared as a singlet at 3.8. The aromatic protons appeared in the region 6.8-7.75.

In the ^{13}C NMR spectrum of this compound, β-lactam carbonyl carbon appeared at 162.9 cm^{-1}. Two methyls of the acetonide group attached to the C-10 carbon appeared at 26.02 and 26.38. The signals from the methoxy group of PMP moiety as well as the *b*-lactam carbon C-4 and carbon bearing the azido group resonated as 3 peaks at 55.17, 58.66, and 66.41. The β-lactam carbons C-3 and the chiral backbone C-7, C-9 appeared at 79.21, 80.23, and 83.21. The anomeric carbon C-6 appeared at 104.24. The C-10 carbon of the acetonide group appeared at 112.14. The aromatic carbons appeared in the region 113.83 to 157.13.
The mass spectral analysis of this compound showed the molecular ion peak at 452 (100%), which is also the base peak.

Preparation of the imine 3.9

The aldehyde **3.8** was prepared from diacetonide-D-glucose in 3 steps following a reported[6-7] procedure. This aldehyde was converted into the imine on treatment with p-anisidine in methylene chloride at RT in presence of $MgSO_4$ (*Scheme 6*). After the completion of the reaction (TLC), filtration and concentration of the filtrate provided the imine **3.9**, which was used as such for the [2+2] cycloaddition step without any purification.

Scheme 6

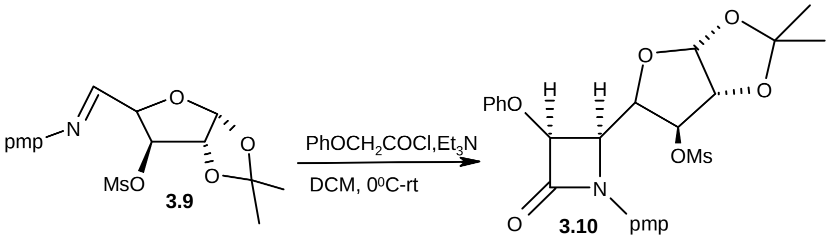


HO
2.1
MsCl,DMAP
pyridine,DCM
MsO
3.6
0.8%H2SO4,MeOH
HO
HO
MsO
3.7
NaIO4,acetone
H
MsO
3.8
R1NH2,MgSO4
DCM
R1
N
MsO
3.9
R1=PMP

Preparation of b-lactam 3.10

A solution of phenoxyacetyl chloride in methylene chloride was added to a solution of the imine (**3.9**), triethylamine at 0 ^{0}C under argon. The resulting mixture was allowed to warm up to rt and stirred overnight, after the usual work up and column chromatography provided β-lactam **3.10** as a single *cis* diastereomer in good yield (*Scheme 7*).

Scheme 7



pmp
N
MsO
3.9
PhOCH2COCl,Et3N
DCM, 0ºC-rt
PhO
H
H
OMs
N
pmp
3.10

The β-lactam **3.10** was isolated as white solid, mp 246 ^{o}C. The IR spectrum of this compound showed a strong band at 1753.17 indicating the presence of the carbonyl group of β-lactam ring.

The ^{1}H NMR spectrum showed methyl protons of the sugar ring as two singlets at 1.3 and 1.5. The anomeric proton H-6 showed a doublet at 6.11 with J=3.4 Hz. The proton H-7 adjacent to the anomeric proton appeared as a doublet at 4.88 with J=3.4 Hz. The peaks due

H-4 proton of the *b*-lactam ring were merged with the proton H-9 of sugar moiety and appeared as a multiplet at 4.6-4.8. The H-8 proton shows a doublet at 5.59 with J=2.5 Hz. The H-3 proton of the *b*-lactam ring showed doublet at 5.42 with J=5.3 Hz. The singlet at 2.95 could be assigned to the mesylate methyl protons, while a singlet at 3.8 to the methoxy of the p-anisyl. The aromatic protons appeared in the region 6.8-7.8.

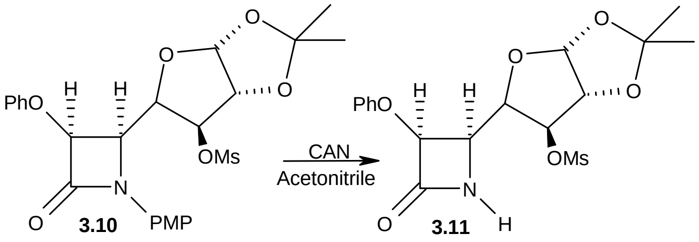
In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl carbon appeared at 163.12. The two methyls of the acetonide group attached to the C-10 carbon appeared at 26.13 and 26.49. The signals from the methoxy group of PMP moiety as well as the β-lactam carbon C-4 and the methyl carbon of the mesylate group resonated as 3 peaks at 38.44, 55.35, and 57.26. The β-lactam carbons C-3 and the chiral backbone C-7, C-8, C-9 appeared at 79.39, 79.98, 82.33, and 83.18. The anomeric carbon C-6 appeared at 104.42. The quaternary carbon, C-10 of the acetonide group appeared at 112.69. The aromatic carbons appeared in the region 114.02 to 157.06.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 505 (100%) as a base peak.

Preparation of N-unsubstituted b-lactam 3.11

To a solution of **3.10** in acetonitrile, was added a solution of CAN[8] in water at 0 ^{0}C and the reaction mixture was stirred at this temperature for 1 hr. After the completion of the reaction, cold water was added to the reaction mixture and extracted with EtOAc and after the usual workup and column chromatography of the crude product gave NH-β-lactam **3.11** as a gummy substance (*Scheme 8*) in good yield.

(*Scheme 8*)



The IR spectrum showed a broad band at 3300 corresponding to the NH stretching of the β-lactam. The β-lactam carbonyl was seen at 1778.25 as a strong band.

The ^{1}H NMR of this compound showed a broad singlet at 6.7 corresponding to the NH proton of the N-unsubstituted β-lactam. The other protons appeared in their usual regions and were consistent with the structure of the compound.

The mass spectral analysis of this compound showed the molecular ion peak at 399 (100%) as a base peak.

3.5 : Summary

A highly diastereospecific synthesis of *b*-lactams was carried out *via* Staudinger reaction, using the imines derived from D-glucose. A single diastereomer with exclusively *cis* stereochemistry was obtained in all the cases.

3.6 : Experimental

All dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Dichloromethane was dried over anhydrous P_2O_5, stored over 4Å molecular sieves. Acetone was purified by distilling over $KMnO_4$, and dried over anhydrous $CaSO_4$, and stored over K_2CO_3.

Synthesis of 3-Azido-3-deoxy-1,2:5,6-di-O-isopropylidene α-D-glucofuranose 3.1

A solution of iodide **2.2** (2.5 g, 6.75 mmol), and sodium azide (3.95 g, 60.8 mmol) in DMF (50 ml) was heated to 105 ^{0}C and kept at this temperature for 18 hrs. The reaction mixture was cooled to room temprature and solvent was removed under reduced pressure. The mass that remains was extracted with EtOAc and washed with water. The aqueous layer was back-extracted with EtOAc several times. The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate upon evaporation gave residue, which was purified by column chromatography to afford the azide **3.1** as a semisolid (1.24 g, 65.60%).

^{1}H NMR ($CDCl_3$) **:** 1.32 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.51 (s, 3H), 3.96
(200 MHz) (dd, J = 4.2 and 4.7 Hz, 1H), 4.08 to 4.28 (m, 4H), 4.61 (d,
J = 3.6 Hz, 1H), 5.85 (d, J = 3.6 Hz, 1H).

Synthesis of 3-Azido-3-deoxy-1, 2–O-isopropylidene α-D-glucofuranose 3.2

To a solution of **3.1** (2.85 g, 10 mmol) in MeOH (35 ml), 0.8% H_2SO_4 (3 ml) was added and stirred at room temprature till the disappearance of the starting material (TLC, ca. 24 hrs). The acid was quenched with triethylamine (3 ml). The solvents was removed by distillation under reduced pressure and the residue was taken up in EtOAc, it was washed with water, saturated solution of brine, dried over sodium sulphate, and concentrated under reduced pressure to give the diol **3.2** (2.1 g, 85%), which was pure enough to be used for the next reaction without further purification.

Synthesis of aldehyde 3.3

To a solution of the diol **3.2** (2.45 g, 10 mmol) in a mixture of acetone (25 ml) and water (25 ml) was added $NaIO_4$ (4.27 g, 20 mmol) in small portions. The white suspension was stirred for an additional 30 min, filtered through a pad of celite and organic solvent was removed under vacuum. The white residue was then extracted with EtOAc and the combined organic extracts were dried and filtered. The removal of the solvent by distillation under reduced pressure afforded the pure aldehyde **3.3** (1.8 g, 84%), which was used as such for the next step.

IR ($CHCl_3$) : 1712.67, 1747.39, 2987.53
^{1}H NMR ($CDCl_3$) : 1.33 (s, 3H), 1.51 (s, 3H), 2.04 (s, 3H), 4.59 (d, 1H, J = 3.4
(200 MHz) Hz), 4.73 (d, 1H, J = 3.4 Hz), 5.49 (d, 1H, J = 3.9 Hz), 6.08
(d, 1H, J = 3.9 Hz), 9.64 (d, 1H, J =0.9 Hz)

Synthesis of imines 3.4

To a solution of the p-anisidine (0.615 g, 5 mmol) in CH_2Cl_2 (25 ml), and anhydrous $MgSO_4$, (1.8 g, 15 mmol) a solution of the aldehyde **3.3** (1.06 g, 5 mmol) in CH_2Cl_2 were added. This mixture was stirred for 4 hrs (TLC). The reaction mixture was filtered through a pad of celite in a sintered glass crucible. The filtrate was concentrated to get the imines **3.4** (1.44 g, 91%), which were used as such for the next step of β-lactam ring formation.

Synthesis of b-lactam 3.5

To a stirred solution of imine **3.4** (0.318 g, 1 mmol) and Et_3N (0.46 g, 4.5 mmol) in dry dichloromethane (15 mL), a solution of phenoxyacetyl chloride (0.25 g, 1.5 mmol) in methylene chloride was added drop-wise at 0 °C over a period of 1 h. The reaction mixture was allowed to warm up to room temperature and stirred overnight. It was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue on column chromatography (silica gel, 230-400 pet. ether / ethyl acetate) gave a single diastereomer of *cis*-***b***-lactam **3.5** as an oil (0.42 g, 92%).

$[a]_D^{25}$: +125.8 (c = 1, $CHCl_3$)
IR (cm^{-1}) : 1761.97, 2113.84
^{1}H NMR : 1.33 (s, 3H), 1.5 (s, 3H), 3.8 (s, 3H), 4.45 (s, 1H), 4.55-4.65
(m, 2H), 4.73 (d, J=3.5 Hz, 1H), 5.5 (d, J=4.7 Hz, 1H), 6.03

(d, J=3.5 Hz, 1H), 6.8-7.75 (m, 9H).

^{13}C NMR : 26.02, 26.38, 55.17, 58.66, 66.41, 79.21, 80.23, 83.21, 104.24, 112.14, 113.83, 115.71, 119.49, 122.69, 129.6, 130.74, 156.51, 157.13, 162.9.

MS (*m/z*) : 452 (M+)

Microanalysis :

$C_{19}H_{22}NO_5I$	Calculated	C: 61.05	H: 5.35	N: 12.38
	Obtained	C: 61.23	H: 5.22	N: 12.56

Synthesis of 3-deoxy-3-Methane sulphonyl-1,2:5,6-di-O-isopropylidene a-D-glucofuranose 3.6

To a solution of the diacetonide **2.1** (2.6 g, 10 mmol) in anhydrous methylene chloride (50 mL) were added triethylamine (1.02 g, 10 mmol), methane sulphonyl chloride (1.37 g, 12 mmol) and a catalytic amount of DMAP (0.73 g, 6 mmol) at 0 ^{0}C. The mixture was stirred for 24 hrs at room temperature. The organic layer was separated and washed several times with water, and brine soln., dried over Na_2SO_4 and concentrated to get the crude acetate, which was then purified by column chromatography to get pure **3.6** as a white solid (3.2 g, 94%).

Synthesis of 3-deoxy-3-Methanesulphonyl-1,2–O-isopropylidene a-D- glucofuranose 3.7

To a solution of **3.6** (3.38 g, 10 mmol) in MeOH (35 ml), 0.8% H_2SO_4 (3.6 ml) was added and stirred at room temperature till the disappearance of the starting material (TLC, ca. 24 hrs). The acid was quenched with triethylamine (3.6 ml). The solvents was evaporated under reduced pressure and the residue was taken in $CHCl_3$, it was then washed with water, saturated solution of brine, dried over sodium sulphate, and concentrated under reduced pressure to give the diol **3.7** (2.7 g, 90%), which was pure enough to be used for the next reaction without further purification.

Synthesis of aldehydes 3.8

To a solution of the diol **3.7** (0.596 g, 2 mmol) in a mixture of acetone (25 ml) and water (25 ml) was added $NaIO_4$ (0.85 g, 4 mmol) in small portions. The white suspension was stirred for an additional 30 min, filtered through a pad of celite and freed of solvents in vacuum. The white residue was then extracted with EtOAc and the combined organic extracts were dried and filtered. Evaporation of the solvent under reduced pressure afforded the pure aldehyde **3.8** (0.5 g, 94%).

Synthesis of imine 3.9

To a mixture of the p-anisidine (0.246 g, 2 mmol) in CH_2Cl_2, and anhyd. $MgSO_4$, (0.96 g, 8 mmol) was added a solution of the aldehyde **3.8** (0.532 g, 2 mmol) in CH_2Cl_2. The mixture was stirred for 4 hrs (TLC). The mixture was filtered through a pad of celite in a sintered glass crucible. The filtrate was concentrated to get the imine **3.9** (0.7 g, 94%) which were used as such for the β-lactam ring formation.

Synthesis of b-lactams 3.10

To a stirred solution of imine **3.9** (0.371 g, 1 mmol) and Et_3N (0.45 g, 4.5 mmol) in dry dichloromethane (15 mL), a solution of phenoxyacetyl chloride (0.255 g, 1.5 mmol) in methylene chloride was added drop-wise at 0 °C over a period of 1 hr. The reaction mixture was allowed to warm up to room temperature and stirred overnight. It was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue on column chromatography (silica gel, 230-400 pet. ether / ethyl acetate) gave a single diastereomer of *cis*-*b*-lactams, which was purified by column chromatography to give **3.10** as an oil (0.48 g, 95%).

[a]$_D^{25}$: -268.29 (c = 1.85, CH_2Cl_2)

IR (cm^{-1}) : 1753.17.

^{1}H NMR : 1.3 (s, 3H), 1.5 (s, 3H), 2.95 (s, 3H), 3.8 (s, 3H), 4.6-4.8 (m, 2H), 4.88 (d, J=3.4 Hz, 1H), 5.42 (d, 5.3 Hz, 1H), 5.59(d, J=2.5 Hz, 1H), 6.11(d, J=3.4 Hz, 1H), 6.8-7.8 (m, 9H).

^{13}C NMR : 26.13, 26.49, 38,44, 55.35, 57.26, 79.39, 79.98, 82.33, 83.18, 104.42, 112.69, 114.02, 116.18, 119.79, 122.91, 129.67, 130.70, 156.76, 157.06, 163.12.

MS : 505 (m+)

Microanalysis :

$C_{24}H_{27}NO_9S$	Calculated	C: 57.02	H: 5.38	N: 2.77
	Obtained	C: 57.14	H: 5.49	N: 2.84

Synthesis of b-lactam 3.11

To a solution of **3.10** (0.489 g, 1 mmol) in acetonitrile (15 mL), a solution of CAN (1.64 g, 3 mmol) in water (10 ml) was added at 0 ^{0}C and the reaction mixture was stirred at this temperature for 1 hr. After the completion of the reaction, cold water was added to the reaction mixture and extracted with EtOAc (3x30 mL) and the combined organic layers were washed with 5% sodium bicarbonate solution, 10% sodium sulphate solution followed by satd. sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product **3.11** as a gummy substance (0.34g, 88%).

M.P. : Oil

$[a]_D^{25}$: +20.15 (c = 1.85, CH_2Cl_2)

IR (cm^{-1}) : 1778.25, 3300

^{1}H NMR : 1.3 (s, 3H), 1.5 (s, 3H), 3 (s, 3H), 4.1-4.25 (m, 1H), 4.5-4.65 (dd, J=2 and 2.4Hz, 1H), 4.82 (d, J=2.9 Hz, 1H), 5.3-5.45 (m, 2H), 6.02 (d, J=2.9 Hz, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 5H).

Mass : 399(m+)

Microanalysis :

$C_{20}H_{24}NO_5I$	Calculated	C: 51.12	H: 5.30	N: 3.51
	Obtained	C: 51.39	H: 5.46	N: 3.69

3.7 : References

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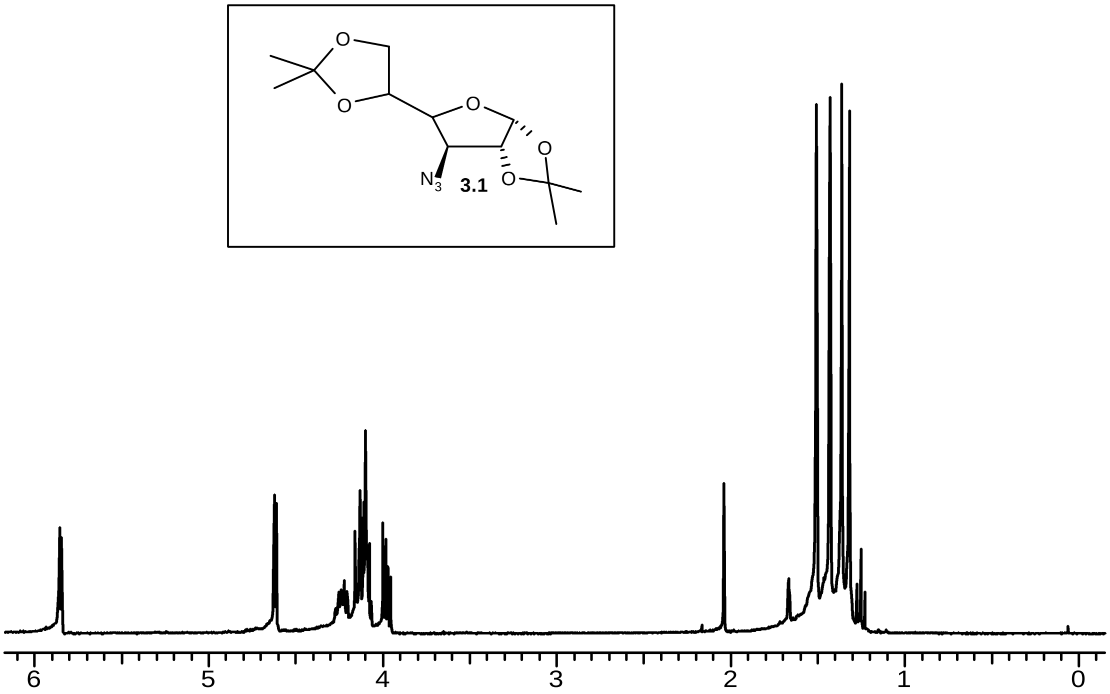
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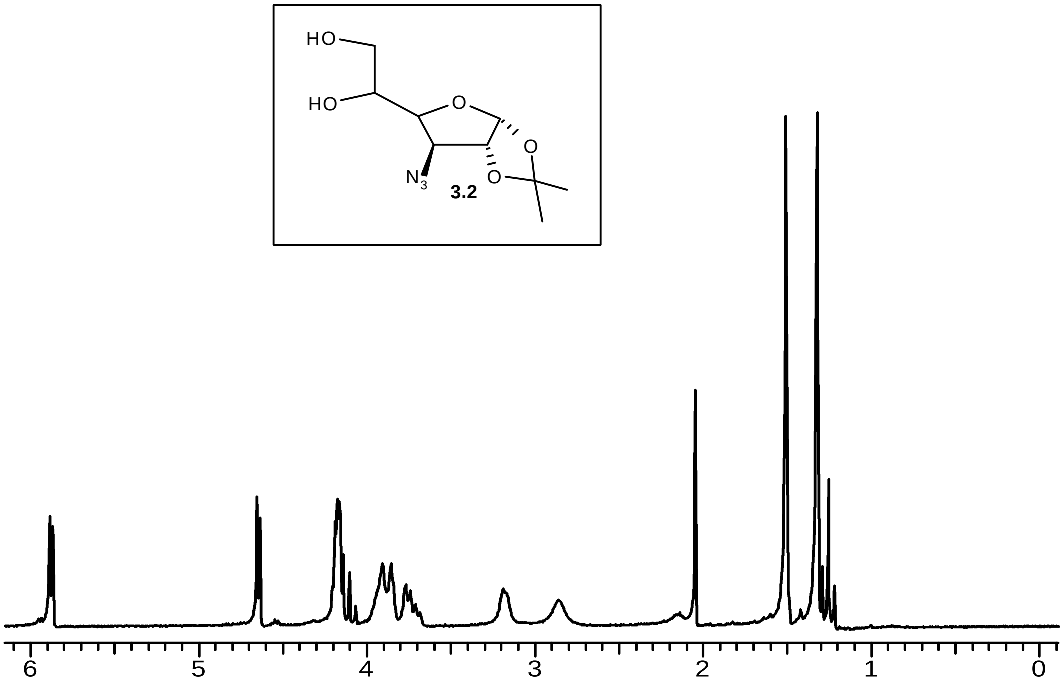
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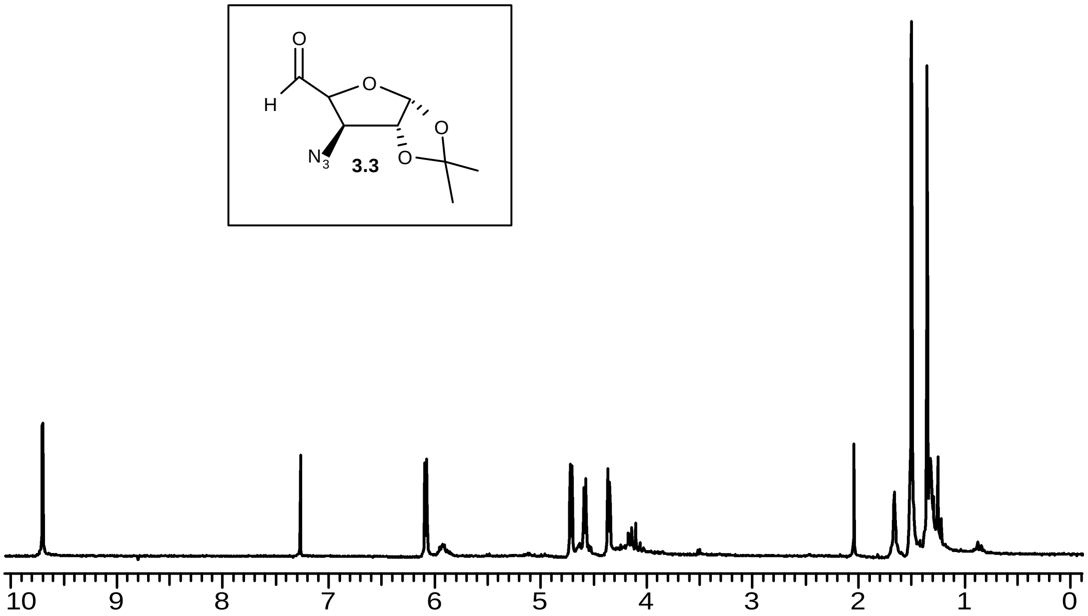
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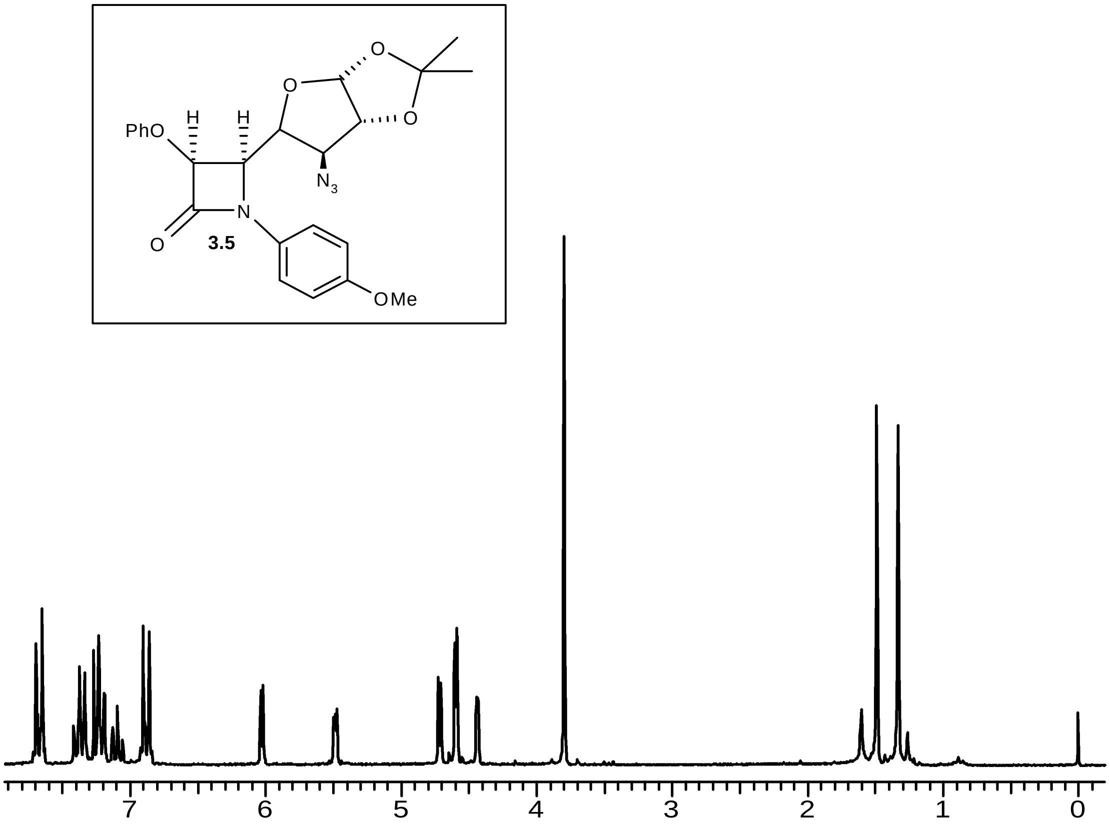
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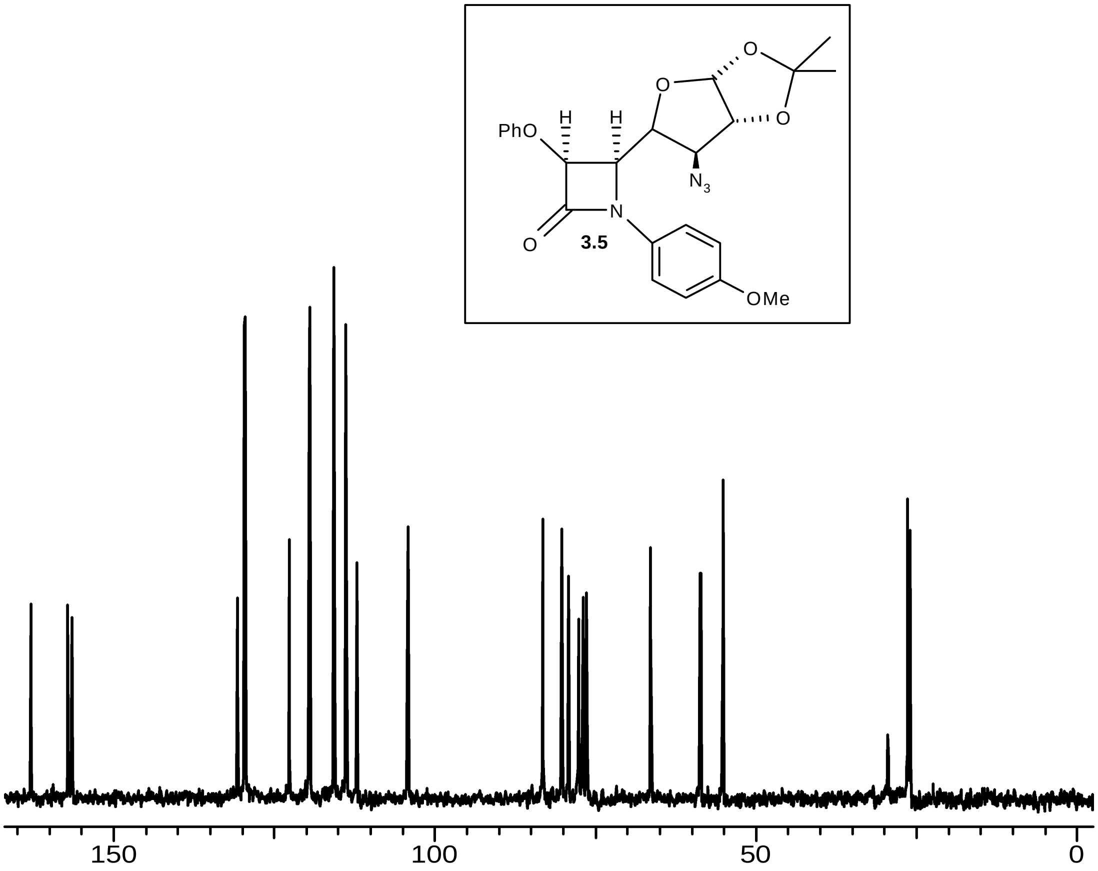
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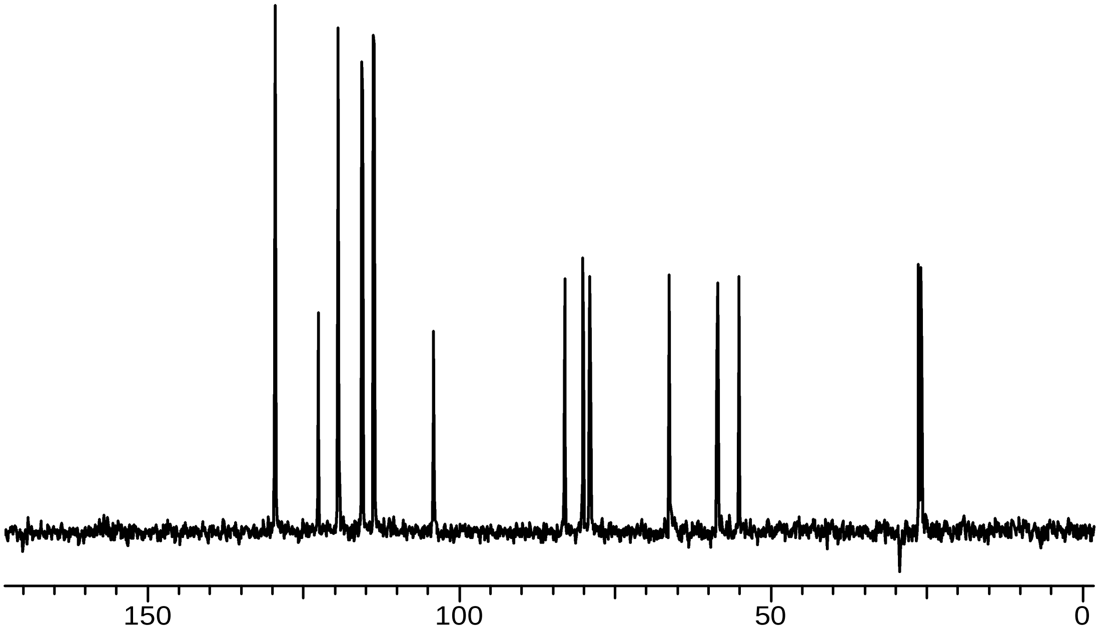
150
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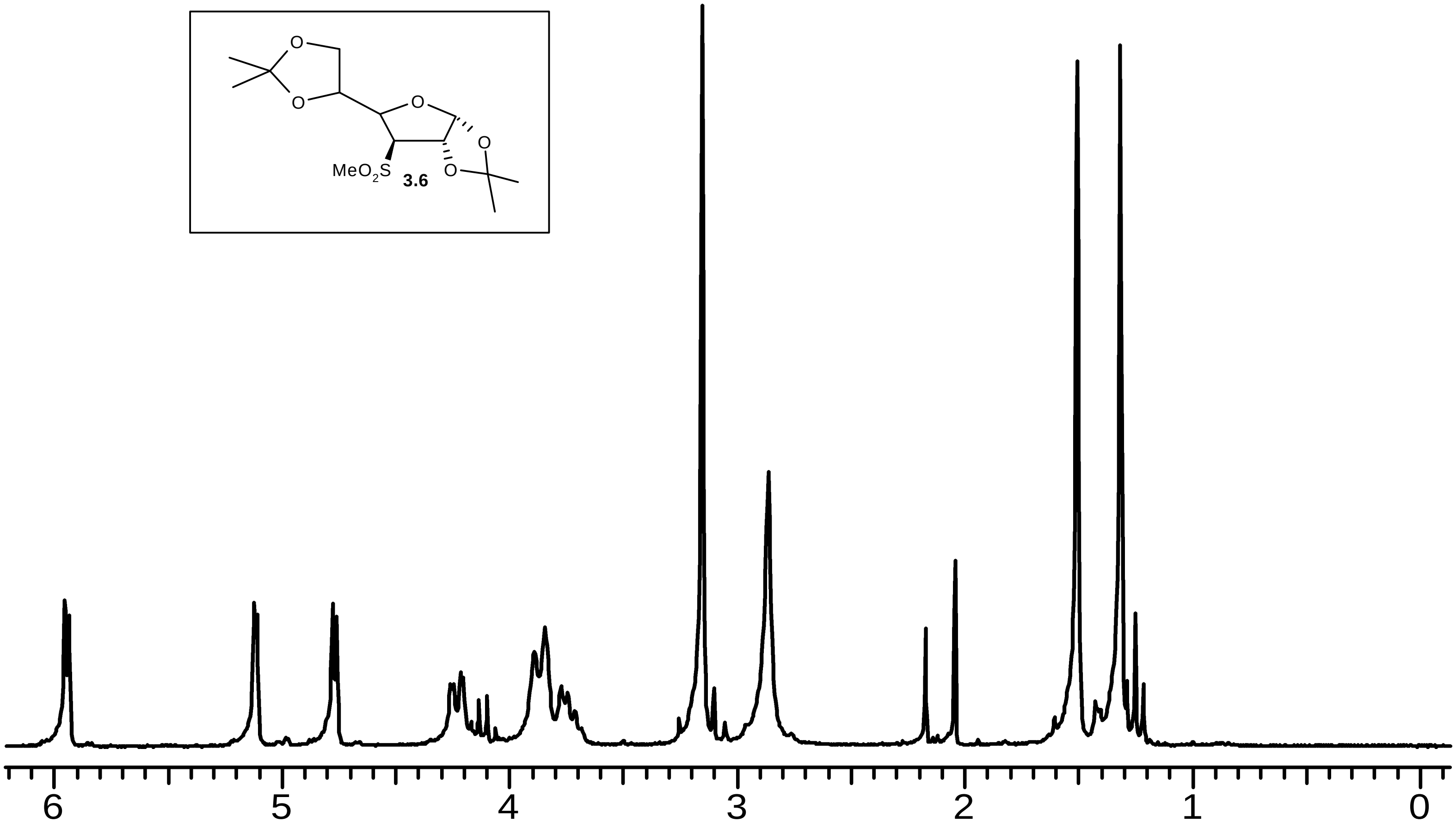
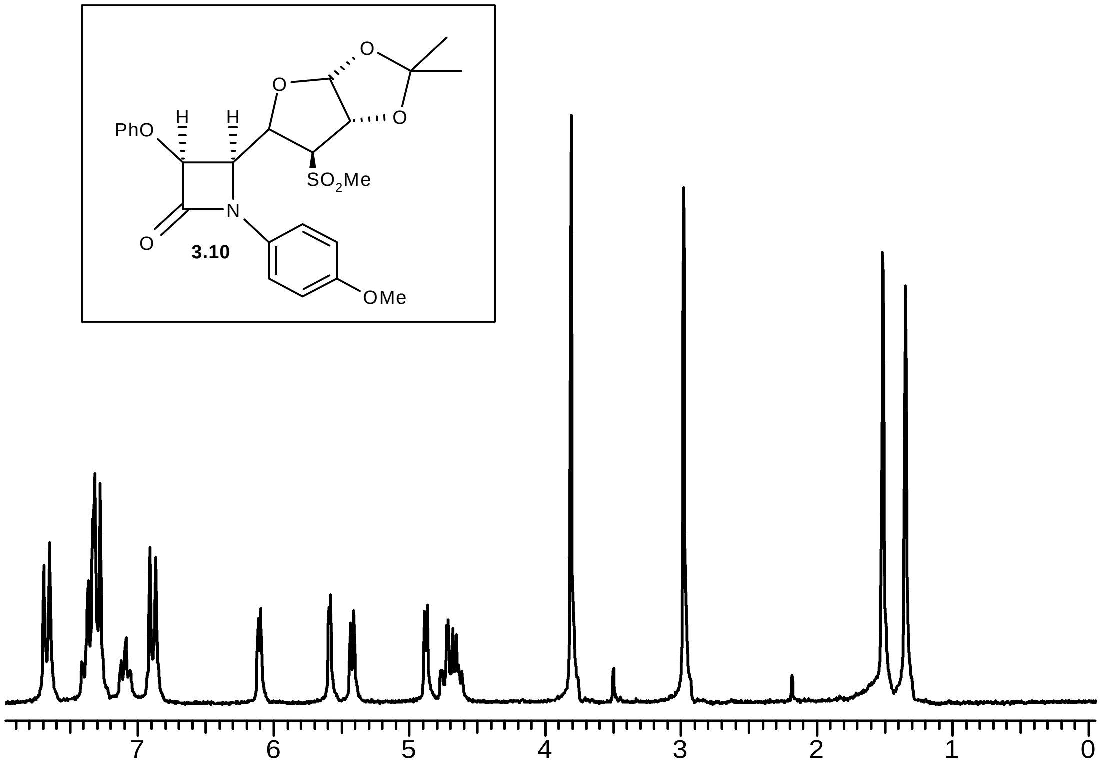
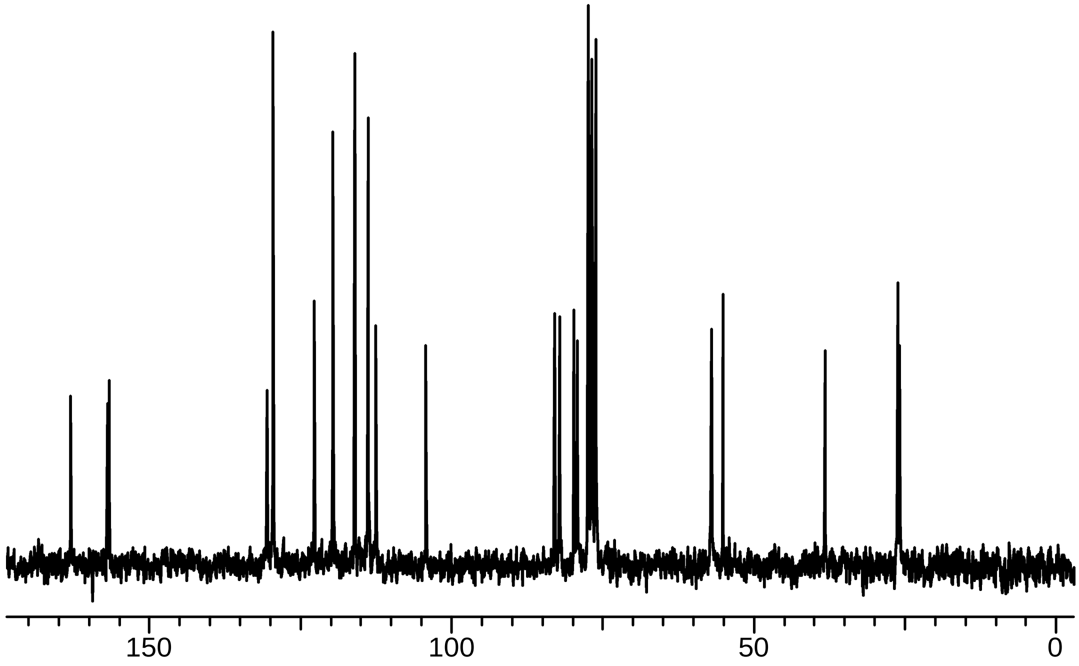
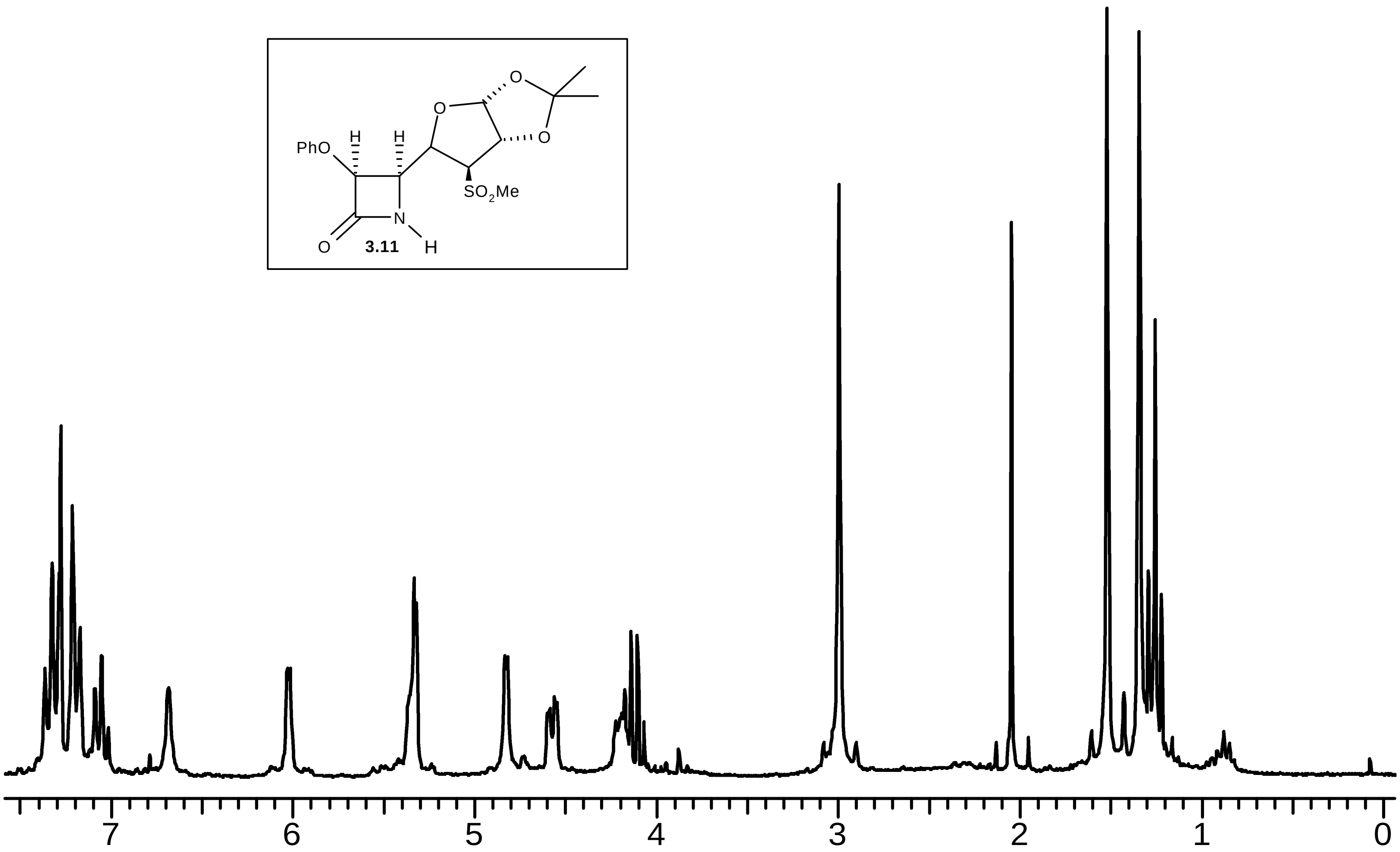


3.6



3.10





3.11

Chapter IV

Diastereoselective synthesis of novel tetracyclic b-lactams via intramolecular radical addition to alkene bond.

4.1 : Abstract

This chapter deals with the radical chemistry of *b*-lactams, which is mainly used as a methodology for the synthesis of bicyclic antibiotics. The *b*-lactams **2.6a**, **2.7a-b**, and **2.12** were suitable radical systems with radical acceptors in the form of allyl double bond at the nitrogen of the *b*-lactam ring and iodo substituted carbohydrate skeleton at C-4 carbon of the *b*-lactam ring as a radical generator. These *b*-lactams on treatment with Bu_3SnH in refluxing toluene under went smooth diastereospecific *7-endo-trig* cyclization to tricyclic *b*-lactams **4.1**, **4.2** and **4.3** in excellent yields.

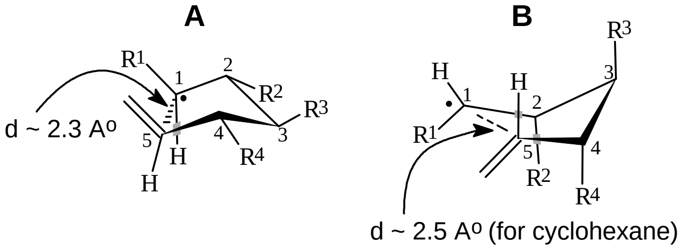
4.2 : Introduction

Almost 100 years ago, Moses Gomberg's paper,[1] 'An Instance of Trivalent Carbon: Triphenylmethyl' appeared in the December 5th, 1900 issue of the *Journal of the American Chemical Society*. The concluding cautionary note of the paper was '*This work will be continued and I wish to reserve the field to myself*'. This was just the beginning of radical chemistry and Gomberg was in true sense the pioneer of radical chemistry.

Initially, radical chemistry was restricted to gas phase reactions due to their erratic, capricious nature and they involved highly reactive species with poor synthetic utility. However, latter on with pioneering work by Julia[2], Kharash[3], Lamb,[4] followed by physical organic work by Ingold,[5] Walling[6] and recently by Curran, Porter, Giese,[7] Newcomb,[8] the concept of radical chemistry has changed dramatically and it has become a powerful branch of synthetic organic chemistry.

Among radical reactions, the ring construction by free radical cyclisation[9] has been accepted as a useful technique and important synthetic methodology, especially in the total synthesis of natural products.[10] A large body of research and systematic studies that has gone into this subject has led to the evolution of certain principles and guidelines[11] regarding the stereochemistry of radical cyclisation. Hexenyl radical[9] cyclisation is the most efficient and well-studied cyclization for mechanistic as well as synthetic applications. The general stereochemical outcome of such kind of cyclisation can be predicted by using Beckwith's transition state model *(Scheme 1).*[11]

Scheme 1



Beckwith's Transition state model for hexenyl radical cyclisation

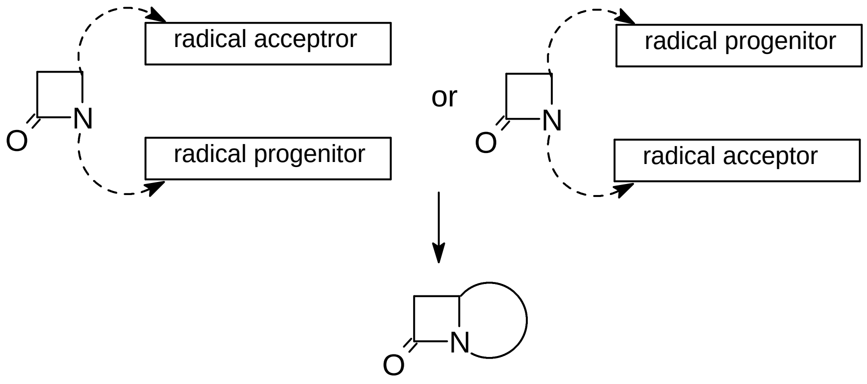
This model invokes a transition state in hexenyl radical cyclisation, which has a long incipient bond (~2.3Å), which is not much different from that between C_1 & C_5 in cyclohexane (ca. 2.5 Å).

Radical Chemistry of b-Lactams:

The increasing bacterial resistance[12] to the classical antibiotics led to the development of novel multicyclic β-lactam systems. Since the biological activity of β-lactam antibiotics is correlated with the enhanced chemical reactivity of the strained 4 membered ring function,[13] the major modification has been in the ring, attached from the nitrogen. The synthesis and biological testing of the novel molecular nuclei, different from the classical β-lactams like penicilins and cephalosporins, led to the discovery of synthetic antibiotics like oxacephems, carbacephems, thienamycin, PS-5 and so on.

The limited stability of these antibiotics to the ionic conditions and susceptibility to nucleophilic reagents made researchers to design their synthetic plans based on the free radical methodology. The free radical based strategy involves the construction of appropriately functionalized and properly substituted β-lactams, which provides molecular framework suitable for cyclization *(Scheme 2).*

Scheme 2

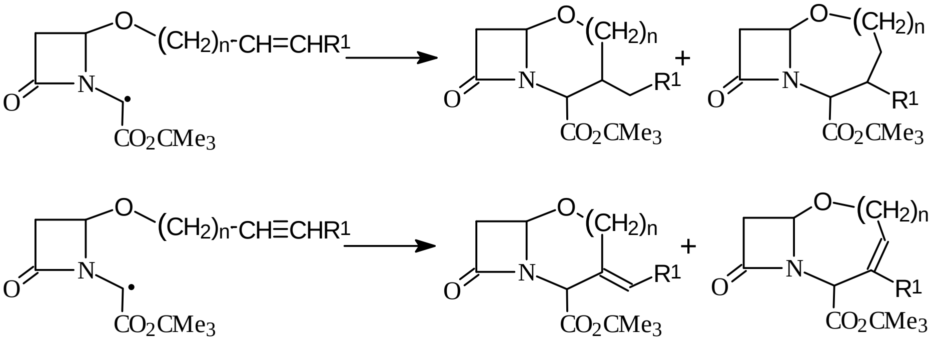


The molecular appendages in the form of substituted double bond attached to the nitrogen or C-4 carbon of the *b*-lactam ring acts as a radical acceptor while functional groups like halo, phenylseleno, phenylthio or acetylenic triple bond acts as a radical progenitor species.

Synthesis of Oxacephams, Oxapenams and Oxabicyclo b-Lactam Derivatives:

Bachi introduced and successfully used radical methodologies in the *b*-lactam field, which he first applied for the synthesis of oxacephems. As most of these antibiotics are highly susceptible towards nucleophilic reagents, he thought that, free radical cyclisation could be a method of choice. His strategy involved use of N-chloromethyl *b*-lactams as substrates for the synthesis of oxacephems. The radical acceptors in the form acetylenic or allylic substituents at C-4 position were used. These derivatives when subjected to the typical radical cyclisation conditions, terminal olefinic derivatives cyclized exclusively in 7-endo fashion, while substituted olefinic derivatives furnished 6 membered ring by 6-exo annelation *(Scheme 3).*[14]

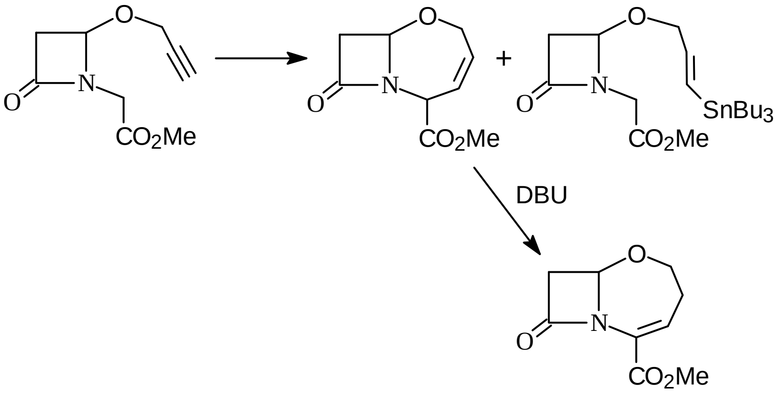
Scheme 3



The instability of N-chloro-*b*-lactams, made him prepare N-phenylseleno and N-phenylthio derivatives.[15] Under typical radical cyclisation conditions these substrates were cyclized in exclusively 7-endo fashion. Similarly, radical acceptors in the form of terminal as well as substituted acetylenic derivatives were prepared and their behavior under radical cyclization conditions was tested.[16] In this case also terminal acetylenic compounds cyclized in 7-endo fashions, while substituted acetylenic derivatives cyclized in 6-exo manners.

Recently, Bachi has reported the synthesis of oxahomocephem, which is obtained by sequential reaction.[17] It involves homolytic intermolecular addition, intramolecular hydrogen transfer, endo intramolecular addition and *b*-elimination as consecutive steps *(Scheme 4).*

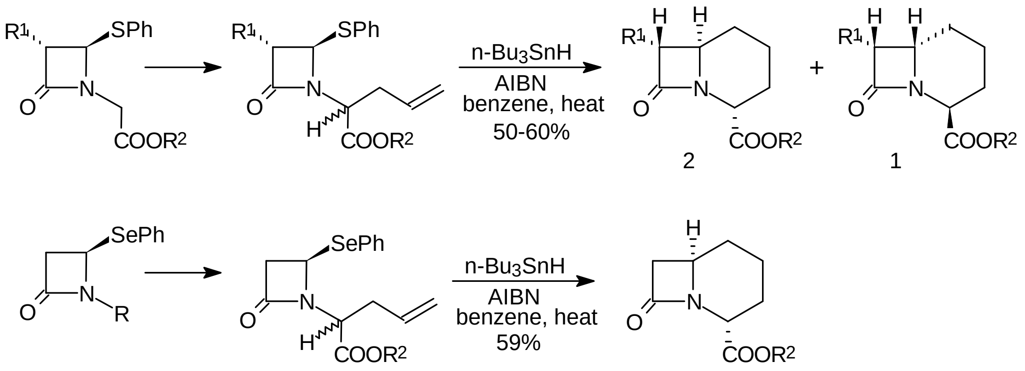
Scheme 4



Carbacephams, Carbapenams and their Derivatives:

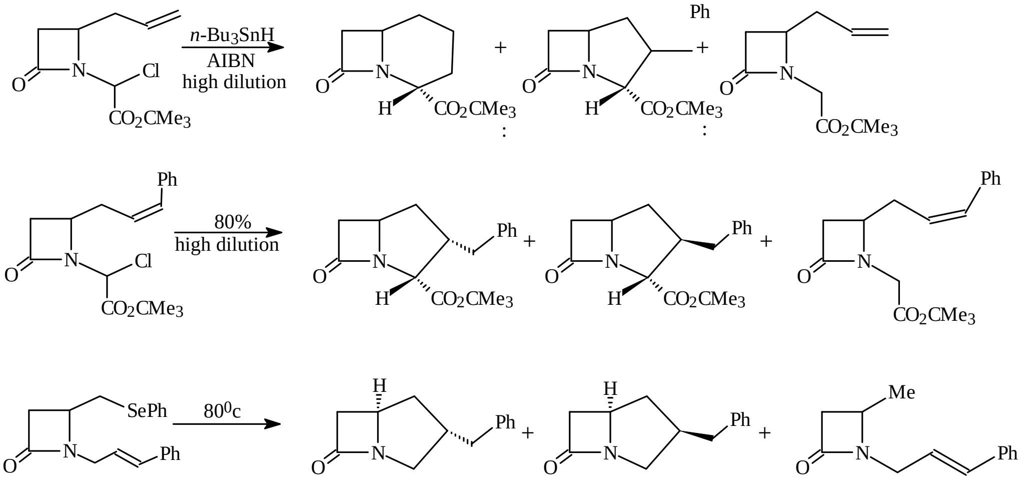
Carbodethia analogues of cephams or penams are called carbapenams or carbacephams.[18] They are proved to be highly effective as *b*-lacatmase inhibitors. Kametani first used radical cyclisation methodology in which he used phenylthio or phenyseleno as radical progenitors. The substituted terminal olefinic or acetylene derivatives attached to the nitrogen of the *b*-lactam core acted as radical acceptors. The olefinic derivatives cyclize efficiently yielding substituted carbacepham in about 66% yield, while acetylenic derivatives cyclized sluggishly. The annulation takes place essentially by 6-endo mode to give [4.2.0] bicyclic ring skeleton (*Scheme 5*).[19]

Scheme 5


R1
SPh
COOR2
H
n-Bu3SnH
AIBN
benzene, heat
50-60%
2
1
SePh
R
59%

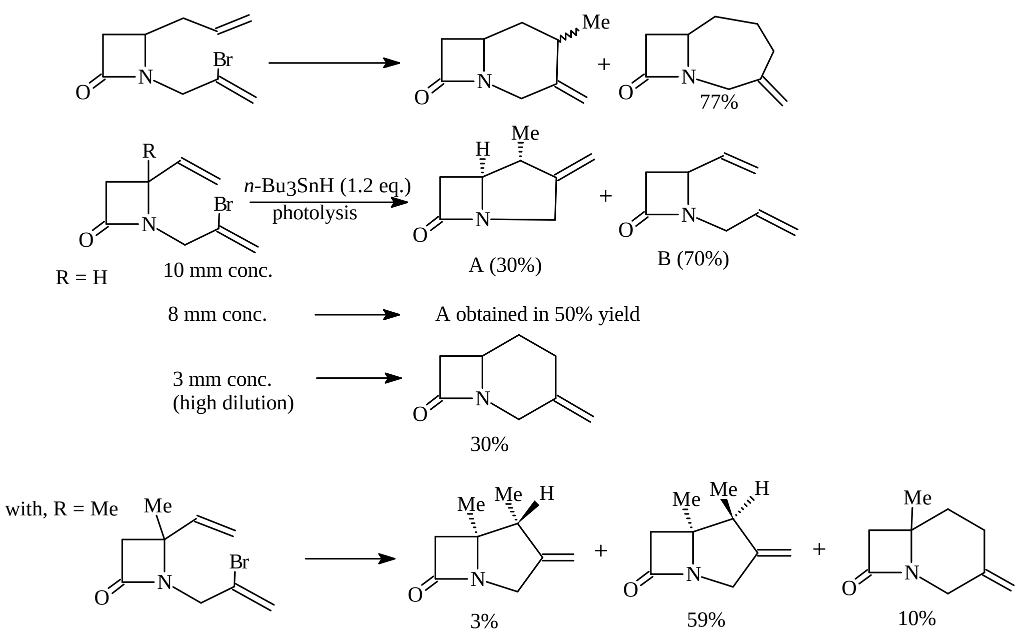
Bachi, has also reported the synthesis of carbapenams and carbacephams by employing modified strategy that he used for the synthesis of oxacephams. He showed that homolytic cyclization of alkenyl *b*-lactams afforded carbapenams by 5-exo addition, when vicinally disubstituted double bond was involved, while carbacephams were the sole products by 6-endo cyclisation when terminal double bond was involved *(Scheme 6)*.[20]

Scheme 6


n-Bu3SnH
AIBN
high dilution
Cl
CO2CMe3
Ph
80%
high dilution
SePh
80⁰c
Me

Parson used strategy based on vinyl radical cyclisation. He used both photochemical as well as thermal conditions for radical cyclisation. In an interesting observation he found that under high dilution conditions the product obtained by 6-endo cyclisation was the major one *(Scheme 7)*.[21]

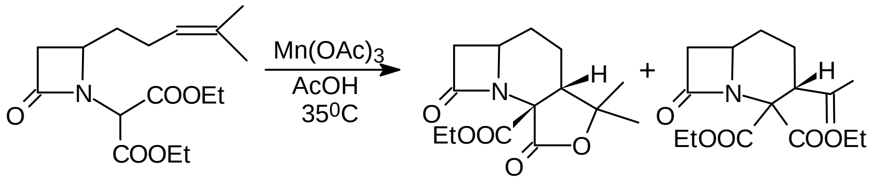
Scheme 7


Me
Br
O
N
+
77%
R
n-Bu3SnH (1.2 eq.)
photolysis
H
Me
A (30%)
B (70%)
R = H
10 mm conc.
8 mm conc.
A obtained in 50% yield
3 mm conc.
(high dilution)
30%
with, R = Me
3%
59%
10%

However, when 4-substituted analogue was cyclized, the product obtained was carbapenam, which was annealed by 5-exo modes. The result was difficult to rationalize on thermodynamic as well as kinetic basis.

Recently, Miller has reported the use of manganese (III) acetate promoted free radical cyclisation methodology for the synthesis of functionalized carbapenams. In the targeted synthesis of Loracarbef, a chloro functionalized carbapenem, he developed a methodology in which the substituted carbapenems were obtained in 60% yield *(Scheme 8)*.[22]

Scheme 8

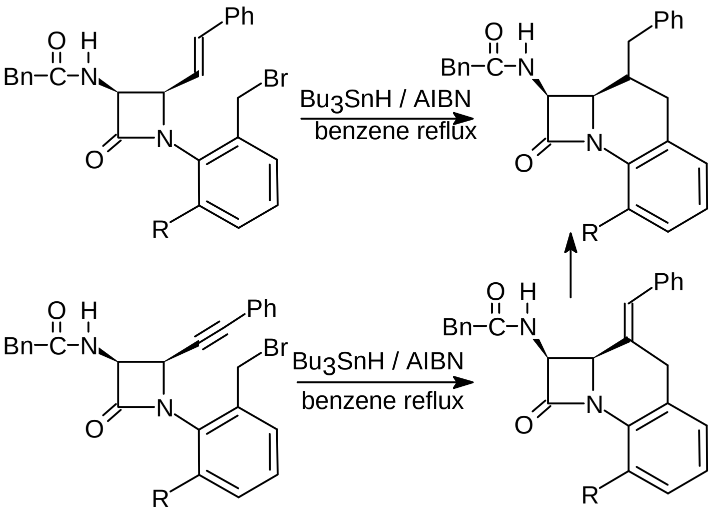

O
N
COOEt
COOEt
Mn(OAc)3
AcOH
35⁰C
H
+
EtOOC
O
COOEt

Synthesis of Bezocarbapenems and Benzocarbacephems:

Benzocarbapenems[23] belong to the class of tricyclic *b*-lactams, which are designed as suicide inactivators of *b*-lactamase. The known instability of these systems under ionic conditions led to the exploration of radical based methodologies for their synthesis.[24]

Just has reported the synthesis of strained tricyclic azetidinone using free radical cyclization based methodology *(Scheme 9).*[25]

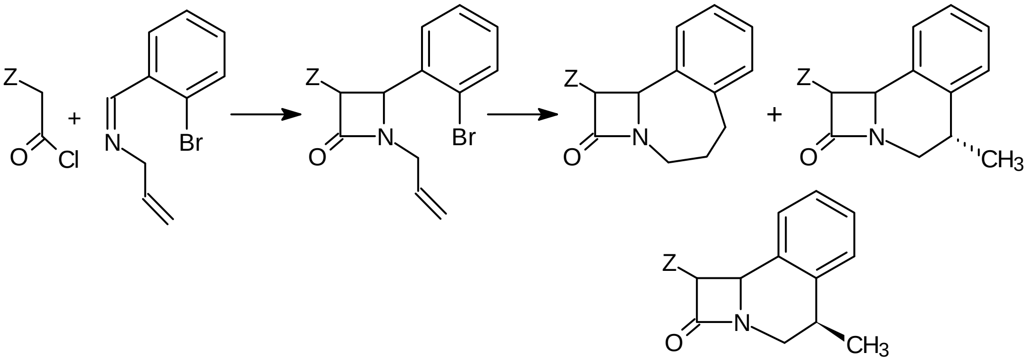
Scheme 9



He observed that the benzocarbapenems, obtained by 5-exo modes were unstable while the benzocarbacephems were stable compounds.

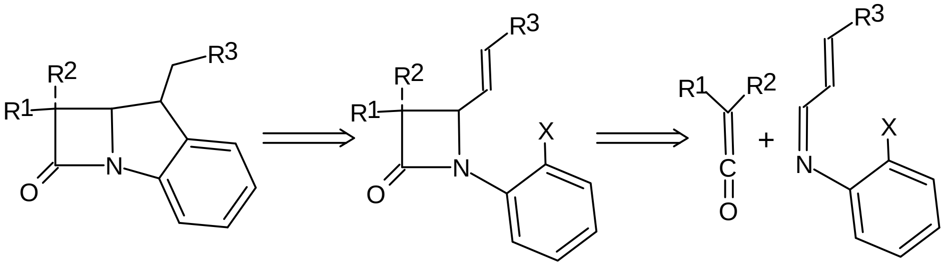
Bose & Manhas used aryl radical cyclization strategy to prepare benzocarbacephems. The use of properly substituted imine, obtainable from o-bromobenzaldehyde and allyl amine was the key step in this methodology. This imine on cycloaddition with acid chlorides afforded *b*-lactams with ideal functionalities for radical cyclisation. Interestingly, 6-exo cyclization was the predominant mode of annulation *(Scheme 10).*[26]

Scheme 10



In another aryl mediated cyclisation strategy, Alcaide, has made use of imines derived from o-bromoaniline and α,β-unsaturated aldehyde. The *b*-lactams cyclized predominantly by 5-exo mode, however, with terminal double bonded derivatives, 6-endo was a competing pathway *(Scheme 11).*[27]

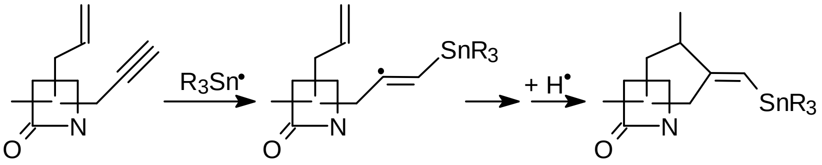
Scheme 11



Recently, Alcaide[28] has reported a novel cyclisation and rearrangement process based on aryl-aryl coupling methodology.

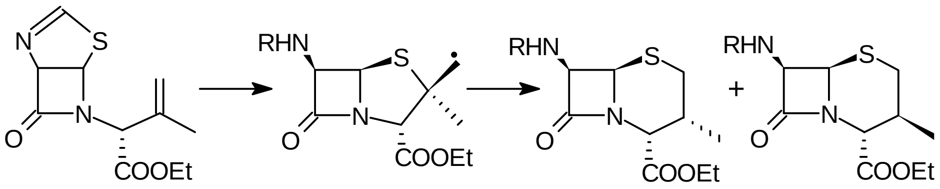
The regio and stereocontrolled radical cyclisation of enyne *b*-lactams to furnish tin functionalized *b*-lactams is reported by using of enynes as radical progenitors. Proteiodestanylation followed by ozonolysis was used to convert these *b*-lactams into the corresponding oxo derivatives *(Scheme 12).*[29]

Scheme 12



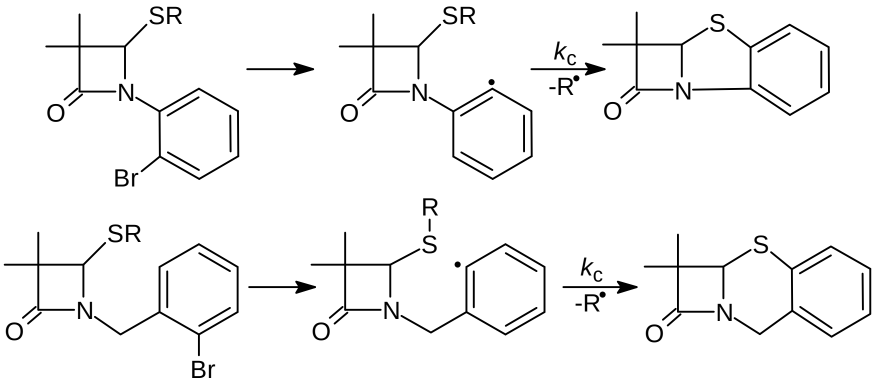
In an other approach, 4-thiyl radical addition onto a substituted N-allyl double bond using Fe (III) and Mn (II) salts is studied. The primary radical formed initially by 5-exo cyclization, rearranges to give 6-membered ring, a cepham derivative in poor to moderate yield *(Scheme 13).*[30]

Scheme 13


N
S
O
N
COOEt
RHN
S
O
N
COOEt
RHN
S
O
N
COOEt
+
RHN
S
O
N
COOEt

Beckwith has studied the formation of fused tricyclic azetidinone by intramolecular radical addition (SH^2 process). In a detailed physiochemical study he determined the approximate rate constants for ring closure, K_c and unimolecular hydrogen atom transfer $K_{1,\,x}$. *(Scheme 14)*[31]

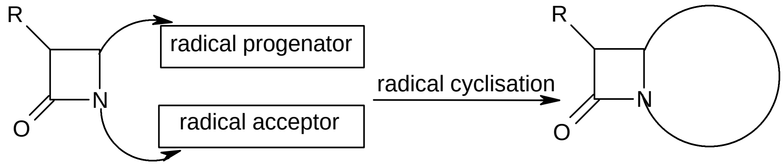
Scheme 14


SR
O
N
Br
SR
O
N
k_c
-R•
S
O
N
SR
O
N
Br
R
S
O
N
k_c
-R•
S
O
N

4.3 : Present Work

The radical chemistry of *b*-lactams is mainly used as a methodology for the synthesis of bicyclic antibiotics. This involves the use of radical generator attached at C-4 carbon and radical acceptor at the nitrogen of the *b*-lactam ring. However, the radical cyclization involving allyl double bond as a radical acceptor and the radical generator at the C-4 of the azetidinone ring *(Scheme 15)* are rarely addressed.

Scheme 15



Earlier two Chapters dealt with the synthesis and use of novel *b*-lactam derivatives, derived from glucose diacetonide. Some of these *b*-lactam derivatives are suitable radical systems with radical acceptors in the form of allyl double bond and iodine attached to the glucose diacetonide skeleton as a radical generator. This chapter describes the reactivity of these *b*-lactams under radical conditions. A study regarding synthesis of novel tetracyclic ring systems and their stereochemistry is presented. The use of NMR spectroscopy as well as single crystal X-ray analysis in the structure determination of the multicyclic *b*-lactam derivatives is also discussed.

4.4 Results & Discussion.

Radical Cyclisation of C 4, 3-Deoxy-3–iodo -1,2;5,6-di-O-isopropylidene-a-D-allofuranose Substituted b-Lactam Derivatives :

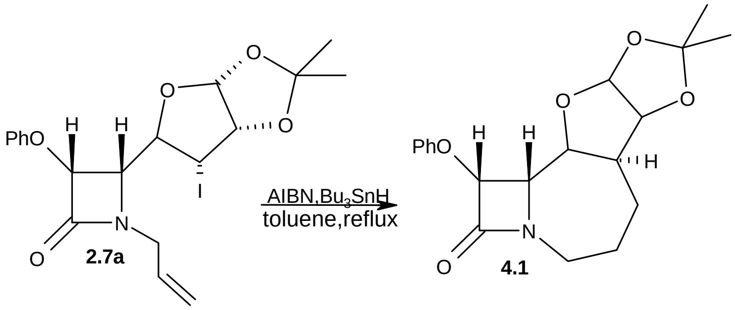
The unique feature associated with all the β-lactam derivatives **2.6a, 2.7a-b** & **2.12** is the presence of iodine at C-4′ centre and presence of allyl double bond attached at nitrogen of the azetidinone nucleus. This system was ideal system for a radical cyclization and it was interesting to study the efficiency of such kind of cyclization.

Radical Cyclization of 2.7a (Synthesis of 4.1)

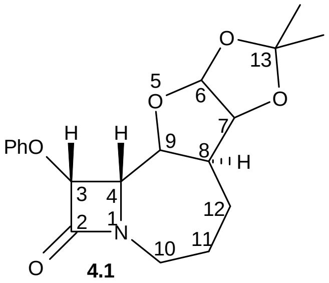
The β-lactam **2.7a** when treated with tributyltin hydride in presence of AIBN in refluxing toluene solution (high dilution conditions and addition *via* syringe pump over 4 hrs) under went smooth radical cyclization to give tetracyclic compound **4.1**. The reaction was over within 1 h after completion of addition as judged from its TLC as well as the analysis of ^{1}H NMR of the crude reaction mixture.

The product could be easily purified by flash column chromatography and the removal of tin impurity was never a problem. It was not necessary to treat the reaction mixture with KF solution and the products obtained were sufficiently pure as could be analyzed from the ^{1}H NMR or the microanalysis of the product **4.1** *(Scheme 16).*

Scheme 16



The cyclized product **4.1** was obtained as colourless oil. The IR spectrum showed a peak at 1764.74 cm^{-1}, which confirmed the presence of *b*-lactam ring.



4.1

The ^{1}H NMR spectrum showed methyl protons of the sugar ring as a singlet at 1.12 and 1.23. A doublet at 5.75, with J = 3.6 Hz was assigned to the anomeric proton H-6. The proton H-7 adjacent to the anomeric proton, appeared at 4.3 as a doublet with J = 3.6 Hz. The proton H-8 appeared as a multiplet at 2.3-2.5. The proton H-9 was seen as a triplet at 4.7 with J=4.4 Hz. The H-4 proton of the *b*-lactam ring was merged with one of the H-10 proton and seen as a multiplet at 3.95-4.1. The other H-10 proton appeared at 2.7-2.9 as a multiplet. The H-3 proton of the *b*-lactam ring appeared at 5.3 as a doublet with J=4.9 Hz. The protons H-11 and H-12 appeared as a multiplet in between 1.5-2.0. The aromatic protons appeared in the region 6.9 to 7.4.

The above assignments are supported by the decoupling Experiment. When the proton H-7 at 4.3 was decoupled, the doublet due to the anomeric proton H-6 at 5.75 collapsed into a singlet. When the β-lactam proton H-4 at 4.05 was decoupled the triplet due to the proton H-9 at 4.7 collapsed into a doublet and the doublet due to the *b*-lactam proton H-3 at 5.3 collapsed into a singlet.

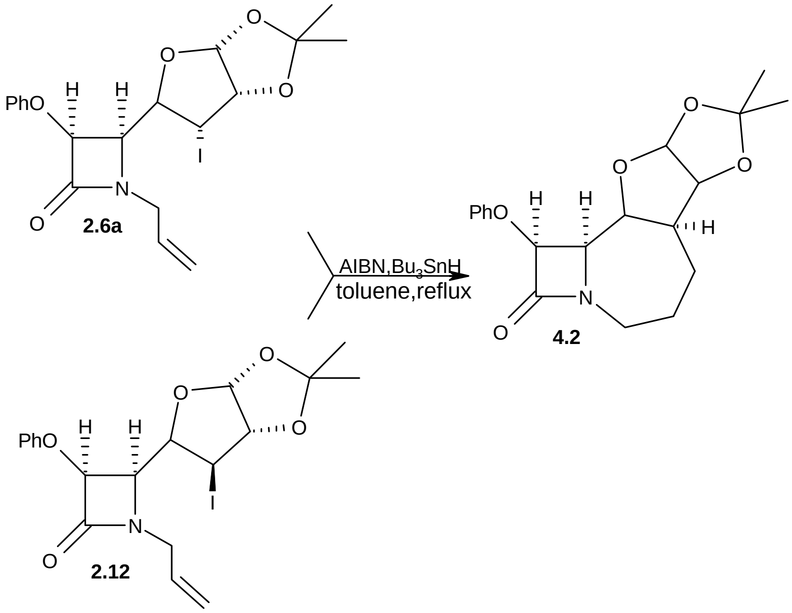
In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl carbon was appeared at 164.56. The two methyls of the acetonide group attached to the C-13 carbon appeared at 26.27. The three methylene carbons of the seven membered ring C-10, C-11, and C-12 were seen at 26.05, 28.77 and 42.56. The β-lactam carbon C-4 appeared at 50.61. The β-lactam carbon C-3 and the chiral backbone C-7, C-9 appeared at 75.27, 80.97, and 87.15. The anomeric carbon C-6 appeared at 104.02. The C-13 carbon of the acetonide group appeared at 111.11. The aromatic carbons appeared in the region 115.38 to 156.77.

The mass spectral analysis of this compound showed the molecular ion peak at *m/z* 345 (100%), which is also the base peak.

Radical Cyclization of 2.6a & 2.12 (Synthesis of 4.2)

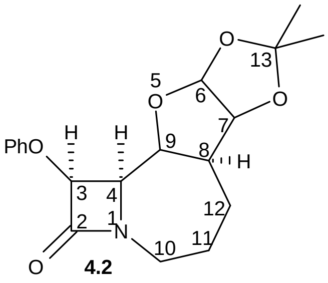
Other diastereomers, **2.6a** & **2.12**, diastereomeric at C-4 bearing iodo group, when subjected independently to the optimized conditions of radical cyclization as described for **2.7a** also underwent smooth cyclization and gave same tetracyclic β-lactam **4.2** *(Scheme 17)*, which was purified by flash column chromatography.

Scheme 17


PhO
H
H
O
O
O
I
N
O
2.6a
AIBN,Bu$_3$SnH
toluene,reflux
PhO
H
H
O
O
O
H
N
O
4.2
PhO
H
H
O
O
O
I
N
O
2.12

The purified product **4.2** was a crystalline solid with mp 174°C. The IR spectrum of this compound showed typical β-lactam amide absorption at 1755.10 cm^{-1}.

The ^{1}H NMR spectrum showed methyl protons of the sugar ring as two singlets at1.15 and 1.25. The anomeric proton H-6 shows a doublet at 5.85 with J=3.6 Hz. The proton H-7 adjacent to the anomeric proton, appeared at 4.31 as a doublet with J=3.6 Hz. The proton H-8 appeared as a multiplet at 2.3-2.4. The proton H-9 was seen as a doublet at 4.33 with J=4.3 Hz. The H-4 proton of the β-lactam ring showed


PhO
H
H
O
13
5
O
6
O
7
9
8
H
3
4
12
2
1
N
10
11
O
4.2

doublet at 4.17 with J=4.3 Hz. The H-3 proton of the *b*-lactam ring appeared at 5.36 as a doublet with J=3.6 Hz. The protons H-11 and H-12 appeared as a multiplet at 1.5-1.9. The protons H-10 appeared as two multiplets at 3.1-3.2 and 3.7-3.8. The aromatic protons appeared in the region 6.9-7.4.

Above assignments are supported by the decoupling Experiments. When the proton H-7 was irradiated at 4.31, the doublet due to the anomeric proton H-6 at 5.85 collapsed into a singlet. When the *b*-lactam proton H-4 at 4.17 was irradiated, the doublets due to the proton H-9 at 4.33 and *b*-lactam proton H-3 at 5.36 collapsed into a singlet.

The structural assignments of **4.2** were further confirmed from the analysis of COSY NMR spectrum (Fig. 1, Table 1).

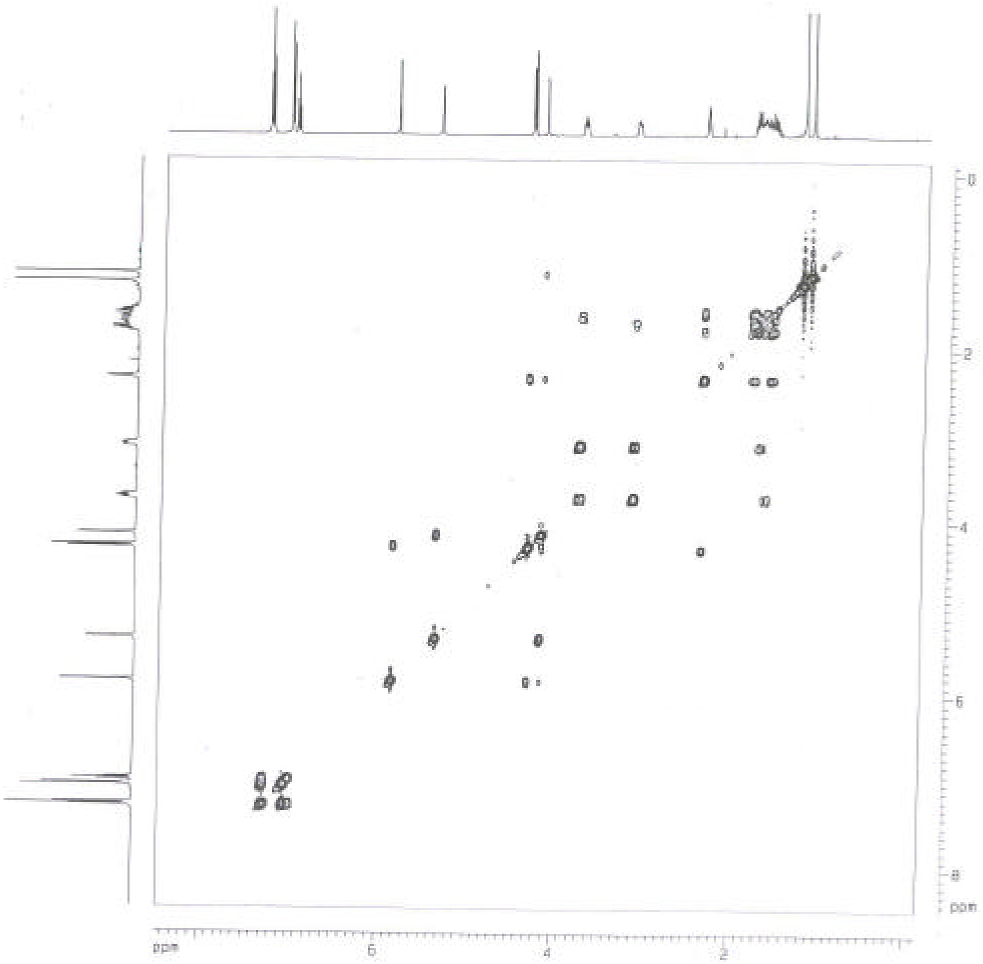
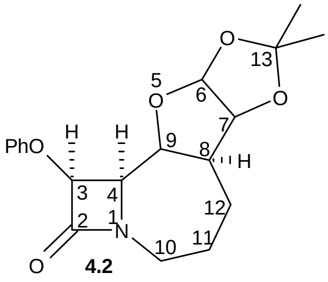


Fig 1. COSY NMR spectrum of **4.2** (selected region shown)

Table 1. Important connectivities in the COSY NMR of **4.2**.

Proton	δ (ppm)	J (Hz)	^{1}H-^{1}H Connectivity
H-6	5.85 (d)	3.6	H-7
H-7	4.31 (d)	3.6	H-6
H-8	2.3-2.4 (m)	-	H-9, H-12
H-9	4.33 (d)	4.3	H-4, H-8
H-4	4.17 (d)	4.3	H-3, H-9
H-10	3.1-3.2 (m), 3.7-3.8 (m)	-	H-11



4.2

In the COSY NMR spectrum (Table 1), The anomeric proton H-6 shows a strong coupling with H-7. The H-8 showed connectivity with H-9 and H-12. The H-9 showed strong coupling with H-8 and a weak interaction with the *b*-lactam proton H-4. The H-3 showed connectivity with the *b*-lactam proton H-4.

In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl carbon appeared at 164.68. Two methyls of the acetonide group attached to C-13 carbon appeared at 26.31. The three methylene carbons, C-10, C-11, and C-12 of the seven membered ring appeared at 23.5, 27.68 and 42.82. The β-lactam carbon C-4 appeared at 57.62. The other β-lactam ring carbon C-3 and the chiral backbone C-7, C-9 appeared at 75.11, 79.32, and 85.3. The anomeric carbon C-6 appeared at 104.59. The quaternary C-13 carbon of the acetonide group appeared at 110.85. The aromatic carbons appeared in the region 115.39 to 157.24. The mass spectrum showed a significant molecular ion peak at *m/z* 345.

X-ray Crystallographic Analysis of 4.2

The compound **4.2** was a crystalline solid. Suitable crystals for X-ray analysis were obtained by the crystallization of **4.2** from isopropanol. The relative stereochemistry was assigned as 3*S*, 4*R*, 6*R*, 7*R*, 8*S*, 9S (corresponding carbon centers C3, C4, C10, C12, C6, C5 in Fig. 3) for β-lactam **4.2** from its single crystal analysis. The absolute stereochemistry at the newly formed centers was established as 3*S*, 4*R*, 8*S* based on known absolute stereochemistry of 6*R*, 7*R*, 9S of sugar residue.

The carbon atoms C7 and C8 are disordered and occupy two positions at C7A, C7B and C8A and C8B with 0.7 and 0.3 occupancy respectively as shown in the ORTEP diagram (F.ig. 3).

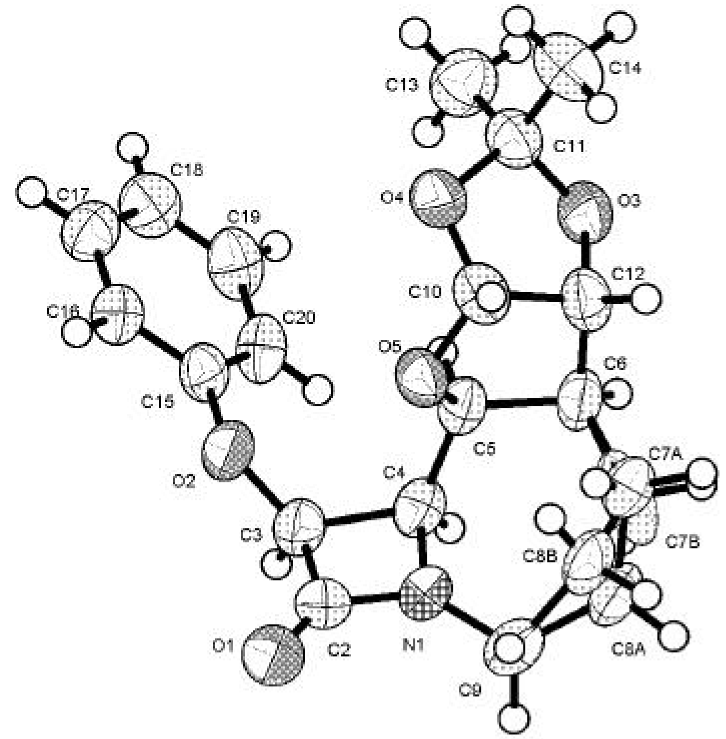


Fig. 3. ORTEP diagram of **4.2a** with 50 % probability.

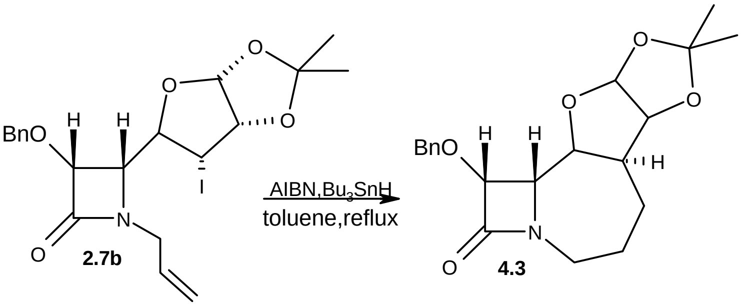
X-Ray diffraction study. X-Ray Structure determination of $C_{19}\,H_{23}\,N\,O_5$: Colorless needles (0.47 X 0.24 X 0.19 mm grown from isopropanol). M = 345.38, orthorhombic, space group $P2_12_12_1$, a = 5.498(2) Å, b = 14.423(5) Å, c = 21.601(8) Å, , V=1712.9(11) Å^3, Z=4, D=1.339 g cm^{-3}, μ=0.097 mm^{-1}, F(000)= 736, T = 293 K. Data were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 28.2°. The structure was solved by direct methods using SHELXTL. Least squares refinement of scale, positional and anisotropic thermal parameters for non hydrogen atom converged to R = 0.0374. Rw = 0.0745 for 3863 unique observed reflections.

Hydrogen atoms were geometrically fixed The refinements were carried out using SHELXL-97 . Largest diff. peak and hole 0.161 and -0.13 e. Å $^{-3}$.

Radical Cyclization of 2.7b (Synthesis of 4.3)

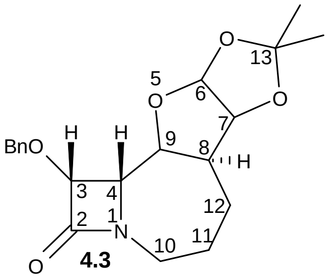
The diastereomer, **2.7b**, on similar radical cyclization conditions as described for **2.7a** gave cyclic product **4.3**, which was purified by flash column chromatography *(Scheme 18).*

Scheme 18



The purified product was isolated as oil. The IR spectrum of this compound showed a typical β-lactam amide absorption at 1758.96 cm^{-1}.

The ^{1}H NMR spectrum showed methyl protons of the sugar ring as two singlets at 1.25 and 1.3. The anomeric proton H-6 shows a doublet at 5.85 with J = 3.6 Hz. The proton H-7 adjacent to the anomeric proton, appeared as a doublet at 4.39 with J=3.6 Hz. The proton H-8 appeared as a multiplet at 2.35-2.5. The proton H-9 and H-3 proton of the *b*-lactam ring were merged and seen as a multiplet at 4.75-4.9. The H-4 proton was also merged as multiplet at 3.75-4.1 with one of the H-10 proton. The other H-10 proton appeared at 2.6-2.9 as a multiplet. The four protons, H-11 and H-12 appeared as a multiplet in the range of 1.45-1.95. The benzylic protons were appeared as a singlet at 4.72. The aromatic protons appeared in the region 7.2-7.6.



In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl appeared at 166.36. The other carbons appeared in their usual regions and were consistent with the structure of the compound.

The mass spectrum showed a significant molecular ion peak at *m/z* 359 (100%).

4.5 : Summary

A series of novel *b*-lactams with N-allyl substituents **2.6a**, **2.7a-b**, and **2.12** were successfully used as precursors for the free radical cyclisation. These *b*-lactams on treatment with Bu_3SnH in refluxing toluene smoothly underwent diastereospecific *7-endo-trig* cyclisation and offered tetracyclic *b*-lactams in excellent yields. In almost all the cases, the products were separated from the tin impurity easily by column chromatography. The structures of these compounds were assigned from their spectral analysis. The absolute stereochemistry of the tetracyclic *b*-lactam **4.2** was determined from the single crystal X-ray analysis.

4.6 : Experimental

General Procedure for the Radical Cyclisation of 2.6a, 2.7a-b & 2.12:

A solution of Bu_3SnH (0.40 mL, 1.5 mmol) in toluene (10 mL) was added to a refluxing solution of β-lactam (1 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (15 mL) over a period of 5 hrs. The reaction mixture was further refluxed for 1-2 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (Silica gel, petroleum ether / ethyl acetate) to give pure cyclized products **4.1, 4.2** & **4.3.**

Preparation of 4.1.

A solution of Bu_3SnH (0.436 g, 1.5 mmol) in toluene (10 mL) was added by syringe pump to a refluxing solution of β-lactam **2.7a** (0.471 g, 1 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (15 mL) over 5 h. The reaction mixture was further refluxed for 1h. After the completion of reaction (TLC), solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate) to give **4.1** (0.32 g, 92%) as oil.

$[a]^{D}_{25}$: +9.52

IR (cm^{-1}) : 1764.74.

^{1}H NMR : 1.12 (s, 3H), 1.23 (s, 3H), 1.5-2.0 (m, 4H), 2.3-2.5 (m, 1H), 2.7-2.9 (m, 1H), 3.95-4.1 (m, 2H), 4.3 (d, 1H, J=3.6 Hz), 4.7 (t, 1H, J= 4.4 Hz), 5.3 (d, 1H, J=4.9 Hz), 5.75 (d, 1H, J=3.6 Hz), 6.9-7.4 (m, 5H).

^{13}C NMR : 26.05, 26.27, 28.77, 42.56, 50.61, 60.86, 75.27, 80.97, 87.15, 104.02, 111.11, 115.38, 122.1, 129.34, 156.77, 164.56.

MS (*m/z*) : 345 (M+)

Microanalysis : M.F. $C_{19}H_{23}NO_5$.

: Calculated C : 66.07 H : 6.71 N : 4.06

Obtained C : 66.27 H : 6.62 N : 4.16

Preparation of 4.2

To a refluxing solution of β-lactam **2.6a** (0.471 g, 1 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (15 mL), a solution of Bu_3SnH (0.436 g, 1.5 mmol) in toluene (10 mL) was added by syringe pump over a period of 5 h. The reaction mixture was further refluxed for 1h. After the completion of reaction (TLC) solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate) to get **4.2** (0.31 g, 90%) as a white solid.

M.P. : 174°C.

$[a]^{D}_{25}$: +1.88

IR (cm^{-1}) : 1755.10.

^{1}H NMR : 1.15 (s, 3H), 1.25 (s, 3H), 1.5-1.9 (m, 4H), 2.3-2.4 (m, 1H), 3.1-3.2 (m, 1H), 3.7-3.8 (m, 1H), 4.17 (d, 1H, J=4.3 Hz), 4.31 (d, 1H, J=3.6 Hz), 4.33 (d, 1H, J=4.3 Hz), 5.36 (d, 1H, J=3.6 Hz), 5.85 (d, 1H, J=3.6 Hz), 6.9-7.4 (m, 5H).

^{13}C NMR : 23.5, 26.31, 27.68, 42.82, 48.28, 57.62, 75.11, 79.32, 85.30, 104.59, 110.85, 115.39, 121.71, 129.25, 157.24, 164.68.

MS (*m/z*) : 345 (M+).

Microanalysis : M.F. $C_{19}H_{23}NO_5$.

: Calculated C : 66.07 H : 6.71 N : 4.06

Obtained C : 66.17 H : 6.87 N : 4.27

Preparation of 4.3

A solution of Bu_3SnH (0.436 g, 1.5 mmol) in toluene (10 mL) was added by syringe pump to a refluxing solution of β-lactam **2.7b** (0.485 g, 1 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (15 mL) over 5 h. The reaction mixture was further refluxed for 1h. After the completion of reaction (TLC), solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate) to give **4.3** (0.300 g, 83%) as oil.

$[a]^{D}_{25}$: +7.6

IR (cm^{-1}) : 1758.96

^{1}H NMR : 1.25 (s, 3H), 1.3 (s, 3H), 1.45-1.95 (m, 4H), 2.35-2.5 (m, 1H), 2.6-2.9 (m, 1H), 3.75-4.1 (m, 2H), 4.39 (d, 1H, J=3.6 Hz), 4.72 (s, 2H), 4.75-4.9 (m, 2H), 5.85 (d, 1H, J=3.6 Hz), 7.2-7.6 (m, 5H).

^{13}C NMR : 26.31, 26.68, 29.58, 42.41, 50.98, 60.72, 72.59, 75.75, 82.26, 87.66, 104.64, 111.22, 127.80, 128.28, 136.77, 166.36.

MS (*m/z*) : 359 (M^{+}).

Microanalysis : M.F. $C_{20}H_{25}NO_{5}$.

: Calculated C : 66.84 H : 7.01 N : 3.90

Obtained C : 66.97 H : 7.34 N : 4.17

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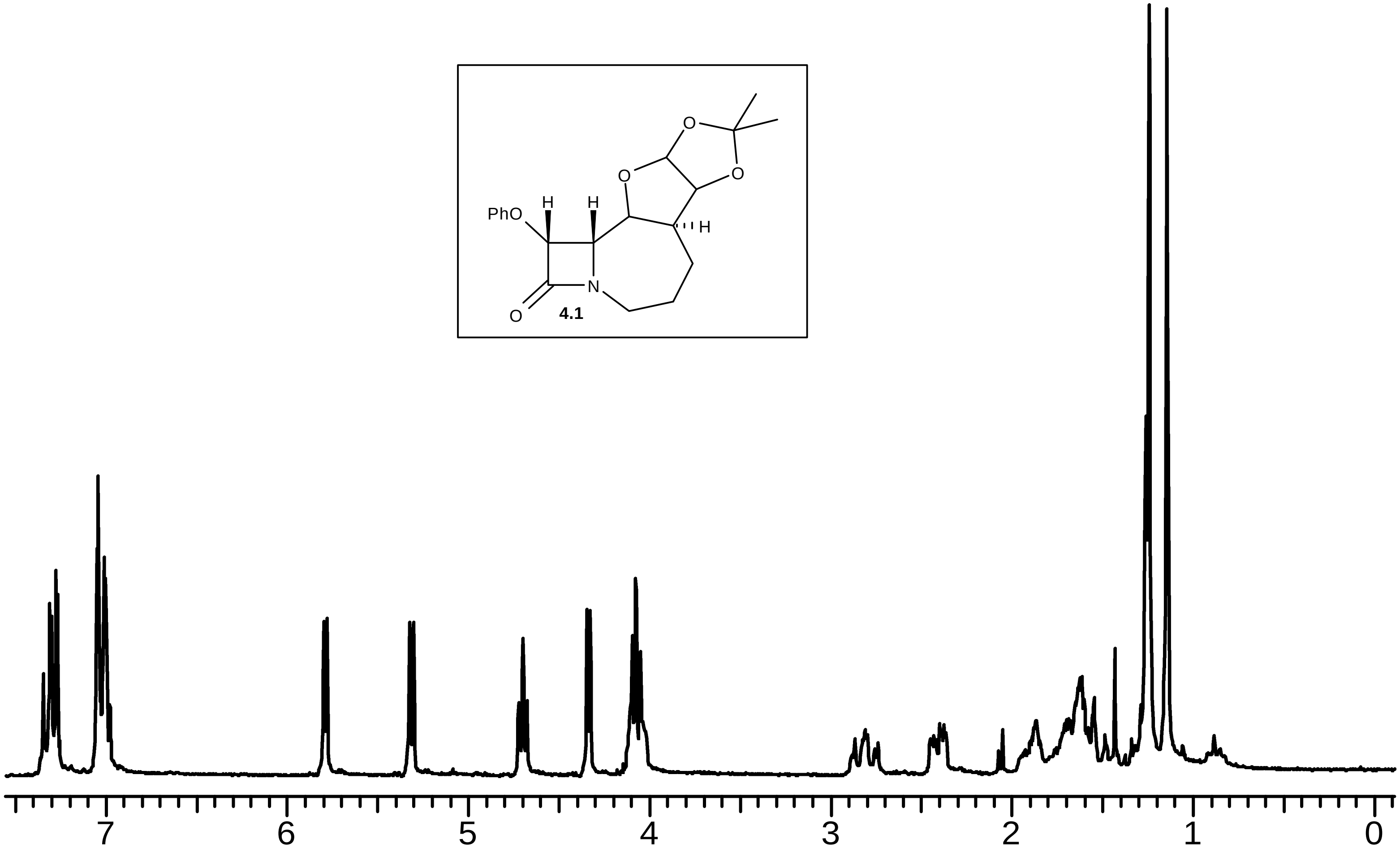

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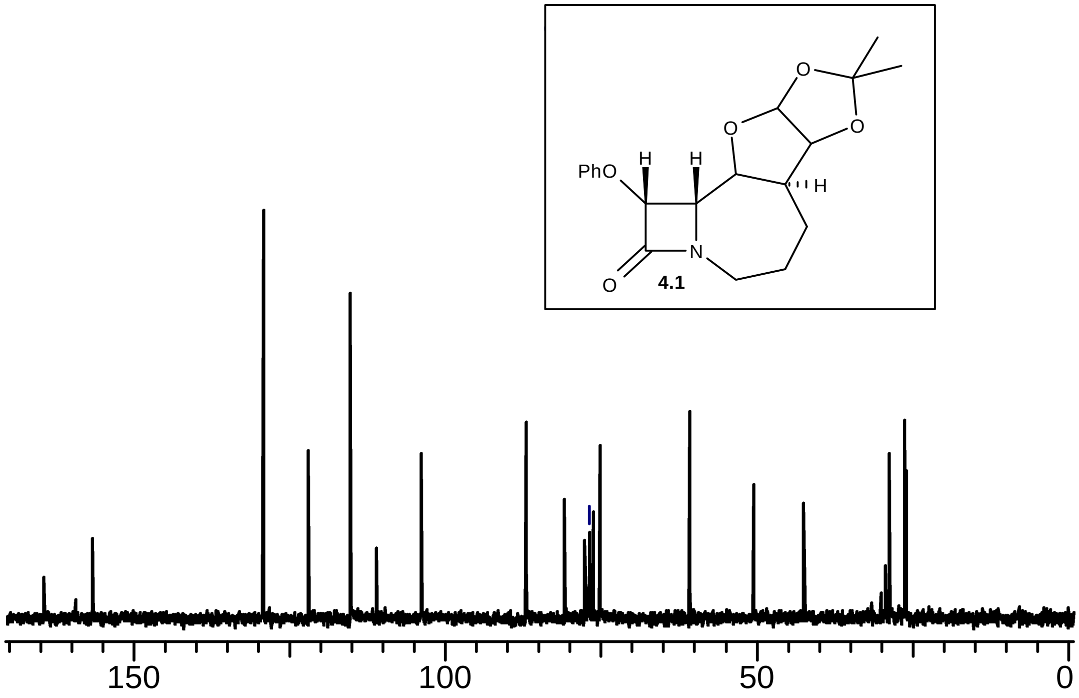

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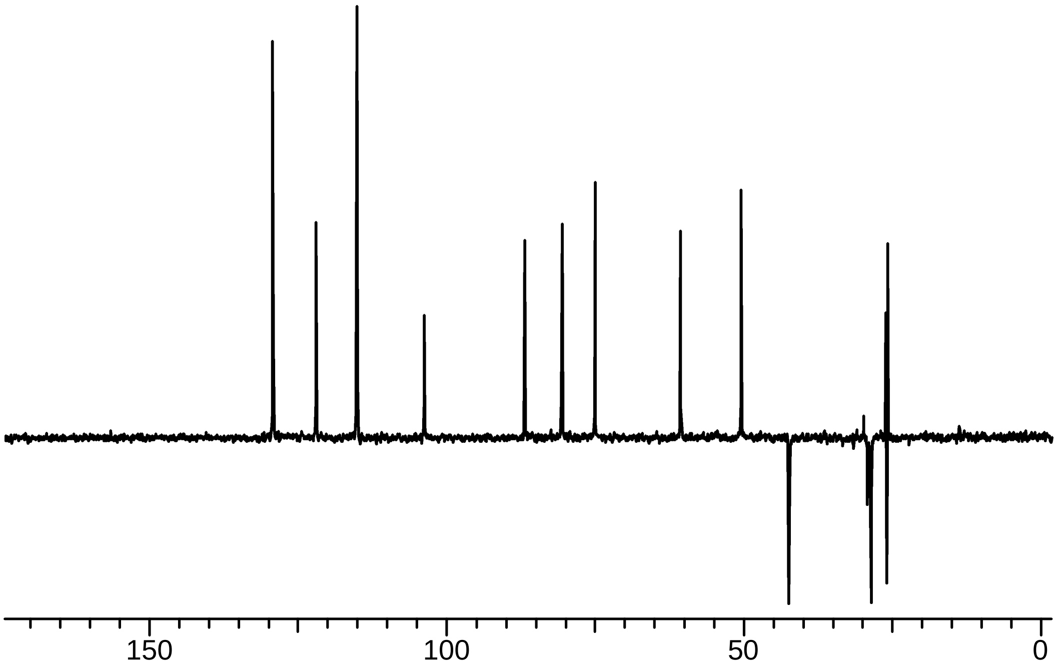

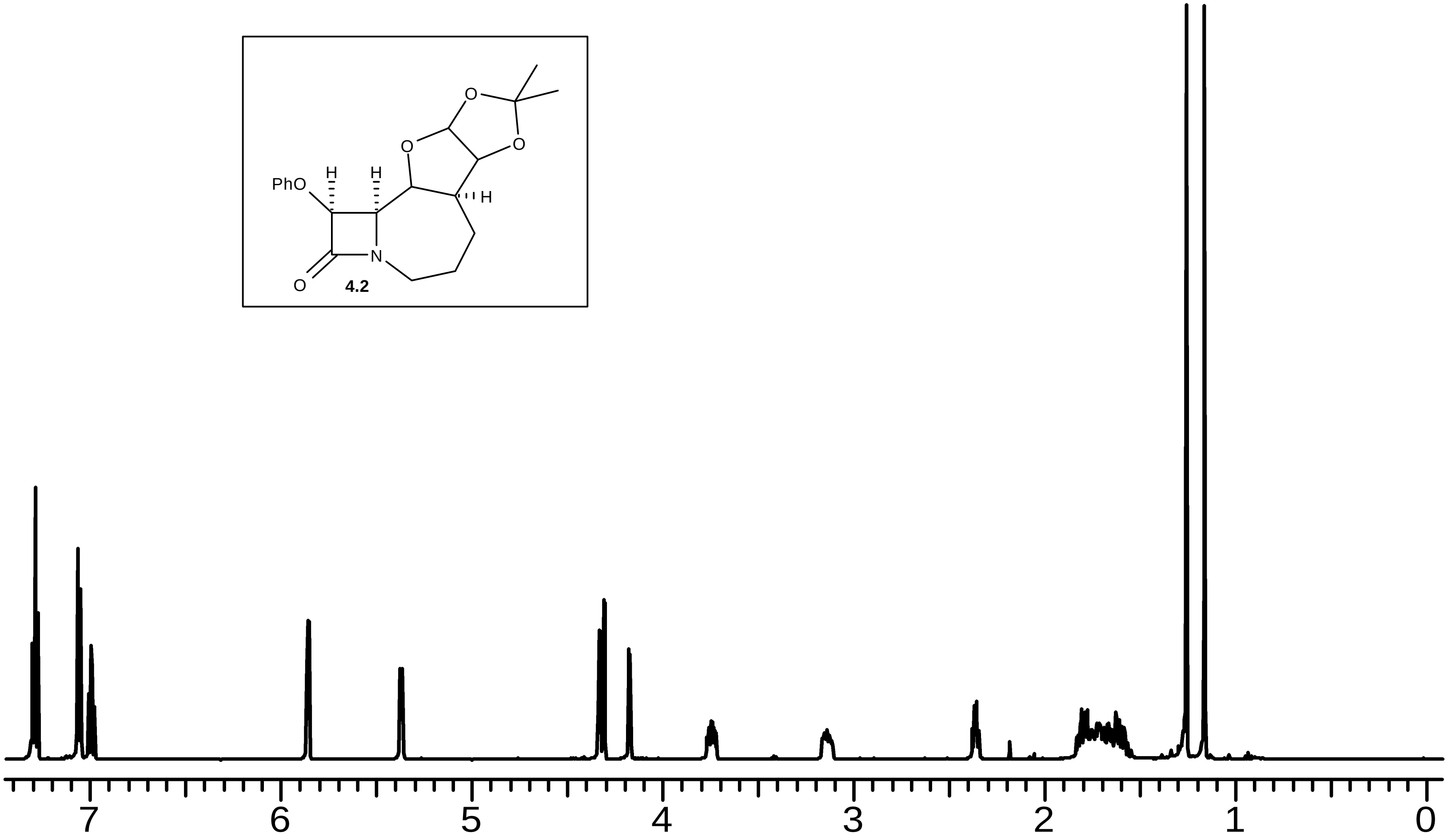
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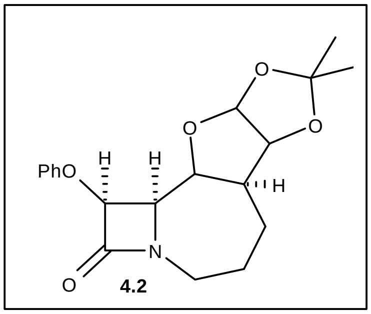
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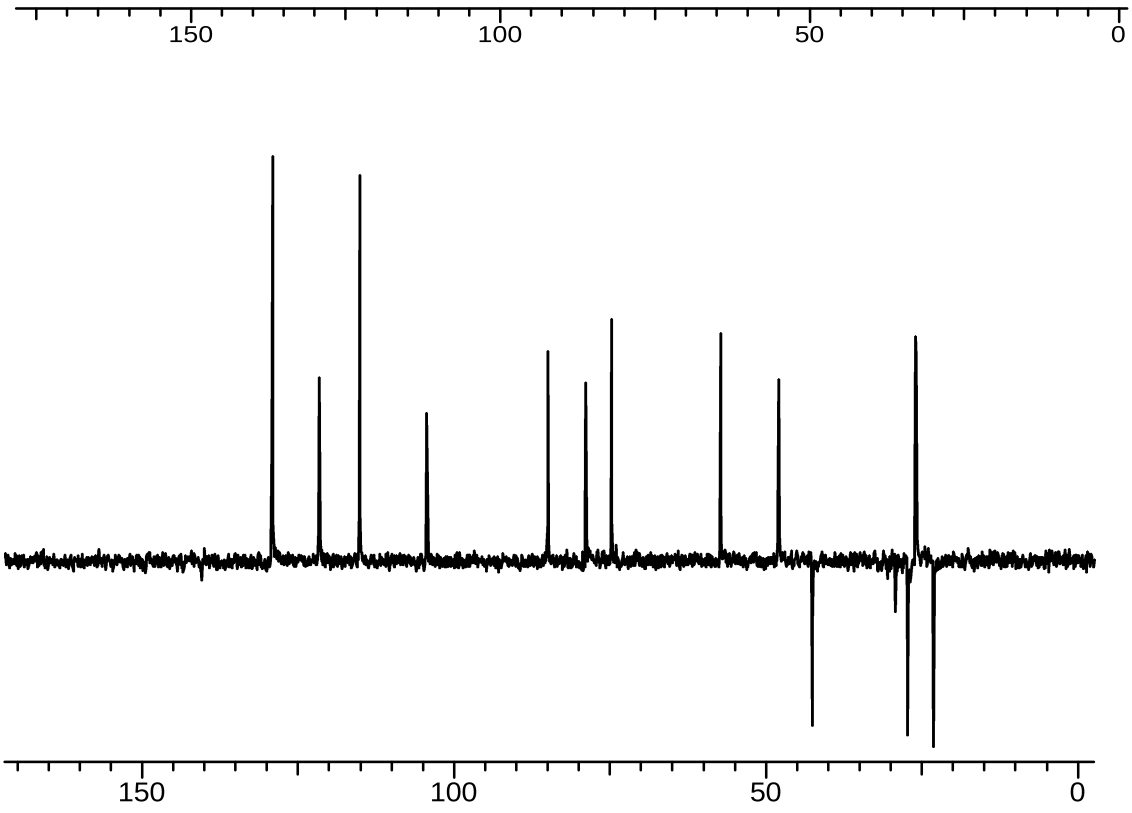

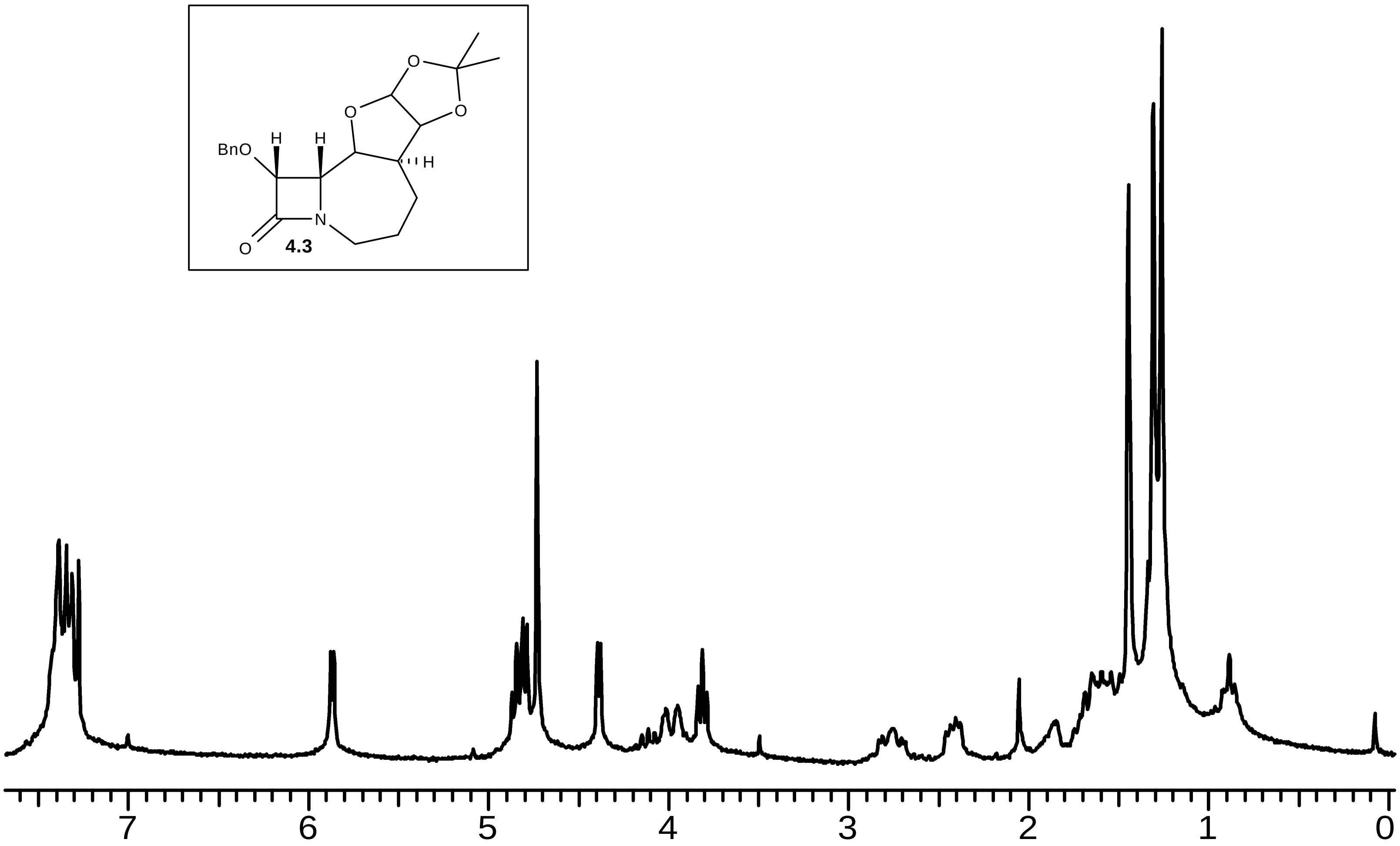
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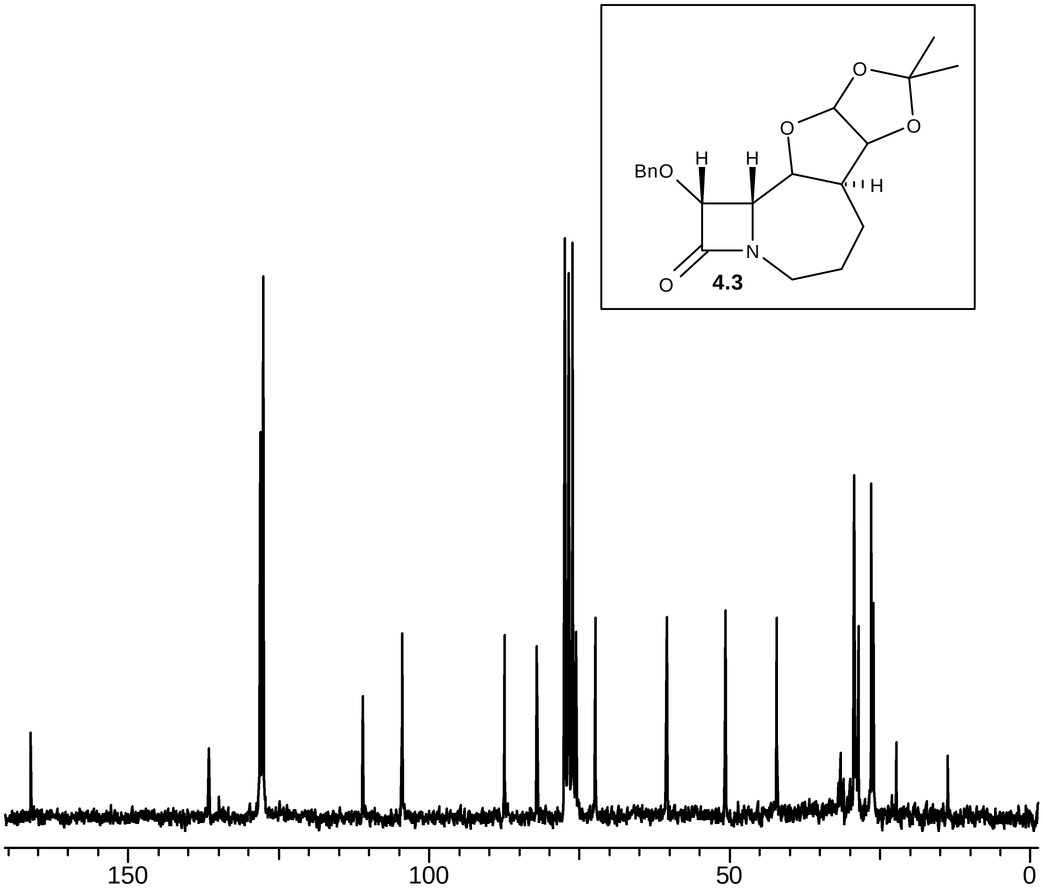

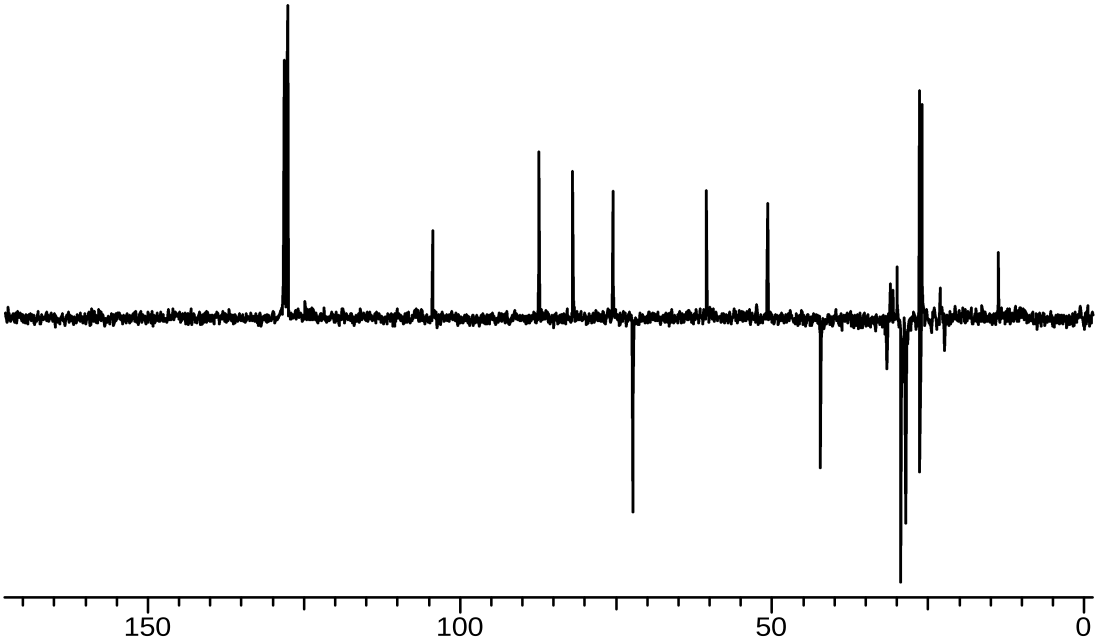4.3