Stereoselective b-lactam Ring construction

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STEREOSELECTIVE b*-LACTAM RING CONSTRUCTION*

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NATIONAL CHEMICAL LABORATORY

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CERTIFICATE

*This is to certify that the work incorporated in the thesis entitled "**Stereoselective b-Lactam ring construction**" submitted by Mr M.Arun 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

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(Dr. B. M. Bhawal)

Research Guide

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M.Arun

CONTENTS

ABBREVIATIONS

Ac	*Acetyl*
Bn	*Benzyl*
CAN	*Ceric AmmoniumNitrate*
DMAP	*N, N'-Dimethylaminopyridine*
DMP	*Dess Martin Periodinane*
DCC	*Dicyclohexylcarbodiimide*
DMF	*N,N'Dimethylformamide*
de	*Diasteromeric excess*
DIPEA	*Diisopropylethylamine*
dr	*Diasteromeric ratio*
EtOAc	*Ethylacetate*
LDA	*Lithium diisopropylamide*
mCPBA	*m-Chloroperbenzoicacid*
Me	*Methyl*
MW	*Microwave*
Pd/C	*Palladium (10%) adsorbed on carbon*
PDC	*Pyridinium dichromate*
Ph	*Phenyl*
PNB	*p-Nitrobenzyl*
PMP	*p-Methoxyphenyl*
PPh_3	*Triphenylphospine*
PTC	*Phase transfer catalyst*
PTSA	*p-Toluene sulfonic acid*
RCM	*Ring closing metathesis*
RT	*Room temperature*
TBDMS	***Tertiarybutyl dimethyl silyl***
TLC	*Thin layer chromatography*
THF	*Tetrahydrofuran*

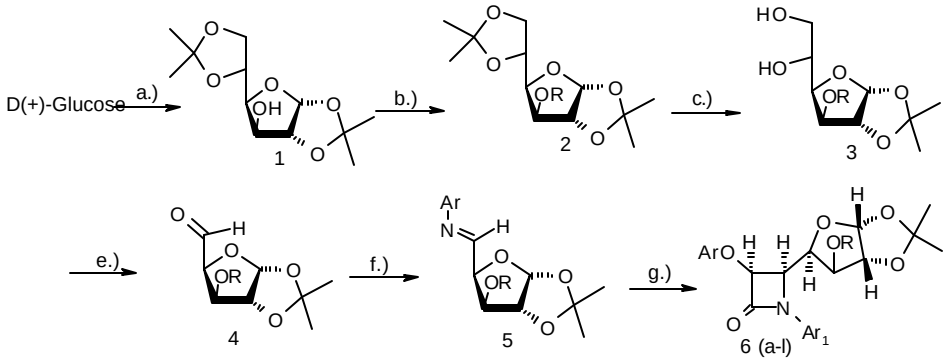
GENERAL REMARKS

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.

Chapter 1 *Stereoselective synthesis of b-lactams using chiral imines derived from 1,2:5,6-diisopropylidenea-D -glucofuranose via Staudinger reaction*

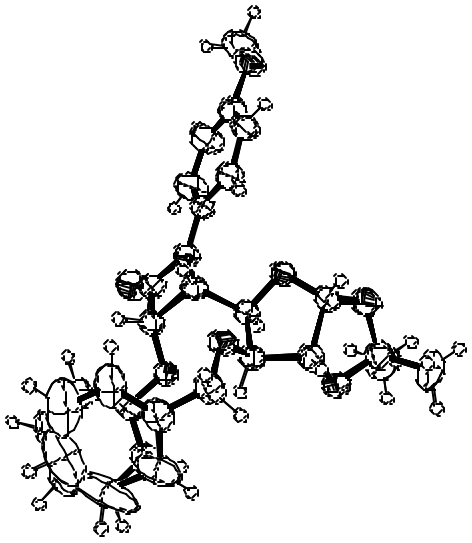
Sterically demanding aldimines were selected in order to probe the effect of steric disposition on the stereoselectivity in the Staudinger reaction for the construction of β-Lactams. We envisaged that the presence of the bulky isopropylidene group could give the necessary steric requirements for facial discrimination and thus could give good diastereoselectivity in the Ketene imine cycloaddition reaction. The chiral aldehyde, 3-O-allyl (or 3-O-benzyl)-1,2-O-isopropylidene-α-D-Xylo-pentadialdo-1, 4-furanose (**4**) was prepared from readily available D-glucose in 4 steps. The imines (**5**) derived from this aldehyde (**4**) when subjected to the *Staudinger reaction* with ketenes, derived from acid chlorides, under went smooth cycloaddition reaction to give *cis*-β-lactams (**6**) in high yields with 100% diastereoselectivity (no trace of the other isomer could be detected, from the ^{1}H NMR spectrum of the crude reaction mixture). The *cis* stereochemistry was ascertained from the coupling constants (5-6 Hz) of the C-3 and C-4 ring protons. The absolute configuration of the β-lactam **6a** was determined from single crystal X-RAY analysis and was found to be 3*S* and 4*R*.

Scheme-1



	R	Ar	Ar_1
a	Bn	Ph	PMP
b	Bn	Ph	Ph
c	Bn	Ac	Ph
d	Bn	Ph	Bn
e	Bn	Ac	Bn
f	Bn	Me	PMP
g	Bn	PhthN	PMP
h	Allyl	Ph	PMP
i	Allyl	Ph	Allyl
j	Allyl	Ac	PMP
k	Allyl	Me	PMP
l	Allyl	Ac	Allyl

Reagents and Conditions : a)Acetone, $ZnCl_2$, H_3PO_4, b)AllylB, aqNaOH, TBAB, CH_2Cl_2, 24hrs / BnCl, NaH, THFc)0.8%H_2SO_4 ,MeOH,24hrs. d) $NaIO_4$ adsorbed on silica gel, CH_2Cl_2 e)$ArNH_2$, $MgSO_4$, CH_2Cl_2
f) $ArOCH_2COCl$,Et_3N,CH_2Cl_2,0^0-rt(15hrs)

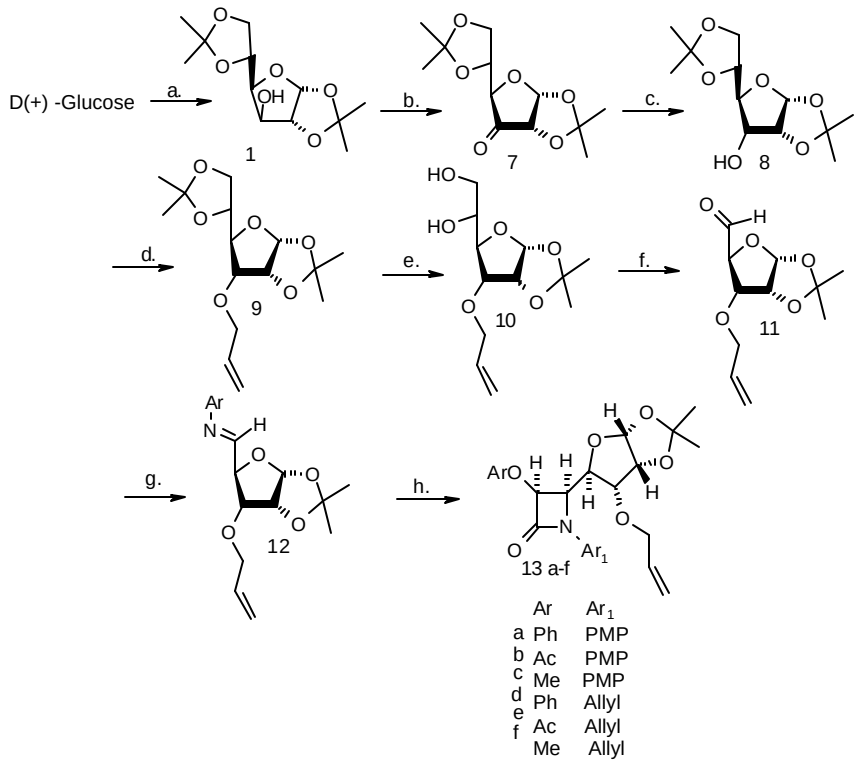


X-Ray Crystal Structure Of 6a

Chapter 2 *Stereoselective Staudinger reaction for the synthesis of b-Lactams using 1,2:5,6 diisopropylidene a-D -Allofuranose*

This chapter deals with the effect of imines derived from D-allose configuration of sugar on diastereoselectivity in the Staudinger reaction. Hence D-glucose was converted to 1,2:5,6 diisopropylidene α-D-Allofuronose using known protocol. The aldehyde 3-O Allyl-1, 2-O-isopropylidene α-D-Arabinopentadialdo- (1, 4) furanose was synthesized from D-Allose, which was then converted to the corresponding imines (12). These imines (**12**) underwent (2+2) cycloaddition reaction with ketenes generated from acid chlorides, to form cis-β-lactams diastereospecifically in good yields.

Scheme2

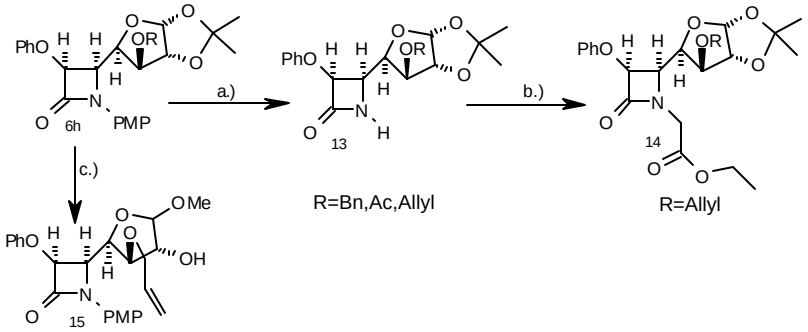


Reagents and Conditions : a)Acetone, $ZnCl_2$, H_3PO_4. b) PDC, CH_2Cl_2. c.) $NaBH_4$, MeOH. d.)AllylBr, aqNaOH, TBAB, CH_2Cl_2 24hrs / BnCl, NaH, THF. e)0.8%H_2SO_4,MeOH,24hrs. f) $NaIO_4$adsorbed on silica gel,CH_2Cl_2. g)$ArNH_2$, $MgSO_4$, CH_2Cl_2 h)$ArOCH_2COCl$, Et_3N, CH_2Cl_2, 0^0-rt(15hrs).

Chapter 3 *Transformations of β-lactams derived from D-glucose*

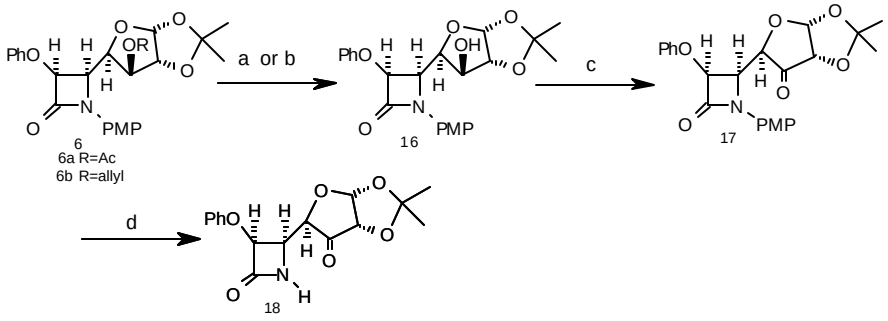
Fused bicyclic structural frameworks represent important substructures in many natural products and the efficient synthesis of functionalized fused bicyclic rings remains an important goal. With this goal in mind we carried out various transformations on the β-lactams derived from D-Glucose to offer key intermediates for the synthesis of polycyclic β-Lactams.

Scheme-3a



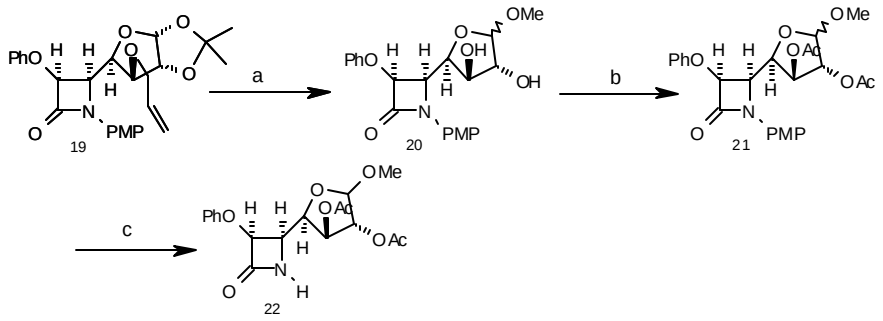
Reagents and conditions: a) CAN,CH_3CN, 0^0C to rt; b) NaH,THF,$BrCH_2COOEt$
c) PTSA, MeOH, reflux.

Scheme-3b



Reagents and conditions: a)K_2CO_3, MeOHPd/C, MeOH, PTSA, reflux24hrs
c)Dessmartin Periodinane, CH_2Cl_2, rt; d) CAN, CH_3CN,0^0 to rt

Scheme-3c

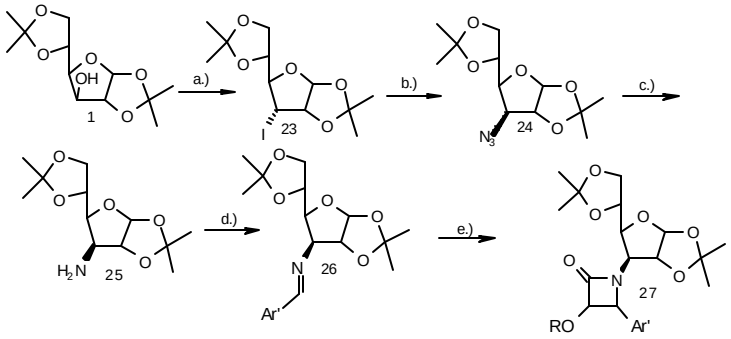


Reagents and conditions: a) MeOH,PTSA, reflux, 4hrs; b) Ac_2O,DMAP,CH_2Cl_2
c) CAN, CH_3CN, 0^0 to rt

Chapter 4 *Diastereoselective Staudinger reaction using imines derived from 3-Amino-3-Deoxy-1, 2:5,6-diisopropylidene α–D-gluco-furanose*

The amine, 3-amino-3-deoxy-1, 2: 5, 6-diisopropylidene α-D-glucofuranose (**25**) was synthesized from the readily available D(+)glucose in 4 steps. This amine was converted into the Schiff's base (**26**) by the reaction of cinnamaldehyde. This Schiff s base (**26**) on annulation with ketene generated from phenoxyacetyl chloride in presence of triethylamine at 0^0C afforded exclusively *cis*-β-Lactam (**27**) in good yield as a single diastereomer.

Scheme-4



R = Ph,AcO
Ar' = Styryl, Ph

Reagents and conditions:a.)I_2,Imidazole,Toluene reflux b.)NaN_3,DMF,105^0C,18hrs c.)Pd/C H_2,MeOH,rt,3hrs d.)Ar'CHO,$MgSO_4CH_2Cl_2$ e.)$ROCH_2COCl$, Et_3N, CH_2Cl_2, 15hrs

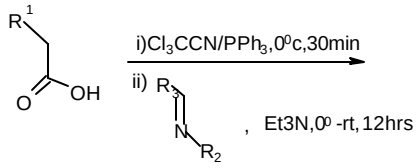
Chapter 5 *Use of acid activators for the synthesis of b-lactams*

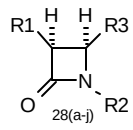
The generation of ketenes can be achieved from suitable precursors in a variety of ways, such as thermally, photochemically, from metal carbenes, or from acid chlorides in the presence of tertiary amines. Alternatively acid activating reagents can be used to generate the ketenes from acids for the synthesis of β-lactams *via* ketene-imine cycloaddition reaction.

Section A *Stereoselective synthesis of b-Lactams using Trichloroacetonitrile - Triphenylphosphine as acid activators*

The annulation of imines with ketenes (generated in situ from various substituted acetic acids using a combination of trichloroacetonitrile and triphenylphospine) provided β-lactams. Thus, drop-wise addition of a solution of trichloroacetonitrile in anhydrous methylene chloride to a combination of the carboxylic acid, and triphenylphospine in anhydrous methylene chloride generated the acid chlorides. These acid chlorides formed the ketenes in presence of triethylamine and reacted with the imines to provide exclusively *cis*-β-lactams in moderate to good yields.

Scheme-5a



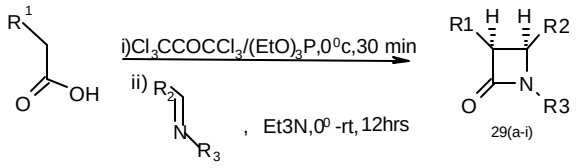


R1	R2	R3
PhO	Ph	PMP
PhO	PMP	Ph
PhO	PMP	PMP
MeO	PMP	Ph
PhO	PMP	Styryl
PhO	Ph	Styryl
PhO	m-Tolyl	Styryl
PhthN	PMP	Styryl
MeO	PMP	Styryl
		Styryl PMP

Section B *Hexachloroacetone-Triethylphospite, a novel acid activator in the stereocontrolled Staudinger reaction*

This section deals with the use of combination of hexachloroacetone and triethylphospite as acid activators in the Staudinger reaction. The acid chlorides were generated *in situ* from the corresponding acids by the drop-wise addition of a solution of triethylphospite in anhydrous methylene chloride at 0^0 C, in presence of hexachloroacetone. The ketenes were then generated from these acid chlorides in presence of triethylamine and reacted with various Schiff's bases to give corresponding β-lactams. The *cis* stereochemistry was ascertained from ^{1}H NMR spectroscopy (coupling constants of 5-6 Hz for the C-3 and C-4 protons).

Scheme-5b



R1	R2	R3
PhO	Ph	PMP
PhO	PMP	PMP
PhO	Styryl	PMP
PhO	PMP	Ph
MeO	Ph	PMP
PhO	Styryl	Benzyl
PhthN	Styryl	m-Tolyl
PhO	Styryl	m-Tolyl
	Styryl	PMP

Note: compound numbers in the synopsis are not related to the numbers in the chapters.

Chapter 1

Stereoselective synthesis of β-lactams using chiral imines derived from 1,2:5,6-diisopropylidene α-D -glucofuranose via Staudinger reaction.

1.1 : Abstract

This chapter deals with the diastereospecific synthesis of β-lactams using D-(+)-glucose derived chiral imines *via* Staudinger reaction. The sterically demanding aldimines 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 (**1.7b**) 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 3*S* and 4*R*.

1.2 : Introduction

1.2.1 Background

The fascinating history of the β-lactam antibiotics began in the late 1920's with Sir Alexander Fleming's historic discovery of the substance capable of destroying pathogenic bacteria. This substance is produced in nature by the mould penicillin notatum and aptly named Penicillin[1]. Fleming, Florey and Chain did pioneering work in developing this 'wonder drug' and received the noble prize for medicine and physiology on December 11, 1945.

The controversy surrounding this molecule raged on until Prof. Dorothy Crowfoot-Hodgkins of Oxford University elucidated the structure by X-ray crystallography. Before Prof. Crowfoot-Hodgkin's major contribution in 1945, few chemists had faith in the proposal that a β-lactam ring structure distinguish penicillin, though considerable evidence has been accumulated during the Anglo-American penicillin project.

Until 1970 Penicillin and Cephalosporin were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7α-methoxycephalosporins from Streptomyces in 1971 stimulated the search for novel antibiotics from microbes. At present β-Lactam antibiotics can be classified into several groups according to their structure (**Chart-1.1**).

- Penicillins (penams)
- Cephalosporins (cephems)
- Cephamycins
- Oxacephems
- Penems
- Oxapenams such as clavulanic acids
- Carbapenems such as thienamycin
- Nocardicins
- Monobactams

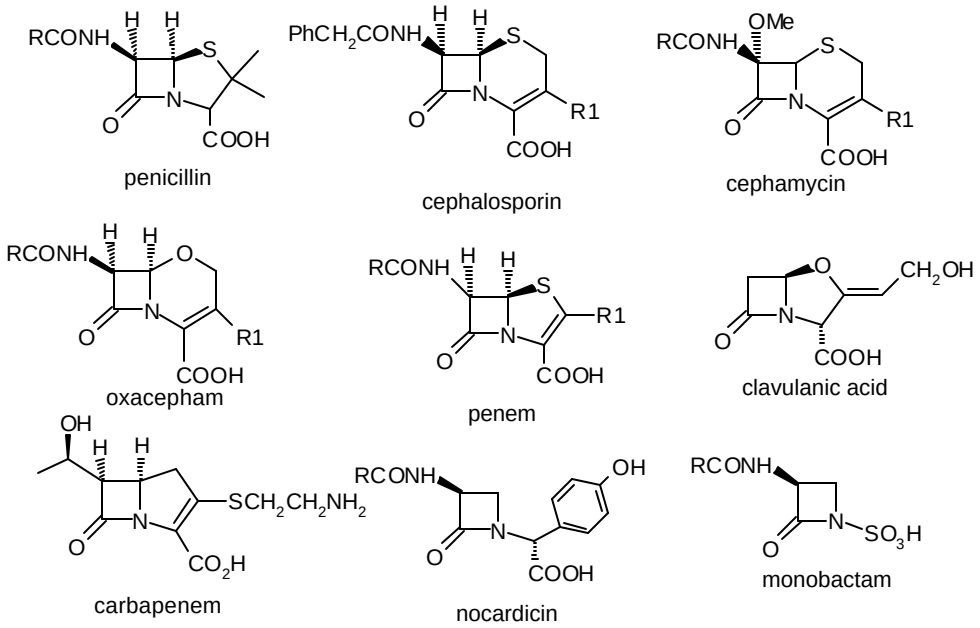


Chart-1.1

1.2.2 Synthesis of b-lactams

The first β-lactam was synthesized by Staudinger and coworkers[2-4] in 1907 *via* 2+2 cycloaddition reaction of ketene and imine and this reaction is termed as the Staudinger reaction. Since the determination of the chemical structure of penicillin and the identification of the β-lactam subunit as the key structural element endowing these compounds with life saving antibacterial activity, the significance of this small ring heterocycle to the field of organic synthesis was established. The discovery of other β-lactam containing antibacterials served to lend further support to the need for efficient methods of construction of the β-lactam ring.

1.2.3 Methods of β-lactam construction

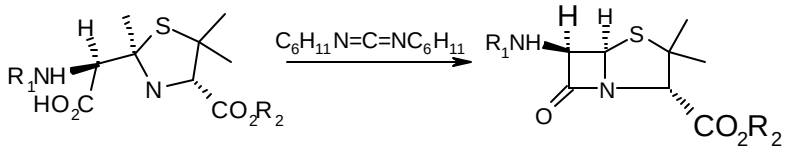
The various approaches to the synthesis of β-lactam ring can be classified into

1. Formation of the (N1-C2) bond
2. Formation of the (C2-C3) bond
3. Formation of the (C3-C4) bond
4. Formation of the (C4-N1) bond

1.2.3a Formation of the Amide (N1-C2) bond

Dehydration of β-amino acids leading to the synthesis of azetidinones seem to be the obvious approach, but in contrast to their γ and δ analogs β-amino acids normally do not cyclize thermally[5] due to the high degree of ring strain of the β-lactam.

Scheme-1.1



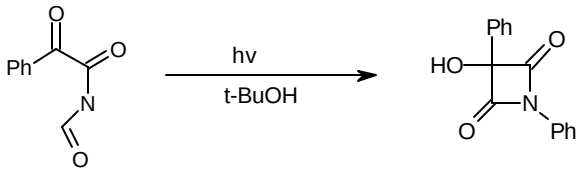
Penicillin

Sheehan and Hess[6,7] used DCC as a condensing agent in their landmark synthesis of Penicillin (Scheme-1.1).

1.2.3b Formation of the (C2-C3) bond

In contrast to the amide bond formation, azetidinone ring formation *via* C2-C3 bond closing is complicated by the inherent difficulty in forming carbon–carbon bond versus an amide bond and hence is the least used method. A photochemical method[8] has been developed that leads to the formation of 4-keto-β-lactams (**Scheme-1.2**).

Scheme-1.2



1.2.3c Formation of the (C3-C4) bond

The formation of C3-C4 bond is as complicated as C2-C3 as discussed earlier, because of the necessity of a stereo selective carbon-carbon bond formation amidst a multi functional array. Bond formation at C3-C4 would involve the formation of nucleophilic center at C3 and an electrophilic center at C4, or vice versa. Sheehan and Bose reported the first example of such an intra molecular nucleophilic displacement reaction. They used malonate anions and halides as nucleophilic and electrophilic components respectively[9] **(Scheme-1.3).**

Scheme-1.3

1.2.3d Formation of the (C4-N1) bond

The synthesis of β-lactam ring *via* formation of the C4-N1 bond is used in nature for the biosynthesis of azetidinone containing antibiotics[10]. New methods for the synthesis of β-lactam ring through the formation of C4-N1 has been dominated by strategies involving the intramolecular displacement of a leaving group attached to the C4 by appropriately activated nitrogen, N1 **(Fig-1).**

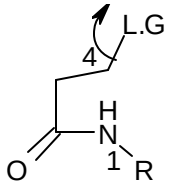
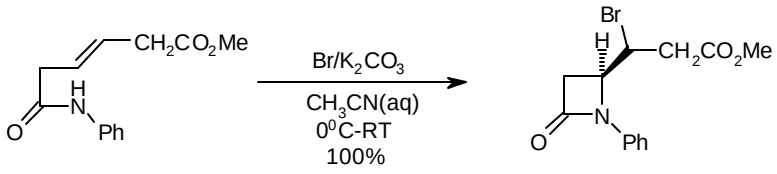


Fig-1

Miller and Rajendra[11] have successfully realized the oxidative cyclization of olefinic amides to β-lactams from oxygen-substituted hydroxymates. The attenuated acidity of the nitrogen in this functionality provided easy access to a number of important azetidinone intermediates **(Scheme-1.4).**

Scheme -1.4



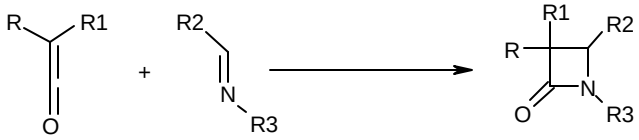
1.2.4 Multiple bond forming reactions

The most significant synthetic approaches to the formation of the β-lactam ring involving multiple bond forming reactions are the ketene-imine cycloaddition reaction (*Staudinger reaction*) and the enolate-imine methodologies.

1.2.4a The Staudinger Reaction

Among the numerous methodologies for the synthesis of β-lactams the annulations of the ketenes with imines has proven to be a versatile procedure for the construction of the β-lactam ring (**Scheme -1.5**).

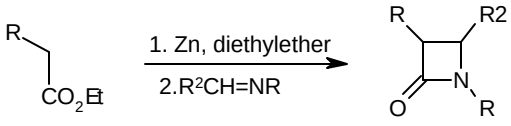
Scheme -1.5



1.2.4b Enolate-imine condensation

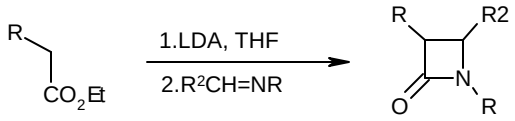
Gilman and Speeter utilized the Reformatsky reaction of alkyl bromoacetates with imines in presence of zinc for the construction of the β-lactam skeleton **(Scheme-1.6)** and obtained the β-lactam in good yields.

Scheme -1.6



Recently metal enolates have been utilized to obtain good selectivities in β-lactam ring construction ***(*Scheme-1.7*).***

Scheme -1.7



1.2.5 Ketenes

The ketenes required for the Staudinger reaction can be generated from suitable precursors in a variety of ways such as thermally, photo chemically from metal carbenes or from acid chlorides and related derivatives in the presence of tertiary amines. An alternate methodology involves the reaction of substituted acetic acids, imines and base in the presence of an activating agent. A brief discussion about acid activators is presented in Chapter **5**.

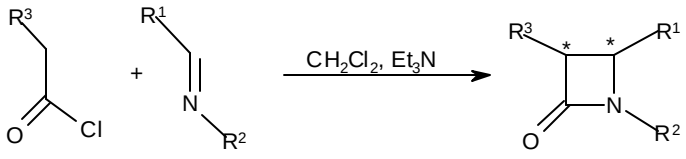
1.2.6 Imines

Imines derived from aldehydes and ketones were used in the Staudinger reaction. Imines were often derived from cinnamaldehyde, methyl glyoxalate, phenyl glyoxal, mandelic aldehyde, etc, so that the C4 substituent functional group provides easy access for further transformations.

1.2.7 Asymmetric Synthesis

The introduction of stereogenic centers into substituents on the imine carbon (R^1), the substituents on the imine nitrogen (R^2), or the substituents on the ketene (R^3) can induce stereoselectivity (**Scheme -1.8**).

Scheme -1.8

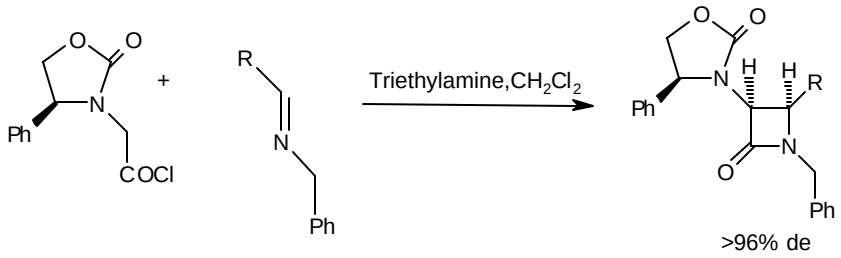


1.2.8 Chiral Ketenes

Over the past several years the Staudinger reaction has been extensively developed by using a combination of either chiral ketenes and achiral imines or achiral ketenes and chiral imines, generally providing good yields with excellent diastereo-selectivity. One example is the cycloaddition reaction of Evans-Sjogren ketenes, generated from chiral

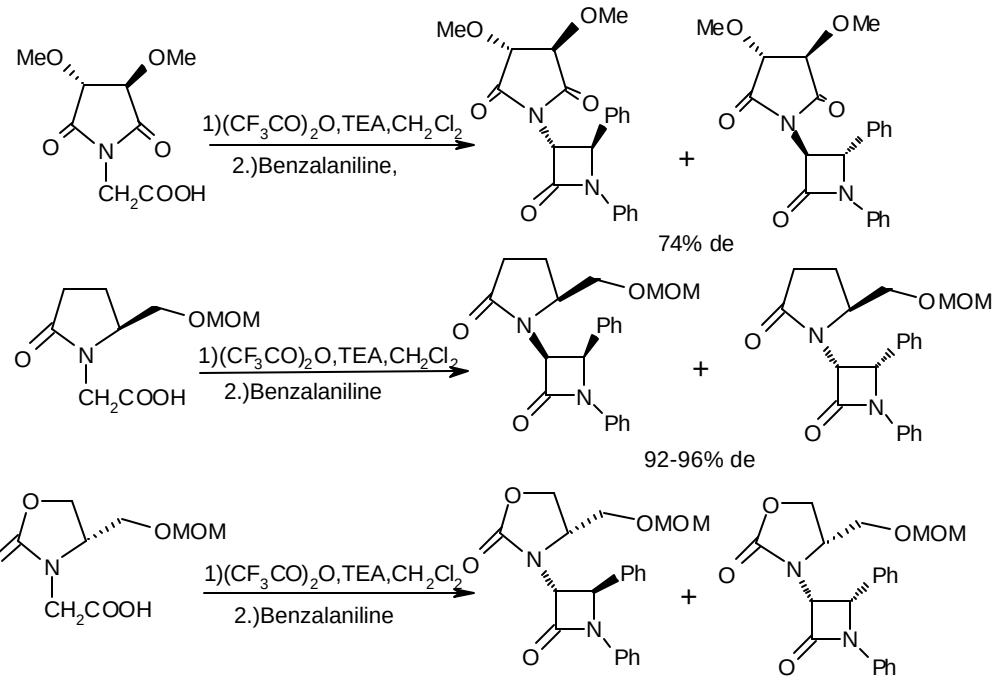
oxazolidinyl acid chlorides and triethylamine, with achiral imines to form optically active β-lactams with high levels of asymmetric induction, typically greater than 96% de **(Scheme -1.9).**

Scheme -1.9



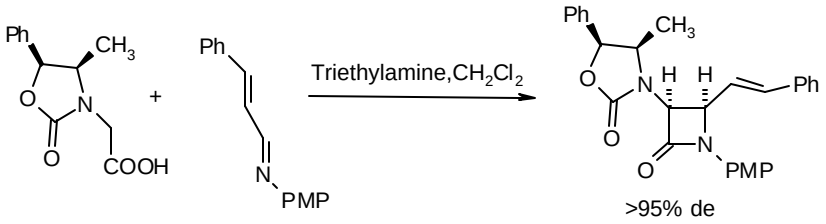
Ikota in a series of papers has reported a highly stereoselective β-lactam formation by asymmetric cyclo-condensation employing chiral heterocycles derived from L-(+)-tartaric acid, (S)-glutamic acid, and (S)-serine as ketene precursors (**Scheme-1.10**). Ikota used these acids in presence of trifluoroacetic anhydride (the mixed anhydride method) in the presence of a base to achieve a high level of diastereoselectivity**.**

Scheme -1.10



Cooper et. al used a norephedrine derived oxazolidone as the chiral ketene (**Scheme-1.11**) and achieved >95% diastereoselectivity in the β-lactam formation

Scheme-1.11

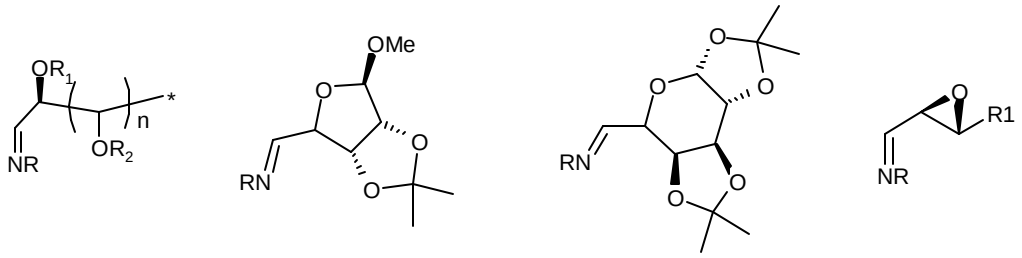


1.2.9 Chiral imines

The asymmetric induction in the reaction of achiral ketenes with chiral imines has been effected from imines derived from chiral aldehydes and achiral amines and also from imines derived from chiral amines and achiral aldehydes. In the latter case β-lactams are often produced, if at all, with low levels of diastereoselectivity [31, 32].

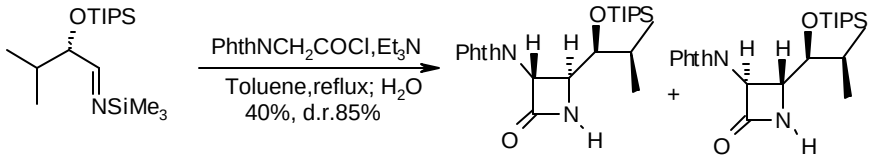
Better diastereoselectivities are obtained when imines derived from chiral aldehydes are used. The common approaches involve the use of α-oxyaldehydes derived imines, sugar-aldehydes and α,β-epoxy imines (**Chart-1.2**). In all these cases the formation of *cis*-β-lactams was reported with high diastereomeric ratio**.**

Chart-1.2



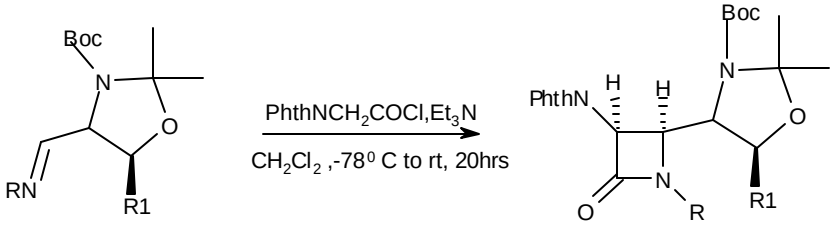
Recently, Panunzio and coworkers[33] have reported preferential *trans*-selectivity in β-lactam ring formation using phthalimidoacetyl chloride with N-trimethylsilyl-imines and triethylamine under toluene reflux conditions **(Scheme-1.12)**.

Scheme-1.12



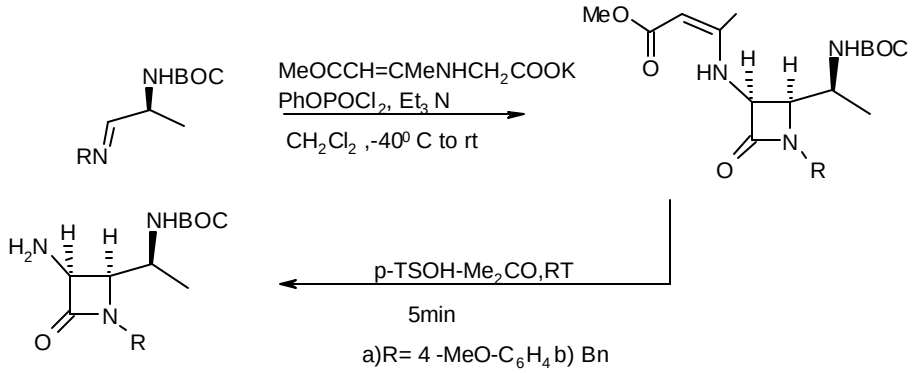
Alternatively the use of N-Boc α-amino imines[34] with phthalimidoacetyl chloride and triethylamine afforded the respective β-lactams as single diastereomers (**Scheme-1.13**).

Scheme-1.13



Similarly, the reaction of the Dane's salt of glycine with chiral imines in the presence of phenyl phosphorodichloridate[35] and triethylamine gave the corresponding vinyl amino-β-lactams in moderate yields. These compounds on treatment with PTSA furnished the 3-amino-β-lactams in high yields ***(*Scheme-1.14*).***

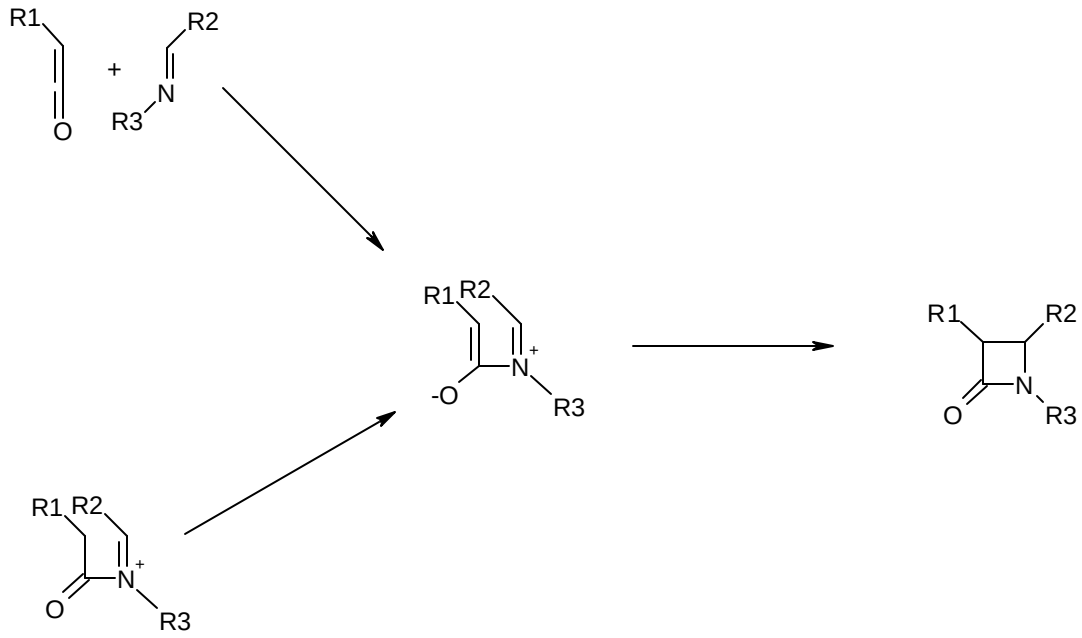
Scheme-1.14



1.2.10 Mechanism

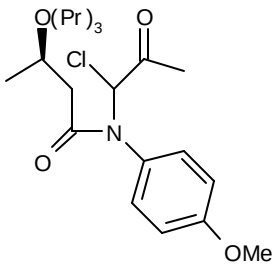
The mechanism of the Staudinger reaction is complex and the stereo chemical course of the reaction is sometimes difficult to predict. The formation of ketenes occurs thermally, photo chemically, or from an acid chloride to form a zwitterionic intermediate. Alternatively, the acid chloride acylates the imines, followed by the proton abstraction to form a zwitterionic intermediate, which then undergoes [2+2] cycloaddition to form β-lactams ***(*Scheme -1.15*).***

Scheme -1.15



1.2.11 Ketene-Imine Mechanism

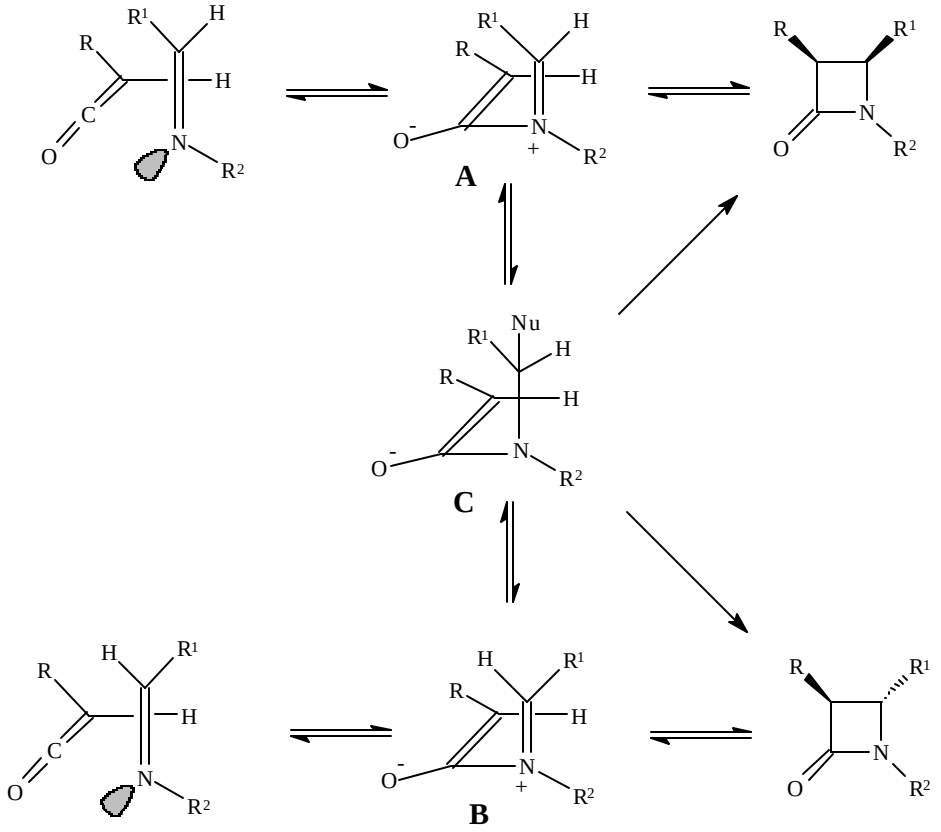
From the kinetic studies of ketene formation from acid chloride and base and the subsequent reaction of this ketene with imine, it has been concluded that the azetidinones arise completely from the ketene intermediate and not *via* direct acylation of the imines with the acid chloride. Reaction between the acid chloride and the imine in the absence of base led to the formation of α-chloroamide and no ketene could be detected spectrophotometrically.



α-chloroamide

It has been postulated that the LUMO of the ketene carbonyl which is coplanar to the substituents of the ketene, is attacked by the imines in an orthogonal approach, thus an intermediate is generated in which the planes of the imine and enolate are perpendicular to each other. It is further believed that the attack of the imine occurs from the least hindered side (hydrogen or small substituent) of the ketene, generating the zwitterionic intermediate A. Con-rotatory ring closure will then generate the thermodynamically less stable β-lactam in which the two hydrogens are *cis* to each other. In the case of the cyclic imines, an orthogonal approach between the two reactants will produce a zwitterionic intermediate B, which on con-rotatory electrocyclization will generate the *trans* product (**Scheme -1.16**)

Scheme -1.16



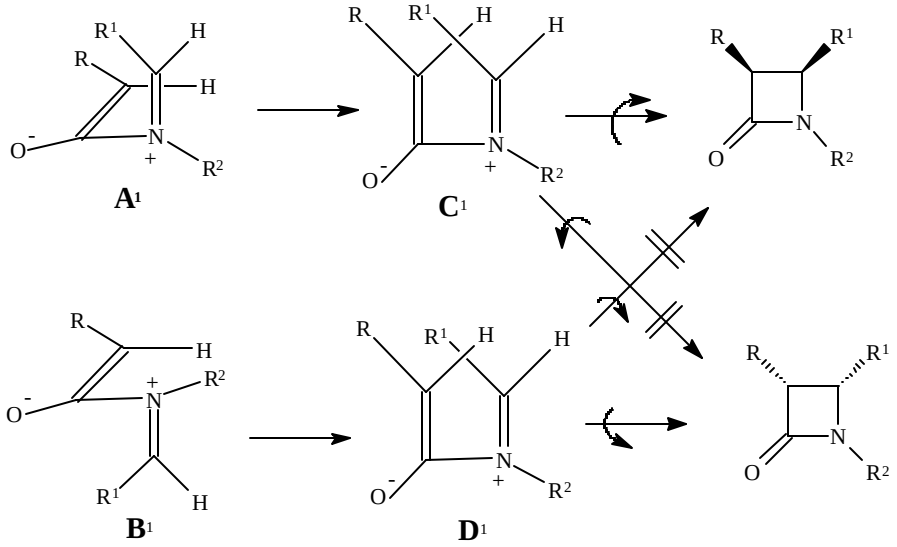
1.2.12 Asymmetric Induction

The ketene can be approached by the imine either form the top face or bottom face to produce two possible zwitterionic intermediates $\mathbf{A^1}$ and $\mathbf{B^1}$ respectively (**Scheme -1.17**). Before the conrotatory ring closure can take place, the intermediates $\mathbf{A^1}$ and $\mathbf{B^1}$ have to undergo the 90° rotation around C-N bond to produce two more intermediates $\mathbf{C^1}$ and $\mathbf{D^1}$ respectively. The conrotatory ring closure of these intermediates $\mathbf{C^1}$ and $\mathbf{D^1}$, will produces *cis*-β-lactams and its enantiomer. This intermediates $\mathbf{D^1}$ and $\mathbf{C^1}$ can also be formed from $\mathbf{A^1}$ and $\mathbf{B^1}$ by rotating through 270° around C-N bond.

According to the principle of least motion, the transformation of **A[1]** to **C[1]** and **B[1]** to **D[1]** is favoured as this transformation needs only 90° rotation.

It has been pointed out by Hegedus et al. that the conrotatory ring closure of intermediate **C[1]** can only occur clockwise[39] as the counterclockwise ring closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is of importance for chiral induction, because a counterclockwise rotation would generate the enantiomeric β-lactam. The opposite is true for intermediate **D[1]**, which can undergo only counterclockwise conrotatory ring closure.

Scheme-1.17



1.3 : Present Work

Earlier reports have clearly indicated that the use of homochiral aldehydes in most of the cases resulted in complete stereo control in the Staudinger reaction. In the asymmetric Staudinger reaction using homochiral aldehydes, it has been postulated that 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.

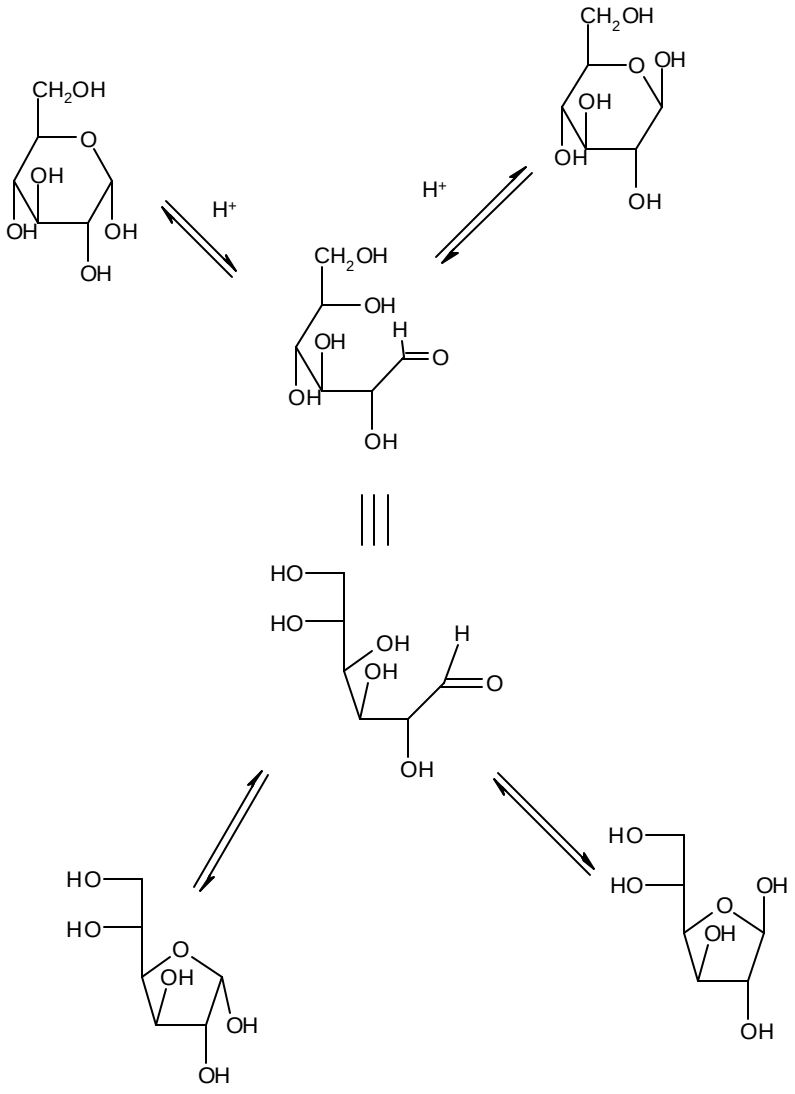
1.4 : Results and discussions

D-Glucose when treated with acetone in presence of $ZnCl_2$ and ortho-phosporic acid afforded the glucose diacetonide **1.2** 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 causes less strain than similar fusion to a pyranoid ring (**Scheme1.17**). 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 proton) respectively. The free hydroxyl was suitably protected using benzyl and the allyl protecting groups. The selective deprotection at C-5 and C-6 position provided the pure glycol **1.4 a-b,** as the other acetonide group was more stable to the reaction conditions. The $NaIO_4$ cleavage of the glycols **1.4a-b** provided the pure aldehydes **1.5a-b** in quantative yields. The aldehydes **1.5a,b** underwent imine formation with amines in methylene chloride in presence of $MgSO_4$. The imines **1.6a-e** were characterized by ^{1}H NMR spectroscopy.

The ^{1}H 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 **1.6a-e** provided the β-lactams **1.7a-l** as a single diastereomer in good yields, with exclusively *cis* stereochemistry as ascertained from the coupling constants (4.9-6 Hz) of the C-3 and C-4 protons in ^{1}H NMR spectra of these compounds.

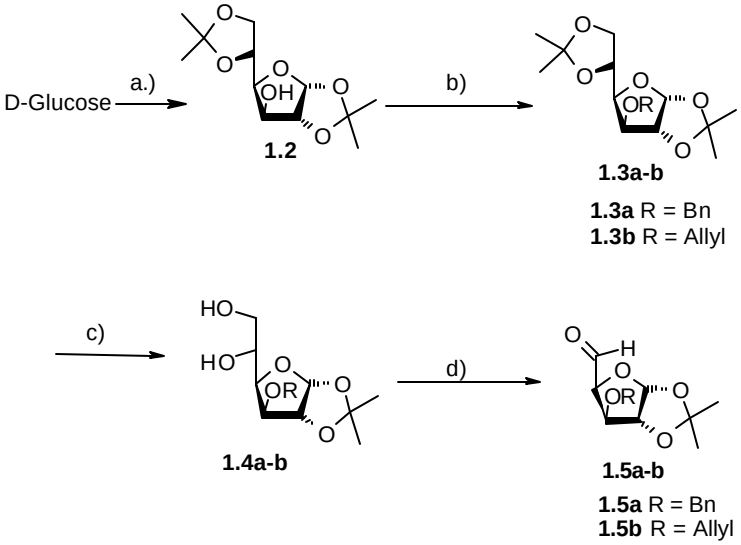
Scheme1.17



1.4.1 Preparation of the aldehyde **1.5**

The hydroxyl group of diacetone-D-glucose was sufficiently protected as the allyl or the benzyl ether **1.3 a-b**. These were then converted to the respective glycols **1.4 a-b**. The aldehydes **1.5 a-b** were prepared from the glycols **1.4 a-b** in good yields on treatment with $NaIO_4$ (**Scheme-1.18**) following reported[36-39] procedures.

Scheme-1.18

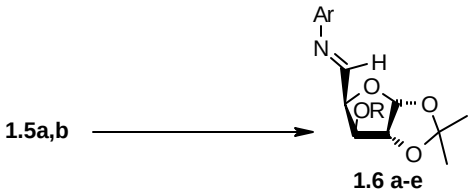


Reagents and conditions:a) $ZnCl_2$,Acetone b) BnBr,NaH,DMF, AllylBromide/aqNaOH, PTC c)aq HOAc or 0.8%H_2SO_4 d)$NaIO_4$ adsorbed on silica gel

1.4.2 Preparation of the imines **1.6 a-e**

The imines **1.6a-e** were prepared by treating the aldehydes **1.5a-b** with various amines (p-anisidine, benzyl amine, ally amine, aniline) in CH_2Cl_2 at RT in presence of $MgSO_4$ (**Scheme-1.19**). 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 without purification.

Scheme-1.19

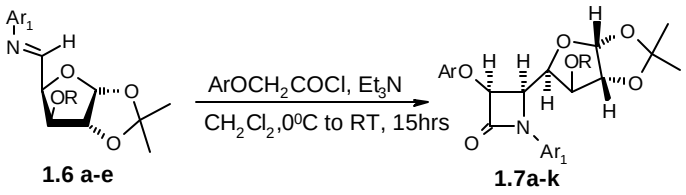


	R	Ar
1.6a	Bn	PMP
1.6b	Bn	Ph
1.6c	Bn	Bn
1.6d	Allyl	PMP
1.6e	Allyl	Allyl

1.4.3 Preparation of b-lactam **1.7a-k**

With the imines **1.6a-e** in hand, stage was set for the synthesis of β-lactams **1.7a-k.** The β-lactams were synthesized by the reaction of imines with acid chlorides in presence of triethylamine (**Scheme -1.20**).

Scheme-1.20



1.6 a-e **1.7a-k**

With the imines **1.6 a-e** in hand stage was set for the preparation of β-lactams. The imines were found to be highly reactive and provided the β-lactams **1.7 a-k** on treatment with the respective acidchlorides in presence of triethylamine, in good yields. Only a single diastereomer with *cis* stereoselectivity was obtained in all the cases, as confirmed from the ^{1}H NMR spectra of the crude compounds.

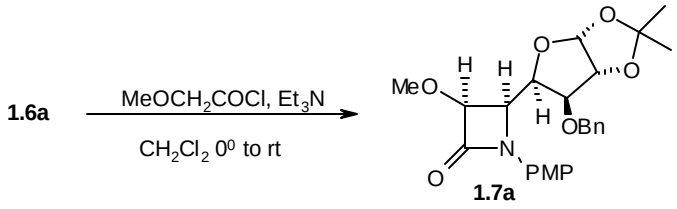
Table 1. Synthesis of β-lactams **1.7a-k** from the imines **1.6a-e** *via* the Staudinger reaction.

b-lactams **1.7 a-k**	R	Ar	Ar_1	Yield (%)
1.7a	Bn	Me	PMP	75
1.7b	Bn	Ph	PMP	75
1.7c	Bn	Ph	Ph	71
1.7d	Bn	Ac	Ph	72
1.7e	Bn	Ph	Bn	74
1.7f	Bn	Ac	Bn	70
1.7g	Allyl	Ph	PMP	79
1.7h	Allyl	Ac	PMP	70
1.7i	Allyl	Me	PMP	72
1.7j	Allyl	Ph	Allyl	69
1.7k	Allyl	Ac	Allyl	68

1.4.3a Preparation of b-lactam **1.7a**

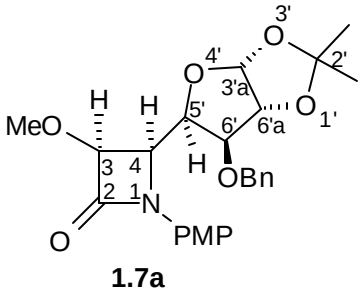
A solution of methoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine**1.6a** and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere (**Scheme-1.21**).

Scheme-1.21

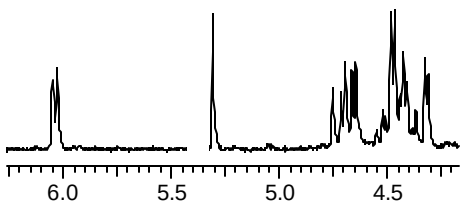


The resulting mixture was allowed to warm up to RT and stirred for 15 hrs. After the usual workup followed by column chromatography, the β-lactam **1.7a** was isolated as oil in 75% yield. The IR spectrum of this compound showed a strong band at 1743.53 cm^{-1}, indicating presence of the carbonyl group of β-lactam ring.

The ^{1}H NMR of the crude compound showed that it is a single diastereomer.



1.7a



The two-methyl groups on the acetonide appeared at 1.32 and 1.46 as two singlets integrating for 3 protons each. The methoxy group at the C-3 position of the β-lactam appeared at 3.47. The methoxyl of the p-anisyl appeared at 3.78 as a singlet integrating for 3 protons. The H-3a' (anomeric) proton of the sugar appeared as a doublet at 6.05 (J = 3.9 Hz). The β-lactam H-3 proton appeared at 4.75 (d, J = 4.9 Hz), while the H-4 ring proton appeared as a dd at 4.64 (J = 4.9 Hz and 3.9 Hz). The H-6'a proton of the sugar appeared as a doublet at 4.50 with a coupling constant J = 3.4 Hz.

In the ^{13}C NMR spectrum of this compound, the β-lactam carbonyl carbon was appeared at 164.90. The aromatic carbon bearing the methoxy group of the p-anisyl appeared at 156.29, and the aromatic carbon attached to the nitrogen of the p-anisyl appeared at

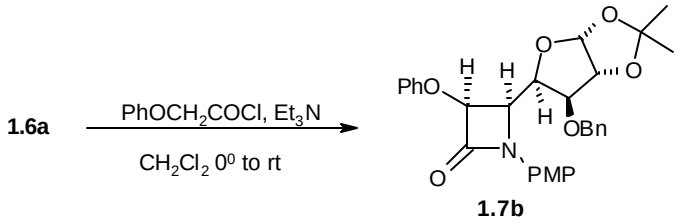
137.34. The other aromatic carbons appeared in the region 131.23 to 104.74. The carbons of the sugar framework appeared at 82.59-81.18. The β-lactam carbons C-3 and C-4 appeared at 81.18 and 71.75 respectively. The two-methoxy groups appeared at 58.75 and 58.41. The two methyls of the acetonide appeared at 26.58 and 26.06. The benzylic carbon was seen at 55.18. The other carbons resonated in the expected regions.

The mass spectral analysis of this compound showed the molecular ion peak at 455 (100%), which also was the base peak.

***1.4.3b Preparation of b-lactam* 1.7b**

A solution of phenoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine**1.6a** 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 followed by column chromatography, the β-lactam **1.7a** was isolated as solid in 75% yield (**Scheme-1.22**).

Scheme-1.22

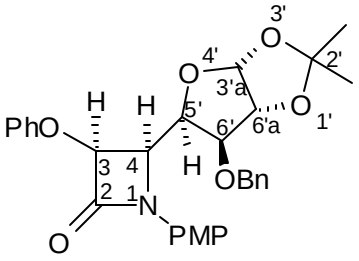


1.7b

The ^{1}H NMR of the crude reaction mixture showed the presence of peaks corresponding to only one diastereomer. The crude product was purified by column chromatography to get a solid, which was further purified by crystallization from dichloromethane/methanol.

The crystallized product was a white solid, m. p. 148 °C. The IR of **1.7b** showed peak at 1749 cm^{-1}, typical of the *b*-lactam carbonyl stretching. ^{1}H NMR showed two singlets at 1.34 & 1.54 belonging to two methyl groups of acetonide. The OMe of the p-anisyl group resonated as a singlet at 3.78. One of the diastereotopic protons from the benzyl group resonated as doublet at 4.3 with coupling constant 11.7 Hz. One of the ring Protons of the sugar skeleton, H-6a'

appeared at 4.45 as a doublet with coupling constant J = 3.0 Hz. The H-3 *b*-lactam proton appeared at 5.31 as a doublet with coupling constant 5.4 Hz. The signals due to H-4 *b*-lactam proton, H-5', H-6' ring protons and one of the benzylic protons appeared as a merged multiplet in the region of 4.5-4.8. A higher coupling constant



1.7b

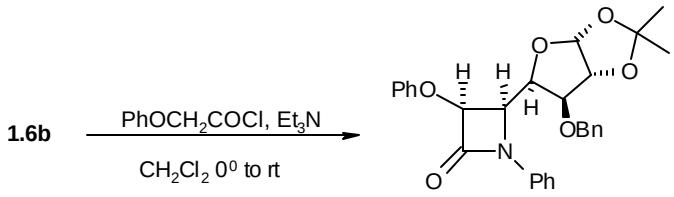
(5.4 Hz) indicated a *cis* stereochemistry of β-lactam ring protons. The H-3'a (anomeric) proton was seen downfield at 6.08, with coupling constant J = 3.9 Hz. The aromatic protons were seen as multiplets in the region of 6.80-7.70.

In the ^{13}C-NMR of **1.7b**, the methyls of the acetonide appeared at 26.29 & 26.83. The C-4 β-lactam carbon and the OMe of the *p*anisyl moiety appeared at 55.40 & 58.47. The rest of the carbons of the chiral backbone as well as the β-lactam i. e. C-5, C-6, C-6a', C-3a' and the methylene carbon of the O-CH_2Ph appeared at 71.95, 79.14, 81.38, 81.86 & 83.14 respectively. The mass spectrum showed presence of molecular ion peak at 517 (5%).

1.4.3c Preparation of b-lactam 1.7c

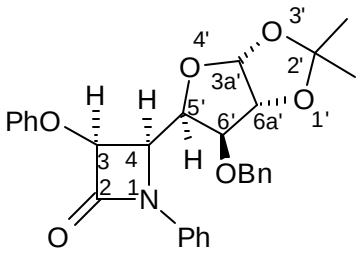
Following a similar procedure the β-lactam **1.7c** was isolated in 71% from the reaction between phenoacetyl chloride and the imine **1.6b** (**Scheme-1.23**).

Scheme-1.23

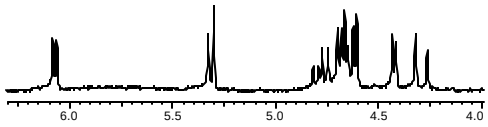


1.7c

The ^{1}H NMR spectrum of crude product showed the presence of a single diastereomer. This was then purified by column chromatography. In the IR spectrum of the compound **1.7c** recorded in nujol, the carbonyl stretching typical of β-lactam was observed as a strong band at 1751.24 cm^{-1}.



1.7c



The ^{1}H NMR spectrum of **1.7c** showed the acetonide peaks at 1.33 and 1.48 as two singlets integrating for three protons each. The H-3 proton appeared as a doublet at 5.29 (J = 5.4 Hz), while the H-4 was seen at 4.74 as a dd (J = 5.3 Hz, 3.4 Hz). The anomeric proton (H-3a') was observed at 6.05 as a doublet with a coupling constant 3.9 Hz. One of the benzylic protons appeared at 4.26 as a doublet (J = 11.2 Hz). The doublet at 4.67 was due to the H-6'a proton (J = 3.4 Hz). The H-6' proton came as a doublet at 4.60 (J = 3.5 Hz). The H-3'a (anomeric) proton appeared downfield at 6.05 as a doublet (J =3.9 Hz). The aromatic protons came as multiplets in the region 6.98 to 7.76 integrating for 15 protons.

The ^{13}C NMR of this compound was recorded in DMSO-d_6. The signal at 164.46 was due to the β-lactam carbonyl carbon, the methyls of the acetonide appeared at 26.12 and 26.76. All the other signals were in the expected regions and were in agreement with the structure of the compound.

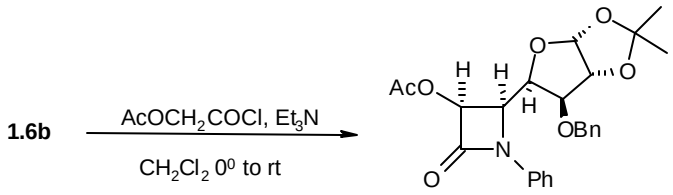
The mass spectral analysis of the compound showed the molecular ion peak at 487 (8%), while the base peak was seen at 91(100%). This compound provided satisfactory elemental analysis.

***1.4.3d Preparation of b-lactam* 1.7d**

Following a similar procedure the β-lactam **1.7d** was isolated in 72% from the reaction between acetoxyacetyl chloride and the imine **1.6b** (**Scheme-1.24**) in presence of triethylamine.

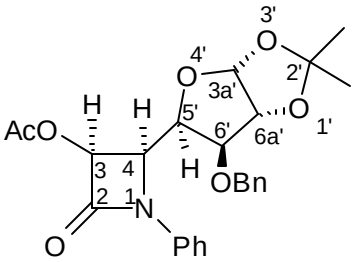
The IR spectrum of the product showed a sharp signal corresponding to the β-lactam carbonyl stretching at 1766.67 cm^{-1}, while the acetate carbonyl was seen at 1735 cm^{-1}.

Scheme -1.24



1.7d

The ^{1}H NMR of the crude compound showed the presence of a single diastereomer.



1.7d

The *cis* stereochemistry of the β-lactam was confirmed from the coupling constants of the H-3 and H-4 protons (J = 5.9 Hz). The β-lactam H-3 proton appeared at 6.07 as a doublet (J = 5.9 Hz), while the H-4 seen at 4.70 as a dd (J = 5.9 Hz, 3.9 Hz). The H-3a' (anomeric) proton appeared at 6.04 (J = 3.9 Hz) as a doublet. Due to the diastereotopic nature, the methylene protons of the benzylic group appeared as two sets of doublets at 4.36 (J = 11 Hz) and 4.63 (J = 11.2 Hz). The other signals appeared at the expected positions.

The ^{13}C NMR spectrum showed the β-lactam and the acetate carbonyl carbons at 162.35 and 168.27 respectively. The other peaks appeared at the expected values.

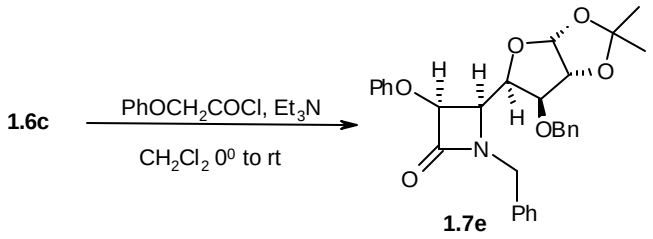
The mass spectral analysis of the compound showed the molecular ion peak at 453 ($M^{+\cdot}$) and the base peak at 91(100%). This compound showed satisfactory elementary analysis.

***1.4.3e Preparation of b-lactam* 1.7e**

Following a similar procedure the β-lactam **1.7e** was isolated in 74% from the reaction between phenoxyacetyl chloride and the imine **1.6c** (**Scheme -1.25**).

The IR spectrum showed the carbonyl peak typical of the β-lactam at 1758.96. The ^{1}H NMR of this compound was recorded in $CDCl_3$ and showed the presence of two singlets at 1.32 and 1.50 for the methyl protons of the acetonide.

Scheme -1.25



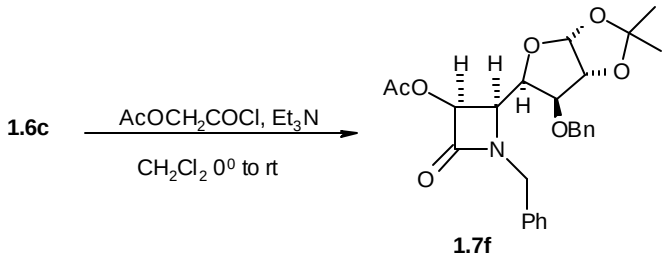
A dd at 4.11 was due to the H-5 proton (J = 4 Hz and 6 Hz). Due to the diastereotopic nature of the benzylic protons, they appeared as three sets of doublets at 4.22 (J = 14 Hz), 4.24 (J = 12 Hz), and 4.30 (J = 14 Hz). The fourth benzylic proton appeared as a multiplet, which was merged with H-4 and H-6' protons at 4.52 and integrated for a total of 3 protons. The H-6a' proton appeared as a doublet at 4.63 (J = 4 Hz). The H-3 β-lactam proton resonated at 5.16 as a doublet (J = 4.9 Hz). The anomeric proton (H-3'a) was seen downfield at 6.03 (J = 4 Hz). The aromatic ring protons appeared as a multiplet in the region 6.90 to 7.49 integrating for a total of 15 protons.

The ^{13}C NMR of this compound showed the signals due to the gem dimethyl of the acetonide at 25.88 and 26.43. The β-lactam C-3 resonated down field at 71.20, while C-4 resonated at 56.06. The two benzylic carbons appeared at 82.01 and 81.67. The 18 carbons of the aromatic rings appeared in the region 104.62 to 159.99 giving a total of 12 signals. The mass spectral analysis of this compound showed the molecular ion peak at 501 (1%), and the base peak at 91 (100%).

***1.4.3f Preparation of b-lactam* 1.7f**

Following a similar procedure, β-lactam **1.7f** was isolated in 70% from the reaction between acetoxyacetyl chloride and the imine **1.6c** (**Scheme -1.26**).

Scheme -1.26



The crude ^{1}H NMR spectrum showed the presence of a single diastereomer. This was then purified by column chromatography. In the IR spectrum of the compound recorded in nujol, the carbonyl stretching typical of β-lactam was observed as a strong band at 1751.24 cm^{-1}.

The ^{1}H NMR spectrum showed the acetonide peaks at 1.36 and 1.51 as two singlets integrating for three protons each. The H-3 proton appeared as a doublet at 5.85 (J = 4.9 Hz), while the H-4 was seen at 4.02 as a dd (J = 4.9 and 5.4 Hz). The anomeric proton (H-3'a) was observed at 5.98 as a doublet with a coupling constant 3.9 Hz. Due to the diastereotopic nature of the benzylic protons, each of the four protons were observed as a doublet in the following regions, 4.21 (d, J = 14.7 Hz), 4.30 (d, J = 12.3 Hz), 4.53 (d, J = 12.3 Hz) and 4.74 (d, J = 14.7 Hz). The doublet at 4.62 was due to the H-6a' proton (J = 3.9 Hz). The H-6' proton came as a doublet at 4.56 (J = 4.4 Hz). The aromatic protons came as multiplets at 7.19 integrating for 10 protons.

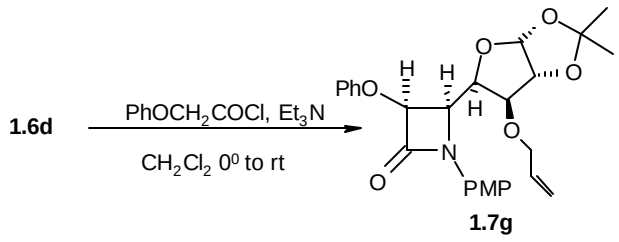
The ^{13}C NMR of this compound was recorded in $CDCl_3$. The signal at 164.10 was due to the β-lactam carbonyl carbon, while the acetate carbonyl resonated at 168.53. The methyls of the acetonide appeared at 26.06 and 26.64. The methyl carbon of the acetate gave a signal at 20.17. The C-3 and the C-4 carbons of the β-lactam resonated at 71.35 and 55.36 respectively. All the other signals were in the expected regions and were in agreement with the structure of the compound.

The mass spectral analysis of the compound showed the molecular ion peak at 467.19 (10%), while the base peak was seen at 91 (100%).

1.4.3g Preparation of b-lactam 1.7g

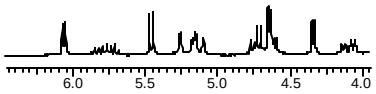
Following a similar procedure, the β-lactam **1.7g** was isolated in 79% from the reaction between phenoxyacetyl chloride and the imine **1.6d** (**Scheme-1.27**). The IR spectrum showed the carbonyl peak typical of the β-lactam carbonyl at 1751.24.

Scheme-1.27



The ^{1}H NMR of this compound showed two singlets at 1.30 and 1.50 for the two methyls of the acetonide. The methoxy protons of the p-anisyl appeared as a singlet at 3.80 integrating for 3 protons. The H-3 β-lactam proton appeared as a doublet at5.46 (J = 5.4 Hz), while the H-4 proton appeared as dd at 4.69 (J = 5.3 Hz, 3.4 Hz). The H-5' proton appeared as a dd at 4.10 (J = 3.4 Hz and 3 Hz). The H-6' proton came as a doublet at 4.33 (J = 3 Hz). The doublet at 4.58 was due to the H-6a' proton (J = 3.4 Hz).

The H-7 proton appeared as a doublet at 4.64 (J = 3.9 Hz), while the anomeric (H-3a') proton seen as a doublet at 6.06 (J = 3.9 Hz). The allyl protons appeared as 3 sets of multiplets at 3.90, 5.10 and 5.75.



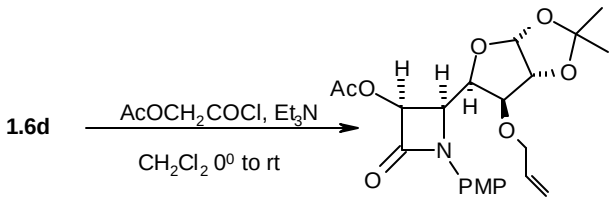
The ring protons of the phenoxy and the p-anisyl appeared in the aromatic region from 6.80 to 7.80 and integrated for 9 protons.

The ^{13}C NMR spectrum of this compound was recorded in $CDCl_3$. The C=O of the β-lactam resonated at 163.34. In the aliphatic regions the two methyls of the acetonide resonated at 26.16 and 26.72. The methoxyl carbon of the p-anisyl resonated at 55.31. The C-3 and C-4 of the β-lactam appeared at 70.68 and 58.58 respectively. The other carbons resonated in the expected regions and were consistent with the structure of the compound. The mass spectral analysis showed the base peak at 149 (100%) and the molecular ion peak at 467 (36%). This compound provided satisfactory elemental analysis.

***1.4.3h Preparation of b-lactam* 1.7h**

Following the standard procedure the β-lactam **1.7h** was isolated in 70% from the reaction between acetoxyacetyl chloride and the imine **1.6d** (**Scheme-1.28**).

Scheme-1.28



1.7h

The crude ^{1}H NMR spectrum showed the presence of a single diastereomer. This was then purified by column chromatography. In the IR spectrum of the compound recorded in nujol the carbonyl stretching typical of β-lactam was observed as a strong band at 1747.39 cm^{-1}. The ^{1}H NMR spectrum showed the acetonide peaks at 1.32 and 1.47 as two singlets integrating for three protons each. The methyl protons of the acetate appeared as a singlet at 2.21 and integrated for 3 protons. The H-3 proton appeared as a doublet at 6.15 (J = 5.6 Hz), while the H-4 was seen at 4.63 as a dd (J = 5.4 and 3.4 Hz). The anomeric proton (H-3a') was observed at 6.01 as a doublet with a coupling constant 3.9 Hz. The allyl protons appeared as 3 sets of multiplets at 3.80, 5.10 and at 5.77. The four aromatic protons came as multiplets in the region 6.83 to 7.63.

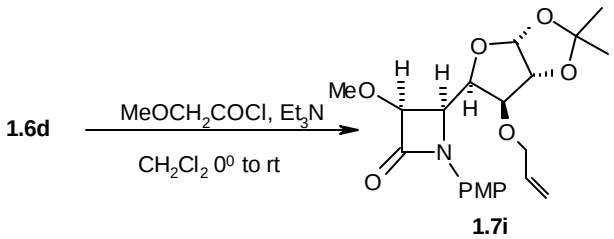
The ^{13}C NMR of this compound was recorded in $CDCl_3$. The signal at 162.02 was due to the β-lactam carbonyl carbon, while the acetate carbonyl resonated at 168.53. The methyls of the acetonide appeared at 26.09 and 26.64. The methyl carbon of the acetate gave a signal at 20.65. The methyl carbon of the p-anisyl resonated at 55.28. The C-3 and the C-4 carbons of the β-lactam resonated at 70.79 and 57.96 respectively. All the other signals were in the expected regions and were well in agreement with the structure of the compound.

The mass spectral analysis of the compound showed the molecular ion peak at 433 (18.75%), while the base peak was seen at 101 (100%).

1.4.3i Preparation of b-lactam **1.7i**

Following a similar procedure using methoxyacetyl chloride and the imine **1.6d** in the presence of triethylamine, the β-lactam **1.7i** was obtained as a gum in 72% yield. The product was purified by column chromatography to get the pure compound. The IR spectrum of this compound showed the C=O stretching of the β-lactam at 1747.39 (**Scheme -1.29**).

Scheme -1.29



The ^{1}H NMR of this compound showed two singlets at 1.31 and 1.44 corresponding to the acetonide. The methoxy of the β-lactam appeared as a singlet at 3.66 integrating for 3 protons. The methoxy group at C-3 position of the β-lactam

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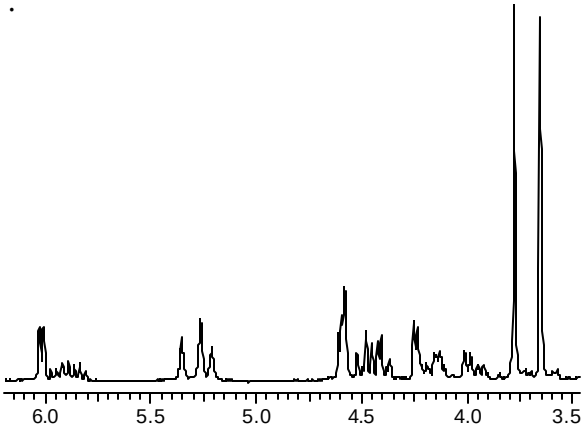


appeared at 3.66 as a singlet integrating for 3 protons. The methoxy group of the p-anisyl resonated at 3.78. The H-5' proton came as a dd at 3.92 (J = 5.8 Hz and 3.4 Hz) The H-3a' proton appeared at 6.02 as a doublet (J = 3.9 Hz). The aromatic protons appeared at

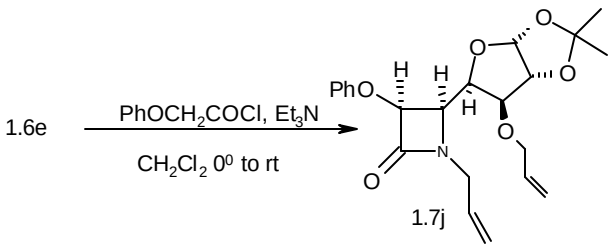
6.82and 7.64 as two signals integrating for 4 protons.

The ^{13}C NMR of this compound recorded in $CDCl_3$ showed a signal at 164.96 corresponding to the C=O carbon of the β-lactam. The two methyls carbons of the acetonide resonated at 26.15 and 26.67. The carbons of the C-3 methoxyl and the methoxyl of the p-anisyl appeared at 55.30 and 58.66 respectively. The C-3 and C-4 carbons of the β-lactam resonated at 70.84 and 58.66 respectively. All the other signals appeared at the expected regions. The mass spectral analysis of the compound showed the base peak at 149 (100%) and the molecular ion peak at 405 (100%).

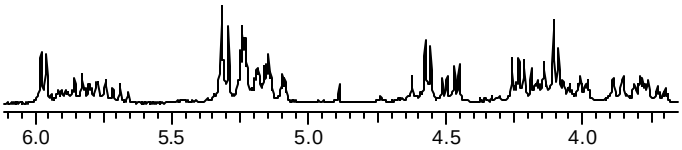
1.4.3j Preparation of b-lactam **1.7j**

Following a similar procedure the β-lactam **1.7j** was isolated in 69% yield by the reaction of phenoxyacetyl chloride with the imine **1.6e** in presence of triethylamine (**Scheme-1.30**).

Scheme-1.30



The β-lactam was purified by column chromatography and isolated as oil. The IR spectrum of the compound showed a strong band at 1758.96 cm^{-1} suggesting the presence of β-lactam ring. In the ^{1}H NMR spectrum of this compound showed two singlets at 1.29 and 1.50 integrating for three protons each could be attributed to the two methyls of the acetonide.



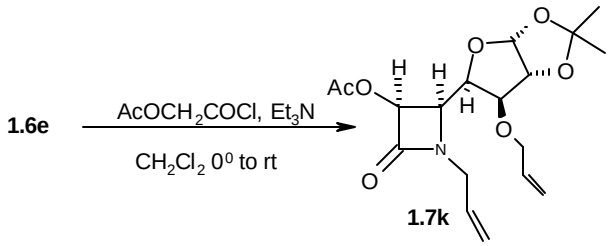
The H-3 β-lactam proton was observed as a doublet at 5.32 (J = 4.9 Hz). The H-5' proton appeared as a dd at 4.47 (J = 3.4 Hz and 3.9 Hz). The H-6' was seen at 4.11 as a doublet (J = 3.4 Hz). The H-6a' and the H-3a' protons were seen as two doublets at 4.57 (J = 3.9 Hz) and 5.96 (J = 3.9 Hz) respectively. The 10-allyl protons were seen as four sets of multiplets in the regions 3.70 to 3.90 integrating for 2 protons, 4.00 to 4.25 integrating for 2 protons, 5.05 to 5.20 integrating for 4 protons and 5.65 to 5.90 integrating for 2 protons.

In the ^{13}C NMR of this compound, the carbonyl carbon of the β-lactam resonated at 165.37. The olefinic and the ring carbons of the phenoxy group were observed in between 104.86 to 157.43. The two methyls of the acetonide resonated at 26.16 and 26.72. The sugar and the β-lactam carbons resonated in the regions of 82.18 to 26.16 and were consistent with the structure of the compound. The mass spectral analysis of the compound showed the molecular ion peak at 401 (2%) and the base peak at 147 (100%).

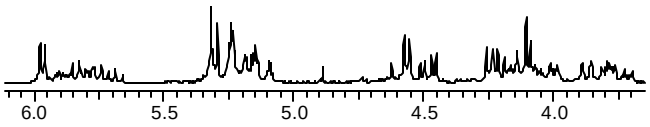
***1.4.3k Preparation of b-lactam* 1.7k**

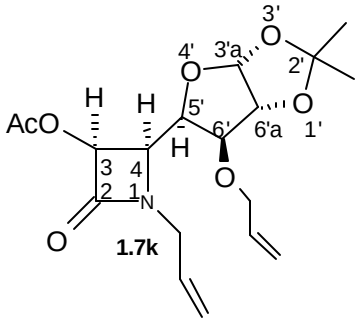
Following a similar procedure the β-lactam **1.7k** was isolated in 68% from the reaction of acetoxyacetyl chloride and the imine **1.6e** (**Scheme-1.31**).

Scheme -1.31



The IR spectrum of **1.7k** showed two bands due to two carbonyls at 1755.10 and 1760, for the acetate and the β-lactam carbonyl respectively. The ^{1}H NMR spectrum of this compound showed acetonide peaks at 1.32 and 1.50 as two singlets integrating for 3 protons each. The methyl protons of the acetate were observed at 2.10 as a singlet integrating for 3 protons. The H-5' and the H-6' protons merged with the multiplets of the allyl protons. The H-6a' was seen at 4.53 (d, J = 4 Hz).





The H-3 proton of the β-lactam appeared as a doublet at 5.99 (J = 4.8 Hz), while the H-4 proton resonated at 4.27 as a dd (J = 4.8 Hz and 3.5 Hz). The H-3a' (anomeric) proton appeared at 5.29 as a doublet (J = 3.6 Hz). The 10 protons of the allyl moieties appeared as three sets of multiplets in the regions 3.75 to 3.90 integrating for 3 protons, 5.15 to 5.30 integrating for 3 protons and 5.69 to 5.90 integrating for two protons.

In the ^{13}C NMR spectrum of this compound, the acetate carbonyl carbon resonated at 168.01 and the β-lactam carbonyl at 163.45. The methyl signal of the acetate appeared at 19.80. The two methyls of the acetonide were observed at 25.50 and 26.09. The other signals appeared in the expected region and were consistent with the structure of the compound. The mass spectrum of the compound showed the molecular ion peak at 367 (1%) and the $M^{+\cdot}$ peak at 368 (7.5%). The base peak was observed at 111 (100%). This compound provided satisfactory elemental analysis.

X-Ray crystal structure determination

In order to ascertain the relative configuration of the molecule, it was necessary to carry out single crystal X-Ray structure analysis of one of the compounds. Since the absolute stereochemistry of the chiral sugar precursor was known, the absolute configuration of the β-lactam could be deduced from the relative stereochemistry of the chiral centers.

To determine the relative stereochemistry of **1.7b**, a single crystal X-ray analysis of **1.7b** was carried out. Suitable Crystals for X-ray analysis were obtained by crystallization of **1.7b** from dichloromethane/methanol solvent system.

The important X-ray data for **1.7b** is as follows.

a = 9.7300 (10) Å, b = 13.598 (3) Å, c = 20.599 (3) Å, $\alpha = 90^0$, $\beta = 90^0$, $\gamma = 90^0$, V = 2725.4 (8) $Å^3$, z = 4, r_{calcd} = 1.261 Mg m^{-3}, wR2 = 0.1235, R1 = 0.0575, T = 293 (2) K, GOF = 1.233.

The data were collected on Enariuf Nonius CAD-4 single crystal X-ray diffractometer using Cu-Kα radiation (λ = 1.54060 Å) and ω-2θ scan mode to a θ range of 3.89 to 59.82^0. The structure was solved by direct positional and anisotropic thermal parameters for non-hydrogen atom converged to R*w* = 0.1235 R1 = 0.0575 for 2314 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference Fourier that was held fixed during the refinement. The refinements were carried out using SHELEX-97.

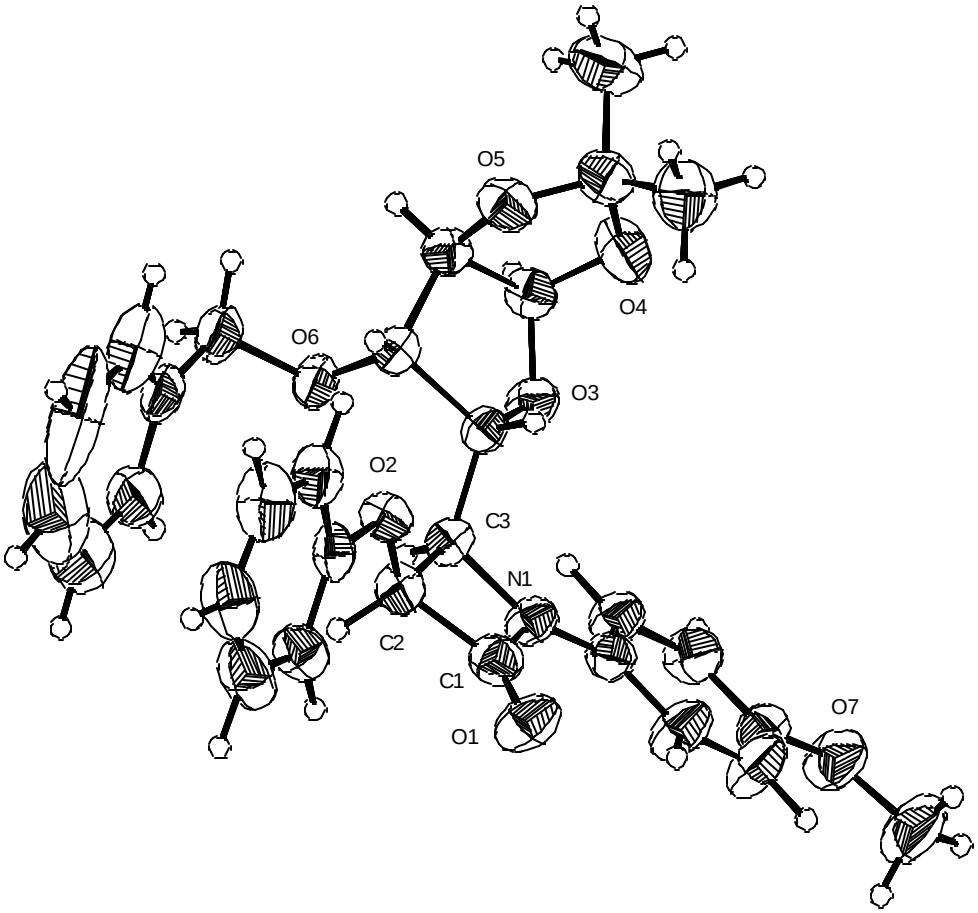


Fig 1.2. ORTEP diagram of the crystals of **1.7b**.

The X-ray analysis further confirmed the assigned structure of **1.7b** (**Fig 1.2**). The absolute stereochemistry of newly formed *b*-lactam ring centers were assigned as 3*S*, 4*R* based on the known absolute stereochemistry of sugar residue present in the molecule. The overall absolute stereochemistry of *b*-lactam **1.7b** was established as 3*S*, 3a'*R*, 4*R*, 5*R*, 6*S*, and 6a'*R*.

1.5 : Conclusion

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 all the cases. The relative stereochemistry at the two new chiral centers was established as 3*S* and 4*R* from X-Ray analysis of one of the *b*-lactams **1.7b**.

1.6 : 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. Zinc Chloride was freshly fused before use.

1.6.1 Synthesis of Diacetone-D-glucose **1.2**

A suspension of 75 g (0.0415 mol) of 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 is 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, is dissolved in 100 ml water and extracted with portions of methylene chloride (5x50 ml). 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).

1.6.2 Synthesis of 3-O-Allyl-1, 2: 5,6 di –O-isopropylidene α-D-glucofuranose **1.3a**

To a solution of the diacetonide **1.2** (10 g, 0.038 mol) and allyl bromide (6.97 g, 4.99 ml, 0.057 mol) in methylene chloride (100 ml) was added 50% aquous NaOH solution (50 ml) and the mixture stirred vigorously. Tetrabutylammonium bromide (catalytic) was then added to this mixture and the stirring continued till the disappearance of the starting material, as indicated by TLC (Ca. 24 hrs). The organic layer was separated and the aqueous layer washed with methylene chloride. The combined organic layers washed with water, dried over anhydrous sodium sulphate and the solvents evaporated under reduced pressure. The crude product containing residual PTC was chromatographed over silica (60-120 mesh) using EtOAc/Pet. Ether (1:4). Removal of solvents under reduced pressure afforded the 3-O-allyl-1, 2:5,6-diisopropylidene α-D-glucofuranose **1.3a** as an oil (11 g, 95.4%).

1.6.3 Synthesis of 3-O-Allyl-1, 2-O -isopropylidene α-D- glucofuranose **1.4a**

3-O-Allyl-1, 2: 5,6 di-O-isopropylidene α-D- glucofuranose **1.3a** (8 g, 0.0115 mol) was dissolved in 20 ml of aqueous acetic acid (75% v/v) and heated to 75 ^{0}C for 3 hrs. The solvents were removed under reduced pressure. The mass that remains was dissolved in $CHCl_3$ and washed repeatedly with water, saturated sodium bicarbonate solution, and saturated brine solution, dried over Na_2SO_4, and concentrated to get (6 g, 86.58%) of the diol **1.4a** as viscous oil which was used as such for the next reaction without further purification.

1.6.4 Synthesis of 3-O-Benzyl-1, 2: 5,6 di-O-isopropylidene α-D- glucofuranose **1.3b**

A solution of the diacetonide **1.2** (5.2 g, 0.02 mol) in anhydrous DMF (100 ml) was added to a suspension of NaH (2 g) under argon atmosphere, with cooling. The suspension was stirred at room temperature for 30 min. and a solution of benzyl chloride was added drop wise. The reaction mixture was stirred for 2.5 hrs at room temperature and the excess reagent was decomposed by the careful addition of MeOH (10 ml), and the solvents were removed. The residue was extracted with $CHCl_3$ (150 ml) and this was washed with water (3x100 ml), saturated brine solution and dried over sodium sulphate. Filtration and evaporation of the solvent under reduced pressure yielded **1.3b** as a syrup (6.8 ***g,*** 97%).

1.6.5 Synthesis of 3-O-Benzyl-1, 2-O -isopropylidene α-D- glucofuranose **1.4b**

Method A: 3-O-Benzyl-1, 2: 5,6 di –O-isopropylidene α-D- glucofuranose **1.3b** (5 gm, 0.0115 mol) was dissolved in aqueous acetic acid (20 ml, 75% v/v) and heated to 75 ^{0}C for 3 hrs. The solvents were removed under reduced pressure. The mass that remains was dissolved in $CHCl_3$ and washed repeatedly with water, saturated sodium bicarbonate solution, and saturated brine solution, dried over Na_2SO_4, and concentrated to get 3.8 g (94%) of the diol **1.4b** as a viscous oil, which was used as such for the next reaction without further purification.

Method B: To a solution of 3-O-Benzyl-1, 2: 5,6 di-O-isopropylidene α-D-glucofuranose **1.3b** (3 g, 8.57 mmol) in MeOH (30 ml), 0.8% H_2SO_4 (3ml) was added and allowed to stir at rt till the disappearance of the starting material (TLC, ca 24 hrs). The acid was quenched with triethylamine (3 ml). The solvents was evaporated under reduced pressure. The residue was taken up in $CHCl_3$, washed with water, Saturated

solution of brine, dried over Sodium Sulphate, and concentrated under reduced pressure to give the glycol **1.4b**, which was pure enough to be used for the next reaction without further purification. For the synthesis of the diol **1.4a**, similar procedures were employed.

1.6.6 General procedure for the preparation of aldehydes **1.5a-b**

The aldehydes were synthesized from the glycols following reported procedures [38,39] as follws: .

Silica gel (230-400 mesh, 10 g) was added to a vigorously stirred solution of $NaIO_4$ (2.57g, 12.0 mmol) dissolved in hot water (~75^0 C). It was cooled and filtered and dried. The resultant silica gel – supported $NaIO_4$ was used in the preparation of aldehydes.

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ (2.0 g) in methylene chloride (5 ml) was added a solution of the glycol (1 mmol) **1.4a,b** in methylene chloride (5 ml). The reaction was monitored by TLC, until the disappearance of the starting material, filtered through sintered glass funnel and the silica gel was washed thoroughly with methylene chloride. Removal of solvent under reduced pressure afforded the pure aldehydes **1.4a,b** respectively. These aldehydes were pure enough and were used as such for the next step.

1.6.7 General procedure for the preparation of imines **1.6a-e**

To a solution of the amine (p-anisidine, benzyl amine, ally amine, aniline) in CH_2Cl_2, and anhydrous $MgSO_4$, was added a solution of the aldehyde **1.5a-b** in CH_2Cl_2. The mixture was stirred for 6-8 hrs (TLC). The reaction mixture was filtered through a pad of celite. The filtrate was concentrated to get the imines **1.6a-e**, which were used as such for the β-lactam reaction.

1.6.8 General procedure for the preparation of b-lactams **1.7a-l**

A solution of the acid chlorides (phenoxyacetyl chloride, acetoxyacetyl chloride, methoxyacetyl chloride and phthalimidoacetyl chloride) (1.5 mmol) in methylene chloride were added to a solution of the imines **1.6a-e** (1 mmol) and triethylamine (4.5 mmol) in CH_2Cl_2 (20 ml) at 0 ^{0}C. After the addition was completed the reaction mixture was 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 the crude β-lactams **1.7a-l**, which were then purified by column chromatography using silica gel (60-120 mesh).

Synthesis of (3a'R, 3S, 4R, 5'R, 6'S, 6a'R,)-4-(6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2', 3',d], [1', 3'] dioxol-5yl)-3-methoxy-1- (4-methoxyphenyl)-azetidine2-one **1.7a**

The imine **1.6a** (0.383 g, 1 mmol) on treatment with methoxyacetyl chloride (0.162 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7a** (0.34 g, 74.72%) as a single diastereomer. It was purified by column chromatography.

M.P. : Oil

[a]$_D^{25}$: -217.19^0 (c = 1, $CHCl_3$)

IR (cm^{-1}) : 1743.53

^{1}H NMR : 1.32 (S, 3H), 1.46 (S, 3H), 3.47 (S, 3H), 3.78 (S, 3H), 4.28 (d, 1H, J = 3.5 Hz), 4.35-4.48 (m, 2H), 4.50 (d, 1H, J = 3.4 Hz), 4.64 (dd, 1H, J = 4.9 Hz and 3.9 Hz), 4.75 (d, 1H, J = 4.9 Hz), 4.78 (d, 1H, J = 11.7 Hz), 6.05 (d, 1H, J = 3.9 Hz).

^{13}C NMR : 26.06, 26.58, 55.18, 58.41, 58.75, 71.75, 81.18, 81.85, 82.07, 82.59, 104.74, 111.49, 113.81, 119.51, 127.66, 127.88, 128.06, 128.33, 131.23, 137.34, 156.29, 164.90

MS : $M^{+\cdot}$ 455 (100%), $M^{+\cdot}$ +1 456 (20%), $M^{+\cdot}$ +2 (33%), 368 (31%), 149 (17%), 91 (44%)

Microanalysis : Calculated C: 65.906 H: 6.421 N: 3.076

$C_{25}H_{29}NO_7$ Obtained C: 66.02 H: 6.57 N: 3.19

Synthesis of (3a'R, 3S, 4R, 5'R, 6'S, 6a'R,)***-4-(6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2', 3',d], dioxol-5'yl)-1-(4-methoxyphenyl)-3-Phenoxyy-azetidine2-one*** **1.7b**

The imine **1.6a** (0.383 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.255 g, 1.5 mmol), in the presence of triethylamine (0.405 g, 4.5 mmol) provided the β-lactam **1.7b** (0.387 g, 75%) as a single diastereomer. It was purified by column chromatography.

MP: : 148

[a]$_D^{24}$	**:**	-245^0 (c = 1.85, CH_2Cl_2)
IR ($CHCl_3$):	**:**	1749
^{1}H NMR ($CDCl_3$): (200 MHz)	**:**	1.34 (s, 3H), 1.54 (s, 3H), 3.78 (s, 3H), 4.3 (d, 1H, J = 1.7 Hz), 4.45 (d, 1H, J = 3.0 Hz), 4.5-4.8 (m, 4H), 5.31 (d, 1H, 5.4 Hz), 6.08 (d, 1H, J = 3.9 Hz), 6.87 (d, J = 8 Hz), 6.9-7.77 (m, 15H).
^{13}C NMR ($CDCl_3$): (200.13 MHz)	**:**	26.29, 26.83, 55.40, 58.47, 71.95, 79.14, 81.38, 81.86, 83.14, 104.96, 111.83, 113.94, 115.62, 119.79, 122.41, 127.57, 127.99, 128.46, 129.62, 131.21, 137.12, 156.55, 157.39, 163.44
MS	**:**	$M^{+\cdot}$ 517 (5%), $M^{+\cdot}$ +1 518 (1%), $M^{+\cdot}$ +2 519 (0.1%), 430 (2%), 149 (41%), 134 (15%), 91 (100%), 77 (12%)
Analysis $C_{30}H_{31}NO_7$	**:**	Calculated: C: 70.04, H: 6.26, N: 2.63 Found: C: 69.85, H6.01, N: 2.49

***Synthesis of (3a', 3S, 4R, 5'R, 6'S, 6a'R,)-4-(6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2', 3',d][1'-3'] dioxol-5'yl)-3-Phenoxyy-1-Phenyl azetidine2-one* 1.7c**

The imine **1.6b** (0.383 g, 1 mmol) on treatment with phenoxyacetylchloride (0.255 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7c** (0.346 g, 71.2%) as a single diastereomer. It was purified by column chromatography.

MP:	**:**	112^0 C
[a]$_D^{24}$	**:**	-285^0 (c = 1, $CHCl_3$)
IR (nujol):	**:**	1751.24
^{1}H NMR ($CDCl_3$): (200 MHz)	**:**	1.33 (S, 3H), 1.48 (S, 3H), 4.26 (d, 1H, J = 11.2 Hz), 4.41 (d, 1H, J = 3 Hz), 4.60 (d, 1H, J = 3.5 Hz), 4.67 (d, J = 3 Hz), 4.74 (dd, 1H, J = 5.3 Hz, 3.4 Hz), 5.29 (d, 1H, J = 5.4 Hz), 6.05 (d, 1H, J = 3.9 Hz), 6.98-7.76 (m, 15H, Ar)
^{13}C NMR (DMSO-D_6) (50.3 MHz)	**:**	26.12, 26.76, 57.74, 67.38, 71.01, 78.92, 81.15, 81.27, 82.40, 104.62, 111.05, 115.51, 118.04, 119.97, 121.37, 122.50, 123.87,124.51, 127.72, 128.36, 128.88, 129.82, 137.52, 137.39,

133.49, 157.23, 157.99, 164.46.

MS : $M^{+\cdot}$ 487 (8%), 354 (12%), 275 (55%), 217 (19%), 161 (28%), 149 (25%), 91 (100%).

Analysis : Calculated: C: 71.44, H: 5.995, N: 2.87

$C_{29}H_{29}NO_6$ Found: C: 71.40, H: 6.09, N: 2.77

***Synthesis of (3a'R, 2R, 3S, 5'R, 6'S, 6a'R, 8R)-3-Aceticacid-2-(6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2',3',d], [1',3'dioxol-5'yl]-4-oxo-1-Phenyl-azetidine2-one* 1.7d**

The imine **1.6a** (0.383 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.204 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7d** (0.32 g, 72%) as a single diastereomer. It was purified by column chromatography.

MP: : Gum

[a]$_D^{27}$: -244.071^0 (c=1, $CHCl_3$)

IR ($CHCl_3$): : 1766

^{1}H NMR ($CDCl_3$) : 1.32 (S, 3H), 1.46 (S, 3H), 2.05 (S, 3H), 3.99 (1H, 3.6 Hz), 4.40-4.36 (d, 11 Hz, benzylic), 4.47 (dd, 1H, 3 Hz each), 4.65-4.62 (d, 1H, J = 3.9 Hz), 4.63 (d, 1H, J = 11.2 Hz), 4.75 (dd, 1H, J = 5.9 Hz and 3.9 Hz), 6.03-6.05 (d, 1H, J = 3.9 Hz), 6.07-6.05 (d, 1H, J = 5.9 Hz), 7.07-7.13 and 7.70-7.68 (m, 10H, aromatic).
(200.13 MHz)

^{13}C NMR ($CDCl_3$): : 20.06, 25.87, 26.38, 57.22, 71.38, 72.77, 80.57, 81.12, 81.85, 104.53, 111.44, 117.95, 124.31, 127.80, 127.98, 128.31, 136.47, 137.21, 162.35, 168.27
(200.13MH_Z)

MS : M+. 453 (15%), 193 (5%), 91 (100%), 77 (15%), 65 (18%).

Analysis : Calculated: C: 66.21, H: 6.00, N: 3.08

$C_{25}H_{27}NO_7$ Found: C: 66.40, H: 6.57, N: 3.19

***Synthesis of (3a'R, 3S, 4R, 5'R, 6'S, 6a'R)-1-Benzyl-4- (6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2', 3',d], [1', 3'] dioxol-5'yl)-3-Phenoxy-azetidine2-one* 1.7e**

The imine **1.6c** (0.367 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 the β-lactam **1.7e** (0.37 g, 74%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Oil
[a]$_D^{25}$	**:**	-206.415^0 (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1758.96
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.32 (S, 3H), 1.50 (S, 3H), 4.11 (dd, 1H, J = 4 Hz, 6 Hz), 4.22 (d, 1H, J = 14 Hz), 4.24 (d, 1H, J = 12 Hz), 4.30 (, d, 1H, J = 14 Hz), 4.53 (m, 2H), 4.63 (d, 1H, J = 4 Hz), 4.79 (d, 1H, J = 18 Hz), 5.16 (d, 1H, J = 4.9 Hz), 6.03 (d, 1H, J = 4 Hz).
^{13}C NMR ($CDCl_3$) ($50.3\ MH_Z$)	**:**	25.88, 26.43, 44.92, 56.06, 71.20, 79.78, 81.06, 81.67, 82.01, 104.62, 111.27, 114.36, 115.18, 121.71, 126.99, 127.88, 128.12, 128.97, 135.66, 136.73, 156.99, 164.90
MS	**:**	$M^{+\cdot}$ (501, 1%), 368 (20%), 275 (25%), 235 (8%), 196 (60%), 161 (20%), 149 (23%), 105 (18%), 91 (100%),
Analysis	**:**	Calculated: C: 71.84; H: 6.23, N: 2.79
$C_{30}H_{31}NO_6$		Found: C: 72.15, H: 6.50, N: 3.05

***Synthesis of (2R, 3a'R, 3S, 5'R, 6'S, 6a'R)-3-Aceticacid-2-(6'-Benzyloxy-2', 2'-Dimethyl-tetrahydrofuro [2',3',d], [1',3'dioxol-5'yl]-1-Benzyl-4-oxo-azetidine-3yl ester* 1.7f**

The imine **1.6c** (0.367 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.204 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7f** (0.326 g, 70%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Oil
[a]$_D^{25}$	**:**	-216.11^0 (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1751.24
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.36 (s, 3H), 1.51 (s, 3H), 1.97 (s, 3H), 3.85 (d, J = 3.5 Hz), 4.02 (dd, 1H, J = 4.9 Hz, 5.4 Hz), 4.21 (d, 1H, J = 14.6 Hz), 4.30 (d, 1H, J = 12.3 Hz), 4.31 (d, 1H, J = 3.5 Hz), 4.53 (d, 1H, J = 11.8 Hz), 4.56 (d, 1H, J = 4.4 Hz), 4.62 (d, 1H, J = 3.9 Hz), 4.74 (d, 1H, J = 14.7 Hz), 5.85 (d, 1H, J = 4.9 Hz), 5.98 (d, 1H, J = 3.9 Hz), 7.19 (m, 10H, Ar)
^{13}C NMR	**:**	20.17, 26.06, 26.64, 45.20, 55.36, 71.35, 74.01, 80.66, 81.24,

($CDCl_3$)	81.55, 104.80, 111.67, 127.39, 127.85, 128.03, 128.36, 135.44,
(200 MH_Z)	136.45, 164.10, 168.53
MS	$M^{+\cdot}$ 467 (10%), 274 (48%), 161 (50%), 129 (30%), 101 (45%), 91 (100%).
Analysis	Calcd. C: 66.797, H: 6.252, N: 2.996
$C_{26}H_{29}NO_7$	Found. C: 66.922, H: 6.472, N: 3.136

Synthesis of (3a'R, 3S, 4R, 5'R, 6'S, 6a'R)-4-(6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-1-(-4-methoxyphenyl)-azetidin-2one **1.7g**

The imine **1.6d** (0.333 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 the β-lactam **1.7g** (0.368 g, 79%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	144-145 ^{0} C
[a $]_D^{29}$	**:**	-242^0 (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1751.24
^{1}H NMR ($CDCl_3$)	**:**	1.30 (S, 3H), 1.50 (S, 3H), 3.80 (S, 3H), 3.90 (m, 2H), 4.04 (dd,
(200.13 MHz)		1H, J = 5.3 Hz each), 4.32 (d, 1H, J = 3 Hz), 4.58 ((d, 1H, J = 3.4 Hz), 4.69 (dd, 1H, J = 5.4 Hz, 3.4 Hz), 5.10 (m, 3H), 5.46 (d, 1H, J = 5.4 Hz), 5.75 (m, 1H), 6.06 (d, 1H, J = 3.9 Hz), 6.80 and 7.8 (m, 9H).
^{13}C NMR	**:**	26.16, 26.72, 55.31, 58.58, 70.68, 79.17, 81.34, 81.82, 82.81,
($CDCl_3$)		104.79, 111.66, 113.87, 115.60, 117.43, 119.71, 122.40,
(50.3 MH_Z)		129.56, 131.11, 133.72, 156.51, 157.39, 163.34
MS	**:**	$M^{+\cdot}$ 467 (35%), 379 (12%), 149 (100%), 134 (38%), 111 (17%), 77 (42%).
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{26}H_{29}NO_7$		Found: C: 66.02, H: 6.57, N: 3.19

Synthesis of (2R, 3a'R, 3S, 5'R, 6'S, 6a'R,)-Acetic acid2- (6'-Allyloxy-2, 2-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-1-(-4-methoxyphenyl)-4oxo-azetidin-3ylester **1.7h**

The imine **1.6d** (0.333 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.204 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7h** (0.303 g, 70%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Oil
[a]$_D^{25}$	**:**	-225.94^0 (c = 1, $CHCl_3$)
IR (nujol)	**:**	1747.39
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.32 (S, 3H), 1.47 (S, 3H), 2.21 (S, 3H), 3.78 (S, 3H), 3.80-3.89 (m, 3H), 3.92 (d, 1H, J = 3.4 Hz), 4.08 (m 1H), 4.41 (dd, 1H, J = 3.4 Hz each), 4.59 (d, 1H, J = 3.8 Hz), 4.63 (dd, 1H, J = 5.4 Hz, 3.4 Hz), 5.10 (m, 1H), 5.77 (m, 1H), 6.01(d, 1H, J = 3.9 Hz), 6.15 (d, 1H, J = 5.6 Hz), 6.83-7.63 (m, 4H)
^{13}C NMR ($CDCl_3$) ($50.3\ MH_Z$)	**:**	20.65, 26.09, 26.64, 55.28, 57.96, 70.79, 72.88, 80.75, 81.52, 81.78, 82.22, 104.72, 111.70, 113.83, 118.24, 119.68, 130.89, 133.42, 156.54, 162.02, 168.53
MS	**:**	433 (18.2%), 387 (3 %), 360 (3.6%), 318 (2.42%), 291 (3.85%), 258 (2.1%), 223 (27.3%), 190 (6%), 174 (22.72%), 149 (64%), 123 (67%), 101 (100%), 83 (27.3%), 73 (75.8%).
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{22}H_{27}NO_8$		Found: C: 66.02, H: 6.57, N: 3.19

***Synthesis of (2R, 3a'R, 3S, 5'R, 6'S, 6a'R)- 4-(6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-3- methoxy-4 (methoxy-phenyl) azetidin-2one* 1.7i**

The imine **1.6d** (0.333 g, 1 mmol) on treatment with methoxyacetyl chloride (0.16 g, 1.5 mmol), in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **1.7i** (0.29 g, 72%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Gum
[a]$_D^{29}$	**:**	-209.07^0 (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1747.39

^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.31 (S, 3H), 1.44 (S, 3H), 3.66 (S, 3H), 3.78 (S, 3H), 3.92 (dd, 1H, J = 5.8 Hz and 3.4 Hz), 4.11 (m, 2H), 4.36 (m, 2H), 4.52 (m, 2H), 5.21 (m, 2H), 5.81 (m, 1H), 6.02 (d, 1H, J = 3.9 Hz)
^{13}C NMR ($CDCl_3$) (200.13 MH_Z)	**:**	26.15, 26.67, 55.30, 58.66, 59.05, 70.84, 81.33, 82.01, 82.25, 82.68, 104.77, 111.49, 113.87, 117.26, 119.54, 131.29, 133.95, 156.32, 164.96
MS	**:**	$M^{+\cdot}$ 405 (45%), 318 (12%), 179 (10%), 149 (100%), 134 (30%), 111 (33%), 99 (10%), 87 (40%), 71 (29%)
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{21}H_{27}NO_7$		Found: C: 66.02, H: 6.57, N: 3.19

***Synthesis of (3a'R, 3S, 4R, 5'R, 6'S, 6a'R)-1-Allyl-4- (6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-3 -phenoxy-azetidin-2one* 1.7j**

The imine **1.6e** (0.267 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.255 g, 1.5 mmol), in the presence of triethylamine (0.405 g, 4.5 mmol) provided the β-lactam **1.7j** (0.276 g, 69%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Oil
[a]$_D^{27}$	**:**	-206.797^0 (c = 1, $CHCl_3$)
IR (neat)	**:**	1758.96
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.29 (S, 3H), 1.50 (S, 3H), 3.70 (m, 2H), 4.00 (m, 2H), 4.11 (d, 1H, J = 3.4 Hz), 4.47 (dd, 1H, J = 3.4 Hz and 3.9 Hz), 4.57 (d, 1H, J = 3.9 Hz), 5.05 (m, 4H), 5.32 (d, 1H, J = 4.9 Hz), 5.96 (d, 1H, J = 3.9 Hz), 5.65 (m, 2H)
^{13}C NMR ($CDCl_3$) (50.3 MH_Z)	**:**	26.16, 26.72, 43.88, 56.60, 70.57, 79.90, 81.34, 82.18, 104.86, 111.63, 115.52, 117.29, 118.32, 122.18, 129.38, 131.29, 133.68, 157.43, 165.37

MS	**:**	$M^{+\cdot}$ 401 (2%), 358 (20%), 318 (10%), 225 (50%), 167 (25%), 147 (100%), 131 (21%), 111 (90), 78 (97%)
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{22}H_{27}NO_6$		Found: C: 66.02, H: 6.57, N: 3.19

***Synthesis of (2R, 3a'R, 3S, 5'R, 6'S, 6a'R)-Acetic acid, 1-Allyl-4- (6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-3-phenoxy-azetidin-2one* 1.7k**

The imine **1.6e** (0.267 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.204 g, 1.5 mmol), in the presence of triethylamine (0.405 g, 4.5 mmol) provided the β-lactam **1.7k** (0.25 g, 68%) as a single diastereomer. It was purified by column chromatography.

MP	**:**	Oil
$[a]_D^{24}$	**:**	-238.88^0 (c = 1, $CHCl_3$)
IR (neat)	**:**	1745, 1755
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.32 (S, 3H), 1.50 (S, 3H), 2.10 (S, 3H), 3.75 (m, 3H), 4.00 (m, 4H), 4.27 (dd, 1H, J = 4.8 Hz, 3.5 Hz), 4.53 (d, 1H, J = 4 Hz), 5.15-5.30 (m, 3H), 5.69-5.90 (m, 2H), 5.29 (d, 1H, J = 3.6 Hz), 5.99 (d, 1H, J = 4.8 Hz)
^{13}C NMR ($CDCl_3$) ($50.3\ MH_Z$)	**:**	19.80, 25.50, 26.09, 43.29, 55.46, 59.36, 70.02, 73.18, 79.94, 81.01, 81.23, 104.27, 110.93, 117.36, 130.89, 133.13, 163.45, 168.01.
MS	**:**	$M^{+\cdot}$ 368 (15%), 352 (12%), 310 (6%), 294 (15%), 269 (7%), 238 (2%), 224 (5%), 210 (1.2%), 184 (2%), 173 (4%), 129 (7), 111 (100%), 98 (16%).
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{18}H_{25}NO_7$		Found: C: 66.02, H: 6.57, N: 3.19

1.7 : References

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Chapter 2

Stereoselective Staudinger reaction for the synthesis of β-Lactams using 1,2:5,6 diisopropylidene α-D -Allofuranose.

2.1 : Abstract

This chapter deals with the asymmetric synthesis of β-lactams from chiral aldimines **2.6a** and **2.6b** derived from 3-O-Allyl-1,2-O-isopropylidene-ribo-1,5-penta dialdo-1,4-furanose. The sterically demanding aldimines **2.6a** and **2.6b** were prepared from glucose diacetonide **1.2** in 7 steps. These imines underwent a highly stereospecific Staudinger reaction with ketenes to provide a single diastereomer of β-lactams **2.7a-f**, 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).

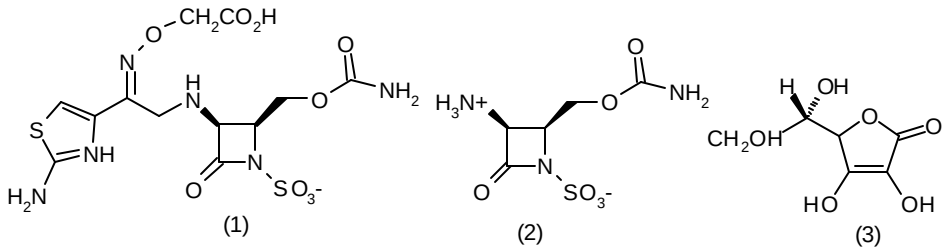
2.2 : *Introduction*

2.2.1 Background

Carbohydrates as chiral precursors to b-lactams

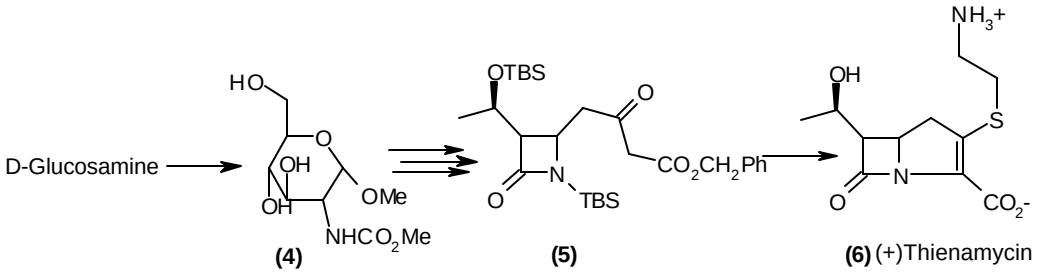
The discovery of sulfazecin[1] (**1**) and related monocyclic β-lactams (monobactams) from microbial sources has spawned considerable effort to generate synthetic analogues with enhanced antibiotic properties. Chung Chen Wei utilized L-ascorbic acid (**3**) as a convenient and inexpensive starting material and converted it into the zwitterionic precursor (**2**) in 7 steps (**Chart 2.1**).

Chart 2.1



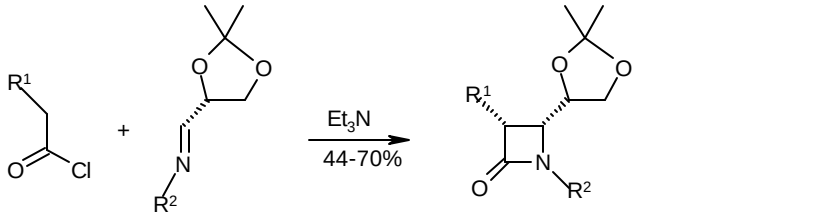
The rapidly expanding family of carbapenems antibiotics has attracted much attention owing to their wide spectrum of antibacterial activity and this consequently stimulated synthetic efforts. Yoshikosi et al[2] have achieved the chiral synthesis of the intermediate of thienamycin, a representative of the family of carbapenem antibiotics, starting from the commercially available D-glucosamine in 10 steps (**Scheme 2.1**).

Scheme 2.1



Bose et al observed complete diastereoselectivity during the cyclocondensation of activated acids with aldimines derived from D- and L-glyceradehyde acetonide[3,4,5.] The β-lactams were isolated in excellent optical and good chemical yields (**Scheme2.2a** and **2.2b**)

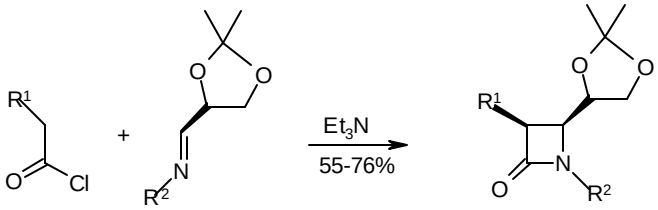
Scheme2.2a



R^1=CH_3O,PhO,AcO,N_3,PhthN,CH_2=CH

R^2=PMP,CH_2COOCH_3,Bn

Scheme2.2b

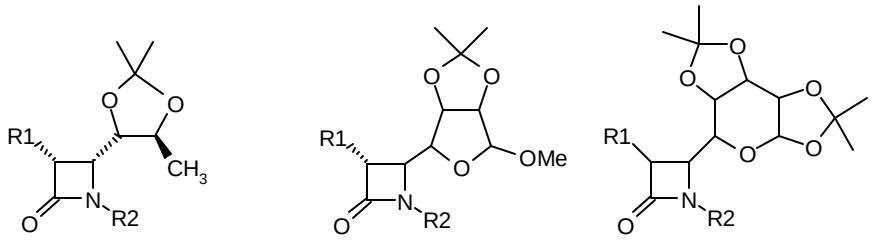


R^1=PhthN

R^2=DMB,PMB,Bn

Bose et al also observed that imines derived from several glyceraldehydes acetonide related aldehydes (**scheme2.3**) led to a single *cis* β-lactams in all the cases [6,7,8], demonstrating that the second chiral center in the aldehyde does not exercise any influence on the stereo chemical course of the annulations reaction.

Scheme2.3



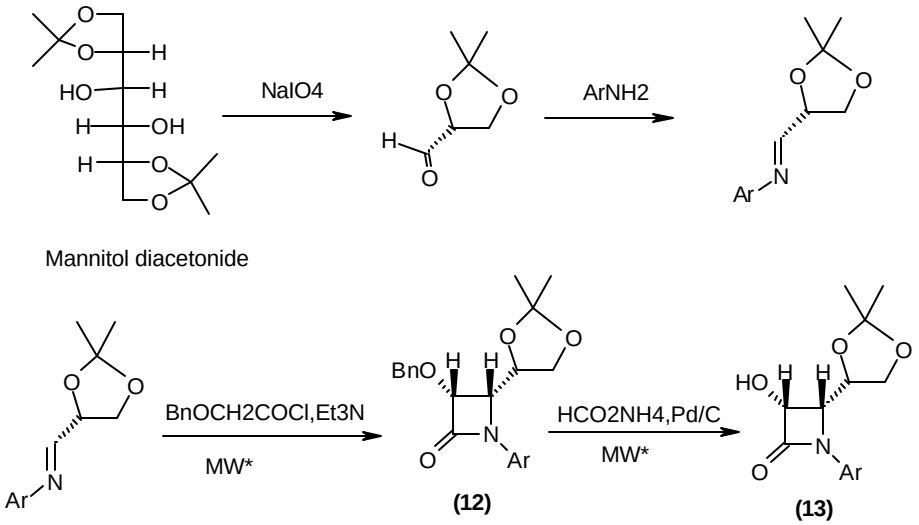
(9) **(10)** **(11)**

R1=OAc,OBn,OCH3,OPh

R2=DMP,Bn

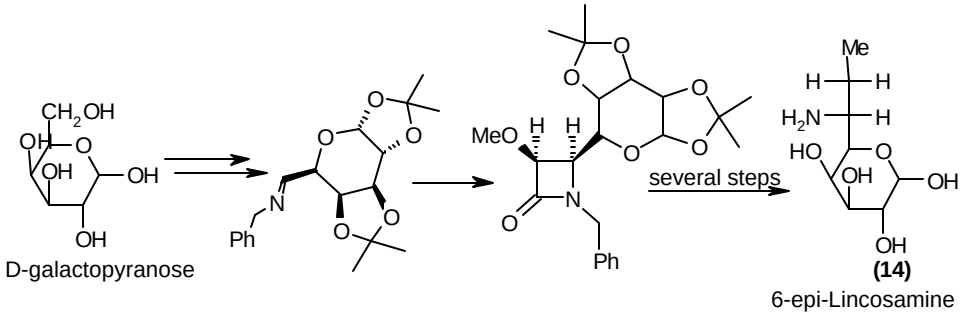
Recently Bose and Manhas[9] have reported the enantiospecific synthesis, of α-hydroxy-β-lactams (13) using Schiff's bases derived from D-glyceraldehyde under microwave irradiation (**Scheme2.4**).

Scheme2.4



They also synthesized *cis*–3-hydroxy-β-lactams[10] starting from optically active aldehydes derived from D-galactopyranose and converted it stereospecifically into 6-epi-lincosamine (**Scheme2.5**).

Scheme2.5



2.3 : Present work

Our present investigation was focused on the stereoselective synthesis of β-lactams using the chiral aldehyde derived from 1, 2: 5, 6-diisopropylidene-α-D-allofuranose, and the C-3 epimer of 1,2:5,6-diisopropylidene-α-D-glucofuranose (inverted stereochemistry of the hydroxyl group at the C-3 position). Our interest in the use of this aldehyde was to study the influence due to the second chiral center on the stereo chemical course of the annulations reaction.

2.4 : Results and discussions

Optically active aldehydes were known to induce high levels of stereoselectivity in the *Staudinger reaction*. The *Staudinger reaction* was also known to proceed with good selectivity providing only the *cis*β-lactams. Recently it has been shown that the chirality at the α-carbon center is necessary for high levels of chiral induction. Hence the stereochemistry at the β-chiral center should not necessarily affect the chiral induction in the *Staudinger reaction*. Having studied the level of stereo selection in the β-lactam formation using the aldehydes **1.5a** and **1.5b** and having obtained a high level of diastereoselectivity, we thought it worthwhile to study the effect of inverting the stereo center at the β-chiral center in the *Staudinger reaction*. We therefore selected the chiral aldehyde 3-O-allyl-1, 2 isopropylidene α-D-arabino-1, 5penta dialdo-1-4-furananose **2.5**, with the required steric bulk, as one face of the aldehyde is completely blocked by the gem dimethyl group.

The aldehyde **2.5** was prepared from D-glucose in 6 steps. D-glucose was converted into its diacetonide using zinc chloride and acetone. The PDC oxidation of the diacetonide **1.2** provided the ketone **2.1**. The crude ketone was then reduced stereospecifically to the

alcohol **2.2** in presence of $NaBH_4$ in MeOH. This alcohol on alkylation with allyl bromide under phase transfer condition, in the presence of tetra butyl ammonium bromide provided the 3-O-allyl diacetonide **2.3**. The selective hydrolysis of the acetonide **2.3** at the 5, 6 positions under acidic conditions provided the glycol **2.4**. $NaIO_4$ oxidation of **2.4** gave the aldehyde **2.5**, with the required steric bulk. The aldehyde **2.5** on treatment with amines formed the respective imines in quantative yields. The imines were found to be reactive and the annulations with the acid chloride in presence of triethylamine at 0 ^{0}C provided the β-lactam **2.7a-f** in good yields. As expected only a single diastereomer with *cis* stereochemistry was formed in the reaction, as observed from the ^{1}H NMR spectrum of the crude product.

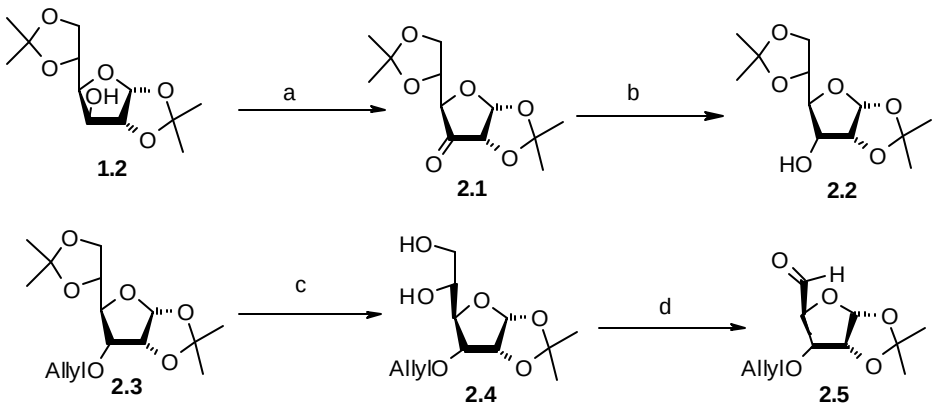
Thus the inversion of the stereo center at the β-chiral center in the aldehyde **1.5b** did not exert any influence on the stereo chemical course of the reaction. Hence it can be safely concluded that the relative stereochemistry at the C-3 and C-4 positions of the β-lactam must be the same i.e. 3*R* and 4*S* for the compounds obtained from both the epimers of the sugar aldehyde.

The diagnostic tool to differentiate spectroscopically the two isomeric sugars at the C-3 position is the ^{1}H NMR. The H-2 proton of the glucose diacetonide derivative appeared as a doublet at 4.5 (J = 3.4 Hz) whereas in the allose di acetonide derivative the H-3 proton appeared as a triplet at 4.5 (J = 3.4 Hz). This can be explained in terms of the Karplaus's equation, which states that the largest vicinal couplings arise with protons in the *trans* coplanar positions ($\phi = 180^0$, where ϕ is the dihedral angle between two vicinal C-H bonds). Vicinal couplings for *cis* coplanar protons are almost as large ($\phi = 0$). Very small couplings arise between the protons at 90^0 to each other. In the case of the glucose derivative the dihedral angle is 90^0 and so no coupling is observed, whereas in the allose derivative the dihedral angle is close to 60^0 hence the H-2 proton couples with both the H-1 and the H-3 giving a triplet.

2.4.1 Preparation of the aldehyde **2.5**

Following the reported procedure, glucose diacetonide[11,12,13] was converted into its diastereomer 1,2:5,6-diisopropylidene-α-D-allofuranose **2.2** in two steps.

Scheme -2.1



Reagents and condition:a)PDC,CH_2Cl_2 b) NaBH4, MeOHc)AllylBromide/aqNaOH,PTC d)aq HOAc or 0.8%H_2SO_4 d)$NaIO_4$ adsorbed on silica gel

The alcohol **2.2** was then alkylated using allyl bromide under phase transfer conditions to get the 3-O-allyl derivative **2.3** in quantative yield. The diacetonide **2.3** was then selectively deprotected using either 70% aq. acetic acid or 0.8% H_2SO_4 solution to get the 5,6-diol **2.4**, which on treatment with $NaIO_4$ afforded the required aldehyde **2.5** in good yields (**Scheme -2.1**).

2.4.2 Preparation of imines **2.6a** *and* **2.6b**

The imines **2.6a** and **2.6b** were prepared by treating the aldehyde **2.5** with p-anisidine or ally amine in methylene chloride in presence of $MgSO_4$ at RT. After the usual workup and concentration the imines were obtained in quantative yields (**Scheme -2.2**). The imines were pure enough to be used as such for the cycloaddition reaction, as confirmed by ^1H NMR spectroscopy. The imine proton appeared as a doublet at 7.82 (J = 4.9 Hz) for **2.6a** and at 7.66 (J = 4.9 Hz) for **2.6b**.

Scheme -2.2

2.6a-b
2.6a: R =PMP
2.6b:R =allyl

2.4.3 Preparation of the b-lactams **2.7a-f**

The β-lactams **2.7a–f** were synthesized using the imines **2.6a-b** on treatment with respective acidchlorides in presence of triethylamine (**Scheme2.3**).

Scheme2.3

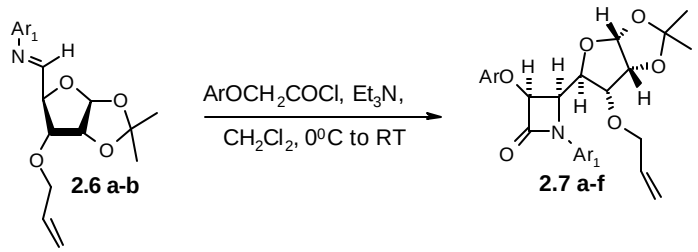


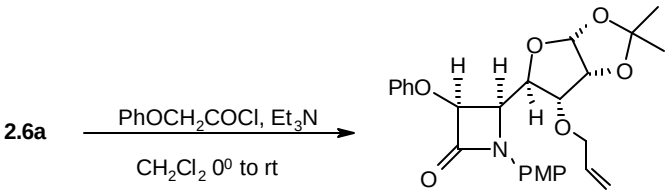
Table 2.1 The syntheses of β-lactams **2.7a–f** from the imines **2.6a-b** *via* the *Staudinger Reaction.*

β-lactams **2.7a –f**	Ar	R	Yield (%)
2.7 a	Ph	PMP	70
2.7 b	Ac	PMP	69
2.7 c	Me	PMP	68
2.7 d	Ph	Allyl	72
2.7 e	Ac	Allyl	69
2.7f	Me	Allyl	71

2.4.3a Preparation of the b-lactam **2.7a**

A solution of phenoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine **2.6a** 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 followed by column chromatography, the β-lactam **2.7a** was isolated as a gum in 70% yield (**Scheme -2.4**). The IR spectrum of this compound showed a strong band at 1747 cm^{-1} corresponding to the β-lactam carbonyl stretching frequency. In the ^{1}H NMR spectrum of this compound showed two gem dimethyl protons of the acetonide at 1.46 and 1.58 as two singlets.

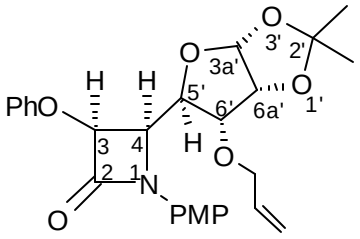
Scheme -2.4



2.7a

The methoxyl protons of the PMP appeared as singlet at 3.90. The H-3 and H-4 protons resonated at 5.63 (d, 1H, J = 5.2 Hz) and 4.90 (dd, 1H, J = 5.1 Hz and 3.9 Hz) respectively. The H-5' proton of the sugar appeared as a dd (J = 3.4 & 3.9 Hz) at 4.18. The H-6a' resonated at 4.62 as a triplet (J = 3.7 Hz). The H-3a' (anomeric proton) appeared as a doublet at 5.61 (d, J = 3.5 Hz). The 5-allyl protons appeared as three sets of multiplets at 3.93, 5.27 and 4.05.

The ^{13}C NMR spectrum of this compound showed the two methyls of the isopropylidene as two signals at 25.54 and 26.09. The methoxy of the p-anisyl resonated at 54.69. The C-3 and the C-4 carbons were seen at 78.54 and 70.05 respectively. The C-6' carbon and the C-5' resonated at 80.71 and 81.19 respectively.



2.7a

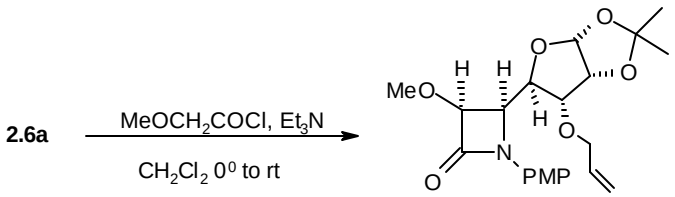
The C-3a' (anomeric) carbon was seen at 104.16. The carbonyl carbon of the β-lactam resonated at 162.72. The aromatic and the olefin carbon resonated in the region 156.76 to 104.16. The mass spectrum of this compound showed the base peak at 149 (100%) and the molecular ion peak at 467.

***2.4.3b Preparation of the b-lactam* 2.7b**

Following the standard procedure the β-lactam **2.7b** was isolated in 69% yield from methoxy acetyl chloride and the imine **2.6b**, the resulting mixture was allowed to warm up to RT and stirred for 15 hrs. After the usual workup followed by column chromatography, the β-lactam **2.7b** was isolated as a gummy substance in 70% yield (**Scheme -2.5**). The IR spectrum of this compound showed a strong band at 1751.24 cm^{-1}

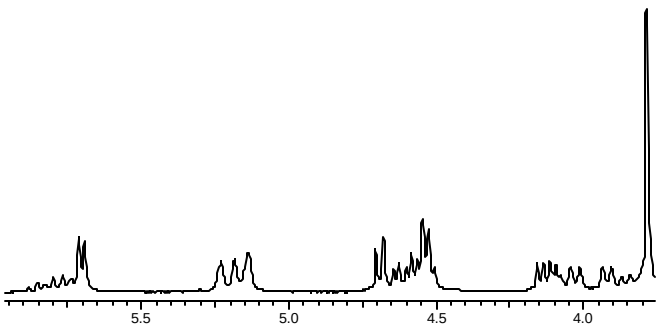
corresponding to the β-lactam carbonyl stretching. The ^{1}H NMR spectrum showed the peaks in the expected regions. Two singlets appeared at 1.35 and 1.60 corresponding to the two methyls of the acetonide. The C-3 methoxy appeared at 3.60 and the methoxy of the p-anisyl seen at 3.80, as two singlets integrating for three protons each.

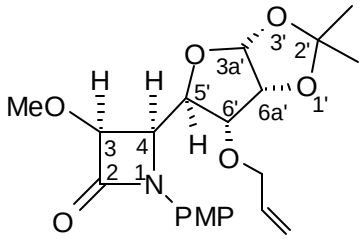
Scheme -2.5



2.7b

The H-3 proton of the β-lactam was seen at 4.70 as a doublet (J = 5.3 Hz). The H-4 proton resonated at 3.93 as a dd (J = 5.4 & 5.8 Hz). A dd at 4.02 (J = 5.8 & 3.9 Hz) corresponded to the H-5' proton. The H-6' proton appeared at 4.56 as a doublet (J = 3.9 Hz). The H-6a' proton appeared as a doublet at 4.64 (t, J = 3.6 Hz). The H-3a' proton (anomeric) resonated at 5.70 (d, J = 3.4 Hz). The five allylic protons appeared as three sets of multiplets in the region of 5.74 - 5.89 integrating for one proton, 5.23-5.34 integrating for two protons and 4.09 - 4.16 integrating for two protons.





2.7b

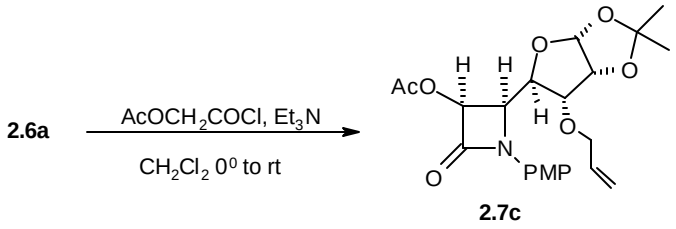
The ^{13}C NMR spectrum of this compound showed the two methyls of the isopropylidene as two signals at 26.58 and 27.10. The methoxy of the p-anisyl resonated at 55.73. The C-3 and the C-4 carbons were seen at 81.76 and 71.26 respectively. The C-3a' (anomeric) carbon was seen at 105.20. The carbonyl carbon of the β-lactam resonated at

156.75, while the acetate carbonyl gave a signal at 165.38. All the other signals appeared in their expected regions.

***2.4.3c Preparation of the b-lactam* 2.7c**

Following the standard procedure the β-lactam **2.7c** was isolated in 68% yield as thick oil, from the [2+2] cycloaddition reaction between acetoxyacetyl chloride and the imine **2.6a** (**Scheme -2.6**).

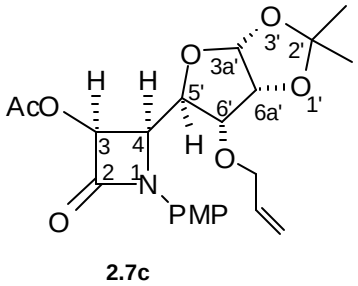
Scheme -2.6



The IR spectrum of this compound (**2.7c**) was recorded in $CHCl_3$, and showed a strong band at 1758.96 cm^{-1} due to the β-lactam carbonyl stretching and another at 1732 cm^{-1} due to the acetate carbonyl.

The ^1H NMR spectrum of **2.7c** showed two singlets for two methyls of the acetonide at 1.32 and 1.48 integrating for 3 protons each. The methyl protons of the acetate resonated at 2.15 as a singlet. The H-3 proton of the β-lactam resonated at 5.96 as a doublet (J = 5.1 Hz), while the H-4 proton came as a dd at 4.14 (J = 5.1 & 5.9 Hz). The H-5' proton appeared as a dd at 4.22 (J = 3.6 & 5.9 Hz). The dd at 3.61 was attributed to H-6' proton (J = 3.6 & 4.4 Hz).

The characteristic triplet due to the H-6a' proton appeared at 4.51 (J = 3.6 Hz). The anomeric proton (H-3a') appeared at 5.70 (J=3.7 Hz). The five allylic protons appeared as three sets of multiplets at 5.88 - 5.98 integrating for one proton, 5.23 - 5.34 integrating for two protons and 3.8 - 3.94 integrating for two protons.



In the ^{13}C NMR spectrum of this compound the carbonyl carbon of the β-lactam appeared at 156.75 while the acetate carbonyl carbon was seen at 165.38. The signals

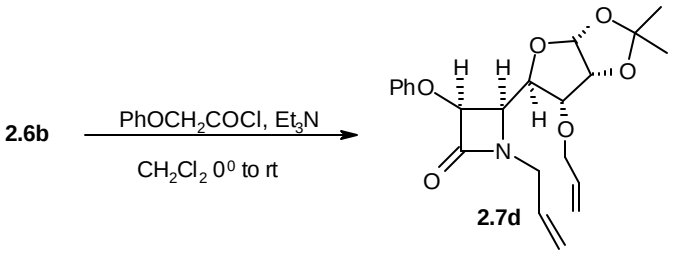
due to the olefinic carbons and the aromatic carbons came in the region 134.38 to 105.20. The carbons on the sugar moiety and the β-lactam ring resonated in the region 83.10 to 26.58. The methyl of acetate resonated at 27.10 while the two methyls of the acetonide gave a signal at 26.15 and 26.69,.

The mass spectrum of this compound exhibited the molecular ion peak ($m^{+\cdot}$) at 405 and the base peak at 149 (100%).

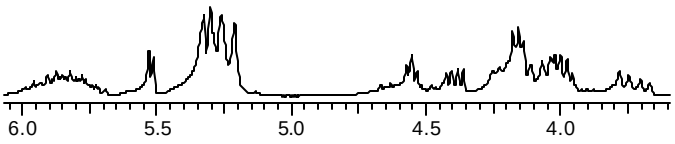
2.4.3d Preparation of the b-lactam **2.7d**

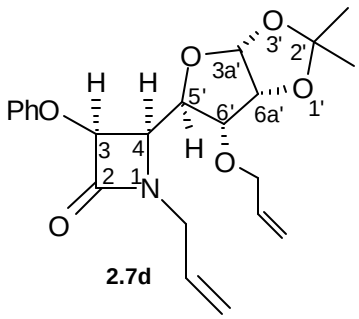
The β-lactam **2.7d** was isolated as viscous oil in 72% yield from phenoxyacetyl chloride and the imine **2.6b** following the standard procedure (**Scheme-2.7**). In the IR spectrum of this compound, a strong band at 1758.96 cm^{-1} indicated the presence of β-lactam C=O stretching. The ^1H NMR spectrum was recorded in $CDCl_3$, which showed two singlets at 1.33 and 1.48 for two methyls of the acetonide.

Scheme-2.7



The H-3 proton of the β-lactam appeared as a dd at 4.42 (J = 4.9 Hz). A dd appeared at 3.70 (J = 3.7 & 3.8 Hz), which could be attributed to the H-5' proton. The characteristic triplet due to the H-6a' proton appeared at 4.55 (J = 3.9 Hz). The anomeric proton (H-3a') resonated at 5.68 as a doublet (J = 3.4 Hz). The H-3 and the H-6' protons were merged with the allylic protons. The allylic protons, a total of ten protons, appeared as three sets of multiplets in the usual pattern, from 5.68 to 5.53 integrating for two protons, 5.31 to 5.33 integrating for 4 protons of the allyl and the H-3 proton of the β-lactam, and 3.97 to 4.17 integrating for 5 protons, four of which were from the allyl and the fifth was the H-5 proton.





2.7d

The ^{13}C NMR spectrum of this compound showed the signal due to the β-lactam C=O carbon at 165.96. the two methyls of the isopropylidene appeared as two signals at 27.07 and 27.25. The other signal appeared at the expected regions.

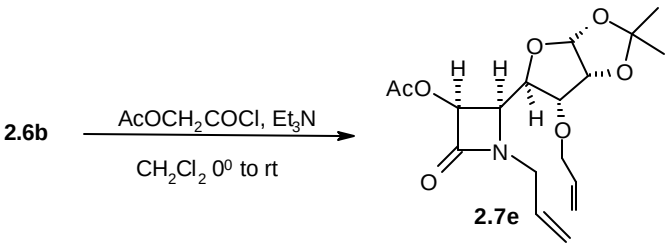
The mass spectral analysis of this compound showed the base peak at 147 (100%) and the molecular ion peak at 401 (5%). This compound provided satisfactory elemental analysis.

2.4.3e Preparation of the b-lactam **2.7e**

Following the standard procedure the β-lactam **2.7e** has been prepared from acetoxyacetyl chloride and the imine **2.6b** in 69% yield (**Scheme-2.8**).

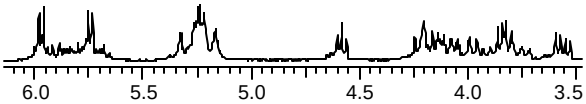
The IR spectrum of this compound showed two carbonyls, β-lactam and the acetate appearing at 1750 cm^{-1} and 1747.39 cm^{-1} respectively.

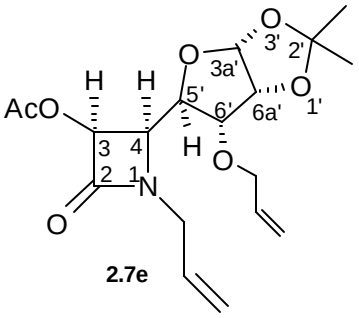
Scheme-2.8



2.7e

The ^{1}H NMR spectrum of this compound showed the acetonide peaks at 1.35 and 1.52. The acetate was seen at 2.15 as a singlet integrating for 3 protons. The H-3 β-lactam proton came as a doublet at 5.98 (J = 4.4 Hz). The H-4 and H-5' protons merged with the allylic multiplets. The H-6 proton appeared at 3.54 as a doublet (J = 4.4 Hz).





2.7e

The H-4 and H-5' protons merged with the allylic multiplets. The H-6 proton appeared at 3.54 as a doublet (J = 4.4 Hz). The characteristic triplet due to the H-6a' proton appeared at 4.58 (J = 4.4 Hz). The anomeric proton (H-3a') resonated at 5.75 as a doublet (J = 3.9 Hz).

The 10 allylic protons appeared as three sets of multiplets in the regions, 3.74 to 4.16 integrating for 4 protons of the allyl moieties and the H-5' proton, a 5-proton multiplet from 5.16 to 5.33 inclusive of 4 allyl protons merged with the H-4 proton, and a two-proton multiplet from 5.68 to 5.91.

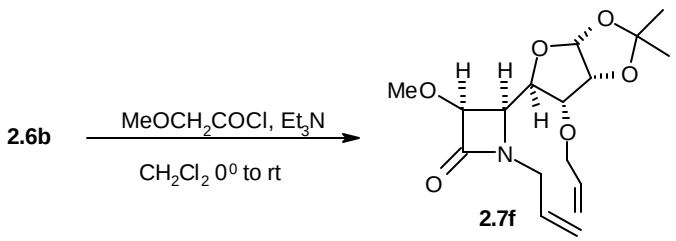
The ^{13}C NMR spectrum of this compound exhibited signals due to the carbonyl carbons of the β-lactam and the acetate at 164.71 and 169.38 respectively. All the other signals were consistent with the structure of the compound.

The mass spectral analysis of this compound showed the molecular ion peak at 367, while the base peak was seen at 111. This compound provided satisfactory elementary analysis.

2.4.3f Preparation of the b-lactam **2.7f**

Following the usual procedure the β-lactam was isolated as a viscous oil in 71% yield from methoxyacetyl chloride and the imine **2.6b** in the presence of triethylamine at 0 ^{0}C (**Scheme -2.9)**.

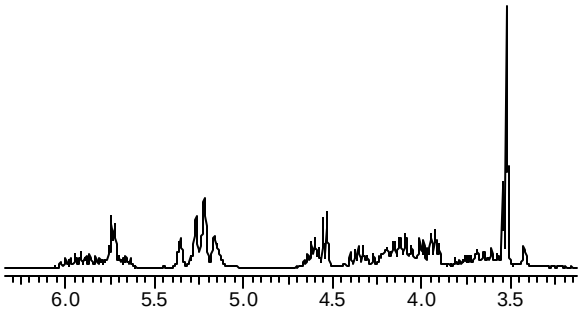
Scheme -2.9

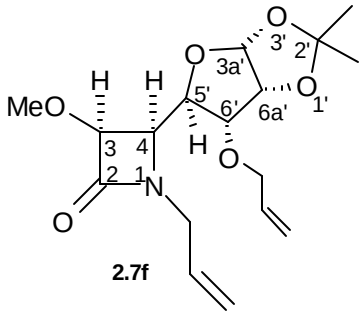


2.7f

The ^{1}H NMR spectrum of the crude product showed signals due to a single diastereomer. Purification of this compound by column chromatography provided oil. The IR spectrum of this compound showed a strong band at 1755.10 cm^{-1} corresponding to the β-lactam carbonyl stretching.

The ^{1}H NMR spectrum recorded in $CDCl_3$ showed the acetonide protons at 1.40 and 1.50 as two singlets integrating for 3 protons each. The methoxy protons resonated at 3.52. The H-3 proton of the β-lactam appeared as a doublet at 4.55 (J = 4.8 Hz). The H-4 β-lactam proton was seen at 4.39 as a dd (J = 4.8 & 3.9 Hz). The H-5' and H-6' protons were merged with the allylic protons. The characteristic triplet at 4.61 (J = 4.4 Hz) corresponded to the H-6a' proton.





2.7f

The anomeric proton (H-3a') was seen at 5.73 (J = 3.4 Hz). The 10 allylic protons appeared as four sets of multiplets, 3.90 to 4.00 and 3.54 to 3.75 integrating for 2 protons each, 5.16 to 5.35 integrating for 4 protons, and a multiplet at 5.65 to 6.01 integrating for 2 protons.

In the ^{13}C NMR of the compound the signal corresponding to the β-lactam carbonyl carbon appeared at 166.51. The two methyls of the isopropylidene gave a signal at 26.16. The methoxy carbon was seen at 42.74. The methylene carbons of the two allyls on the nitrogen and oxygen resonated at 56.78 and 58.84 respectively. The C-3 and the C-4 carbons of the β-lactam resonated at 76.01 and 70.79 respectively. The other carbons resonated in the expected regions.

The mass spectral analysis of the compound showed the base peak at 87 (100%), while the molecular ion peak appeared at 339 (3%).

2.5 : Conclusion

A highly diastereospecific synthesis of *b*-lactams was achieved, *via Staudinger reaction*, using D-allose derived imines. As only a single diastereomer was obtained, the relative stereochemistry at the two new chiral centers must be the same as that of the compounds obtained from the epimeric aldehydes **1.5a,b**. Hence the relative stereochemistry at the two new centers must be 3*R* and 4*S*.

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. PDC was synthesized freshly from anhydrous pyridine and CrO_3 and recrystallized from anhydrous acetone.

2.6.1 Synthesis of 1,2: 5,6-Di-O-isopropylidene -α -D-ribo – hexofuranose-3-ulose **2.1**

To a stirred solution of the diacetonide **1.2** (3.12 g, 12.1 mmol) in anhydrous methylene chloride (80 ml) was added slowly PDC (6.85 g, 18.2 mmol), 10 g of freshly activated molecular sieves (3 Å), followed by 0.5 ml of anhydrous acetic anhydride at RT. The reaction mixture was stirred for 24 hrs, after which celite (6 gm) was added and stirred for 30 min. Filtered and co-evaporated with toluene under reduced pressure to remove pyridine and acetic anhydride. The resulting dark brown residue was treated with diethyl ether and filtered through anhydrous $MgSO_4$ and evaporated to get the crude ketone **2.1** (3 g), which was used, as such for the reduction step.

2.6.2 Synthesis of 1,2: 5,6-Di-O-isopropylidene -α -D-allofuranose **2.2**

To the crude syrupy oxidation product **2.1** (3.5 g, 12.5mmol) is added 10ml of EtOH and the solution was cooled to 0^0C, $NaBH_4$ (0.47 g, 12.7 mmol) was added to the cold magnetically stirred solution. After the addition is complete the cooling bath is removed and stirring continued for 1hr. The reaction mixture is concentrated under reduced pressure extracted with $CHCl_3$ and the combined organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the alcohol **2.2** (3 g, 85%), as a white solid (m.p. 75 ^{0}C).

2.6.3 Synthesis of 3-OAllyl-1, 2: 5,6 di – O-isopropylidene α -D- allofuranose **2.3**

To a solution of the diacetonide **2.2** (3g, 11.53 mmol) and allyl bromide (1.4 g, 0.99 ml, 17.11 mmol) in methylene chloride was added 50% aquous NaOH solution (15 ml) and the mixture stirred vigorously. Tetrabutylammonium bromide (catalytic amount) was then added to this mixture and the stirring continued till the disappearance of the starting material, as indicated by TLC (Ca. 24 hrs). The Organic layer was separated and the aqueous layer washed with methylene chloride. The combined organic layers washed

with water, dried over anhydrous sodium sulphate and the solvents evaporated under reduced pressure. The crude product containing residual PTC was chromatographed over silica (60-120 mesh) using EtOAc/Pet. Ether (1:4). Removal of solvents under reduced pressure afforded the pure allyl ether **2.3** (3.28 g, 95%).

2.6.4 Synthesis of 3-O-Allyl-1, 2–O-isopropylidene α-D- glucofuranose **2.4**

To a solution of **2.3** (3.28 g, 10.96 mmol) in MeOH (35 ml), 0.8% H_2SO_4 (3.3 ml) was added and stirred at rt till the disappearance of the starting material (TLC, ca 24 hrs). The acid was quenched with triethylamine (3.3 ml). The solvents was evaporated under reduced pressure and the residue was taken in $CHCl_3$, it was washed with water, saturated solution of brine, dried over sodium sulphate, and concentrated under reduced pressure to give the glycol **2.4** (2.64 g, 93%), which was pure enough to be used for the next reaction without further purification.

2.6.5 Synthesis of 3-O-allyl-1, 2 isopropylidene α-D-arabino-1, 5penta dialdo-1-4-furanose **2.5**

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ (8 g) in methylene chloride (50 ml) was added a solution of the glycol **2.4** (2.64 g, 10.16 mmol) in methylene chloride (5 ml). The reaction mixture was filtered through sintered glass funnel and the silica gel was washed thoroughly with methylene chloride. The solvent was removed under reduced pressure to afford the pure aldehyde **2.5** (2.19 g, 95%). This was then used as such for the next step without any purification.

2.6.6 General procedure for the synthesis of imines

To a solution of the amine (4.38 mmol of p-anisidine/allyl amine) in CH_2Cl_2, and anhydrous $MgSO_4$, was added a solution of the aldehyde **2.5** (1 g, 4.38 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 **2.6a,b**, which were used as such in the *Staudinger reaction*.

2.6.7 General procedure for the synthesis of β-lactams **2.7a-f**

A solution of the acid chloride (1.5 mmol) in methylene chloride (10 ml) was added to a solution of the imines **2.6 a, b** and triethylamine in CH_2Cl_2 (20 ml) at 0 ^{0}C. After the addition was completed, the reaction mixture was 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. Concentration followed by purification of resultant crude product by column chromatography provided the β-lactams **2.7a-f** in 68-72% yields.

***Synthesis of (3S, 3a'R 4R, 5'R, 6'R, 6a'R)-4-(6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-1-(-4-methoxyphenyl)-azetidin-2one* 2.7a**

The imine **2.6a** (0.33 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.25 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **2.7a** as a single diastereomer (0.32g, 70%) as a gummy substance.

MP : Gum

$[\alpha]_D^{24}$: $+24.24^0$ (c = 0.61, $CHCl_3$)

IR ($CHCl_3$) : 1747

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.46 (s, 3H), 1.58 (s, 3H), 3.90 (s, 3H), 3.95 (m, 2H), 4.18 (dd, 1H, J = 4.4 Hz each), 4.62 (t, 1H, J = 3.7 Hz), 4.90 (dd, 1H, J = 5.1 Hz and 3.9 Hz), 5.27 (m, 2H), 5.61 (d, 1H, J = 3.5 Hz), 5.63 (d, 1H, J = 5.2 Hz), 5.83 (m, 1H)

^{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 : 467 (20%), 149 (100%), 77 (49%), 111 (3%), 134 (30%)

Analysis : Calculated: C: 66.797, H: 6.252, N: 2.996

$C_{26}H_{29}NO_7$ Found: C: 66.86, H: 6.34, N: 3.086

***Synthesis of (2R, 3S, 3a'R 5'R, 6'R, 6a'R)-Acetic acid2- (6'-allyloxy –2',2' dimethyl-tetrahydro-furo [2',3'-d][1',3'] dioxol-5'yl)-1-(4-methoxyphenyl)-4-oxo (2R, 3S) azetidin-3yl ester* 2.7b.**

The imine **2.6a** (0.33 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.204 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) at 0 ^{0}C provided the β-lactam **2.7b** as a single isomer (0.29 g, 69%) as a gummy substance.

MP	**:**	Oil
[a]$_D^{27}$	**:**	+33.28^0 (c = 1, $CHCl_3$)
IR ($CDCl_3$)	**:**	1758.96
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.35 (s, 3H), 1.60 (s, 3H), 3.61 (dd, 1H, J = 3.6 Hz, 4.4 Hz), 3.8 (m, 2H), 3.93 (dd, 1H, J = 5.8 Hz and 5.4 Hz), 4.02 (dd, 1H, J = 5.8 Hz, 3.9 Hz), 4.09-4.16 (m, 2H), 4.22 (dd, 1H, J = 3.6 Hz, 5.9 Hz), 4.56 (d, 1H, J = 3.9 Hz), 4.64 (t, 1H, J = 3.6 Hz), 5.23-5.34 (m, 2H), 5.70 (d, 1H, J = 3.4 Hz), 5.74-5.89 (m, 1H).
^{13}C NMR ($CDCl_3$)	**:**	26.58, 27.10, 55.73, 59.09,59.48, 71.26, 81.76, 82.43, 82.68, 83.10, 105.20, 111.91, 114.29, 117.68, 119.97, 131.72, 134.38, 156.75, 165.38
MS	**:**	433 (15%), 101 (100%), 73 (92%), 83 (40%), 123 (87%), 149 (85%), 174 (22%), 223 (25%)
Analysis	**:**	Calculated: C: 60.962; H: 6.279; N: 3.231
$C_{22}H_{27}NO_8$		Found: C: 61.09; H: 6.429, N: 3.31

***Synthesis of (3S, 3a'R, 4R, 5'R, 6'R, 6a'R)-4-(6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-3 methoxy-1- (-4-methoxyphenyl)-azetidin-2one* 2.7c**

The imine **2.6a** (0.33 g, 1 mmol) on treatment with methoxyacetyl chloride (0.16 g, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) at 0 ^{0}C provided theβ-lactam **2.7c** as a single isomer (0.27 g, 68%) as Oil.

MP	**:**	Oil
[a]$_D^{27}$	**:**	+37.202^0 (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1751.24

^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.32 (s, 3H), 1.48 (s, 3H), 3.61 (dd, 1H, J = 3.6 Hz and 4.4 Hz), 3.8-3.94 (m, 2H), 4.14 (dd, 1H, J = 5.1 Hz and 5.9 Hz), 4.22 (dd, 1H, J = 3.6 Hz and 5.9 Hz), 4.51 (t, 1H, J = 3.6 Hz), 5.23-5.34 (m, 2H), 5.70 (d, 1H, J = 3.7 Hz), 5.88-5.98 (m, 1H), 5.96 (d, 1H, J = 5.1 Hz)
^{13}C NMR		26.69, 26.15, 55.30, 58.66, 59.05, 70.84, 81.33, 82.01, 82.25, 82.68, 105.20, 111.49, 113.87, 117.26, 119.54, 134.38, 156.75,165.38.
MS	**:**	405 (30%), 362 (5%), 318 (10%), 179 (8%), 149 (100%), 134 (32%), 111 (27%), 87 (40%), 71 (30%)
Analysis	**:**	Calculated: C: 65.906, H: 6.421, N: 3.076
$C_{26}H_{29}NO_7$		Found: C: 66.11, H: 6.67 , N:3.30

***Synthesis of (3S, 3a'R, 4R, 5'R, 6'R, 6a'R)-1-Allyl-4- (6'-allyloxy –2', 2' dimethyl-tetrahydro-furo [2',3'-d][1',3']dioxol-5'yl)- 3-phenoxyazetidin-2-one* 2.7d**

The imine **2.6b** (0.33 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.25 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) at 0 ^{0}C provided the β-lactam **2.7d** as a single diastereomer (0.28 g, 72%).

MP	**:**	Oil
[a]$_D^{24}$	**:**	+7.72^{0} (c = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1758.96
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.33 (s, 3H), 1.48 (s, 3H), 3.70 (dd, 1H, J = 3.7 Hz, 3.4 Hz), 3.97 (m, 5H), 4.42 (d, 1H, J = 4.9 Hz), 4.55 (t, 1H, J = 3.9 Hz), 5.21 (m, 5H), 5.53 (m, 2H), 5.68 (d, 1H, J = 3.4 Hz), 7.29 (m, 5H)
^{13}C NMR ($CDCl_3$)	**:**	27.07, 27.25, 44.28, 57.65, 71.81, 76.69, 77.43, 77.85, 79.56, 80.85, 104.59, 113.59, 116.07, 116.31, 118.45,

119.06, 122.44, 129.68, 131.97, 134.62, 157.94, 165.96

MS : 401 (5%), 358 (9%), 225 (32%), 167 (25%), 147 (100%), 11 (79%), 78 (87%)

Analysis : Calculated: C: 65.820, H: 6.779, N: 3.489

$C_{26}H_{29}NO_7$ Found: C: 65.877, H: 6.95, N: 3.63

Synthesis of (2R, 3S, 3a'R, 5'R, 6'R, 6a'R)-Acetic acid1-allyl-2- (6'-Allyloxy-2', 2'-dimethyl-tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl)-4-oxo (2R, 3S) azetidin-3yl ester **2.7e.**

The imine **2.6b** (0.33 g, 1 mmol) on treatment with acetoxyacetyl chloride (0.25 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) at 0 ^{0}C provided the β-lactam **2.7e** as a single isomer (0.32 g, 70%).

MP : Oil

$[\alpha]_D^{27}$: $+9.274^0$ (c = 1.03, $CHCl_3$)

IR (neat) : 1747, 1753

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.35 (s, 3H), 1.52 (s, 3H), 3.54 (d, 1H, J = 4.4 Hz), 3.74-4.16 (m, 6H), 4.58 (t, 1H, J = 4.4 Hz), 5.16-5.33 (m, 5H), 5.68-5.91 (m, 2H), 5.75 (d, 1H, J = 3.9 Hz), 5.98 (d, 1H, J = 4.4 Hz)

^{13}C NMR ($CDCl_3$) : 20.69, 26.64, 43.89, 59.24, 71.35, 73.46, 70.06, 80.24, 104.32, 113.07, 118.51, 131.57, 134.25, 164.71, 169.38

MS : 367 (8%), 352 (2%), 294 (7%), 224 (5%), 173 (3%), 111 (100%), 98 (15%), 83 (48%)

Analysis : Calculated: C: 58.846; H: 6.859; N: 3.812;

$C_{26}H_{29}NO_7$ Found: C: 59.00; H: 6.957; N: 4.01;

Synthesis of (3S, 3a'R, 4R, 5'R, 6'R, 6a'R)-1-Allyl-4- (6'-allyloxy –2', 2' dimethyl-tetrahydro-furo [2', 3'-d][1', 3'] dioxol-5'yl)- 3-methoxyazetidin-2-one **2.7f**

The imine **2.6b** (0.33 g, 1 mmol) on treatment with methoxyacetyl chloride (0.267 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) at 0 ^{0}C provided a single isomer of β-lactam **2.7f** (0.32 g, 70%) as a gummy substance.

MP : Oil

$[\alpha]_D^{27}$: $+12.212^0$ (c = 1, $CHCl_3$)

IR (neat)	**:**	1747, 1753
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.40 (s, 1H), 1.50 (s, 1H), 3.52 (s, 3H), 3.54 (m, 2H), 3.90-4.00 (m, 2H), 3.54-3.75 (m, 2H), 4.39 (dd, 1H, J = 4.8 Hz and 3.9 Hz), 4.55 (d, 1H, J = 4.8 Hz), 4.61 (t, 1H, J = 4.4 Hz), 5.16-5.35 (m, 4H), 5.65-6.01 (m, 2H), 5.73 (d, 1H, J = 3.4 Hz)
^{13}C NMR ($CDCl_3$)	**:**	26.16, 42.74, 56.78, 58.84, 70.70, 76.01, 78.84, 83.58, 103.72, 112.47, 117.84, 131.11, 133.72, 166.51
MS	**:**	339 (3%), 324 (15%), 241 (5%), 157 (2%), 145 (6%), 111 (70%), 87 (100%), 71 (30%)
Analysis	**:**	Calculated: C: 60.16, H: 7.42, N: 4.13
$C_{17}H_{25}NO_6$		Found: C: 60.37, H: 7.72, N: 4.40

2.7 : References

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Chapter 3

Transformations of b-lactams derived from D-glucose

3.1 : Abstract

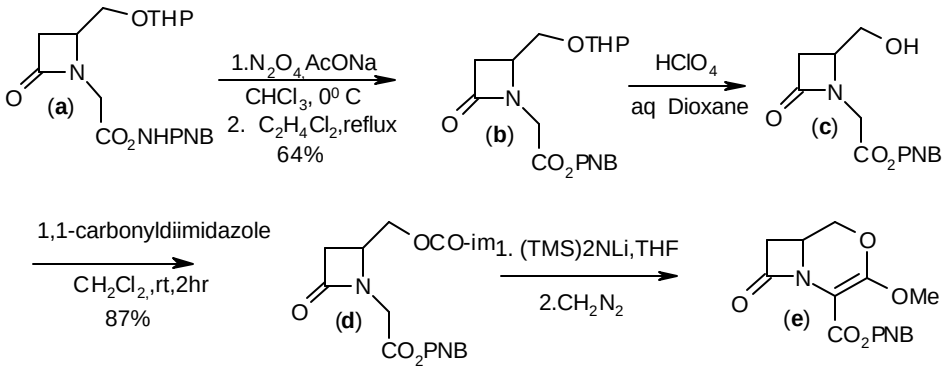
This chapter deals with the transformations of optically active β-lactams whose synthesis has been described in Chapter **1** into various derivatives. Deprotection of the β-lactams **1.7g/ 3.5** afforded the 6-hydroxy β-lactam **3.6**, which was then oxidized to the ketone **3.7** using Dess-Martin Periodinane. Alternately, a one pot deprotection of the allyl and the acetonide of **1.7g** afforded the methyl glycosides in the ratio 46:54, as confirmed by ^{1}H NMR spectrum. This anomeric mixture was then converted into the diacetate **3.11**. The oxidative cleavage of the above β-lactams using CAN afforded the N-unsubstituted β-lactams in high yields. The subsequent alkylation of the ring nitrogen of the **3.14** with ethyl bromoacetate provided the ethyl carboxylate **3.16**.

3.2 : Introduction

The unique structural and chemotherapeutic properties of the β-lactam antibiotics continue to attract attention of the synthetic community as they present a variety of synthetic challenges. During the last few decades much of the effort was 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-lactam with an appropriate tether for ring closure. As a result of their impressive biological activity, polycyclic β-lactams has become interesting targets for synthesis.

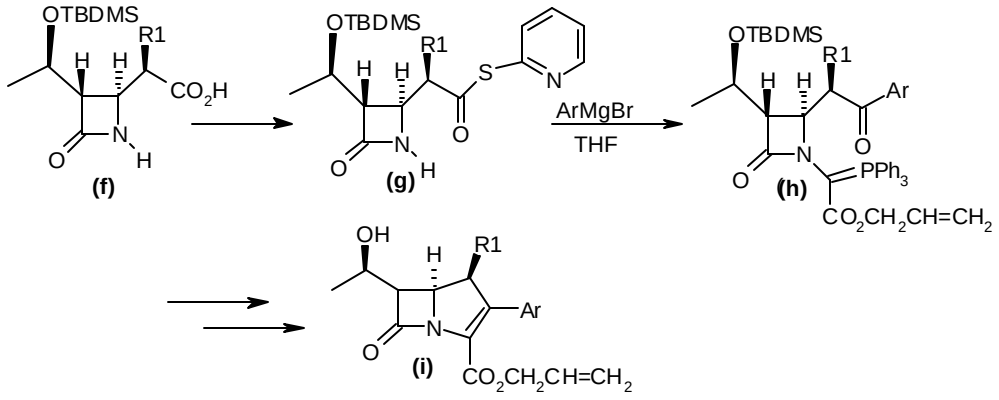
Hatanaka and coworkers[1] reported the synthesis of the O-2, 3-methoxy isocephem (**e**) via an intermolecular acylation reaction .The key Azetidinone- (**a**) synthesized using an Ugi condensation reaction, was converted to the PNB ester (**b**) Deprotection to the alcohol (**c**) followed by the treatment with 1,1[1]-carbonyldiimidazole afforded the carbamate (**d**) which was cyclised on treatment with 2 equivalents of base (**scheme-3.1**). The crude ester was then directly converted to the carbapenem (**e**) on reaction with diazomethane.

Scheme -3.1



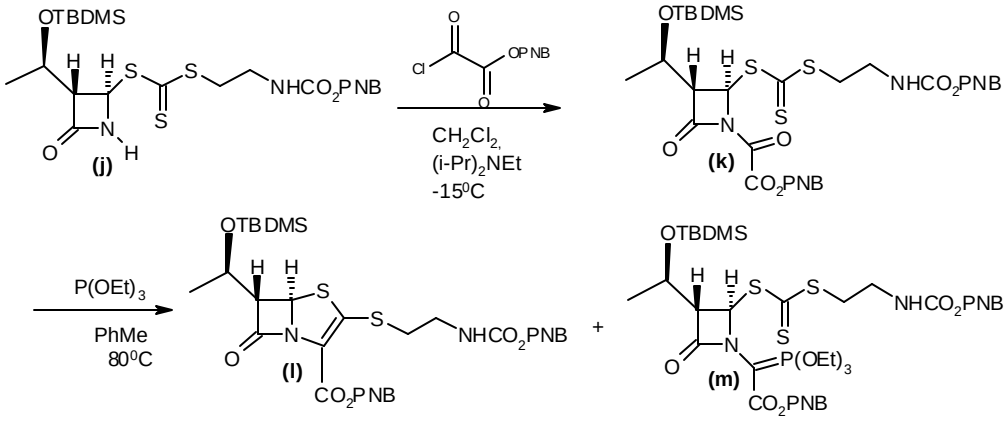
Merck researchers[2] have reported the syntheses and antibacterial activities of a number of C-2 aryl substituted carbapenems (**Scheme-3.2**) Intramolecular Wittig strategy was employed to provide the carbapenems (**i**) in 58-90%yields.

Scheme -3.2



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 $-15\ ^0C$ gave (**k**) in 77% yield (**scheme-3.3**). Reductive cyclization in toluene at 80^0 C for 1hr with 5 equivalents of P $(OEt)_3$ afforded the penem (**i**) and the phosphorane (**m**).

Scheme -3.3



3.3 : Present work

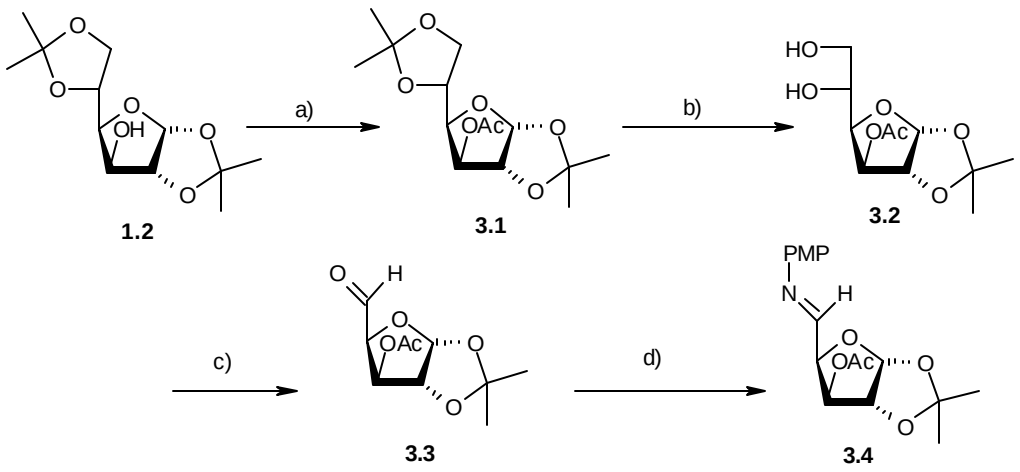
Fused bicyclic structural framework represent important substructures in many natural products and the efficient synthesis of functionalized fused bicyclic rings remains an important goal. With this goal in mind we carried out various transformations on the b-lactams derived from D-glucose to offer key intermediates for the synthesis of polycyclic b-lactams.

3.4 : Results and discussions

3.4.1 Preparation of the imine *3.4*

The optically active aldehyde **3.3** was prepared from Diacetone-D-glucose (**1.2**) in 3 steps following a reported procedure[5]. This aldehyde was converted into the imine **3.4** on treatment with p-anisidine in methylene chloride at RT in presence of $MgSO_4$ (**Scheme-3.4**). After 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 step without further purification.

Scheme -3.4

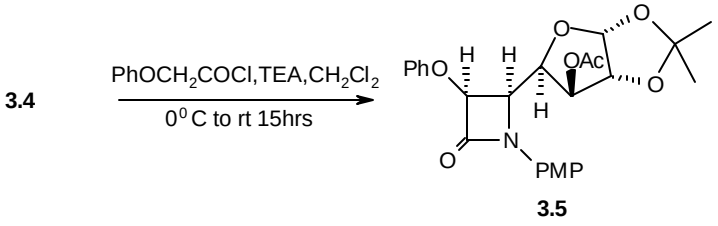


Reagents and conditions: a) Ac_2O,TEA,CH_2Cl_2, b)50%aqHOAc,24hrs, c)$NaIO_4$,MeOH, d)p-Anisidine,CH_2Cl_2,$MgSO_4$

3.4.2 Preparation of β-lactam 3.5

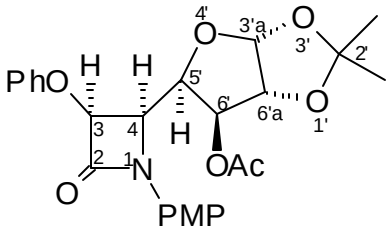
A solution of phenoxyacetyl chloride in methylene chloride was added to a solution of the imine 3.1, triethylamine in methylene chloride at 0 ^{0}C under argon. The resulting mixture was allowed to warm up to rt and stirred overnight, after the usual workup and purification by column chromatography, the product was isolated in 75% yield (**scheme -3.5**). The IR spectrum showed a sharp signal at 1747 cm^{-1} corresponding to β-lactam carbonyl stretching**.**

Scheme -3.5

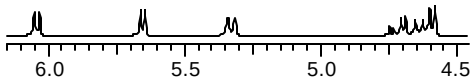


The ^{1}H NMR spectrum of this compound showed the presence of two singlets at 1.5 and 1.32 corresponding to the two methyls of the acetonide. The singlet at 2.0 could be assigned to the acetate, while the methoxy of the p-anisyl appeared as singlet at 3.75. The anomeric (H-3a') proton appeared as a doublet at 6.03 (J = 3.9 Hz). The H-3 β-lactam proton appeared as a doublet at 5.4 (J = 4.9 Hz). The H-4 β-lactam proton

appeared as a dd at 4.74 (J = 4.9 Hz and 3.9 Hz). The H- 6' proton of the sugar moiety came as a doublet at 5.65 (J = 3.9 Hz).



3.5



The ^{13}C NMR spectrum of this compound showed two signals corresponding to two carbonyls. The β-lactam carbonyl was seen at 162.94 while the acetate carbonyl appeared at 168.86. The methyl of the acetate appeared at 20.06 while the two methyls of the isopropylidene were seen at 25.59 and 26.16. The OCH_3 of the p-anisyl appeared at 54.84. All the other signals appeared at the expected regions.

The mass spectrum of this compound showed the molecular ion peak $M^{+\cdot}$ at 469 (5%), the base peak was seen at 59 (100%).

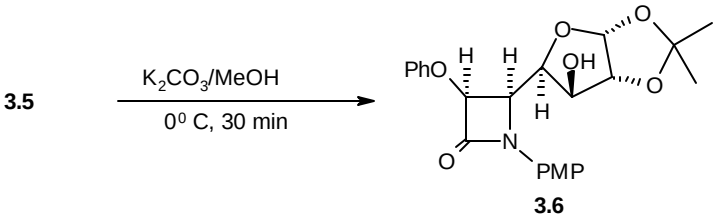
3.4.3 Preparation of 6-hydroxy-b-lactam 3.6

This compound was prepared by two methods; the first method involves the base catalyzed cleavage of the acetate **3.5**. The second method involves the use of Pd/C (10%) catalyzed cleavage of the allyloxy compound **1.7h.**

Method A

A methanolic solution of β-lactam 3.5 was stirred at 0 ^0C in presence of K_2CO_3 (Scheme-3.6) till the disappearance of the starting material (TLC). The reaction mixture was filtered through celite and the filtrate was concentrated to get the 6-hydroxy-β-lactam 3.6 in quantative yield.

Scheme-3.6



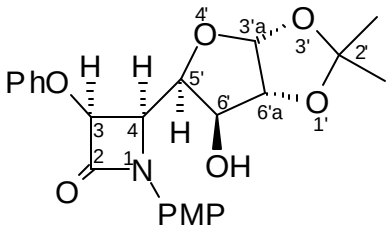
3.6

Method B

A suspension of β-lactam **1.7h** and Pd/C in MeOH was refluxed vigorously till the disappearance of the starting material (TLC). Filtration of the catalyst through a pad of celite and concentrated gave propenyl ether 3.6a[7]. This vinyl ether was then subjected to mCPBA[6] in methylene chloride. Triethylamine was added after 15 min and stirred for 12 hrs. The reaction mixture on filtration through a short bed of silica using methylene chloride and concentration provided alcohol 3.6 in 90%yield as a white solid.

The ^{1}H NMR spectra of 3.6 obtained from both the methods were similar. The IR spectrum of this compound showed a strong band at 3400 cm^{-1} corresponding to the hydroxy stretching frequency and a strong band at 1743 cm^{-1} showing the β-lactam carbonyl stretching.

The ^{1}H NMR of the product displayed a broad hump at 2.5 indicating the presence of the hydroxyl group. Two singlets at 1.30 and 1.46 were seen correspond to the two methyls of the isopropylidene group. The methoxy of the p-anisyl appeared as a singlet at 3.79.



3.6

The H-4 proton of the β-lactam appeared as dd merging with the protons of sugar moiety in the range of 4.49 to 4.65 and integrated for 4 protons. The H-3 protons of the β-lactam appeared as doublet at 5.42 (J = 5.4 Hz) and the anomeric (H-3a') proton of the sugar resonated at 6.05 as doublet (J = 3.9 Hz). The ring protons of the p-anisyl appeared as two set of doublets at 6.87 to 7.36.

The ^{13}C NMR spectrum of this compound showed a signal at 163.64 corresponding to the β-lactam carbonyl carbon. All the signals appeared at the expected regions.

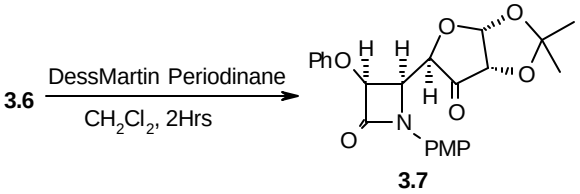
The mass spectral analysis showed molecular ion peak at 427 (100%), which was also the base peak. This compound provided satisfactory elemental analysis.

***3.4.4 Preparation of 6-Keto b-lactam* 3.7**

The 6-hydroxy β-lactam **3.6** was dissolved in anhydrous methylene chloride and added drop wise to a suspension of the Dess Martin Periodinane reagent[8]. After completion of the reaction (TLC, c.a. 2 hrs), the reaction mixture was filtered through a short bed of silica gel and then washed with saturated solution of sodium thiosulphate and concentrated to provide 6-keto compound **3.7** as a white solid ***(*Scheme -3.7*).***

The IR spectrum of this compound showed a strong band at 1745.46 corresponding to the β-lactam carbonyl and another at 1704.96 typical of ketone carbonyl stretching frequency.

Scheme-3.7



3.7

The ^{1}H NMR of the compound taken in $CDCl_3$ showed two singlets at 1.35 and 1.42 corresponding to the acetonide methyls. The methoxyl group of the p-anisyl showed a singlet at 3.81. The anomeric (H-3a') proton appeared as doublet at 5.68 (J = 4.4 Hz). The C-3 proton of the β-lactam seen as a doublet at 5.45 (J = 4.8 Hz), while the C-4 proton appeared at 4.87 as a dd (J = 4.8 and 3.9 Hz). The H-5 proton appeared as a doublet at 4.78 (d, J = 3.9 Hz). The p-anisyl and the phenoxy ring protons appeared in the aromatic region 6.89-7.40.

The ^{13}C NMR of the compound in $CDCl_3$ showed a signal at 208.23 corresponding to the ketone. The β-lactam carbonyl carbon appeared at 162.70. The aromatic carbons and the sugar carbons resonated at the expected regions.

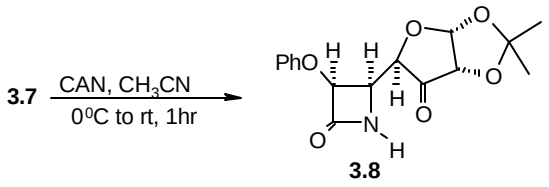
The mass spectrum showed the molecular ion peak at 425 while the base peak appeared at 149. This compound showed satisfactory elemental analysis.

3.4.5 Preparation of N-unsubstituted 6-Keto b-lactam **3.8**

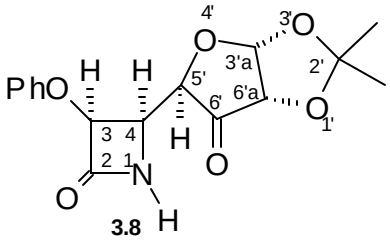
To a solution of **3.7** in acetonitrile, was added a solution of CAN[9] in water at 0 ^{0}C and the reaction mixture was stirred at that temperature for 1hr. After the completion of the reaction cold water was added to the reaction mixture and extracted with EtOAc and after the usual workup and column chromatography the product was isolated as a gummy substance in 93.33% yield (**Scheme-3.8**).

The IR spectrum showed a broad band at 3300 corresponding to the NH stretching of the β-lactam. The β-lactam carbonyl appeared at 1778.25 as a strong band, while the ketone appeared at 1720.

Scheme -3.8



The ^{1}H NMR of this compound showed two singlets at 1.38 and 1.48 corresponding to the two methyls of the acetonide. A broad singlet at 6.75 corresponded to the NH proton of the N-unsubstituted β-lactam.



The H-3 proton appeared at 5.43 as a doublet with a coupling constant 4.9 Hz, while the H-4 appeared at 4.85 as a dd (J = 4.8 Hz and 4.9 Hz). The H-5' proton resonated at 4.78 as a doublet with a coupling constant 4.8 Hz, whereas the H- 6a' appeared as a doublet at 4.13 (J = 4.4 Hz).

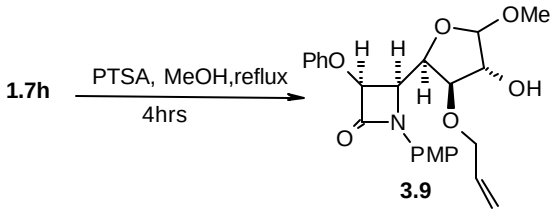
The ^{13}C spectrum of the compound showed the signals due to C=O carbon of the β-lactam at 166.72 while the other signals were consistent with the structure.

***3.4.6 Preparation of the methyl glycoside* 3.9**

A solution of 1.7h in MeOH was treated with catalytic amount of PTSA and refluxed for 4 hrs. After the completion of the reaction (TLC), the solvents were removed under reduced pressure and residue was column chromatographed to get a anomeric mixture (46:54) of methoxy compound **3.9** (**Scheme -3.9**). The IR spectrum of this compound showed a broad band at 3400 confirming the presence of the hydroxyl group. The β-lactam carbonyl-stretching band appeared at 1743.

The presence of two anomers was confirmed by ^{1}H NMR spectroscopy. The two anomers were separated by column chromatography. The spectrum of the minor isomer showed a singlet at 3.30 in the ^{1}H NMR for the anomeric methoxy group.

Scheme -3.9



The methoxy of the p-anisyl appeared at 3.85 as singlet. The anomeric proton appeared as a doublet at 5.49 (J = 5.4 Hz). The allyl group appeared as two multiplets at 5.6 and 5.05. The H-4 β-lactam protons appeared as a dd (J = 5.4 Hz and 5.3 Hz) the other protons of the sugar showed multiplets at 4.05 to 4.28 and 4.57 to 4.65. The ring protons of the p-anisyl and phenoxy appeared in the aromatic region. The major anomer showed a singlet at 3.50 corresponding to the anomeric methoxy group. The methoxy group of the p-anisyl appeared at 3.85 as singlet. The other protons appeared at their respective regions and were consistent with the structure.

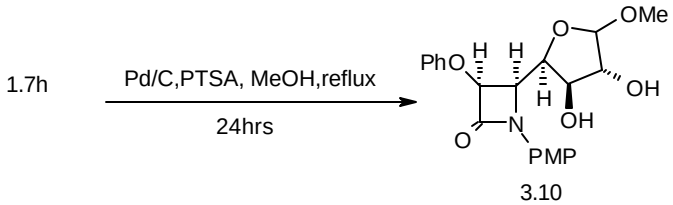
The ^{13}C NMR of the major compound was taken in $CDCl_3$, and showed a signal at 163.93 corresponding to the β-lactam carbonyl. The methoxy at the anomeric position appeared at 55.31, while the methoxy of the p-anisyl came at 56.23. The alkene carbons and the aromatic carbons appeared in their respective regions. The β-lactam and the sugar carbons resonated in the aliphatic region (60-100)

The mass spectral analysis of this compound showed the molecular ion peak at 441 ($M^{+\cdot}$) and the base peak at 77 (100%)

***3.4.7 Preparation of the Diol* 3.10**

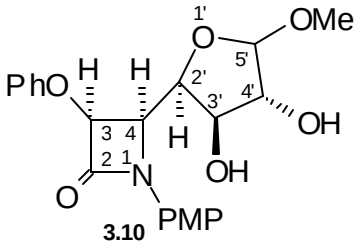
A solution of the β-lactam **1.7h** in MeOH was treated with Pd/C and PTSA, and refluxed for 24 hrs, after filtration and usual workup, the crude product was column chromatographed to give the pure diol **3.10** ***(Scheme -3.10).***

Scheme -3.10



The IR spectrum of 3.10 showed a strong band at 1753.17 cm^{-1} corresponding to the β-lactam carbonyl stretching. The ^{1}H NMR of this compound showed two sets of signals indicating the presence of two diastereomers (anomers). The anomeric ratio was found to be 46:54 from the integration of the methoxy group at the anomeric position. The anomeric methoxy group of the minor isomer appeared as a singlet at 3.80, while the major appeared at 3.50. The methoxy protons of the p-anisyl group appeared as a singlet at 3.82 integrating for 6 protons. The hydroxyls at the C-4' position appeared as two sets of singlets at 2.81 and 2.86, while the two sets of hydroxyls at the C-3' position appeared as doublets at 2.17 (J = 4 Hz) and 2.25 (J = 3.9 Hz).

The H-3 protons of the anomeric mixture of β-lactams appeared as a multiplet at 5.42 integrating for two protons. The two anomeric (H-5') protons appeared as two sets of doublets at 5.87 and 5.85 with coupling constants (J = 3.5 Hz and 3.9 Hz) respectively.



3.10

The other protons appeared as complex sets of multiplets from 4.68 to 5.35 integrating for 10 protons.

The ^{13}C NMR spectrum of this compound was recorded in DMSO-d_6, the methyl protons of the two anomers appeared at 55.47 and 58.81. The C-3a' (anomeric) carbons of the mixture appeared at 110.72 and 114.02. The two C-3 β-lactam carbons resonated at 79.44 and 79.62, while the two C-4 carbons gave a single signal at 59.44. The C-5' carbon appeared as two sets of signals at 76.49 and 77.89. The β-lactam carbonyl carbon appeared as a single signal at 164.09 for the two anomers.

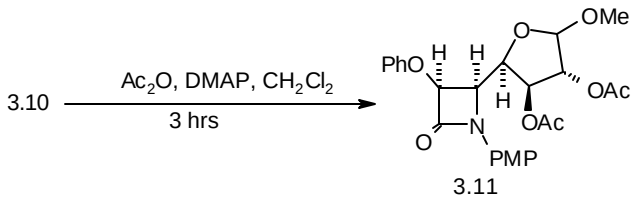
The aromatic carbons appeared in the region 115.97 to 157.91 and were consistent with the structure of the compound.

***3.4.8 Preparation of the Diacetate* 3.11**

A solution of the diol 3.10 in methylene chloride was treated with acetic anhydride, triethylamine, and catalytic amount of DMAP and stirred at RT for 3 hrs (Scheme-3.11). After the completion of the reaction, it was quenched with saturated NH_4Cl solution and

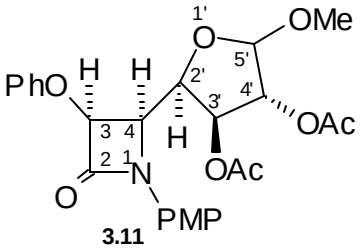
worked up in the usual manner. Filtration of crude product through a pad of silica gel followed by concentration provided the pure diacetate 3.11 in quantitative yield.

Scheme -3.11



3.11

The IR spectrum showed a strong band at 1753.17 cm^{-1} corresponding to the β-lactam carbonyl stretching. The ^{1}H NMR of this compound showed two sets of signals indicating the presence of two diastereomers (anomers). The anomeric ratio was found to be 46:54 from the integration of the methoxy group at the anomeric position. One of the acetate appeared as two singlets at 1.94 and 1.90 in the ratio 46:54 indicating their relative abundance. The other acetate appeared as two singlets at 2.17 and 2.13 in the same ratio.



3.11

The glycosidic methyl appeared as two sets of singlets at 3.26 and 3.52 in the ratio 46:54. The methoxy of the p-anisyl group appeared as a singlet at 3.82 integrating for 6 protons. The H-3 protons of the β-lactam appeared as a doublet at 5.65 (1H, J = 5.4 Hz). The two-anomeric protons appeared as two sets of doublets at 5.87 and 5.85 with coupling constants (J = 3.5 Hz and 3.9 Hz) respectively. The other protons appeared as complex sets of multiplets from 4.68 to 5.35 integrating for 10 protons.

The ^{13}C NMR of the compound was recorded in $CDCl_3$ and showed two sets of signals. The carbonyl of the acetate resonated at 167.46 and 166.58. The carbonyls of the β-lactam appeared at 160.73 and 156.99. The anomeric ratio was found to be 46:54, well in agreement with the ^{1}H NMR. The diastereomeric excess of the reaction was only 12%. The two diastereomers could not be separated by column chromatography.

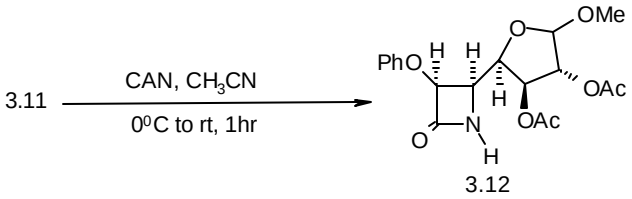
The mass spectral analysis of the compound displayed the molecular ion peak at 485 (3%). The base peak appeared at 149 (100%).

3.4.9 Preparation of N-unsubstituted b-lactam 3.12

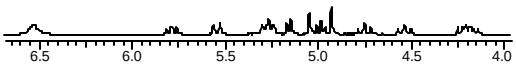
A solution of CAN was added to an ice cooled solution of the diacetate 3.11 in acetonitrile, stirred for 30 min at 0 ^{0}C, and then worked up as usual (Scheme-3.12). Column chromatography of the crude compound provided the N-unsubstituted β-lactam 3.12 in 95.23% yield as a yellow gummy substance.

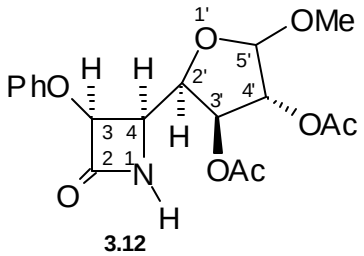
The TLC of this compound showed a single spot even after several trials. The IR of this compound showed a strong band at 1753.17 cm^{-1} corresponding to the β-lactam C=O stretching frequency. The NH stretching of the β-lactam was observed as a strong band at 3415.70 cm^{-1}.

Scheme-3.12



The ^{1}H NMR of this compound showed two sets of signals corresponding to a pair of anomers. One of the methyl groups of the acetates appeared as two sets of singlets at 1.92 and 1.95. The other acetate appeared at 2.15 integrating for 6 protons. The methoxyls at the anomeric position appeared as two singlets at 3.40 and 3.45. At 4.13 two sets of merged dd were seen with J = 4.8, 4.9, 4.9, 6.0 Hz. Two triplets appeared at 4.53 (J = 6.9 Hz) and 4.7 (J = 6.4 Hz). A four-proton multiplet appeared at 4.92 to 5.04. One of the H-3 ring protons of the β-lactam appeared at 5.74 as a doublet (J = 4.9 Hz), while the other appeared at 5.78 as a doublet (J = 4.9 Hz). The two N-H protons appeared as a broad singlet at 6.5 integrating for two protons. The 10 aromatic protons resonated down field at 6.95 to 7.40 as a set of multiplets.





In the ^{13}C NMR of this compound recorded in $CDCl_3$, the four-methyl groups of the acetyls appeared as two signals at 17.78 and 17.89. The two-anomeric methoxyl carbons were appeared as two signals at 52.67 and 53.51. The C-4 carbons of the two β-lactams appeared at 55.83 and 57.44. The C-3 carbons of the β-lactam appeared at 76.30 and 79.76. The anomeric (C-5') carbon appeared at 98.03 and 105.01. The 10 aromatic carbons appeared in the region 111.18 to 156.99. The carbonyl carbons of the β-lactam resonated at 160.62 and 160.73. The four acetate carbonyls gave three signals at 166.47, 166.58, and 167.46.

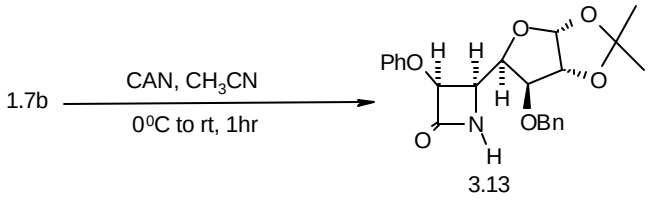
The mass spectral analysis of the compound showed the molecular ion peak at 379 (8.33%) and the base peak at 149 (100%). This compound provided satisfactory elemental analysis.

***3.4.10 Preparation of N-unsubstituted b-lactam* 3.13**

A solution of CAN was added to an ice cooled solution of the β-lactam 1.7b in acetonitrile, stirred for 30min at0^0 C, and then worked up as usual (Scheme-3.13). Column chromatography of the crude compound provided the N-unsubstituted β-lactam 3.12 in 89% yield as a white gum.

The IR of this compound showed a strong band at 1753.17 cm^{-1} corresponding to the

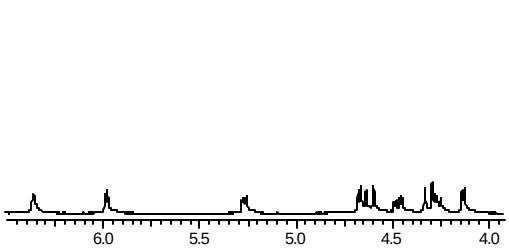
Scheme-3.13

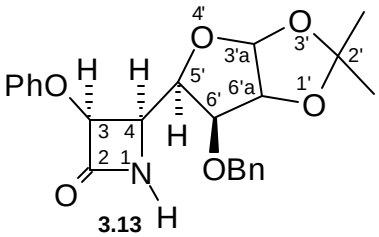


β-lactam C=O stretching frequency. The NH stretching of the β-lactam seen as a strong band at 3415.70 cm^{-1}.

The ^1H NMR of this compound showed two singlets corresponding to methyl protons of the acetonide at 1.39 and 1.56 integrating for three protons each. The H-3 proton of the β-lactam appeared at 5.29 as a doublet (J = 5.1 Hz), while the H-4 resonated up- field at 4.30 as a dd (J = 3.3 Hz and 5.1 Hz). The H-5' proton was seen as a dd at 4.49 (J = 3.3 Hz each). The H-6' proton resonated at 4.17 as a doublet (J = 3.3 Hz), while the H-6'a was seen at 4.70 (d, 1H, J = 4.1Hz). The anomeric (H-3'a) proton appeared at 6.01 as a

doublet at 6.01 (J = 3.7 Hz). The two benzylic protons appeared as two sets of doublets at 4.33 (J = 11.4 Hz), and at 4.63 (J = 11.8 Hz), due to their diastereotopic nature. The N-H proton appeared as a broad singlet at 6.40. The 10 aromatic protons resonated down field at 7.06 to 7.34 as a set of multiplets.





3.13

The ^{13}C NMR of this compound was recorded in $CDCl_3$, and showed the two-methyl carbons of the acetonide at 26.18 and 26.70. The C-4 carbon of the β-lactam appeared at 52.95, while the C-3 carbon of the β-lactam appeared downfield at 71.66. The anomeric (C-3'a) carbon appeared at 104.59. The 12 aromatic carbons appeared in the region 111.94 to 157.21. The carbonyl carbon of the β-lactam resonated at 166.33.

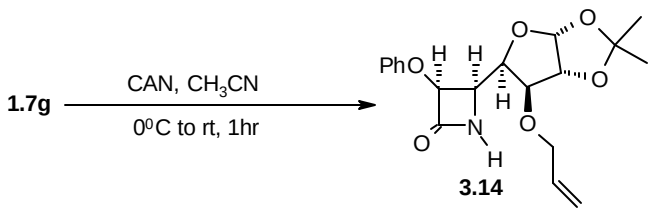
The mass spectral analysis of the compound showed the molecular ion peak at 411 (17%) and the base peak at 91 (100%). This compound provided satisfactory elemental analysis.

3.4.11 Preparation of N-unsubstituted b-lactam 3.14

A solution of CAN was added to an ice cooled solution of the β-lactam 1.7h in acetonitrile, stirred for 30min at 0 ^{0}C, and then worked up as usual (**Scheme-3.14**).

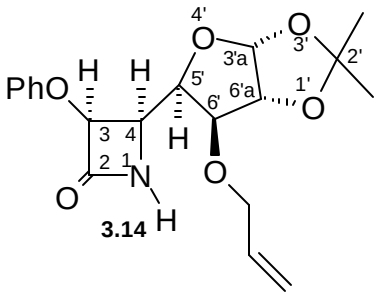
Column chromatography of the crude compound provided the N-unsubstituted β-lactam 3.12 in 98.3% yield as a white gum.

Scheme-3.14

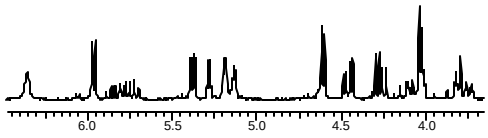


3.14

The IR of this compound showed a strong band at 1753.17 cm^{-1} corresponding to the β-lactam C=O stretching frequency. The NH stretching of the β-lactam was observed as a strong band at 3415.70 cm^{-1}.



3.14



The ^{1}H NMR of this compound showed two singlets corresponding to methyl protons of the acetonide at 1.34 and 1.51 integrating for three protons each. The H-3 proton of the β-lactam appeared at 5.35 as a doublet (J = 4.9 Hz), while the H-4 resonated up- field at 4.25 as a dd (J = 4.9 Hz, 3.4 Hz). The H-5' proton was seen as a dd at 4.42 (J = 3.4 Hz). The H-6' proton resonated at 4.02 as a doublet (J = 3.4 Hz), while the H-6'a was seen at 4.59 (d, 1H, J = 3.9 Hz). The anomeric (H-3'a) proton appeared at 5.94 as a doublet (J = 3.9 Hz). The 5 allylic protons appeared as three sets of multiplets at 4.12, 5.71 and 5.94. The N-H proton appeared as a broad singlet at 6.35. The 5 aromatic protons resonated down field at 7.01 to 7.36 as a set of multiplets.

The ^{13}C NMR of this compound was recorded in $CDCl_3$, and showed the two-methyl carbons of the acetonide at 26.21 and 26.76. The C-4 carbon of the β-lactam appeared at 52.27, while the C-3 carbon of the β-lactam appeared downfield at 70.03. The anomeric (C-3'a) carbon appeared at 104.28. The 6 aromatic carbons and the two olefinic carbons appeared in the region 111.01 to 157.43. The carbonyl carbon of the β-lactam resonated at 166.43.

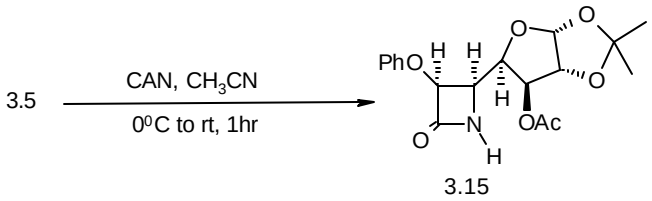
The mass spectral analysis of the compound showed the molecular ion peak at 363 (2%) and the base peak at 149 (100%). This compound provided satisfactory elemental analysis.

3.4.12 Preparation of N-unsubstituted b-lactam **3.15**

A solution of CAN was added to an ice cooled solution of the β-lactam 3.5 in acetonitrile, stirred for 30 min at0 ^{0}C, and then worked up as usual (Scheme-3.15).

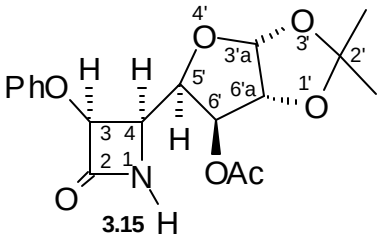
Column chromatography of the crude compound provided the N-unsubstituted β-lactam 3.12 in 77.77% yield as a white gum.

Scheme-3.15



3.15

The IR of this compound showed a strong band at 1753.17 cm^{-1} corresponding to the β-lactam C=O stretching frequency. The NH stretching of the β-lactam was seen as a strong band at 3415.70 cm^{-1}. The ^{1}H NMR spectrum of this compound showed two singlets integrating for three protons each, at 1.33 and 1.54 for two-methyl groups of the acetonide. The methyl protons of the acetate resonated at 2.07 as a singlet. The H-3 proton was observed at 5.36 as a doublet (J = 4.5 Hz). The H-3'a and H-6'a were seen downfield at 5.90 and 5.26 as two doublets (J = 3.4 Hz each).



3.15

The H-4 resonated up field at 4.5 as a dd (J = 4.5 and 3.4 Hz). The other protons resonated at 4.09 to 4.18 as multiplet. The NH proton appeared downfield at 6.47 as a broad singlet. The 5 aromatic protons resonated at 7.01 to 7.35 as a complex multiplet.

In the ^{13}C NMR spectrum of this compound, two carbonyl carbons of the acetate and the β-lactam carbonyl resonated at 169.26 and 166.54 respectively. The aromatic carbon attached to oxygen appeared at 157.21.

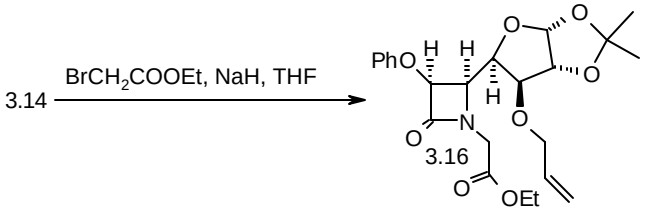
The methyls of the acetonide appeared at 25.98 and 26.42. The methyl carbon of the acetate resonated at 20.39. The C-3 and C-4 carbons were observed at 76.41 and 52.59. All the other carbons resonated in the expected regions and were consistent with the structure of the compound.

The mass spectrum of the compound showed the molecular ion peak at 379 (8.33%), and the base peak at 149 (100%).

3.4.13 Preparation of N-ethyl carboxylate **3.16**

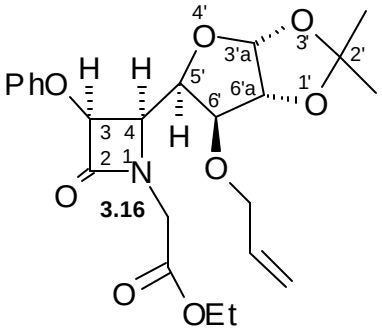
A solution of β-lactam **3.12** in anhydrous THF was added to 50% suspension of NaH in mineral 0 ^{0}C oil at and refluxed for 2 hrs. The reaction mixture was then cooled to 0 ^{0}C and ethyl bromoacetate was added. The reaction mixture was then refluxed gently for 8 hrs. After the usual workup and column chromatography compound 3.16 was obtained an oil (**Scheme -3.16**).

Scheme -3.16



The IR spectrum showed the presence of two carbonyl peaks. The β-lactam carbonyl appeared at 1749 cm^{-1} while the ester carbonyl was observed at 1730 cm^{-1}.

The ^{1}H NMR of this compound was recorded in $CDCl_3$, the two methyls of the isopropylidene were merged with the triplet of the ethyl ester and seen as a multiplet integrating for 9 protons. The methylene on the nitrogen resonated at 1.50 as a singlet integrating for 2 protons.



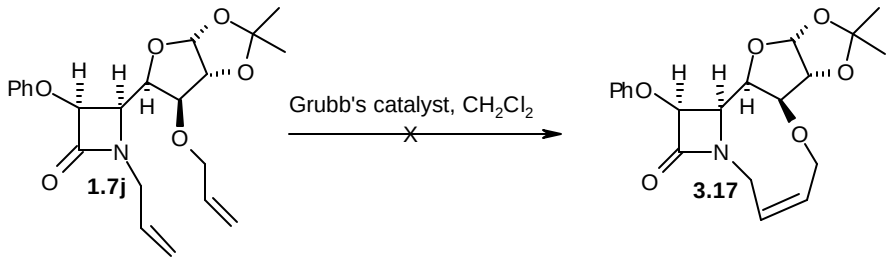
The H-3 β-lactam proton appeared at 5.42 as a doublet (J = 4.9 Hz). The H-4 β-lactam proton appeared as a dd (J = 4.9 Hz and 3.9 Hz). A complex set of multiplets appeared from 4.00 to 4.56 integrating for 6 protons (inclusive of the allyl). The allyl protons appeared as three sets of multiplets at 5.10 and 5.65 and the third set at 4.00 to 4.56. The H-3'a (anomeric) proton resonated at 5.92 as a doublet (J=3.9 Hz)

The ^{13}C NMR spectrum of 3.16 showed the β-lactam carbonyl carbon at 165.66 while the ester appeared at 167.64. The methyl of the ester appeared up field at 13.78, while those of the acetonide resonated at 25.94 and 26.46. The (OCH_2) methylene of the ester appeared at 42.45, while the allyl CH_2 resonated at 57.08 and CH_2 on the nitrogen

appeared at 61.05. The other signals appeared at the expected regions and were consistent with the structure of the compound. The mass spectral analysis of this compound showed both the molecular ion peak $M^{+\cdot}$ and the base peak at 447 ***(***100%***).***

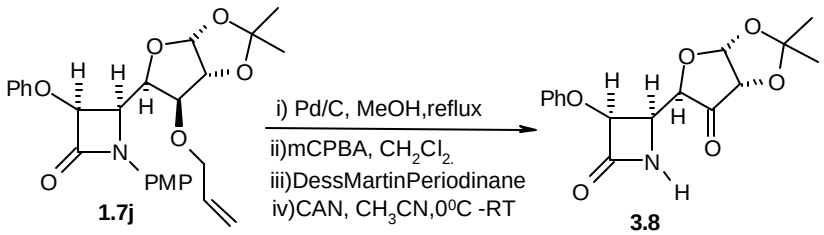
In an effort to synthesize novel polycyclic compounds with β-lactam backbone, we envisaged that the β-lactams derived from D-glucose would be suitable precursors. Therefore, an attempt was made to synthesize polycyclic β-lactams by ring closing metathesis (RCM) using Grubb's catalyst. However, the β-lactam **1.7j** failed to undergo RCM under standard conditions (**Scheme -3.17**), in all probability due to the strain involved in the formation of a 9 membered ring sandwiched between a four membered and a five membered ring.

Scheme -3.17



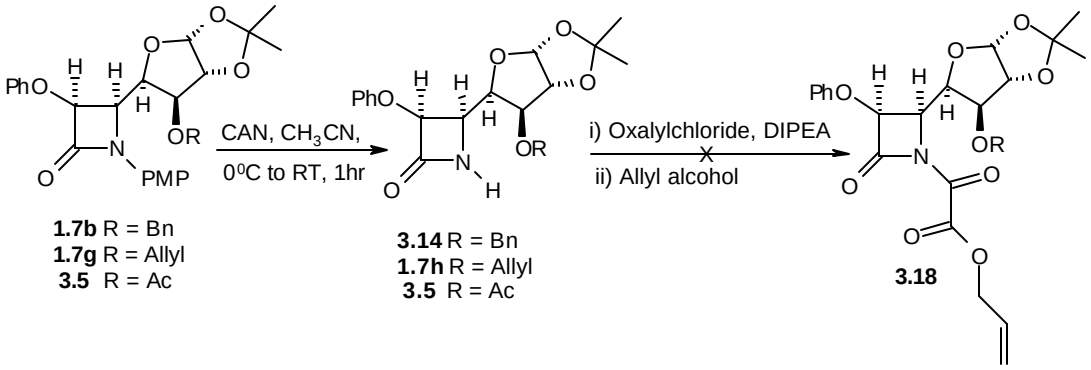
We then focused our attention on the β-lactam **1.7g**, where sufficient deprotection of the allyl and the PMP could provide a tether for cyclization. The isomerisation of the allyl ether followed by the removal of the propenyl ether using mCPBA in methylene chloride afforded the 6-hydroxy β-lactam **3.6.** The hydroxyl group was then oxidized to ketone **3.7** using DMP (**Scheme -3.18**).

Scheme -3.18

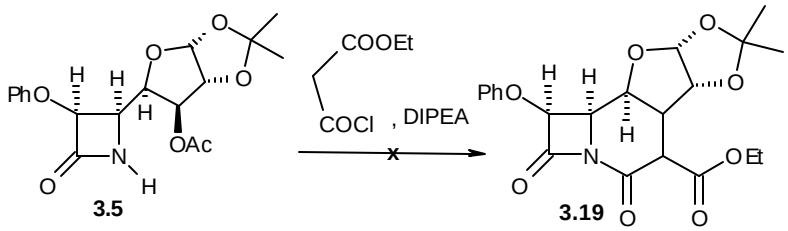


The p-anisyl of **3.7** was oxidatively cleaved to give the N-unsubstituted β-lactam **3.8**. Oxidative dearylation of the p-anisyl was carried out using CAN on the β-lactams **1.7b, 1.7h, and 3.5** to get the respective N-unsubstituted β-lactams. An attempted acylation of these β-lactams with oxalyl chloride and DIPEA, followed by the addition of allyl alcohol failed to provide the corresponding N-acylated allyl esters (**Scheme -3.19**).

Scheme -3.19



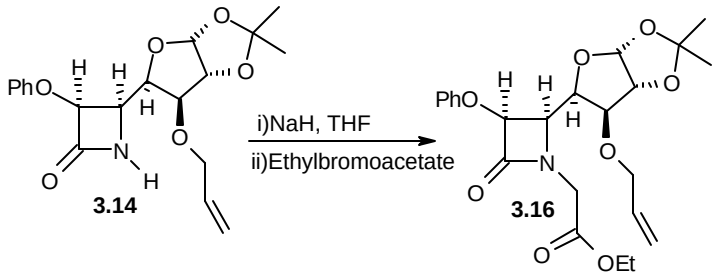
It was also envisaged that use of ethyl malonyl chloride for N-acylation of **3.5** should in one step provide a polycyclic system. But to our dismay no reaction was observed and the starting material was recovered (**Scheme -3.20**).



Scheme -3.20

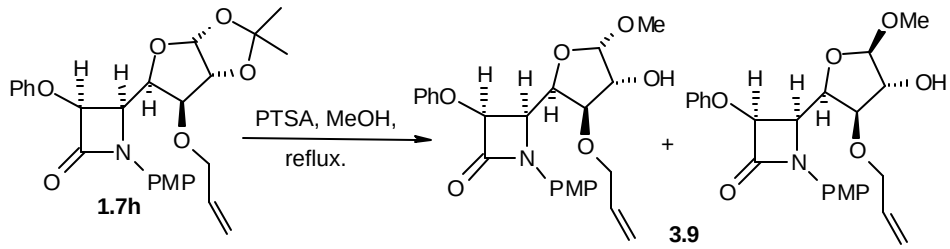
Based on these results we thought that the alkylation of the β-lactam nitrogen would be more feasible, with a stronger base than the acylation. Hence the alkylation of **3.14** was carried out using ethyl bromoacetate and NaH in THF; the reaction proceeded smoothly in 70%yield and afforded the corresponding N-ethyl carboxylate as oil (**Scheme -3.21**).

Scheme -3.21



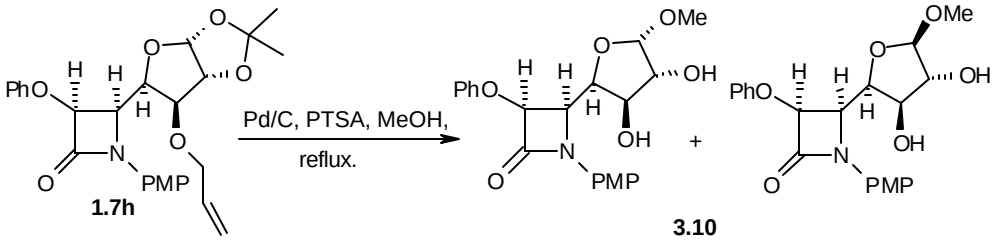
The compound **1.7h** was converted into a mixture of methyl glycosides **3.7,** by refluxing with PTSA in MeOH and the two anomers were separated by column chromatography (**Scheme -3.22**).

Scheme -3.22



In a similar way the compound **1.7h** on refluxing with Pd/C, and PTSA in MeOH provided a mixture of methyl glycosides **3.10** in the ratio 46:54. The two anomers could not be separated by column chromatography (**Scheme 3.23**).

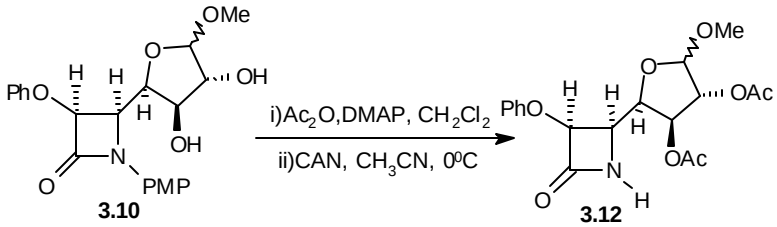
Scheme -3.23



It was thought that the derivatisation of the diol to its diacetate (**Scheme -3.24**) could help in the seperation of the two compounds, but unfortunately the two anomers could not be separated on TLC even after several elutions with non-polar solvents.

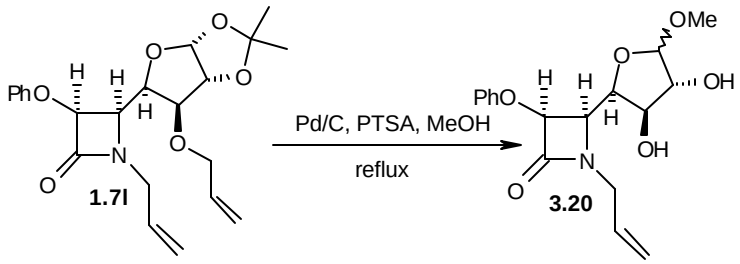
The diacetate was therefore subjected to oxidative cleavage by CAN giving the N-unsubstituted β-lactam, but again the two anomers were of the same polarity and could not be separated.

Scheme-3.24



Under similar reactions conditions of Pd/C, PTSA in refluxing MeOH the diallyl compound **1.7l** was envisioned to provide a diol with N- unsubstituted β-lactam (**Scheme-3.25**). But to our dismay we found that the N-allyl remained intact under the reaction conditions, only the O-allyl and the acetonide got deprotected under reaction conditions providing an inseparable mixture of anomers.

Scheme-3.25



3.5 : *Conclusion*

Various β-lactam derivatives were synthesized to serve as precursors for polycyclic ring systems with a β-lactam core. However, attempts to cyclize these derivatives to polycyclic compounds were unsuccessful.

3.6 : Experimental

All dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. THF was freshly distilled over sodium benzophenone ketyl. Dichloromethane was dried over anhydrous P_2O_5., Pd/C (10%) was purchased from Aldrich, USA and used as received.

***Synthesis of 3-O-Acetyl-1, 2: 5,6-diisopropylidene-α-D-glucofuranose* 3.1**

To a solution of the diacetonide **1.2** (2.6 g, 10 mmol) in anhydrous methylene chloride (50 ml), at 0 ^{0}C were added triethylamine (3.03 g, 4.18 ml, 30 mmol), acetic anhydride (1.22 g, 1.13 ml, 12 mmol) and a catalytic amount of DMAP. The mixture was stirred for 3 hrs, quenched with sat. NH_4Cl soln .The organic layer was separated and washed several times with water, and sat. Brine soln., dried over Na_2SO_4 and concentrated to get the crude acetate, which was then purified by column chromatography to get **3.1** as a white solid (m. p 2.91 g, 96.55%).

IR ($CHCl_3$) : 1747.39

^{1}H NMR ($CDCl_3$): (200 MHz) : 1.30-1.55(4 s, 12H, 4 methyls), 2.10 (s, 3H,OAc), 4.04 (d, 1H, J = 4.9 Hz), 4.19 (m, 2H), 4.48 (d, 1H, J = 3.4 Hz), 5.22 (d, 1H,J=2Hz), 5.86 (d, 1H, J = 3.9 Hz)

***Synthesis of 3-O-Acetyl-1, 2-O-isopropylidene-α-D-glucofuranose* 3.2**

2.91gm (9.63mmol) of **3.1** 3-O-Acetyl-1, 2: 5,6 di –O-isopropylidene α-D-glucofuranose was dissolved in 20ml of aqueous acetic acid (50%v/v) and stirred for 24hrs at RT. The solvents were removed under reduced pressure. The mass that remains was dissolved in $CHCl_3$ and washed repeatedly with water, Saturated sodium bicarbonate solution, and saturated Brine solution, dried over Na_2SO_4, and concentrated to get 2.096 g (83.33%) of white solid **3.2** which was used as such for the next reaction without further purification.

IR ($CHCl_3$) : 3463.92 (br), 1737.74 (s)

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.30 (s, 3H), 1.50 (s, 3H), 2.15 (s, 3H, OAc), 3.50 (s, 2H, br, OH), 3.69 (m, 2H), 3.84 (m, 1H), 4.14 (dd, 1H, J = 2.9 Hz, 2.4 Hz), 4.56 (d, 1H, J = 3.9 Hz), 5.26 (d, 1H, J = 2.4 Hz), 5.89 (d, 1H, J = 3.5 Hz)

***Synthesis of 3-O-Acetyl 1, 2-O-isopropylidene-α-D-xylo pento-dialdo-furanose* 3.3**

To a solution of the diol **3.2** (2.00 g, 9.08 mmol) in a mixture of MeOH (25 ml) and water (25 ml) was added $NaIO_4$ (2.91 g, 13.6 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 **3.3** (1.35 g, 100%) and was used for the next step without any purification

IR ($CHCl_3$) : 1712.67, 1747.39, 2987.53

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.33 (s, 3H), 1.51 (s, 3H), 2.04 (s, 3H), 4.59 (d, 1H, J = 3.4 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 imine* 3.4**

To a solution of the p-anisidine (0.165 g, 1.34 mmol) in CH_2Cl_2, and anhydrous $MgSO_4$ (0.31 g), was added a solution of the aldehyde **3.3** (0.31 g, 1.34 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 imine **3.4** (0.45 g, 1.34 mmol) which were used as such for the β-lactam reaction.

***Synthesis of Acetic acid 5'-(1-(4-methoxy phenyl)- 4-oxo-3-Phenoxy- azetidin-2yl)-2', 2'-dimethyl tetrahydrofuro [2', 3'-d][1', 3'] dioxol-6'yl-ester* 3.5**

A solution of the phenoxyacetyl chloride (0.343 g, 0.277 ml, 2.01 mmol) in anhydrous methylene chloride 10 ml was added to a solution of the imine **3.4** (0.45 g, 1.34 mmol) and triethylamine (0.610 g, 0.84 ml, 6.03 mmol) in CH_2Cl_2 (20 ml) at 0 ^{0}C. After the addition was completed the reaction mixture was 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 the crude β-lactam that was then purified by column chromatography to get **3.5** as a white solid (75%).

M.P	**:**	171^0 C
[a]$_D^{25}$	**:**	-235.64, (C=1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1747.39
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.35 (s, 3H), 1.50 (s, 3H), 2.05 (s, 3H) 3.80 (s, 3H), 4.57 (d, J= 3.9 Hz), 4.62 (d, 1H, J = 5.4 Hz), 4.68 (dd, 1H, J = 3 Hz, 3.5 Hz), 5.33(d, 1H, J = 4.9 Hz), 5.64 (d, 1H, J = 2.9 Hz), 6.02 (d, 1H, J = 3.9 Hz), 6.89-7.25 (m, 9H, Ar).
^{13}C NMR ($CDCl_3$)	**:**	20.06, 25.69, 26.16, 54.84, 57.92, 77, 79.13, 79.61, 82.88, 104.02, 111.66, 113.54, 115.71, 119.20, 122.32, 129.16, 130.48, 156.18, 157.02, 162.94, 168.86.
Ms	**:**	469 (5%), 59 (100%)
Analysis	**:**	Calculated: C: 63.94, H: 5.80, N: 2.98
$C_{25}H_{27}NO_8$		Found: C: 64.06, H: 5.97, N: 3.12

Synthesis of the (3S, 4R, 5R, 6S, 7R, 8R) 4-(2,2-Dimethyl-6-propenyloxy-tetrahydro-furo [2,3, -d][1,3] dioxol-5yl)-1-(4-methoxy-phenyl)-3phenoxy-azetidin-2-one **3.6a**

The β-lactam **1.7h** (0.94 g, 2.0 mmol) was treated with Pd/C (0.094 g) in MeOH (20 ml) and the suspension was refluxed vigorously till the disappearance of the starting material (~24 hrs). The catalyst was filtered through a pad of celite and the solvent evaporated under reduced pressure to afford a white solid **3.6a** (90%).

^{1}H NMR ($CDCl_3$) (200 MHz)	:	1.33 (s, 3H, 1.50 (s, 3H), 1.57 (d, 3H, J = 5.8 Hz), 3.81 (s, 3H), 4.47-4.72 (m, 3H), 4.87 (q, 1H, J = 6.8 Hz), 5.40 (d, 1H, J = 4.9 Hz), 5.82 (d, 1H, J = 7.4 Hz), 6.07 (d, 1H, J = 3.5 Hz), 6.87-7.75 (m, 9H).

Synthesis of (3S, 3a', 4R, 5R, 6S, 6a'R, 8R)-4-(6'-hydroxy-2', 2' dimethyl tetrahydrofuro [2', 3'(d)[1', 3'] dioxol-5'yl)-1-(4-methoxy phenyl)-3-Phenoxy-azetidin-2-one **3.6**

The vinyl ether 3.6a (0.817 g, 1.75 mmol) was dissolved in anhydrous methylene chloride (15 ml) and added (0.603 g, 1.75 mmol) mCPBA (50%). triethylamine (0.5 ml)

was added after 15 min and stirred for 12hrs. Upon filtration through a short bed of silica using methylene chloride and evaporation of the solvent under reduced pressure the alcohol 3.6 was obtained as a white solid (0.67 g, 91%).

MP	**:**	162 ^{0}C
[a]$_D^{25}$	**:**	-211.25 (C = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1751, 3250
^{1}H NMR		1.30 (s, 3H), 1.46 (s, 3H), 2.50 (s, 1H), 3.79 (s, 3H), 4.48-
($CDCl_3$)	**:**	4.69 (m, 4H), 5.39 (d, 1H, J = 5.4 Hz), 6.03 (d, 1H, J = 3.9
(200 MHz)		Hz), 6.84-7.71 (m, 9H, Ar).
^{13}C NMR		26.16, 26.72, 29.55, 55.39, 75.42, 79.39, 81.56, 85.60,
($CDCl_3$)	**:**	104.64, 111.77, 114.09, 115.82, 120.01, 122.58, 129.60, 131.03, 156.80
Ms	**:**	$M^{+\cdot}$ 427 (100%)
Analysis	**:**	Calculated: C: 64.61, H: 5.89, N: 3.27
$C_{23}H_{25}NO_7$		Found: C: 64.31, H: 6.00, N: 3.43

***Synthesis of (3S, 3a'R, 4R, 5R, 6a'R)-4-(2', 2' dimethyl-6'-oxo- tetrahydrofuro [2', 3'-d][1', 3'] dioxol-5'yl] 1-(4-methoxy phenyl)-3-Phenoxy-azetidin-2-one* 3.7**

A solution of **3.6** (0.210 g, 0.49 g) in anhydrous methylene chloride was added drop wise to a suspension of Dess Martin Periodinane (0.417 g, 0.98 mmol) in methylene chloride (20 ml). After 2 hrs the reaction mixture was filtered through a short bed of silica gel and then the elutant was washed with saturated solution of sodium thiosulphate. It was dried (Na_2SO_4) and filtered and filtrate upon concentration gave 6-keto compound **3.7** as a white solid (0.198 g, 95%).

MP	**:**	176 ^{0}C
[a]$_D^{27}$	**:**	+22.20 (C = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	1744.46, 1704.96

^{1}H NMR	**:**	1.35 (s, 3H), 1.42 (s, 3H), 3.81 (s, 3H, OMe), 4.12 (d,
($CDCl_3$)		1H, J = 4.4 Hz), 4.76 (d, 1H, J = 3.9 Hz), 4.83 (dd, 1H, J
(200 MHz)		= 3.6 Hz, 4.4 Hz), 5.43 (d, 1H, J = 4.8 Hz), 5.66 (d, 1H, J
		= 4.4 Hz), 6.88-7.39 (m, 9H, Ar)
^{13}C NMR	**:**	26.16, 26.72, 29.55, 55.39, 75.42, 79.39, 81.56, 85.60,
($CDCl_3$)		104.64, 111.77, 114.09, 115.82, 120.01, 122.58, 129.60,
		131.03, 156.80
Ms	**:**	425 (2%), 149 (100%).
Analysis	**:**	Calculated: C: 64.919, H: 5.452, N: 3.294
$C_{23}H_{23}NO_7$		Found: C: 65.00, H: 5.64, N: 3.46

***Synthesis of (3S, 3a'R, 4R, 5R, 6a'R)-4-(2', 2'-dimethyl-6'-oxo- tetrahydrofuro[2',3'-d][1',3']dioxol-5'yl)- 3 -Phenoxyazetidin-2-one* 3.8**

To a solution of **3.7** (0.1 g, 0.23 mmol) in acetonitrile (10 ml), was added a solution of CAN (0.38 g, 0.7 mmol) in water at 0 ^{0}C and the reaction mixture was stirred at that 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 sulphite solution followed by 10% sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product **3.8** as a gum (0.07 g, 93.33 %).

MP	**:**	Gum
[a]$_D^{25}$	**:**	+32.72 (C = 1, $CHCl_3$)
IR ($CHCl_3$)	**:**	4214.17, 3413, 3018, 2927, 2401, 1778.25
^{1}H NMR($CDCl_3$)	**:**	1.38 (s, 3H), 1.48 (s, 3H), 4.13 (d, 1H, J = 4.4 Hz), 4.78
(200 MHz)		(d, 1H, J = 4.8 Hz), 5.43 (d, 1H, J = 4.9 Hz), 5.69 (d, 1H,
		J = 4.4, Hz), 6.75 (br, s, 1H), 7.04 -7.37 (m, 5H, Ar).
^{13}C NMR	**:**	27.38, 29.62, 54.95, 75.16, 76.71, 81.45, 103.13, 114.24,
($CDCl_3$)		115.52, 115.96, 123.02, 129.75, 157.10, 166.72, 166.87.

Analysis	**:**	Calculated: C: 60.16, H: 5.36, N: 4.38
$C_{16}H_{17}NO_6$		Found: C: 60.32, H: 5.43, N: 4.55

***Synthesis of (3S, 4R, 2'R, 3'S, 4'R)-4-(3'-Allyloxy-4'-hydroxy-5'-methoxy-tetrahydro-furan-2'yl)-1-(4-methoxy-phenyl)-3-Phenoxy-azetidin-2-one* 3.9**

A solution of **1.7g** (0.33 g, 0.7 mmol) in MeOH was treated with catalytic amount of PTSA and refluxed for 4 hrs. After the completion of the reaction (TLC), the solvent was removed under reduced pressure to afford the crude compound, which was column chromatographed to get **3.9** as a mixture of anomers in the ratio 46:54 (yield 0.29 g, 93.54%).

MP	**:**	Gum
[a]$_D^{25}$	**:**	-132.17 (c = 0.5, $CHCl_3$)
IR ($CHCl_3$)	**:**	3400, 1743
^{1}H NMR	**:**	2.17 (d, 1H), 2.25 (d, 1H, J = 3.9 Hz), 2.67 (s, 1H), 2.86
($CDCl_3$)		(s, 1H), 3.40 (s, 1H), 3.55 (s, 3H), 3.85 (s, 6H), 4.19 (1H,
(200 MHz)		m), 4.20 (1H, d, J = 3.4 Hz), 4.43 (m, 1H), 4.52 (m, 1H),
		4.66 (m, 2H), 4.85 (s, 1H), 5.09 (d, 1H, J = 4.4 Hz), 5.42
		(m, 2H), 6.80-7.75 (m, 18H, Ar)
^{13}C NMR	**:**	55.47, 58.81, 59.44, 75.87, 75.87, 76.49, 77.89, 79.44,
($DMSOd^6$)		79.62, 80.50, 83.41, 103.47, 110.72, 114.02, 115.97,
		119.87, 122.26, 129.72, 131.45, 156.22, 157.91, 164.09
Ms	**:**	401 (5%), 369 (1%), 189 (2%), 165 (8%), 149 (23%),
		134 (9%), 95 (16%), 69 (40%), 57 (100%).
Analysis	**:**	Calculated: C: 65.28, H: 6.16, N: 3.17
$C_{24}H_{27}NO_7$		Found: C: 65.44, H: 6.30, N: 3.29

***Synthesis of (3S, 4R, 2'R, 3'S, 4'R)-4-(3', 4'-Dihydroxy-5'-methoxy-tetrahydro-furan-2'yl)-1-(4-methoxy phenyl)-3-Phenoxy-azetidin-2-one* 3.10**

A solution of the β-lactam **1.7h** (1.77g, 3.79 mmol) in 20 ml MeOH was treated with 10%Pd/C (0.177 g) and PTSA (0.177 g), and refluxed for 24hrs. After the completion of the reaction the catalyst was filtered and the filtrate concentrated on the

rotary evaporator to get the crude product was column chromatographed to give (1.24 g, 82%) of the pure diol **3.10** as a white solid.

MP	**:**	158-159 ^{0} C
[a]$_D^{27}$	**:**	-117.20 (c = 0.90, $CHCl_3$)
IR ($CHCl_3$)	**:**	3400, 1749
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.70 (s, 1H), 2.17 (d, 1H, J = 4 Hz each), 2.25 (d, 1H, J = 3.9 Hz), 2.81 (s, 1H), 2.86 (s, 1H), 3.80 (s, 3H, minor), 3.50 (s, 3H, major), 3.80 (s, 6H), 4.19 (m, 2H), 4.37(m, 1H), 4.52 (m, 1H), 4.66 (m, 3H), 5.11 (d, 1H, J = 4.4 Hz each), 4.90 (s, 1H), 5.42 (m, 2H), 6.60 (m, 18H)
^{13}C NMR (DMSO-D_6)	**:**	55.47, 58.81, 59.44, 75.87, 76.49, 77.89, 79.44, 79.62, 80.50, 83.41, 103.47, 110.72, 114.02, 115.97, 122.26, 129.72, 131.45, 156.22, 157.91, 164.09
Ms	**:**	401 (5%), 369 (1%), 189 (2%), 165 (8%), 149 (23%), 134 (10%), 95 (16%), 69 (40%), 57 (100%)
Analysis	**:**	Calculated: C: 62.82, H: 5.77, N: 3.49
$C_{21}H_{23}NO_7$		Found: C: 62.99, H: 5.85, N:3.66

***Synthesis of Acetic acid4-acetoxy-2-methoxy-5- [1'-(4'-methoxy-phenyl-)-4'-oxo-3'-phenoxy-azetidin-5yl)-tetrahydro-furan-3-yl-ester* 3.11**

A solution of the diol **3.10** (0.35 g, 0.87 mmol) in methylene chloride was treated with acetic anhydride (0.24 ml, 2.61 mmol), triethylamine (0.729 ml, 5.23 mmol) and catalytic amount of DMAP and stirred at RT for 3 hrs. After 3hrs the reaction was quenched with saturated NH_4Cl solution. The organic layer was then separated and washed thoroughly with water, sat brine soln, dried over Na_2SO_4, filtration through a pad of silica followed by evaporation of the solvent provided the pure diacetate **3.11** (0.4 g, 95.23 %).

MP	**:**	Gum
[a]$_D^{25}$	**:**	-76.628 (C = 0.89, $CHCl_3$)
IR ($CHCl_3$)	**:**	1753.17

^{1}H NMR	**:**	1.85 (s, 3H, minor), 1.90 (s, 3H, major), 2.15 (s, 3H,
($CDCl_3$)		major), 2.20 (s, 3H, minor), 3.25 (s, 3H, OMe, minor),
(200 MHz)		3.50 (s, 3H, major), 4.80 (s, 6H), 4.67-4.88 (m, 4H), 4.92 (s, 1H), 5.00 (m, 2H), 5.21 (d, 1H, J = 4.4 Hz), 5.30 (m, 2H), 5.26 (d, 1H, J = 5.4 Hz).
^{13}C NMR	**:**	17.78, 26.90, 26.67, 53.51, 55.83, 57.44, 72.99, 73.73,
($CDCl_3$)		74.35, 74.72, 74.98, 76.30, 76.78, 98.03, 105.01, 111.26, 113.24, 117.18, 117.65, 120.08, 126.92, 127.91, 154.01, 154.19, 154.78, 156.99, 160.73, 166.58, 167.46.
Ms	**:**	485 (2%), 149 (100%),
Analysis	**:**	Calculated: C: 61.83, H: 5.60, N: 2.88
$C_{25}H_{27}NO_9$		Found: C: 61.99, H: 5.80, N: 2.97

***Synthesis of Acetic acid4-acetoxy-2-methoxy-5- (-4'-oxo-3'phenoxy-azetidin-2yl)-tetrahydrofuran-3-yl-ester* 3.12**

To a solution of **3.11** (0.42 g, 0.86 mmol) in 20 ml acetonitrile, was added a solution of CAN (1.42 g, 2.59 mmol) in water at 0 ^{0}C and the reaction mixture was stirred at that temperature for 1 hr. After the completion of the reaction cold water was added to the reaction mixture and extracted with EtOAc (3x40 ml) and the combined organic layers were washed with 5% sodium bicarbonate solution, 10% sodium sulphite solution followed by 10% sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product as a gummy substance (0.23 g, 71.87 %).

MP	**:**	Gum
[a]$_D^{27}$	**:**	-93.32 (c =0.60, CHCl3)
IR ($CHCl_3$)	**:**	3415, 3298.05, 3020.32, 1753.17

^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	1.90 (s, 3H), 1.95 (s, 3H), 2.15 (s, 6H), 3.40 (s, 3H), 3.45 (s, 3H), 4.13 (2H, two dd's merged, J = 4.8, 4.9, 4.9, 6.0 Hz), 4.53 (t, 1H, J = 6.9 Hz), 4.7 (t, 1H, J = 6.4 Hz), 4.92-5.04 (4H, m), 5.14 (d, 1H, J = 4.3 Hz), 5.23 (m, 2H), 5.52 (d, J = 6.4 Hz), 5.74 (d, 1H, J = 4.9 Hz), 5.78 (d, 1H, J = 4.9 Hz), 6.5 (br, s, 2H, NH), 6.95-7.40 (m, 10H, Ar)
^{13}C NMR (CDCl3)	**:**	17.78, 17.89, 52.67, 53.51, 55.83, 57.44, 72.99, 73.73, 74.35, 74.72, 74.98, 76.30, 79.76, 98.03, 105.01, 111.18, 111.26, 113.24, 113.39, 117.18, 117.65, 119.97, 120.08, 126.92, 127.91, 128.13, 154.01, 154.19, 154.78, 156.99, 160.62, 160.73, 166.47, 166.58, 167.46.
Ms	**:**	379 (9%), 149 (100%),
Analysis	**:**	Calculated: C: 56.97, H: 5.58, N: 3.69
$C_{18}H_{21}NO_8$		Found: C: 57.12, H: 5.67, N: 3.82

***Synthesis of (3S, 3a'R, 4R, 5R, 6S, 6a'R)-4-(6'-Benzyloxy-2', -2'–dimethyl-tetrahydrofuro[2,3,d][1,3],dioxol-5yl)-3-phenoxyazetidin-2-one* 3.13**

To a solution of **1.7b** (0.2 g, 0.38 mmol) in acetonitrile, was added a solution of CAN (0.63 g, 1.16 mmol) in water at 0 ^{0}C and the reaction mixture was stirred at that 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 10% sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product **3.13** as a gummy substance 89% yield.

MP	**:**	137 ^{0} C
[a]$_D^{25}$	**:**	-190.70 (c =1, C HCl$_3$)
IR (CHCl$_3$)	**:**	3405, 3285, 3020.32, 1749

^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	1.39 (s, 3H), 1.56 (s, 3H), 4.17 (d, 1H, J = 3.3 Hz), 4.30 (dd, 1H, J = 3.3 Hz, 5.1 Hz), 4.33 (d, 1H, J = 11.4 Hz) 4.50 (dd, 1H, J = 3.3 Hz each), 4.63 (d, 1H, J = 11.8 Hz), 4.70 (d, 1H, J = 4.10 Hz), 5.29 (d, 1H, J = 5.1 Hz), 6.01 (d, 1H, J = 3.7 Hz), 6.40 (s, 1H), 7.06-7.34 (m, 10H, Ar)
^{13}CNMR (CDCl3)	**:**	26.18, 26.70, 52.95, 71.66, 80.63, 80.85, 81.97, 82.31, 104.59, 111.94, 115.39, 122.20, 127.33, 127.85, 128.36, 129.40, 136.97, 157.21, 166.33
Ms	**:**	411 (5%), 368 (3%), 275 (58%), 217 (22%), 161 (38%), 149 (70%), 91 (100%),
Analysis	**:**	Calculated: C: 67.14, H: 6.12, N: 3.40 Found: C: 67.40, H: 2.35, N: 3.59

***Synthesis of (3S, 3a'R, 4R, 5R, 6S, 6a'R) 4 -(6'-Allyloxy-2', 2'–dimethyl-tetrahydrofuro [2', 3',d][1', 3'], dioxol-5'yl)-3-phenoxy-azetidin-2-one* 3.14**

To a solution of **1.7h** (0.23 g, 0.49 mmol) in acetonitrile, was added a solution of CAN (0.81 g, 1.47 mmol) 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 (3x30 ml) and the combined organic layers were washed with 5% sodium bicarbonate solution, 10% sodium sulphate solution followed by 10 % sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product **3.14** as a gummy substance (0.175g, 98.3%).

MP	**:**	Gum
[a]$_D^{29}$	**:**	-189.20 (c = 0.60, $CHCl_3$)
IR (CHCl$_3$)	**:**	3410, 3289, 3011, 1751.23
^{1}H NMR (CDCl$_3$) (200 MHz)	**:**	1.34 (s, 3H), 1.51 (s, 3H), 3.79 (dd, 1H, J = 5.4 Hz each), 4.02 (d, 1H, J = 3.4 Hz), 4.25 (dd, 1H, J = 4.9 Hz, 3.4 Hz), 4.44 (d, 1H, J = 3.4 Hz each), 4.59 (d, 1H, J = 3.9 Hz), 5.12 (m, 2H), 5.28 (m, 1H), 5.35 (d, 1H, J = 4.9 Hz), 5.71 (m, 1H), 5.94 (d, 1H, J = 3.9 Hz), 6.35 (s, 1H, NH), 7.01-7.36 (m, 5H, Ar)

^{13}CNMR (CDCl3)	**:**	26.21, 26.76, 52.27, 70.03, 79.29, 80.61, 80.87, 81.57, 81.97, 104.28, 111.01, 115.46, 115.83, 117.04, 122.18, 122.18, 129.72, 134.57, 157.43, 166.40
Ms	**:**	361 (7%), 318 (12%), 320 (16%), 318 (6%), 268 (39%), 225 (17%), 200 (13%), 161 (23%), 149 (100%), 77 (60%).
Analysis $C_{19}H_{23}NO_6$	**:**	Calculated: C: 63.13, H: 6.41, N: 3.87 Found: C: 63.27, H: 6.59, N: 4.03

***Synthesis of (3S, 4R, 5R, 6S, 7R, 8R) Acetic acid 2', 2'-dimethyl-5'- (4-oxo-3-phenoxy-azetidin-5'-yl)- tetrahydrofuro[2',3'-d][1',3']dioxol-6'ylester* 3.15**

To a solution of **3.5** (0.24 g, 0.51 mmol) in 15 ml acetonitrile, was added a solution of CAN (0.84 g, 1.53 mmol) in water (10 ml) 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 10% sodium bicarbonate solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated and column chromatography of the crude provided the product **3.15** as a gummy substance (0.14g, 77.77%).

MP:	**:**	Gum
[a]$_D^{27}$	**:**	-205.17 (c = 1, $CHCl_3$)
IR ($CHCl_3$):	**:**	3415, 3018.39, 2925.81, 2854.45, 1747.39
^{1}H NMR ($CDCl_3$): (200 MHz)	**:**	***1.33 (s, 3H), 1.52 (s, 3H), 2.05 (s, 3H), 4.07-4.22 (m, 2H), 5.36 (d, J = 3.4 Hz), 5.94 (d, 1H, J = 3.4 Hz), 6.47 (s, 1H), 7.01 - 7.35 (m, 5H)***

^{13}CNMR (CDCl3):	**:**	20.39, 25.98, 26.42, 52.29, 76.69, 79.13, 81.15, 83.54, 104.13, 112.18, 115.71, 122.43, 129.38, 157.21, 166.54, 169.26

Ms	**:**	363 (2%), 348 (18%), 320 (22%), 260 (42%), 231 (32%), 218 (16), 202 (8%), 191 (17%), 149 (100%), 131 (27%), 105 (12%), 94 (19%), 77 (42%)
Analysis	**:**	Calculated: C: 59.48, H: 5.82, N: 3.85
$C_{18}H_{21}NO_7$		Found: C: 59.69, H: 6.02, N: 3.97

3.16 Synthesis of (3S, 3a'R, 4R, 5R, 6S, 6a'R) [2-(6'-Allyloxy-2', 2'-dimethyl-tetrahydro-furo [2', 3'-d][1', 3'] dioxol-5'yl)-4-oxo-3-phenoxyazetidin-1-yl]-acetic acid ethyl ester.

To a solution of the β-lactam **3.12** (0.78 g, 2.16 mmol) in anhydrous THF (10 ml) was added to 50% suspension of NaH in mineral oil at 0 ^{0}C and refluxed for 2 hrs. The reaction was then cooled to 0 ^{0}C and a solution of ethyl bromoacetate (1.19 ml, 0.01 mol) in anhydrous THF (10 ml) was added slowly. The reaction mixture was then refluxed gently for 8 hrs. The excess reagent was quenched at 0 ^{0}C with MeOH (5 ml), diluted with excess of water and extracted with EtOAc (3x25 ml). The organic layers were then washed with water, sat brine soln, dried over Na_2SO_4, filtered and concentrated to get the crude ethyl carboxylate. The excess of ethyl bromoacetate was then removed by adsorption on silica gel and elution with pet ether (60-80^0 C). Elution with 10% EtOAc/Pet ether and concentrating the solvents on the rotary evaporator afforded the pure compound **3.15** as an oil (0.67 g, 70%).

MP	**:**	Oil
$[\alpha]_D^{25}$	**:**	-96.01 (c = 0.72, $CHCl_3$)
IR ($CHCl_3$)	**:**	1730, 1749
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.29 (m, 9H), 1.50 (s, 3H), 3.68 (dd, 1H, J = 5.3 Hz, 6.9 Hz), 4.00 (m, 2H), 4.17 (dd, 1H, J = 3.9 Hz, 3.4 Hz), 4.38 (dd, 1H, J = 4.9 Hz), 4.53 (dd, 1H, J = 5.3 Hz, 3.4 Hz), 5.15 (m, 3H), 5.40 (d, 1H, J = 4.9 Hz), 5.70 (m, 1H), 5.90 (d, 1H, J = 3.9 Hz), 6.90 (m, Ar)
^{13}CNMR (CDCl3)	**:**	13.78, 25.94, 26.46, 42.45, 57.08, 61.05, 70.31, 80.01, 80.60, 81.78, 104.64, 115.23, 115.45, 117.21, 122.03, 129.23, 133.46, 157.13, 165.66, 167.64

Ms	**:**	$M^{+\cdot}$ 447 (100%), 417 (23%), 368 (34%), 327 (17%), 313 (43%), 298 (12%).
Analysis	**:**	Calculated: C: 47.67, H: 8.93, N: 4.28
$C_{23}H_{29}NO_8$		Found: C: 47.83, H: 9.07, N: 4.40.

3.7 : References

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Chapter 4

Diastereoselective Staudinger reaction using imines derived from

3-Amino-3-Deoxy-1,2:5,6-diisopropylidene-α–D-glucofuranose

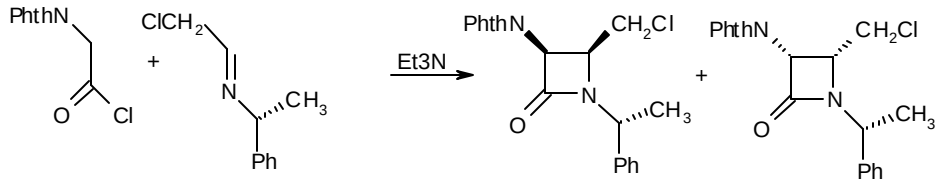
4.1 : Abstract

This chapter deals with the stereoselective synthesis of β-lactam using imines derived from 3-amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-glucofuranose. The imines were synthesized from glucose diacetonide in 4 steps. These imines underwent a highly stereospecific *Staudinger reaction* with ketenes to form a single diastereomer of β-lactam with *cis* stereochemistry. The *cis* stereochemistry was ascertained from the coupling constants (^{1}H NMR) of the C-3 and C-4 protons (J=5-6 Hz).

4.2 : Introduction

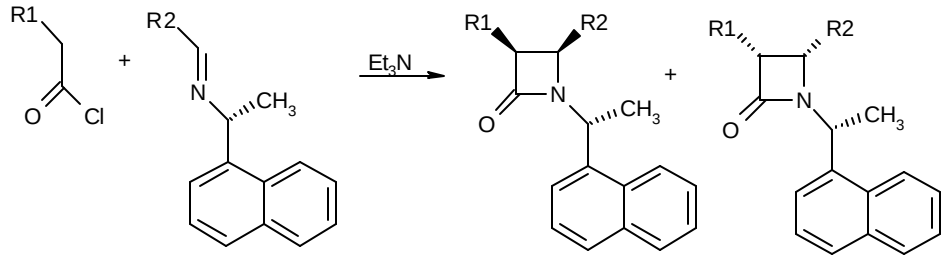
The imines derived from chiral aldehydes were known to proceed with total diastereoselectivity and is widely explored[1]. The extent of diastereoselectivies induced by the imines derived from chiral amines in the *Staudinger reaction* is less exploited. The limited examples revealed only moderate selectivity. Various researchers have reported use of imines derived from the readily available and inexpensive optically active α-methylbenzyl amine in the Staudinger reaction[2-4]. However, moderate diastereoselectivities were observed with these imines. The best result was obtained in the reaction between phthalimidoacetyl chloride and the imine derived from α-chloroacetyaldehyde, which gave isomeric mixture of *cis:trans* β-lactams in the ratio of 9:10 (**scheme-4.1**). The isomeric ratio was found to be dependent on the solvent used, chloroform gave the best results.

Scheme-4.1



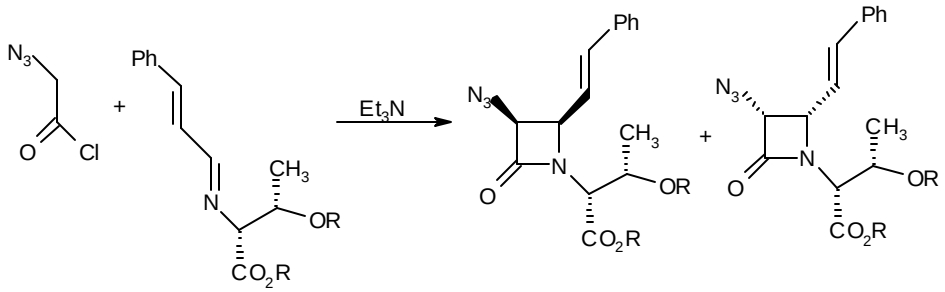
The closely related but more expensive 1-napthylethylamine was found to give similar results. However, benzene, toluene, and chlorobenzene were found to be the best solvents for this reaction and gave about 83:17 ratio of diastereomers[5,6] (**Scheme-4.2**).

Scheme -4.2



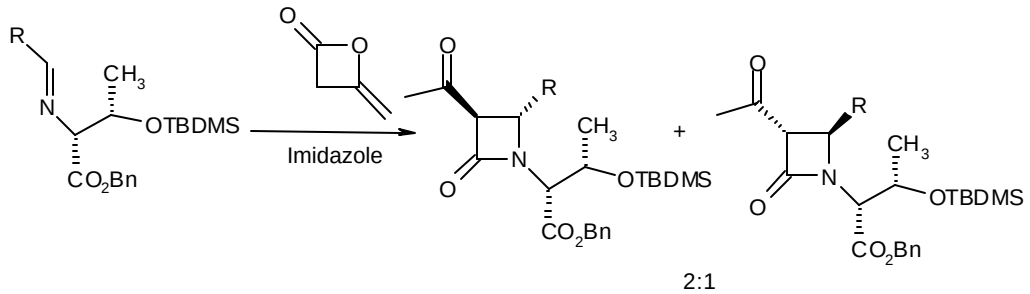
Amino acid derived imines were extensively exploited by various groups[7]. Bose et al effectively used the imines derived from D-threonine and it was observed that the diastereoselectivities depended on the size of the hydroxyl-protecting group (**Scheme -4.3**).

Scheme -4.3



Reaction of diketenes with imines derived from propargyl aldehydes and TBDMS ether of D-threonine offered two *trans* diastereomers in the 2:1 ratio (**scheme -4.4**).

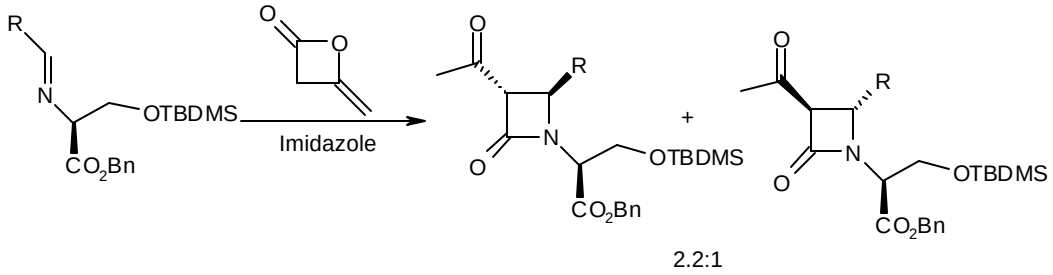
Scheme -4.4



Hirai and Fujimoto observed that cycloaddition of a propargylidene schiff's base derived from L-serine with diketenes gave a mixture of *trans* and *cis* β-lactams (**scheme -4.5**) in

the ratio of 2.2:1[9]. While contradictory reports from Just and Liak[10,11] claimed that the chiral auxiliary of the protected L-serine cinnamaldimine schiff's base racemised in the reaction with azidoacetyl chloride and triethylamine.

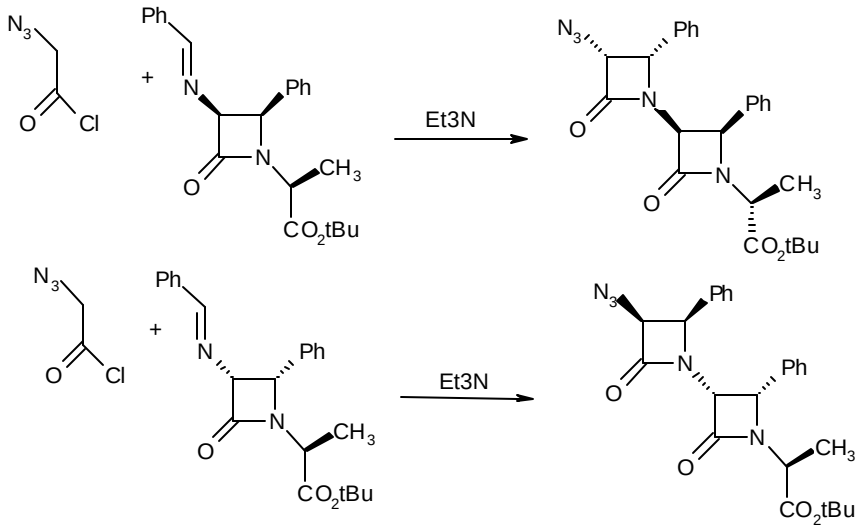
Scheme -4.5



2.2:1

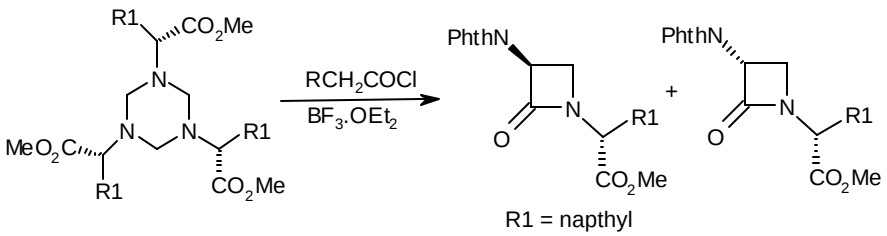
Hatanaka and Ojima have reported a stereospecific cycloaddition reaction of azidoketene to the imines bearing a chiral β-lactam as the back-bone (**scheme -4.6**), which in turn was synthesized from t-butyl alaninate[10].

Scheme -4.6



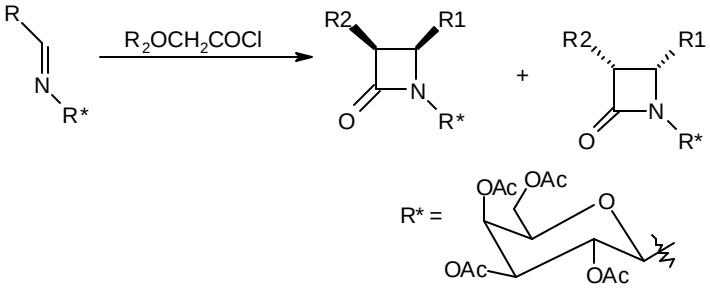
The asymmetric synthesis of 4-unsubstituted β-lactams was achieved from a triazine in the presence of $BF_3.OEt_2$. Maximum selectivity of 10:1 was achieved with phthalimidoketene and α-napthylglycine[11] (**Scheme -4.7**).

Scheme -4.7



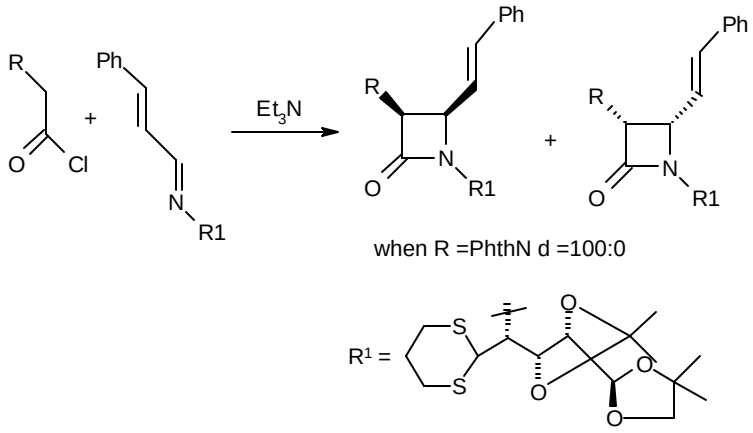
George et al used carbohydrate-derived imines as the chiral auxiliary and achieved moderate selectivities (**Scheme -4.8**).

Scheme -4.8



Barton et al[13] utilized chiral imines derived from 3,4:5,6-di-O-isopropylidene-glucosamine propanedithioacetal and cinnamaldehyde. Virtually total selectivity was obtained in this approach using phthalimidoketene.

Scheme -4.9



4.3 : Present work

We envisaged that the imines derived from glucose diacetonide with the bulky acetonide protecting groups will differentiate the two faces of the ketene to ensure a highly diastereoselectivity in β-lactam ring formation. Therefore, we decided to utilize the imines derived from 3-amino-3-deoxy-1, 2:5,6-diisopropylidene-α-D-glucofuranose in the [2+2] cycloaddition reaction.

4.4 : Results and discussions

Earlier reports have clearly shown that the use of imines derived from chiral amines in the [2+2] cycloaddition reaction leads to none to modest asymmetric induction. A good amount of stereo control was observed whenever one face of the imine was blocked by bulky protecting groups of the chiral amine. Hence we envisioned that the sugar derived amine, 3-amino-1, 2:5,6-diisopropylidene-α-D-glucofuranose **4.3** with the two bulky acetonide groups should sufficiently differentiate the two faces of the imine and induce good levels of stereoselectivity in the [2+2] cycloaddition reaction.

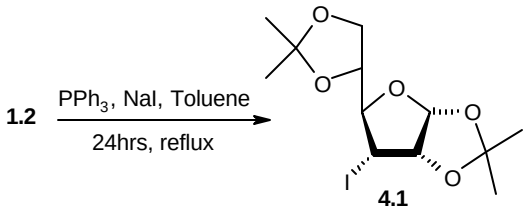
The amine **4.3** was synthesized from D-glucose in four steps. The chiral amine was very reactive and readily formed the imines **4.4a,b** with the aldehydes (cinnamaldehyde and benzaldehyde). Cycloaddition with phenoxyacetylchloride and acetoxyacetylchloride in presence of triethylamine at 0 ^{0}C afforded the β-lactams **4.5a-c** in high yields (75-79%). The ^{1}H NMR spectrum of the crude displayed a single set of diastereomer indicating formation of only one diastereomer. The coupling constants of the C-3 and the C-4 protons indicated *cis* stereochemistry (J = 5-6 Hz).

Unfortunately, none of the compounds could provide X-ray quality crystals, and so the relative configuration of the β-lactams with respect to the absolute stereochemistry of the sugar could not be established.

4.4.1 Preparation of the Iodide **4.1**

The diacetonide **1.2** was converted into iodide **4.1** using reported procedure[14]. The diacetonide **1.2** was refluxed in toluene in the presence of NaI and triphenyl phosphine for 24 hrs. After the completion of the reaction (TLC), the reaction mixture was worked up as usual and resultant product was purified by column chromatography to provided pure iodide **4.1** (**Scheme-4.10**).

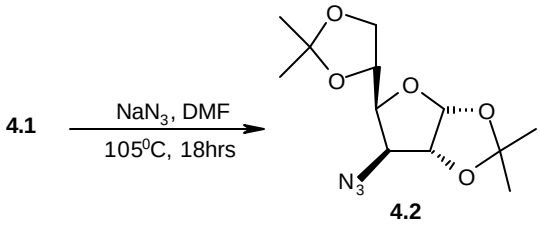
Scheme-4.10



4.4.2 Preparation of the azide 4.2

The iodide **4.1** was dissolved in DMF and treated with sodium azide and heated to 105 ^{0}C for 18 hrs. The solvent was then removed by distillation under reduced pressure and the residue was extracted with $CHCl_3$. The organic extract was then washed thoroughly with water, dried over Na_2SO_4 and filtered. The filtrate upon concentration provided the crude azide **4.2** (**Scheme-4.11**), which was purified by column chromatography.

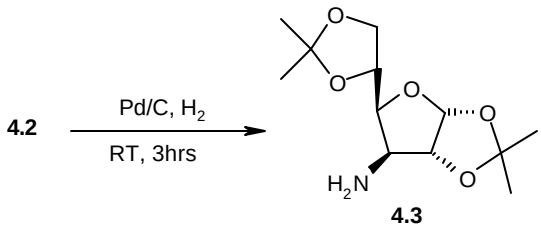
Scheme-4.11



4.4.3 Preparation of the amine*4.3*

A suspension of Pd/C (10%) and the azide **4.2** was taken in MeOH and stirred at RT for 3 hrs in hydrogen atmosphere. After the completion of the reaction the catalyst was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to afford the pure amine **4.3** (**Scheme-4.12**).

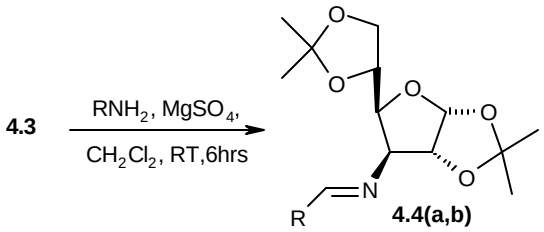
Scheme-4.12



4.4.4 Preparation of the imines **4.4a, b**

The imines **4.4a,b** were prepared by treating the amine **4.3** with the aldehydes, (cinnamaldehyde and benzaldehyde) in presence of $MgSO_4$ (**Scheme -4.13**).

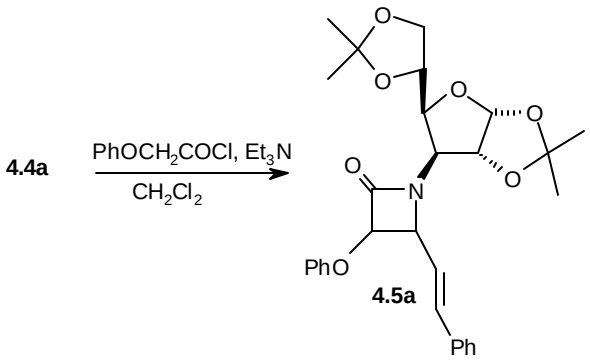
Scheme -4.13



4.4.5 Preparation of the β**-lactam** ***4.5a***

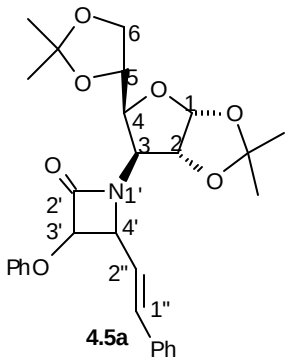
A solution of phenoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine **4.4a** and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere. The resulting solution was warmed up to RT and stirred for 12 hrs. After the usual workup and purification by column chromatography yielded pure β-lactam **4.5a** in 70% yield as a white solid (**Scheme-4.14**).

Scheme-4.14



The IR spectrum of this compound showed a strong band at 1758.96 cm^{-1} indicating the presence of the β-lactam carbonyl. The ^{1}H NMR of the crude compound indicated that it is a single diastereomer as only one set of signals were observed. The methyl protons of the 2 isopropylidene groups appeared at 1.24, 1.30 1.31 and 1.50 as four singlets integrating for 3 protons each.

The H-1 proton (anomeric) of the sugar appeared as a doublet at 5.90 (J = 3.9 Hz). The H-2 proton of the sugar appeared as a doublet at 4.67 (J = 3.9 Hz). The H-3, H-4, H-5, and the methylene protons at C-6 appeared as a five-proton multiplet from4.03 to 4.22. The β-lactam H-3' proton appeared at 5.41 as a doublet (J = 4.9 Hz), while the H-4' ring proton appeared as a dd at 4.59 (J = 4.9 & 4.4 Hz).



4.5a

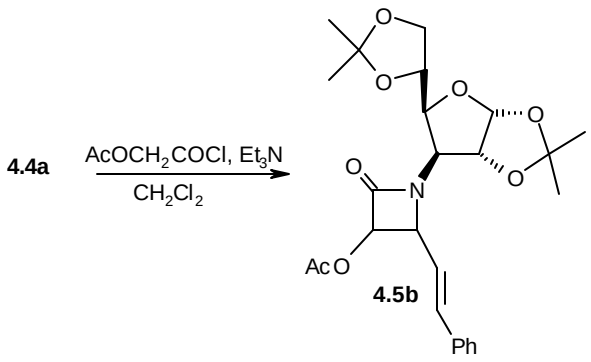
The H-2'' proton appeared at 6.36 as a dd with high coupling constants (J = 4.4 & 15.7 Hz), and the H-1'' proton resonated at 6.77 as a doublet (J = 15.7 Hz)

In the ^{13}C NMR spectrum of this compound the β-lactam carbonyl appeared at 164.85.The four methyl carbons of the diacetonide appeared in the regions 25.06, 25.83, 26.38, 26.68 integrating for three protons each. The β-lactam C-3' carbon resonated at 80.31, while the C-4' carbon appeared at 58.40. The two carbons of the styryl were seen at 123.06 and 126.58. The mass spectral analysis of the compound showed the base peak at 356 (100%) and the molecular ion peak M+. at 507 (5%). This compound provided satisfactory elemental analysis.

4.4.6 Preparation of the b-lactam *4.5b*

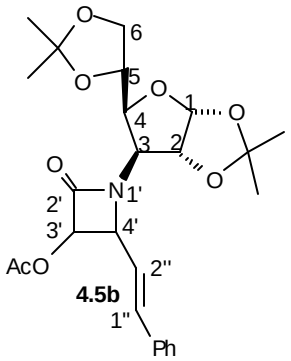
A solution of acetoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine **4.4a** and triethylamine in methylene chloride at 0 ^0C under argon atmosphere. The resulting solution was warmed up to RT and stirred for 12 hrs. After the usual workup and column chromatographic purification provided the pure β-lactam **4.5a** in 80% yield (**Scheme-4.14**).

Scheme-4.14



The IR spectrum of this compound showed a strong band at 1751.53 cm^{-1} indicating the presence of the β-lactam. The ^{1}H NMR of the crude compound showed that it is a single diastereomer.

The methyl protons of the 2 isopropylidene groups appeared at 1.22, 1.29 1.31 and 1.48 as four singlets integrating for 3 protons each. The H-1 proton (anomeric) of the sugar appeared as a doublet at 5.88 (J = 3.4 Hz). The H-2 proton of the sugar appeared as a doublet at 4.66 (J = 3.9 Hz). The H-3, H-4, H-5 and the methylene protons at C-6 appeared as a five-proton multiplet from 4.16 to 3.99.The β-lactam H-3' proton appeared at 5.07 as a doublet (J = 4.9 Hz), while the H-4' ring proton appeared as a dd at 4.47 (J = 4.9 & 4.4 Hz). The H-2'' proton appeared at 6.41 as a dd with high coupling constants (J = 4.4 & 16.1 Hz), and the H-1'' proton resonated at 6.68 as a doublet (J = 16.1 Hz).



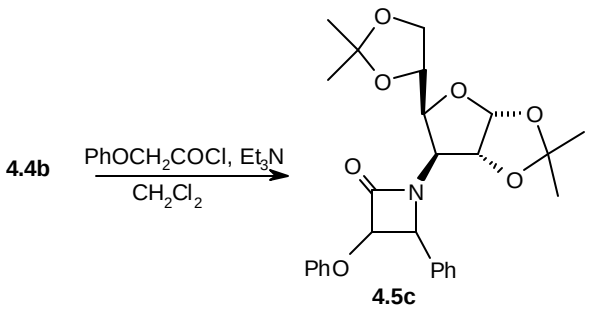
In the ^{13}C NMR spectrum of this compound was recorded in DMSO-d6. The β-lactam carbonyl appeared at 168.83 and the acetate was seen at 168.98. The four-methyl carbons of the diacetonide resonated in the regions 25.50, 25.99, 26.47, and 26.95. The methyl carbon of the acetate resonated at 56.28. The β-lactam C-3' carbon resonated at 83, while the C-4' carbon appeared at 63.96. The two carbons of the styryl were seen at 126.30 and 126.85. The aromatic carbons resonated in between 126.30 to 168.98.

The mass spectral analysis of the compound showed the molecular ion peak $M^{+\cdot}$ at 473 (7%), and the base peak at 399 (100%). This compound provided satisfactory elemental analysis.

4.4.7 ***Preparation of the b-lactam* 4.5c**

A solution of phenoxyacetyl chloride in anhydrous methylene chloride was added to a solution of the imine **4.4b** and triethylamine in methylene chloride at 0 ^{0}C under argon atmosphere. The resulting solution was warmed up to RT and stirred for 12 hrs. After the usual workup and column chromatography gave pure β-lactam **4.5c** in 75% yield (**Scheme -4.14**).

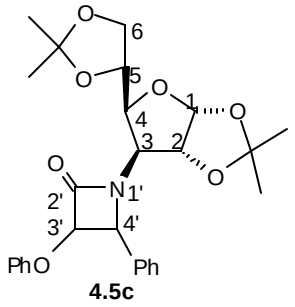
Scheme -4.14



4.5c

The IR spectrum of this compound (**4.5c**) showed a strong band at 1749 cm^{-1} typical of β-lactam carbonyl. The ^{1}H NMR of the crude compound showed that it is a single diastereomer. The methyl protons of the 2-isopropylidene groups appeared as two singlets at 1.39, and 1.44 integrating for 6 protons each. The H-1 proton (anomeric) of the sugar appeared as a doublet at 5.11 (J = 3.9 Hz). The H-2 proton of the sugar appeared as a doublet at 4.51 (J = 3.4 Hz). The H-3, H-4, H-5 and the methylene protons at C-6 appeared as two sets of multiplets in the regions 4.18 to 4.25 integrating for 2 protons, and at 4.00 to 4.10 integrating for three protons.

The β-lactam H-3' proton appeared at as a doublet at 5.09 (J = 4.9 Hz). The H-4' proton appeared as a doublet at 4.29 (J = 4.9 Hz)



4.5c

In the ^{13}C NMR spectrum of this compound the β-lactam carbonyl appeared at 165.84. The four-methyl carbons of the diacetonide resonated at 25.24, 25.61, 26.24, and 26.75 giving 4 signals. The β-lactam C-3' carbon resonated at 80.27, while the C-4' carbon appeared at 67.92. The C-1 (anomeric) carbon appeared at 109.82. The aromatic carbons appeared in the region 111.66 to 156.65. The aromatic carbon attached to oxygen resonated down field at 156.65. All the other carbons resonated in the expected regions. The mass spectrum of this compound showed the molecular ion peak at $M^{+\cdot}$ 481 (17%),

and the base peak at 134 (100%). This compound provided satisfactory elemental analysis.

4.5 : Conclusion

These results demonstrate that high diastereofacial selectivity in the ketene-imine cycloaddition reaction can be achieved by the use of homochiral amines with the necessary steric bulk.

4.6 : 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 and stored over 4Å molecular sieves. DMF was freshly distilled under reduced pressure just before use.

4.6.1 Synthesis of (1R, 2R, 3R, 4R, 5S)-3-Deoxy-3-iodo-1,2:5,6-di-O-isopropylidene-α-D-allofuranose **4.1**

A mixture of glucose diacetonide **1.2** (5g, 19.23 mmol), triphenylphospine (15.1 g, 57.69 mmol), imidazole (3.9 g, 57.35 mmol), and iodine (9.7 g, 38.15 mmol), toluene (375 ml) was refluxed for 18 hrs. The reaction mixture was then washed with sat. $NaHCO_3$ soln (25 ml), $Na_2S_2O_3$ (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 phospine oxide. Column chromatography of the crude provided the pure iodide **4.1** (4.98 g, 70%).

^{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 and 4.4 Hz), 4.06 (m, 2H), 4.23 (m, 2H), 4.59 (t, 1H, J = 3.9 Hz), 5.81 (d, 1H, J = 3.4 Hz).

4.6.2 Synthesis of (1R, 2R, 3S, 4R, 5S)-3-Azido-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **4.2**

A solution of iodide **4.1** (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 on a Kugelrohr apparatus. 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 **4.2** as a semisolid (yield 1.24 g, 65.60%).

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.32 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.51 (s, 3H), 3.96 (dd, 1H, J = 4.7 Hz each), 4.08 to 4.28 (m, 4H), 4.61 (d, 1H, J = 3.7 Hz), 5.85 (d, 1H, J = 3.6 Hz).

4.6.3 Synthesis of (1R, 2R, 3S, 4R, 5S)-3-Amino-3-deoxy-1, 2: 5,6 di-O-isopropylidene a **-D- glucofuranose *4.3***

The azide **4.2** (1 g, 3.5 mmol), was dissolved in methanol (15 ml) and treated with 10% Pd/C (0.1 g, Aldrich) and stirred at RT for 3 hrs under hydrogen atmosphere. The catalyst was then filtered over celite in a sintered crucible, and the filtrate was concentrated under reduced pressure afforded the pure amine **4.3** as oil (0.908 g, 100%).

IR ($CHCl_3$) : 3587.35, 3380.98, 3321.19

^{1}H NMR ($CDCl_3$) : 1.30 (s, 6H), 1.35 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 3.55 (d, 1H, J = 3.5 Hz), 3.97 (m, 2H), 4.14 (m, 2H), 4.40 (d, J = 3.4 Hz), 5.89 (d, 1H, J = 3.4 Hz).

(200 MHz)

***4.6.4 General procedure for the synthesis of imines* 4.4a-b**

To a solution of the amine **4.3** in CH_2Cl_2, and anhydrous $MgSO_4$, was added a solution of the aldehyde (cinnamaldehyde, benzaldehyde) in CH_2Cl_2. The mixture was stirred for 6-8 hrs (TLC). The mixture was filtered through a pad of celite. The filtrate was concentrated to get the imines **4.4a-b**, which were used as such for the β-lactam formation.

4.6.5 General procedure for the synthesis of b-lactams

A solution of the acid chloride in methylene chloride was added to a solution of the imines **4.4a-b** and triethylamine in CH_2Cl_2 (20 ml) at 0 ^{0}C. After the addition was completed the reaction mixture was 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 the crude β-lactams **4.5a-c**, which were then purified by column chromatography using silica gel (60-120 mesh).

Synthesis (1R, 2R, 3S, 4R, 5S)-1-[5-(2,2-Dimethyl-[1,3] dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3] dioxol-6 yl]-3phenoxy-4-styryl-azetidin-2-one

4.5a

The imine **4.4a** (0.33 g, 1 mmol) on treatment with phenoxyacetyl chloride (0.25 g, 0.207 ml, 1.5 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-Lactam **4.5a** as a single isomer (0.32 g, 70%) as a white solid.

MP : 182^0 C

IR ($CHCl_3$) : 1758.96

-13.75 (c = 0.85, $CHCl_3$).

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.24 (S, 3H), 1.30 (S, 3H), 1.31(S, 3H), 1.50 (S, 3H), 4.03-4.22 (m, 5H), 4.59 (dd, 1H, J = 4.9 Hz, 4.4 Hz), 4.67 (d, 1H, J = 3.9 Hz), 5.41(d, 1H, J = 4.9 Hz), 5.90 (d, 1H, J = 3.9 Hz), 6.23 (dd, 1H, J = 9.2 Hz, 9.7 Hz), 6.77 (d, 1H, J = 15.7 Hz).

^{13}C NMR ($CDCl_3$) : 25.06, 25.83, 26.38, 26.68, 58.40, 63.25, 67.63, 72.77, 76.38, 80.31, 82.18, 83.69, 105.19, 109.49, 111.63, 115.67, 122.18, 123.06, 126.55, 128.46, 129.31, 135.74, 136.92, 157.21, 164.85.

MS : M+. 507 (5%), 492 (15%), 414 (12%), 399 (42%), 390 (52%), 356 (100%), 322 (48%), 298 (72%), 266 (44%).

Analysis : Calcd for $C_{26}H_{29}NO_7$: C: 68.60; H: 6.55; N: 2.76.

Found: C: 68.78; H: 6.37; N: 2.85.

***Synthesis of (1R, 2R, 3S, 4R, 5S)-1- [5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxol-6-yl]-2-oxo-4-styryl-azetidin-3ylester* 4.5b**

The imine **4.4a** (0.33g, 1mmol) on treatment with acetoxyacetyl chloride (0.25g, 0.207ml, 1.5mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) provided the β-lactam **4.5b** as a single isomer (0.32 g, 70%) as a white solid.

MP : 198^0 C

IR ($CHCl_3$) : 1751.53

-21.21 (c = 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.22 (S, 3H), 1.29 (S, 3H), 1.31 (S, 3H), 1.48 (S, 3H), 2.18 (S, 3H), 4.16-3.99 (m, 5H), 4.47 (dd, 1H, J = 4.9 Hz, 4.4 Hz), 4.66 (d, 1H, J = 3.9 Hz), 5.07 (d, 1H, J = 4.9 Hz), 5.88 (d, 1H, J = 3.4 Hz), 6.41 (dd, 1H, J = 4.4 Hz and 16.1 Hz), 6.68 (d, 1H, J = 16.1 Hz).
^{13}C NMR (DMSO-d_6)	**:**	25.50, 25.99, 26.47, 26.95, 56.28, 63.96, 69.14, 78.22, 78.74, 83, 104.58, 111.01, 126.30, 126.85, 128.29, 128.98, 135.31, 136.48, 168.83, 168.98
Mass	**:**	$M^{+\cdot}$ 473 (7%), 458 (32%), 430 (17%), 415 (27%), 399 (100%), 358 (21%), 339 (28%)
Analysis Calcd	**:**	Calcd for $C_{26}H_{29}NO_7$ C: 63.39; H: 6.00; N: 2.95
		Found C: 63.48; H: 6.18; N: 3.11

Synthesis of (1R, 2R, 3S, 4R, 5S)-1-[5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-d][1,3]dioxol-6-yl]-3,4-diphenyl-azetidin-2-one **4.5c**

The imine **4.4b** (0.4 g, 1.15 mmol) on treatment with phenoxyacetylchloride (0.29 g, 0.238 ml, 1.72 mmol) in the presence of triethylamine (0.52 g, 0.72 ml, 5.18 mmol) provided the β-Lactam **4.4c** as a single isomer ().

MP	**:**	Gum
IR ($CHCl_3$)	**:**	1749
		-33.17 (c = 0.90, $CHCl_3$)
^{1}H NMR ($CDCl_3$) (200 MHz)	**:**	1.39 (S, 6H), 1.44 (S, 6H), 4.00- 4.10 (m, 3H), 4.18-4.25 (m, 2H), 4.29 (d, 1H, J = 4.9 Hz), 4.51 (d, 1H, J=3.4 Hz), 5.09 (d, 1H, J = 4.9 Hz), 5.11 (d, 1H, J = 3.9 Hz)
^{13}C NMR ($CDCl_3$)	**:**	25.24, 25.61, 26.24, 26.75, 57.74, 64.39, 67.92, 72.92, 80.27, 81.89, 82.18, 104.61, 109.82, 111.66, 114.57, 115.52, 122.03, 128.02, 129.12, 129.38, 133.06, 156.65, 165.84
Mass	**:**	$M^{+\cdot}$ 481 (17%), 466 (21%), 408 (7%), 347 (10%), 317 (12%), 285 (27%), 134 (100%), 77 (43%), 91 (18%).
Analysis	**:**	Calcd for $C_{26}H_{29}NO_7$ C: 65.90; H: 6.42; N: 3.07;
		Found C: 66.01; H: 6.64; N: 3.30;

4.7 : References

1. a.) Hubschwerlen, C,; Schimid, G. *Helv. Chim.Acta.,* **1983,** *66*, 2206. b.) Wagle, D. R; Garai, C.; Chiang, J.; Monteleone, M. G.,; Kurys, B. E.; Stromeyer, T. W.; Hegde, V.R.; Manhas, M. S.,; Bose, A.K. *J.Org.Chem***, 1988,***53*, 4227.
2. Thomas. R. C. *Tetrahedron Lett,* **1989**, *30*, 5239.
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4. Asjodi, J. ; Bonnet, A.,; Chantot, J. F.,; Costerousse, G.; Teutsch, G in *Recent advances in the chemistry of b-lactam Antibiotics*; BentleyP. H. ; Southgate.R. Eds; Roy. Soc.Chem.; London, **1989,**pp 350-364.
5. D. H.R. Barton A.Gatau-Olster, J. Anaya-Mateos, J. Cleophax, S.D. Gero, A. Chiaroni, C. Riche, *J. Chem. Soc., Perkin Trans1.,* **1990,** 3211-3212. J.I.M.Hernando, N.M.Laso, J.Anaya, S.D. Gero, M. Grande, *Synlett***, 1997**, 281-282. J. Anaya, S.D. Gero. M. Vander veen, S.S.Bari, D.R. Wagle, *Tetrahedron*, **1992**, *48*, 4831-4844.
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7. T. E. Gunda, F. Sztaricskai, *Tetrahedron***, 1997,** *53*, 7985-7998.

Chapter 5

Use of Acid Activators for the Synthesis of β-Lactams

Section A: *Stereoselective Synthesis of β-Lactams Using Trichloroacetonitrile-Triphenylphosphine as Acid Activators*

Section B: *Hexachloroacetone-Triethylphospite, a Novel Acid Activator in the Stereocontrolled Staudinger Reaction*

5.1 : Abstract

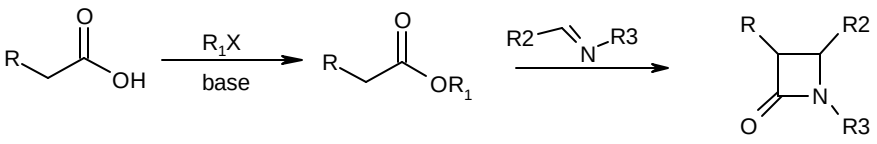
This chapter consists of two sections. *Section-A* ***deals with the use of trichloroacetonitrile and triphenylphospine as acid activators in the Staudinger reaction, while*** *section-B* ***deals with the use of hexachloroacetone -triethylphosphite as acid activators. Both the sections deal with the*** **in situ** ***generation of acid chlorides from various carboxylic acids and their annulations with imines*** **via** ***[2+2] cycloaddition reaction to provide the*** *b* ***-lactams with exclusive*** **cis** ***stereochemistry. The*** **cis** ***stereochemistry was ascertained from the coupling constants of the C-3 and C-4*** *b* ***-lactam ring protons (J = 5-6 Hz).***

5.2 : Introduction

One of the most efficient methods for the construction of the β-lactam ring is the reaction between an activated carboxyl acids with an imine in the presence of a tertiary base[1]. This reaction, which is often referred to as the Staudinger reaction, typically proceeds with good stereoselectivity[2], depending on reaction conditions[3] and substituents[4].

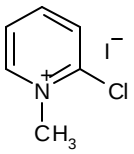
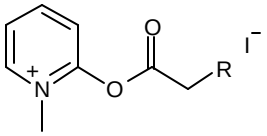
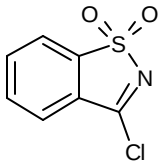
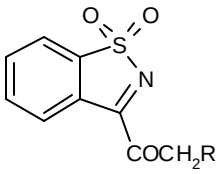
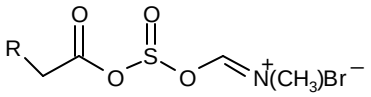
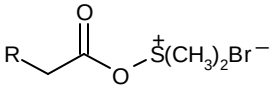
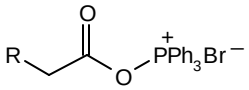
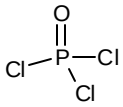
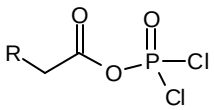
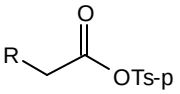
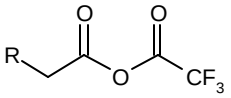
In addition to the utilization of acid chlorides[2] and the *in situ* formation of acid halides, a variety of other methods have been described to activate carboxylic acids for in *it situ* generation of ketenes (**Scheme -5.1**). This is particularly convenient strategy when the acid chloride is not commercially available, difficult to prepare or explosive as is the case with azidoacetyl chloride.

Scheme -5.1



An alternate synthesis of β-lactam that circumvents the use of acid chlorides involves the use of carboxylic group activating agents. Acid activating agents include several phosphorous derived reagents[7], ethyl chloroformate[8], trifluoroacetic anhydride[9] and p-toluenesulphonyl chloride[10]. In 1979, Manhas [12] has reported the use of readily available Mukaiyama reagent[12] (2-chloro-N-methylpyridiniumiodide) as an activating agent in the reaction between carboxylic acids and imines in the presence of triethylamine in refluxing dichloromethane, to yield β-lactams in moderate yields (~55%). **Table -5.1** shows various reagents that have been used as carboxylic acid activator in the Staudinger reaction.

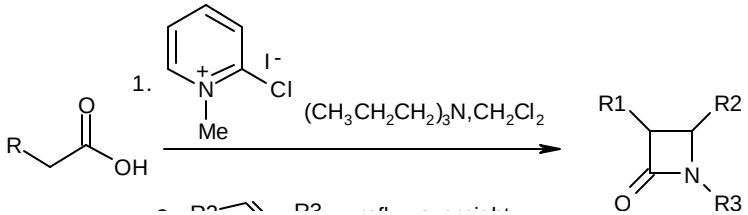
Table -5.1: Reagents that have been used as carboxylic acid activator in the Staudinger reaction.

Reagents	Possible reactive intermediates
	
	
$SOCl_2$-DMF	
$(CH_3)_2SBr_2$	
Ph_3PBr_2	
	
p-TsCl	
$(CF_3CO)_2O$	

It has been observed that the reactions carried out with acid activating agents generally follow the same stereo chemical pattern of the resulting β-lactams as observed in the reactions with acid chlorides.

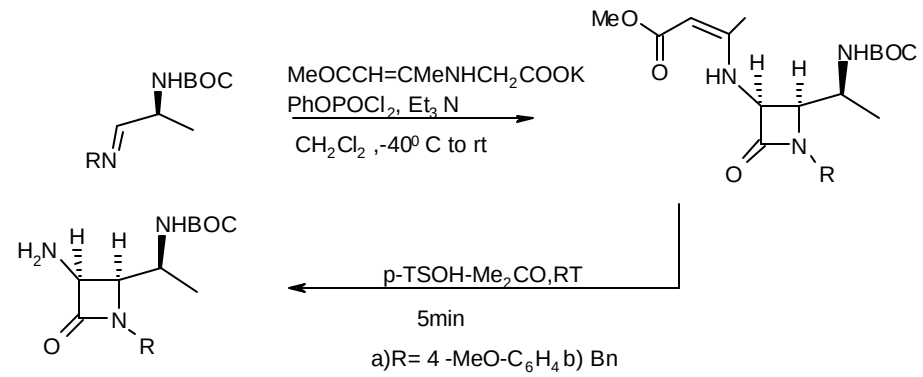
Georg has reportd an improved methodology by using 2-chloro-N-methylpyridinium iodide as an activating agent with tripropylamine as a base to synthesize multi substituted β–lactams (**Scheme -5.2**).

Scheme -5.2



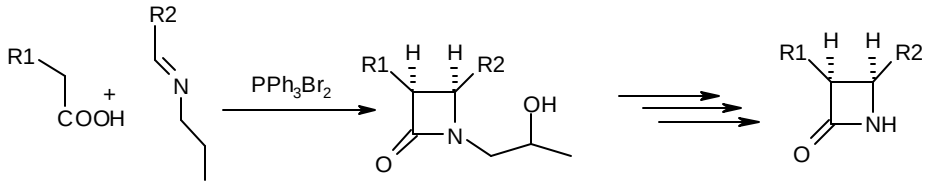
Palomo et al have reported an efficient synthesis of some α-amino-β–lactams from Dane's salts and imino compounds. Treatment of a Dane's salt of amino acids and an appropriate imine in equi-molar quantities with phenyl dichlorophosphate in the presence of triethylamine gave the corresponding 3-vinylamino-β–lactams. Hydrolysis of the side chain with PTSA in acetone-water followed by the acylation with acid chloride provided 3-amido-β–lactams (**scheme-5.3**).

Scheme-5.3



Palomo et al have also used triphenylphosphine dibromide and dimethyl sulphide dibromde for the direct synthesis of variously substituted β-lactams in moderate yields (40-60%) (**Scheme-5.4**).

Scheme-5.4



Section A : Stereoselective synthesis of b-Lactams using Trichloroacetonitrile- Triphenylphosphine as acid activators

5.3a : Present Work

Among the several methods for the synthesis of β-lactams, the cycloaddition reaction of ketenes with imines (*Staudinger reaction*) for the construction of β-lactam ring has found wide acceptance. This is mainly because of its simplicity, predictability of stereo chemical outcome and proven utility of this method for the synthesis of a large number of monocyclic, bicyclic, tricyclic and spiro cyclic β-lactams.

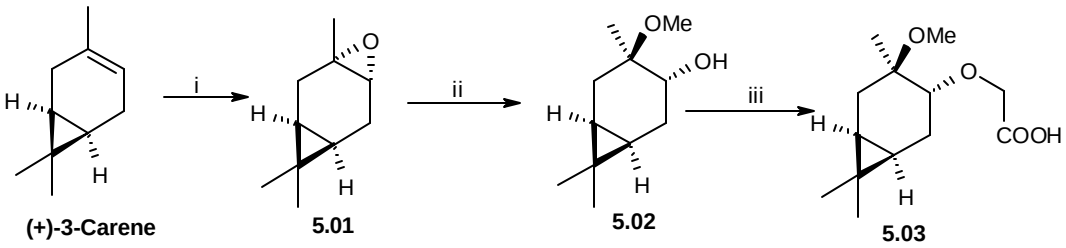
The ketenes are usually generated from acid halides (preformed or generated *in situ*) in the presence of tertiary amines. Alternatively acid activating agents, like ethyl chloroformates, trifluoroacetic anhydride, p-toluenesulfonyl chloride, phosphorus derived reagents, Mukaiyama reagent, cyanuric chloride, and several others have been used. This section decides the application of trichloroacetonitrile-triphenylphosphine as a mild reagent for *in situ* generation of acid chlorides from carboxylic acids and their utility for the synthesis of azetidin-2-ones (β-lactams) *via* ketene-imine cycloaddition reaction.

5.4a : Results and discussions

5.4a.1 Preparation of acid **5.03**

The (+)-3-carene oxide **5.01** was opened with methanolic PTSA to afford methoxy alcohol **5.02** in excellent yield. The alcohol **5.02** on alkylation with chloroacetic acid in presence of NaH in dry toluene gave acid **5.03** (**Scheme -5.5**) in 62% yield, which was purified by distillation, b.p. 180 °C/10mm.

Scheme -5.5



(+)-3-Carene **5.01** **5.02** **5.03**

Reagents and conditions: i.)ClCOOEt/H_2O_2/Na_3PO_4, CH_2Cl_2 ii.) CH_3OH, PTSA, 2h
iii.) Na/$ClCH_2COOH$, Toluene

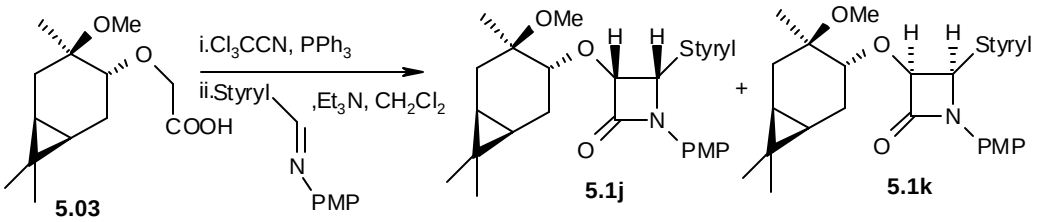
The ^1H NMR spectrum of **5.03** showed two singlets at 0.95 and 1.05 for the *gem* dimethyl group of the carene moiety. The angular methyl and methoxy groups were

observed at 1.25 and 3.38 respectively. The methine and methylene protons of the chiral auxiliary were appeared as multiplets in between 1.2 and 2.4. The methylene protons attached to the carboxylic group appeared as doublet at 3.90 and 4.35 (J = 17.6 Hz) due to their diastereotopic nature. The carboxylic acid proton appeared as a broad singlet at 9.3.

***5.4a.2 Preparation of b-lactams* 5.1j** and **5.1k**

The acid **5.03** on annulations reaction with imine derived form *trans*-cinnamaldehyde and *p*-anisidine in the presence of triethylamine at 0 °C afforded a β–lactam (**Scheme -5.6**) in 55% yield. The analysis of the crude product by ^{1}H NMR and HPLC showed the presence of two diastereomers **5.1j** & **5.1k** in the ratio of 60: 40. The major diastereomer **5.1j** was separated by crystallization (pet. ether/acetone).

Scheme -5.6



The ^{1}H NMR spectrum of the β-lactam **5.1j** showed two singlets at 0.71 and 0.87 of three protons each, corresponding to a gem dimethyl group. The angular methyl group appeared as a singlet at 1.27. Several multiplets appeared in between 1.02 and 2.15 for seven protons of the chiral auxiliary. The methoxy proton of the chiral moiety and that of the *p*-anisyl group appeared at 3.27 and 3.75 respectively. A doublet of doublet was observed at 4.70 corresponding to the C4 proton of the β-lactam (J = 4.8 & 9.7 Hz). The C-3 proton of the β-lactam appeared as a doublet at 5.42 (J = 4.8 Hz). The stereochemistry of the β-lactam was assigned as *cis* from the coupling constant value of 4.8 Hz of C-3 and C-4 protons. One of the styryl protons appeared as a doublet of doublet at 6.37 with J values of 8.5 & 14.4 Hz. A multiplet appeared at 6.85 accounting for three protons, two from aromatic and one from styryl moiety. The multiplets appearing in between 7.15 and 7.55 were assigned to seven protons of the aromatic ring. The IR spectrum of the compound showed a strong band at 1740 cm^{-1} corresponding to the β-lactam carbonyl group.

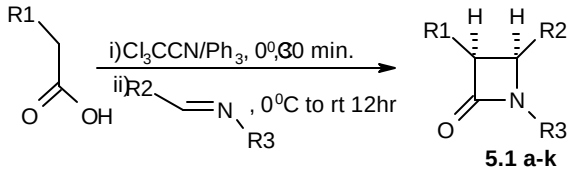
The ^{13}C NMR spectrum of **5.1j** showed a peak at 164.0 corresponding to the β-lactam carbonyl. The aromatic quaternary carbon bearing the methoxy group appeared at 156.1. The other quaternary aromatic carbon attached to the nitrogen atom of the β-lactam ring resonated at 135.9. The styryl olefinic carbon attached to the phenyl group appeared at 135.5. The quaternary carbon of the aromatic carbon was observed at 131.5. The other styryl carbon and aromatic carbons appeared at 128.7, 128.2 126.5, 125.1, 118.5 and 114.2. The C-4 and C-3 carbons of the β-lactam ring were observed at 81.9 and 84.2. The quaternary carbon of the chiral auxiliary-bearing methyl and methoxy groups appeared at 78.2. The methine carbon atom of the carene moiety, which was attached to an oxygen atom, appeared at 61.5. The methoxy carbon of the *p*-anisyl resonated at 55.4. The methoxy group of the chiral auxiliary was observed at 48.9. The methylene carbons of the chiral moiety appeared at 29.7 and 26.2. The two methine carbons of the cyclopropyl group appeared at 28.2 and 20.5. The methyl carbon of the chiral auxiliary was observed at 19.1.The quaternary carbon of the cyclopropyl group appeared at 17.6. The *gem* dimethyl group was observed at 15.5 and 14.8. This compound gave satisfactory microanalysis.

The use of acid **5.03**, derived from secondary alcohol **5.02** as chiral ketene precursor, gave only moderate diastereoselectivity (60: 40) in β-lactam ring formation.

5.4a.3 Preparation of the b-lactams **5.1 a-k**

The annulations of the imines with ketenes, generated from various substituted acetic acids by using triphenylphospine and trichloroacetonitrile provided variously substituted β-lactams in good yield. In a typical experiment, addition of a solution of triphenylphospine to a mixture of trichloroacetonitrile and carboxylic acids in anhydrous methylene chloride at 0 ^{o}C generated the acid chlorides. This mixture was then added to a solution of the imines and triethylamine in methylene chloride at 0 ^{0}C. After completion of the reaction (TLC), the reaction mixture was worked up in the usual manner. Column chromatography of the crude product provided pure β-lactams in moderate to good yields (**Scheme -5.7**).

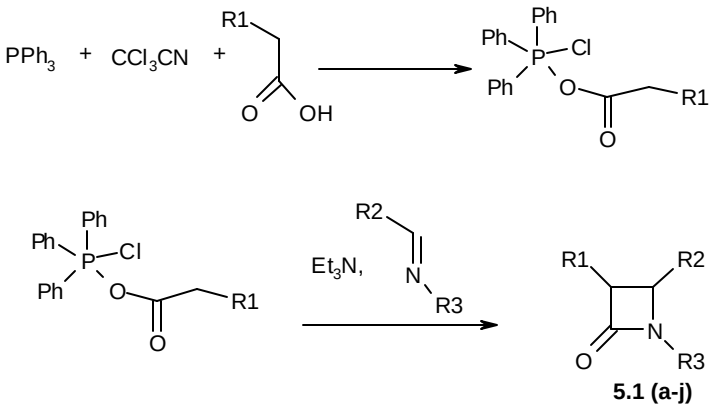
Scheme -5.7



5.1 a-k

The IR of the β-lactams showed the usual C=O stretching typical of β-lactams in the expected region1760 to 1740. The ^{1}H NMR showed two sets of doublets in the region 5.50 to 4.50 for β-lactam ring protons with coupling constants 5-6 Hz indicating the *cis* stereochemistry.

Mechanism

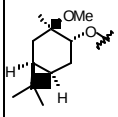


5.1 (a-j)

To explore the generality of this method, several substituted β-lactams **5.1 a-j** were synthesized in good yields (**Table -5.1**). This method can also be used for the

synthesis of β-lactams derived from acids, which are sensitive to mineral acids or thionyl chloride (see entry 10).

Table-5.1: Synthesis of β-lactams **5.1a-j** from acids and imines.

Entry No.	R^1	R^2	R^3	Product	Yield (%)[a]	M.p. (°C)[b]
1	**PhO**	PMP	Ph	**5.1a**	61	150-151 (149-150)[10]
2	PhO	Ph	PMP	**5.1b**	59	185-186
3	PhO	PMP	PMP	**5.1c**	56	166-167
4	MeO	Ph	PMP	**5.1d**	65	159-161
5	PhO	Styryl	PMP	**5.1e**	62	178-180
6	PhO	Styryl	Ph	**5.1f**	65	193-194 (193-195)[11]
7	PhO	Styryl	m-Tolyl	**5.1g**	71	161-162
8	PhthN	Styryl	PMP	**5.1h**	61	191-193 (192-194)[6e]
9	MeO	Styryl	PMP	**5.1i**	62	139-141
10		Styryl	PMP	**5.1j**	70[c]	232-233[d]

[a] Isolated yield of pure products. [b] The figures in parenthesis refers to the literature melting points. [c] Isolated yield of diastereomeric mixture (7:3). [d] M.p. of major diastereomer obtained in 45% yield by single crystallization from acetone-pet. ether (3:7).

5.5a : Conclusions

Trichloroacetonitrile and triphenylphospine were successfully employed as acid activators in the stereoselective synthesis of β-lactams. A series of β-lactams were synthesized in good yields, only *cis* β-lactams were obtained. The above reagents were found to be mild and could be used in reactions where substrates were sensitive to mineral acids.

5.6a : Experimental

5.6.1 Preparation of alcohol **5.02**

To a solution of (+)-3-carene oxide **5.01** (1.0 g, 6.5 mmol) in methanol (25 mL), a catalytic quantity of PTSA (30 mg) was added at 0 °C and the reaction mixture was stirred for 2 h. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4. It was filtered and filtrate was concentrated to give the crude product **5.02**, which on purification by column chromatography (silica gel, 60 - 120, 5% EtOAc in pet. ether) gave 1.1 g (90%) of pure alcohol **5.02**.

5.6.2 Preparation of Acid **5.03**

To a solution of **5.02** (1.84 g, 10 mmol) in dry toluene (25 mL), clean sodium pieces (0.500 g) were added and gently refluxed for 15 h. The solution was cooled and the excess of sodium was removed by filtration through glass wool. The filtrate was heated to 85 – 90 °C with stirring and a solution of chloroacetic acid (0.470 g, 5 mmol) in dry toluene (30 mL) was added in such a way that the refluxing should not be vigorous. A heavy precipitate of sodium chloroacetate was formed immediately. The reaction mixture was refluxed under stirring for an additional 48 h. The reaction mixture was diluted with toluene (30 mL) and extracted with water (3 x 25 mL) and the aqueous layer was acidified with 20% HCl. The crude product, which collected as brown oil on the top, was extracted with benzene. It was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude product as oil, which was purified by fractional distillation under reduced pressure to afford 1.5 g (62%) of the acid **5.03**.

^{1}H NMR (200.13 MHz) : 0.95 (s, 3H, CH_3); 1.05 (s, 3H, CH_3); 1.25 (s, 3H, CH_3); 3.38 (s, 3H, OCH_3); 1.2 - 2.4 (m, 7H, CH_2 & CH); 3.90 (d, J = 17.6 Hz, 1H); 4.35 (d, J = 17.6 Hz, 1H); 9.3 (bs, 1H).

5.6.3 General procedure for the preparation of b-lactams **5.1a-k**

To a solution of acid (1 mmol) and trichloroacetonitrile (2 mmol) in dry CH_2Cl_2 (5 ml), a solution of triphenylphospine (2 mmol) in dry CH_2Cl_2 (3 ml) was added at 0 °C and stirred for 30 min. This mixture was then slowly added to a solution of imine (0.5 mmol) and triethylamine (6 mmol) in CH_2Cl_2 (20 ml) at 0 °C over a period of 15 min. The reaction mixture was allowed to warm-up to room temperature and stirred further for 12

h. It was washed successively with water (20 ml) satd. $NaHCO_3$ (20 ml) and brine (10 ml). The organic layer was dried (Na_2SO_4), concentrated and the product was purified by crystallization from methanol or column chromatography to give pure β-lactams **5.1a-k** in 56 to 71% yields.

***Synthesis of 4-p-Anisyl-3-phenoxy-1-phenylazetidin-2-one* 5.1a**

The β-lactam **5.1a** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and aniline in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1739 cm^{-1}

^{1}H NMR (200.13 MHz) : 3.75 (s, 3H), 5.35 (d, J = 5.4 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 6.75-7.50(m, 14H).

Analysis : Calculated C: 76.49; H: 5.54: N, 4.05.

$C_{22}H_{19}NO_3$ Found C: 76.31; H: 5.18; N: 3.85.

***Synthesis of 1-p-Anisyl-3-phenoxy-4-phenylazetidin-2-one* 5.1b**

The β-lactam **5.1b** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisidine and benzaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1753 cm^{-1}

^{1}H NMR (200.13 MHz) : 3.75 (s, 3H), 5.40 (d, J = 5.4 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 6.70-7.50 (m, 14H).

Analysis : Calculated C: 76.49; H: 5.54: N, 4.05.

$C_{22}H_{19}NO_3$ Found C: 76.23; H: 5.21; N: 3.93.

***Synthesis of 1,4-Bis (p-anisyl)-3-phenoxyazetidin-2-one* 5.1c**

The β-lactam **5.1c** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and p-anisidine in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1739 cm^{-1}

^{1}H NMR (200.13 MHz) : 3.85 (s, 6H), 5.40 (d, J = 5.4 Hz, 1H), 5.60 (d, J = 5.4 Hz, 1H), 6.80-7.50 (m, 13H)

Analysis : Calculated C: 73.57; H: 5.64: N, 3.73.

$C_{23}H_{21}NO_4$ Found C: 73.20; H: 4.81; N: 3.56.

***Synthesis of 1-p-Anisyl-3-methoxy-4-phenylazetidin-2-one* 5.1d**

The β-lactam **5.1d** was prepared following the standard procedure between methoxyacetic acid and the imine derived from p-anisidine and benzaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1741 cm^{-1}

^{1}H NMR (200.13 MHz) : 3.15 (s, 3H), 3.70 (s, 3H), 4.75 (d, J = 5.5 Hz, 1H), 5.15 (d, J = 5.5 Hz, 1H), 6.70-7.50 (m, 9H)

Analysis : Calculated C: 72.06; H: 6.01: N4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H6.04; N: 4.75.

***Synthesis of 1-p-Anisyl-3-phenoxy-4-styrylazetidin-2-one* 5.1e**

The β-lactam **5.1e** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisidine and cinnamaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1751 cm^{-1}

^{1}H NMR (200.13 MHz) : 3.75 (s, 3H), 5.00 (dd, J = 4.4 & 8.1 Hz, 1H), 5.50 (d, J = 4.4 Hz, 1H), 6.30 (dd, J = 8.1 & 15.7 Hz, 1H), 6.75-7.50 (m, 15H).

Analysis : Calculated C: 77.59; H: 5.70: N: 3.77.

$C_{24}H_{21}NO_3$ Found C: 77.38; H: 5.42; N: 3.80.

***Synthesis of 3-Phenoxy-1-phenyl-4-styrylazetidin-2-one* 5.1f**

The β-lactam **5.1f** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from aniline and cinnamaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1739 cm^{-1}

^{1}H NMR : δ 5.60 (dd, J = 5.4 & 8.1 Hz, 1H), 6.15 (d, J = 5.4 Hz, 1H),

(200.13 MHz) 6.50 (dd, J = 8.1 & 15.0 Hz, 1H), 6.70 (d, J = 15 Hz, 1H), 6.75-7.80 (m, 15H).

Analysis : Calculated C: 80.90; H: 5.61; N: 4.10.

$C_{23}H_{19}NO_2$ Found C: 80.51; H: 5.45; N: 3.87.

***Synthesis of 3-Phenoxy-4-styryl-1-m-tolylazetidin-2-one* 5.1g**

The β-lactam **5.1a** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from m-toluidine and cinnamaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1755 cm^{-1}

^{1}H NMR (200.13 MHz) : δ 2.35 (s, 3H), 5.00 (dd, J = 5.2 & 8.1 Hz, 1H), 5.50 (d, J = 5.2 Hz, 1H), 6.20 (dd, J = 8.1 & 15.7 Hz, 1H), 6.75-7.50 (m, 15H).

Analysis : Calculated C: 81.09; H: 5.96: N: 3.94.

$C_{24}H_{21}NO_2$ Found C: 81.00; H: 6.34 N: 3.77.

***Synthesis of 1-p-Anisyl-3-phthalimido-4-styryl azetidin-2-one* 5.1h**

The β-lactam **5.1h** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and aniline in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1743, 1728 cm^{-1}

^{1}H NMR (200.13 MHz) : δ 3.75 (s, 3H), 5.00 (dd, J = 5.8 & 8.8 Hz, 1H), 5.67 (d, J = 5.8 Hz, 1H), 6.31 (dd, J = 8.8 & 16.1 Hz, 1H), 6.79 (d, J = 16.1 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.25-7.35 (m, 3H), 7.46 (d, J = 8.8 Hz, 2H), 7.71-7.85 (m, 4H).

Analysis : Calculated C: 72.06; H: 6.01: N4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H6.04; N: 4.75.

***Synthesis of 1-p-Anisyl-3-methoxy-4-styryl azetidin-2-one* 5.1i**

The β-lactam **5.1i** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisidine and cinnamaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1745 cm^{-1}

^{1}H NMR (200.13 MHz) : δ 3.50 (s, 3H), 3.70 (s, 3H), 4.70-4.85 (m, 2H), 6.30 (dd, J = 7 & 15 Hz, 1H), 6.75-7.00 (m, 3H), 7.20-7.50 (m, 7H).

Analysis : Calculated C: 73.76; H: 6.19 N: 4.52

$C_{19}H_{19}NO_3$ Found C: 73.38 H: 5.98 N: 4.35.

Synthesis of 1-p-Anisyl-4-styryl-3- [3′, 7′, 7′-trimethyl-3′-methoxy]bicyclo(4.1.0)hept-4′-yl-oxy]azetidin-2-one *5.1 j*

The β-lactam **5.1j** was prepared following the standard procedure between the acid **5.03** and the imine derived from p-anisidine and cinnamaldehyde in presence of triethylamine, using the trichloroacetonitrile and triphenylphospine as acid activators.

IR : 1740 cm^{-1},

^{1}H NMR (200.13 MHz) : 0.71 (s, 3H), 0.87 (s, 3H), 1.02 (m, 1H), 1.27 (s, 3H), 1.55-2.15 (m, 6H), 3.27 (s, 3H), 3.75 (s, 3H), 4.70 (dd, J = 4.8 & 9.5 Hz, 1H), 5.42 (d, J = 4.8 Hz, 1H), 6.37 (dd, J = 8.5 & 14.4 Hz, 1H), 6.85 (m, 3H), 7.15-7.55 (m, 7H);

Analysis : Calculated C: 72.06; H: 6.01: N4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H6.04; N: 4.75.

d **[**a **]$_D^{25}$** : -3.3 (c 1.2, CH_2Cl_2).

Section B :

Hexachloroacetone-Triethylphospite, a Novel Acid Activator in the Stereocontrolled Staudinger Reaction

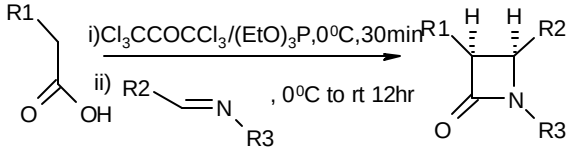
5.3B : Present work

Having studied the combination of trichloroacetonitrile-triphenylphospine as activators and obtained good yields in the [2+2] cycloaddition reaction, we thought it worthwhile to study the synthetic utility of hexachloroacetone-triethylphosphite as mild reagents for the activation of acids in the *Staudinger reaction*. This methodology offers acid free reaction conditions and simple work-up procedure, since the by-products formed in the reaction are water-soluble.

5.4b : Results and discussions

Hexachloroacetone in combination with triphenylphospine is recently used for the preparation of acid chloride form acids[9]. We employed this reagent for one-step cycloaddition reaction of acids and imines to get β-lactams. We found the reaction to be messy, and it gave poor yields of β-lactams. Also, the triphenylphospine oxide formed has to be removed by tedious column chromatography. A combination of hexachloroacetone and triethylphosphite, on the other hand, not only gave improved yields of β-lactams **5.2a-j** (**Table-5.2**), but also the work-up procedure was simplified to mere washing of the organic extract with water to remove all the water soluble by-products (**Scheme-5.8**).

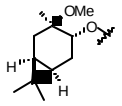
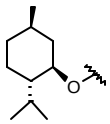
Scheme-5.8



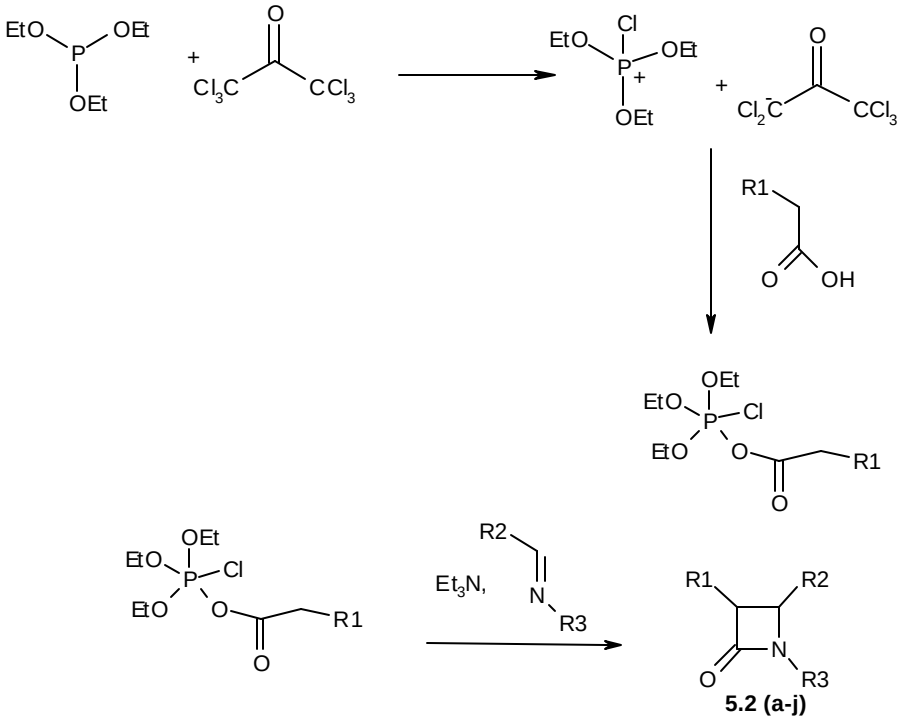
5.1 a-e, 5.1j, 5.1l-o

The cycloaddition reaction was found to be stereoselective and only *cis*-β-lactam formation was observed. To explore the generality of this method, several substituted β-lactams were synthesized in good yields (**Table-5. 2**).

Table-5.2: Synthesis of β-lactams (**5.1a-e, 5.1j, 5.1l-o)** from acids and imines using Hexachloroacetone and triethylphosphite as acid activators.

S.no	R^1	R^2	R^3	Product	Yield (%)	M. P. (^oC)
1	PhO	PMP	Ph	**5.1a**	52.8	151
2	PhO	Ph	PMP	**5.1b**	63.8	185
3	PhO	PMP	PMP	**5.1c**	40.5	166
4	MeO	Ph	PMP	**5.1d**	61.1	161
5	PhO	Styryl	PMP	**5.1e**	60.5	180
6		Styryl	PMP	**5.1j**	61.6	232
7	PhO	Styryl	Benzyl	**5.1l**	54.5	87
8	PhthN	Styryl	m-Tolyl	**5.1m**	52.2	197
9	PhO	Styryl	m-Tolyl	**5.1n**	45.6	162
10		Ph	PMP	**5.1o**	60	148 - 150°C

Mechanism:

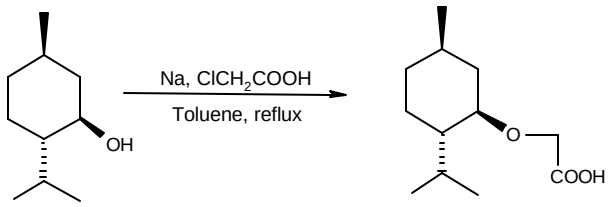


5.4b.1 L- (-)-Menthyl derived ketene precursor.

The optically pure menthyloxyacetic acid **5.05** was selected as a model chiral ketene precursor for the diastereoselective synthesis of β-lactams.

***Preparation of menthyloxyacetic acid* 5.05**.

The alkylation of secondary alcoholic group of L-(-)-menthol **5.04** with chloroacetic acid using sodium metal in dry toluene under reflux condition gave menthyloxyacetic acid **5.05** in good yield[16] (**Scheme -5.9**).



5.04 **5.05**

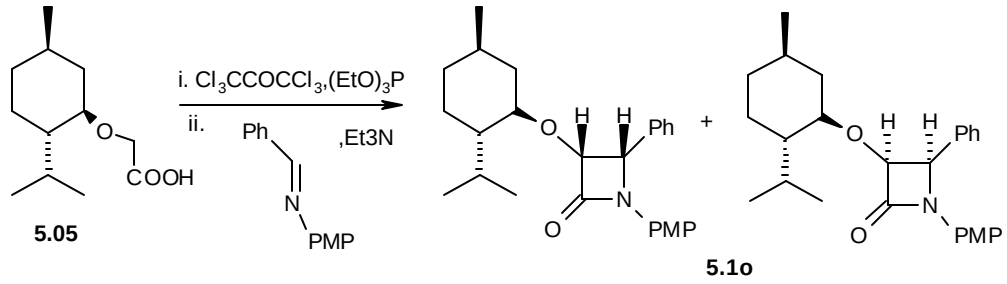
Scheme -5.9

The IR spectrum of **5.05** showed a broad band at 3600-2800 for OH stretching and 1730 for the acid carbonyl stretching. The ^{1}H NMR spectrum of **5.05** showed two doublets at 0.53 and 0.65, each for three protons of *gem* dimethyl group with 8 Hz coupling constant. The angular methyl group appeared as doublet at 0.70. Several multiplets appeared in between 0.75 and 2.93 for the methine and methylene protons. Due to diastereotopic nature, the methylene protons adjacent to carboxylic group appeared as two doublets at 3.75 and 3.90 with 16 Hz coupling constant. A broad singlet appeared at 7.0 was interpreted for carboxylic proton.

5.4b.2 Preparation of b-lactams 5.1o.

The acid **5.05** on annulations reaction with the imine using trichloroacetonitrile and triphenylphospine at 0 ^{o}C gave **5.1o** as a diastereomeric mixture of β-lactams **5.1o** in good yield (**Scheme-5.10**). However, the diastereoselectivity obtained in this reaction was very poor as confirmed by ^{1}H NMR spectral data of the crude reaction mixture, which showed the presence of two diastereomers in almost equal proportions. Moreover, these diastereomers could not be separated either by column chromatography or by crystallization.

Scheme 5.10



Reagents and Conditions*:* i) Et_3N/PhO-P (O)-Cl_2/dry CH_2Cl_2, 0℃ to r. t.

The structure of the diastereomeric mixture **5.1o** was confirmed from IR and ^{1}H NMR spectral and analytical data of the mixture. The ^{1}H NMR spectrum of **5.1o** showed two sets of signals, implying the presence of two diastereomers. The *gem* dimethyl groups of the chiral auxiliary appeared as two sets of doublets at 0.55 & 0.85 and 0.75 & 0.87 with J value of 7 Hz. each set integrating for a total of three protons. The angular methyl group was appeared as doublets at 0.93 & 0.98 for two diastereomers. The ratio of these diastereomers was found to be 1:1 from the relative peak integration. The methylene and methine protons of the chiral auxiliary were appeared as multiplets in between 1.05 and 2.40, integrating for a total of nine protons. The methine proton adjacent to the oxygen atom appeared as a multiplet in between 3.22 and 3.50, integrating for a total of one proton. The methoxy proton appeared as a singlet at 3.75 integrating for three protons. The C-4 proton of the diastereomeric mixture appeared as a multiplet at 4.78, integrating for total one proton. The C-3 proton of the β-lactam ring was appeared as doublets at 4.93 and 4.97 for two isomers with J value of 5 Hz. Two of the aromatic protons appeared as doublets at 6.83. Several multiplets appearing in between 7.22 and 7.50 accounted for total seven protons of the aromatic groups. The IR spectrum showed a band at 1740 for the β-lactam carbonyl stretching. This compound gave satisfactory microanalysis.

5.4b Conclusions

The combination of hexacloroacetone and triethylphosphite was successfully employed in the [2+2] cycloaddition reaction, which provided *cis* β-lactams in good yields. These reagents were found to be mild and could be used in reactions where substrates were sensitive to mineral acids (carene derived acid, entry no 6, Table- **5.2**).

5.5b Experimental

5.5b.1 Preparation of acid **5.05**

To a solution of l-(-)-menthol **5.04** (10 g, 65 mmol) in dry toluene (60 mL), clean sodium pieces (2 g) were added and gently refluxed for 15 h. The reaction mixture was stirred at such a rate that the sodium was broken into fine globules. The reaction mixture was cooled to room temperature and the unreacted sodium was removed by filtration through glass wool. The filtrate was heated to 85 – 90 °C and a solution of chloroacetic acid (2.4 g, 25 mmol) in dry toluene (50 mL) was added with stirring in such a way that the refluxing should not be vigorous. A heavy precipitate of sodium chloroacetate forms immediately. After the addition of chloroacetic acid, the reaction mixture was refluxed for 48 h. The reaction mixture was cooled and diluted with toluene (200 mL). It was then extracted with water (3 x 250 mL). The aqueous layer was acidified with 20% HCl. The crude menthyloxyacetic acid, which separates as brown oil on the top, was extracted with benzene (2 x 30 mL). The removal of benzene by distillation under reduced pressure afforded crude product, which was purified by fractional distillation and the fraction boiling at 100 - 115°C/8-10 mm gave 9.0 g (65%) of required acid **5.05**.

IR : 3600-2800, 1730.

^{1}H NMR **(200.13 MHz)** : 0.53 (d, *J* = 8 Hz, 3H, CH3); 0.65 (d, *J* = 8 Hz, 3H, CH3); 0.7 (d, *J* = 6 Hz, 3H, CH3); 0.75- 0.90 (m, 3H); 0.95 - 1.20 (m, 2H, CH_2); 1.27 - 1.50 (m, 2H, CH_2); 1.70 - 1.90 (m, 1H, CH); 1.93 - 2.2 (m, 1H, CH); 2.93 (m, 1H, CH); 3.75 & 3.90 (d, *J* = 16 Hz, 1H, CH_2); 7.0 (bs, 1H, OH).

5.5b.2 General procedure for the preparation of b-lactams 5.1a-e, 5.1j, 5.1l-o

To a solution of the acids (2 mmol) and hexachloroacetone (4 mmol) in dry CH_2Cl_2 (5 ml), a solution of triethylphosphite (3 mmol) in dry CH_2Cl_2 (5 ml) was added at 0 ^{0}C and stirred for 30 min. This mixture was then slowly added to a solution of imine (1 mmol) and triethylamine (6 mmol) in CH_2Cl_2 (20 ml) at 0 ^{0}C over a period of 15 min. The reaction mixture was then stirred at room temperature for 12 h. It was washed successively with water (20 ml), satd. $NaHCO_3$ (20 ml) and brine (10 ml). The organic

layer was dried (Na_2SO_4), concentrated and the product was purified by crystallization or column chromatography to give the β-lactams (**5.1 a-e, 5.1 j, 5.1 l-o)** in 40 to 64% yields. The data for the compounds **5.1 a-e, 5.1 j** was discussed in the previous section.

This method has also been used for the synthesis of β-lactams derived from acids, which are sensitive to mineral acids or thionyl chloride (see entry 6).

***Preparation of b-lactam* 5.1 o.**

To a mixture of l-(-)-menthyloxyacetic acid **5.05** (0.257 g, 1.2 mmol), and hexachloroacetone (4 mmol) in dry CH_2Cl_2 (5 ml), a solution of triethylphosphite (3 mmol) in dry CH_2Cl_2 (5 ml) was added at 0 ^{0}C and stirred for 30 min. This mixture was then slowly added to a solution of imine (1 mmol) and triethylamine (6 mmol) in CH_2Cl_2 (20 ml) at 0 ^{0}C over a period of 15 min. The reaction mixture was then stirred at room temperature for 12 h. It was washed successively with water (20 ml), satd. $NaHCO_3$ (20 ml) and brine (10 ml). The organic layer was dried over Na_2SO_4. It was filtered and filtrate on concentration under reduced pressure provided the β-lactam **5.1o** as a diastereomeric mixture (0.315 g, 60%). This diastereomeric mixture could not be separated either by column chromatography or crystallization. The spectral and analytical data for the diastereomeric mixture is as follows:

M.P.	**:**	148 - 150°C
IR	**:**	1740.
^{1}H NMR (200.13 MHz)	**:**	0.55 & 0.85 (d, J = 7 Hz, total 3H, CH_3); 0.75 & 0.87 (d, J = 7 Hz, total 3H, CH_3); 0.93 & 0.98 (d, J = 7 Hz, total 3H, CH_3); 1.05 - 1.70 (m, total 6H, CH_2); 1.97 - 2.40 (m, total 3H, CH); 3.22 & 3.50 (m, total 1H, CH); 3.75 (s, total 3H, OCH_3); 4.78 (m, total 1H, C4H of major & minor isomers); 4.93 & 4.97 (two d, J = 5 Hz, total 1H, C3H of major & minor isomers); 6.83 (d, J = 10 Hz, 2H, Ar); 7.22 - 7.50 (m, 7H, Ar).
Analysis	**:**	M. F. $C_{28}H_{35}O_3N$ Calculated: C, 77.55; H, 8.14; N, 3.23. Found: C, 77.18; H, 8.33; N, 3.34.

***Synthesis of 1-Benzyl-3-phenoxy-4-styryl-azetidine-2-one* 5.1 l**

The β-lactam **5.1a** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and aniline in presence of triethylamine, using the reagents hexachloroacetone and triethylphosphite as acid activators.

IR : 1747

^{1}H NMR (200.13 MHz) : 4.09 (d, 1H, J = 14 Hz), 4.41 (dd, 1H, J = 4 Hz each), 4.74 (d, 1H, J = 14 Hz), 5.35 (d, 1H, J = 4 Hz), 6.11 (dd, 1H, H = 6 Hz, 8 Hz), 6.56 (d, 1H, J = 16 Hz).

Analysis : Calculated C: 72.06; H: 6.01: N4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H6.04; N: 4.75.

***Synthesis of 3-phthalimido-4-styryl-1-m-tolyl-azetidin-2-one* 5.1m**

The β-lactam **5.2h** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and aniline in presence of triethylamine, using the reagents hexachloroacetone and triethylphosphite as acid activators.

IR : 1770, 1753.

^{1}H NMR (200.13 MHz) : 2.35 (s, 3H), 5.10 (dd, 1H, J =5.1 Hz, 11 Hz), 6.3 (dd, J = 8.3 Hz, 16.1 Hz), 6.75 (d, 1H, J = 16.1 Hz), 6.95-7.90 (m, 13 H).

Analysis : Calculated C: 72.06; H: 6.01; N4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H6.04; N: 4.75.

***Synthesis of 1-m-tolyl-3-phenoxy-4-styryl-azetidin-2-one* 5.1n**

The β-lactam **5.1a** was prepared following the standard procedure between phenoxyacetic acid and the imine derived from p-anisaldehyde and aniline in presence of triethylamine, using the reagents Hexachloroacetone and triethylphosphite as acid activators.

IR : 1749.23

^{1}H NMR (200.13 MHz) : 2.30 (s, 3H), 5.0 (dd, 1H, J =4.9 Hz, 11 Hz), 5.50 (d, 1H, J = 4.9 Hz), 6.25 (dd, 1H, J = 14.2 Hz, 8.5 Hz), 6.95 (d, 1H,

J =14.2 Hz), 7.0-7.50 (m, 14H).

Analysis **:** Calculated C: 72.06; H: 6.01; N: 4.94.

$C_{17}H_{17}NO_3$ Found C: 71.96; H: 6.04; N: 4.75.

5.8 : References

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3. Bose, A.K.; Manhas, M.S.; Amin, S.G.; Kapur, J.C.; Kreder, J.; Mukkavilli, L.; Ram, B.; Vincent, J.E. *Tetrahedron Lett.* **1979**, 2771.
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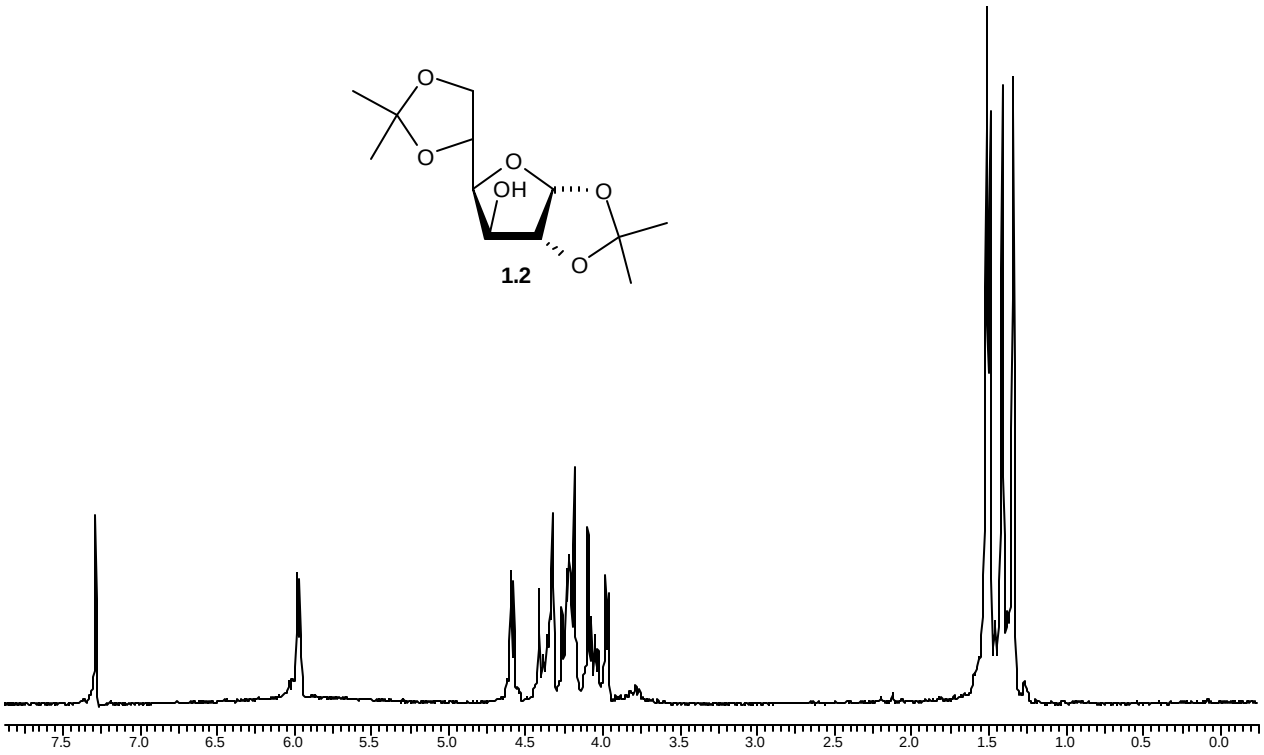
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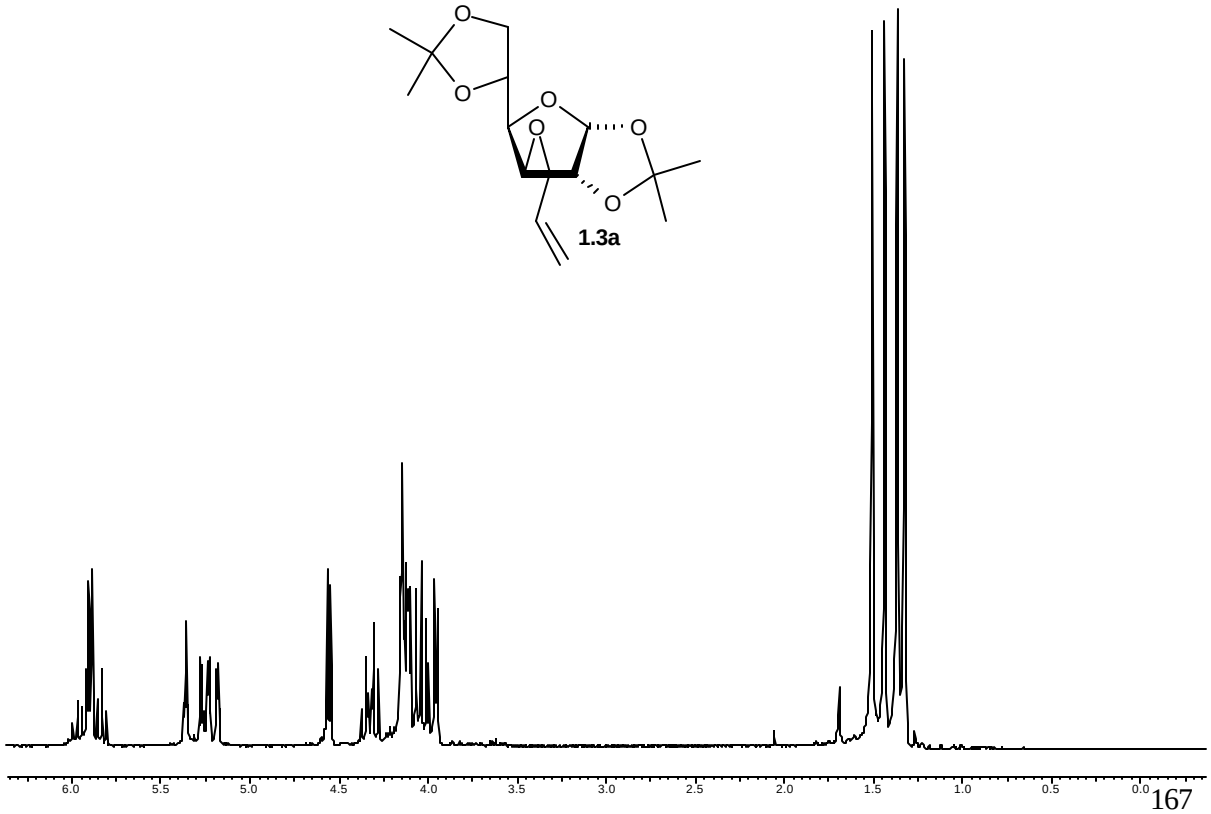
1.2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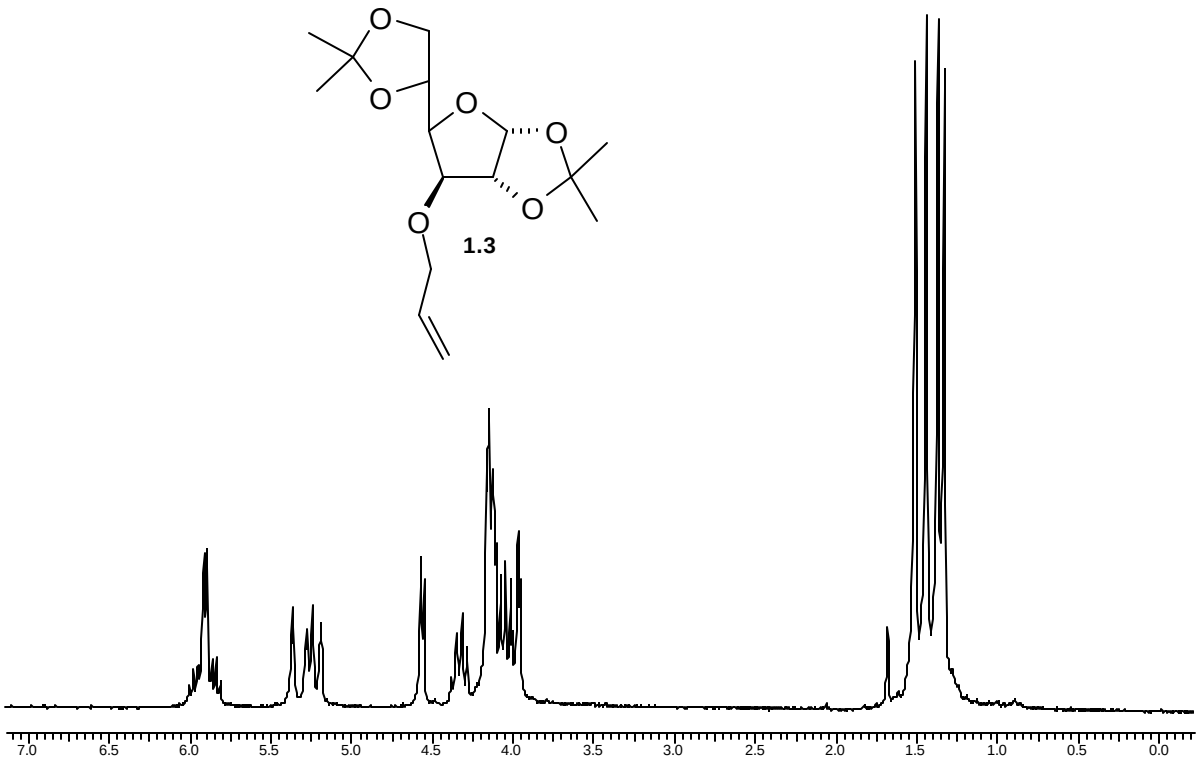
1.3a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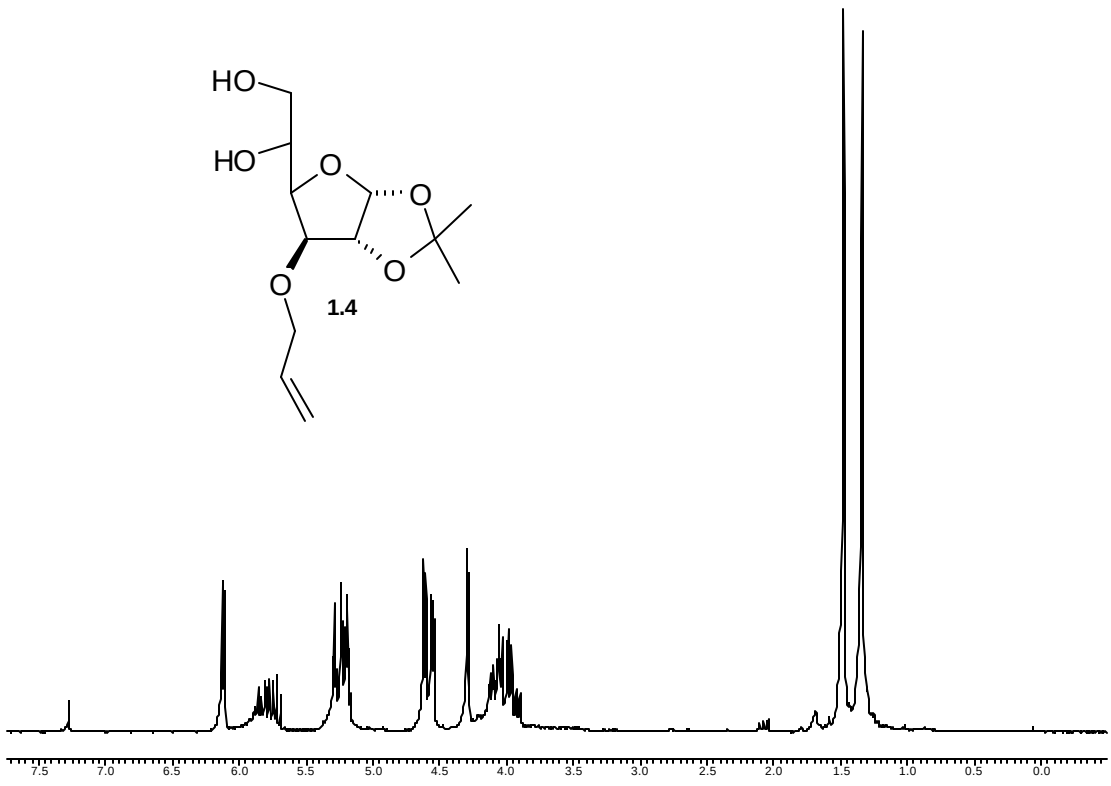
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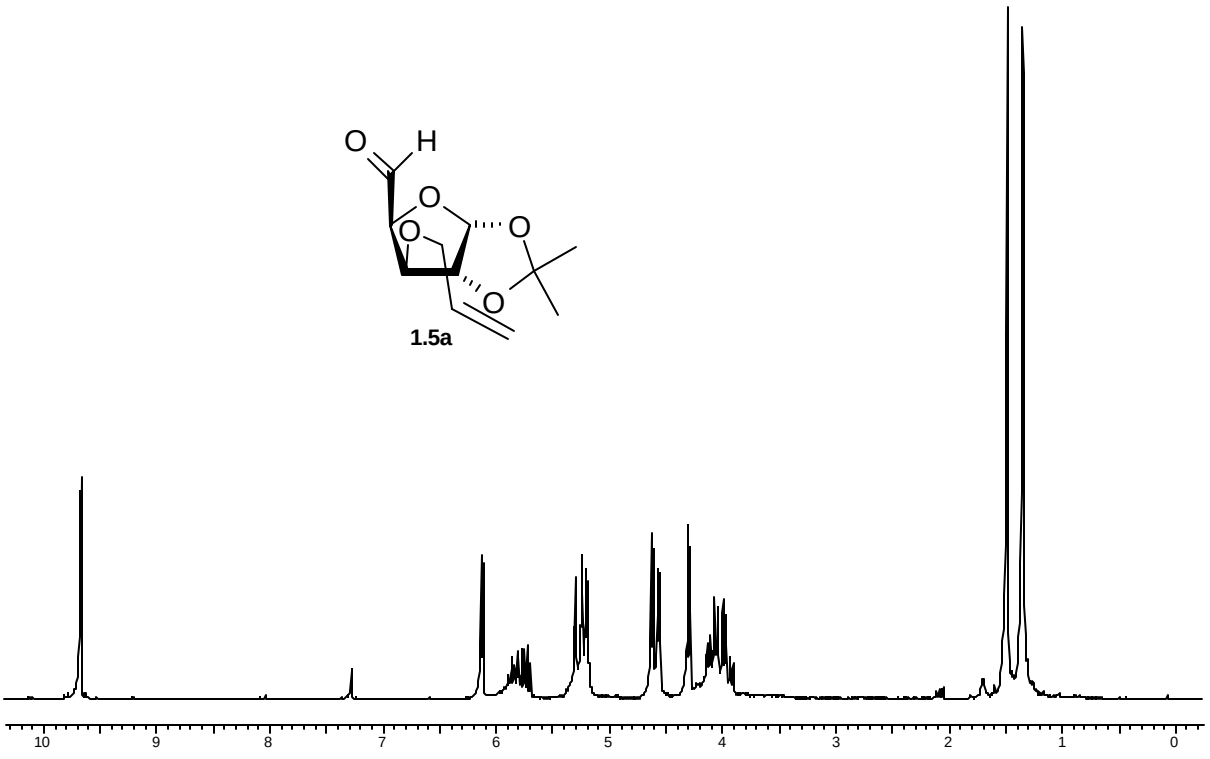
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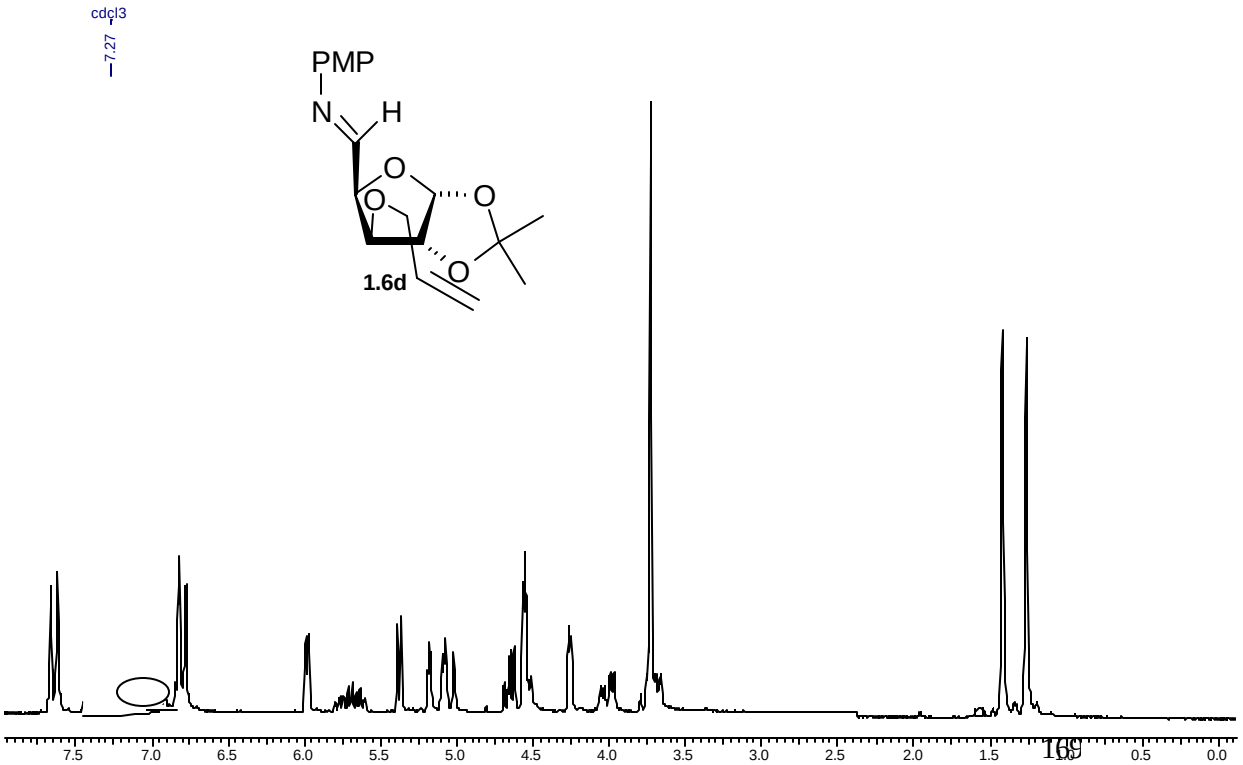
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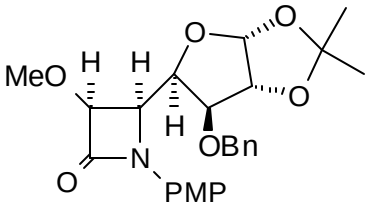

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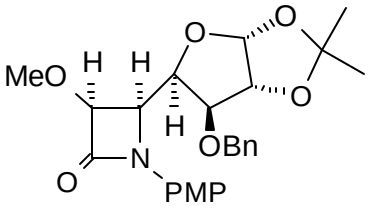
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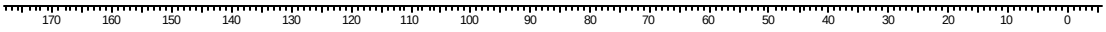
1.7a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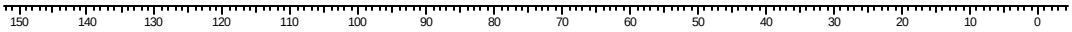
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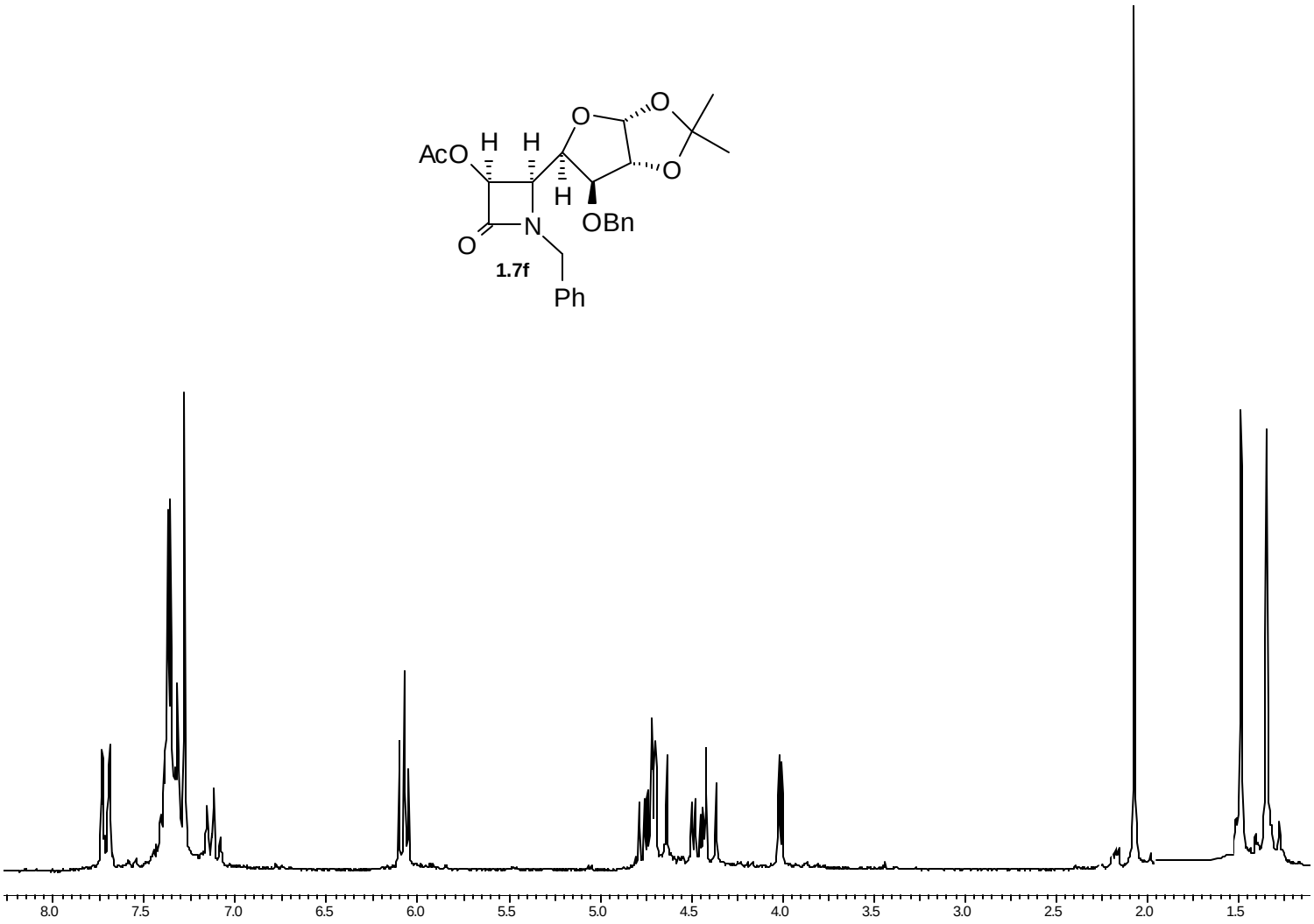

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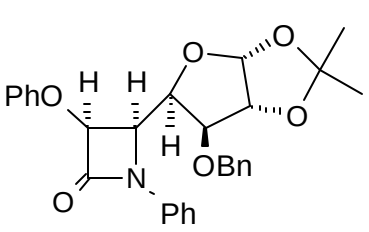
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1.7c

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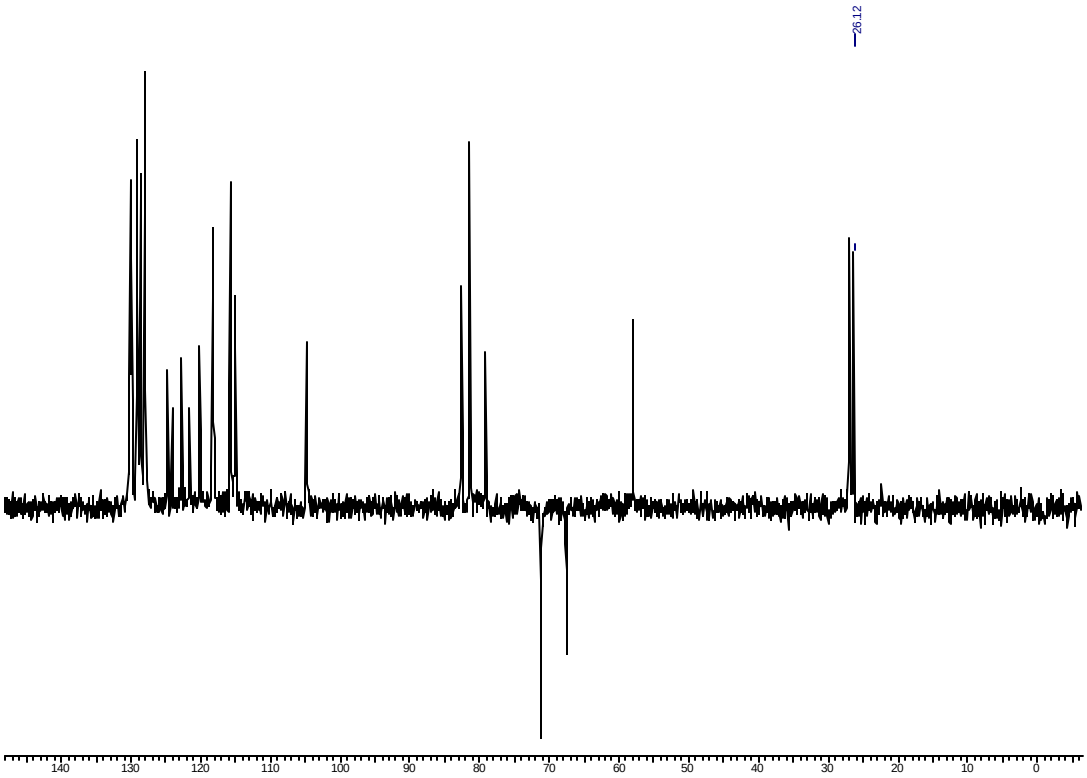
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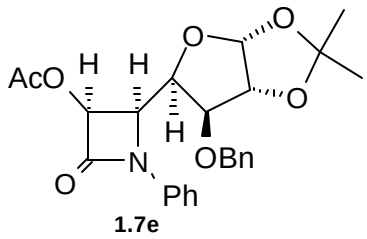
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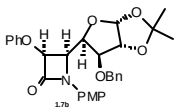
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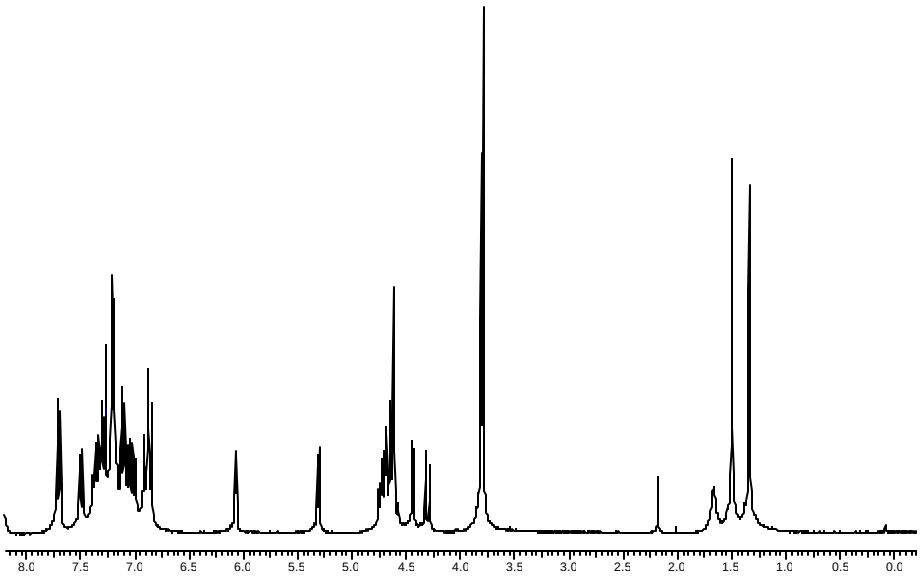
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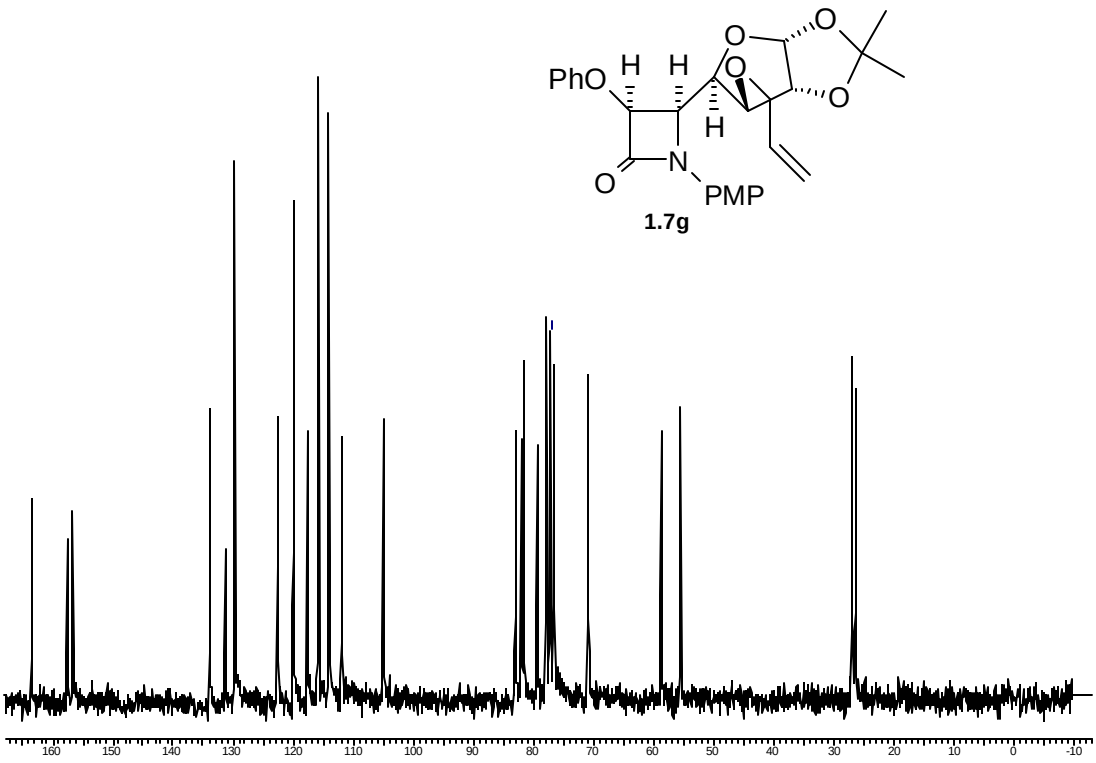
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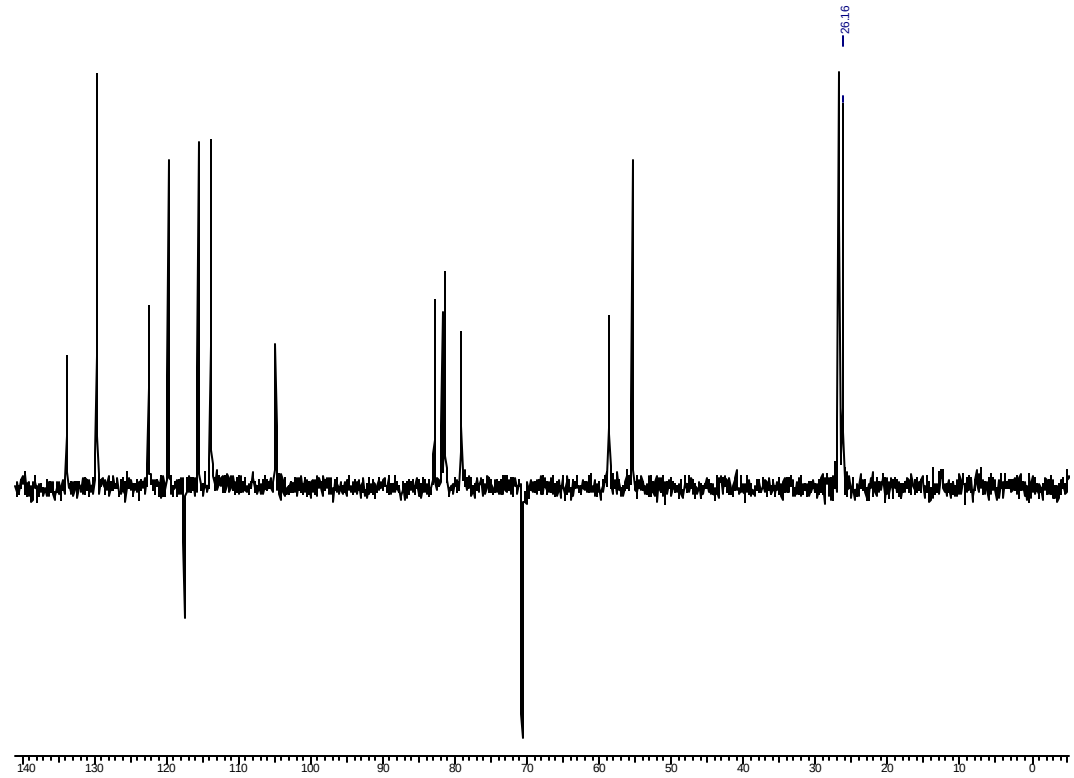
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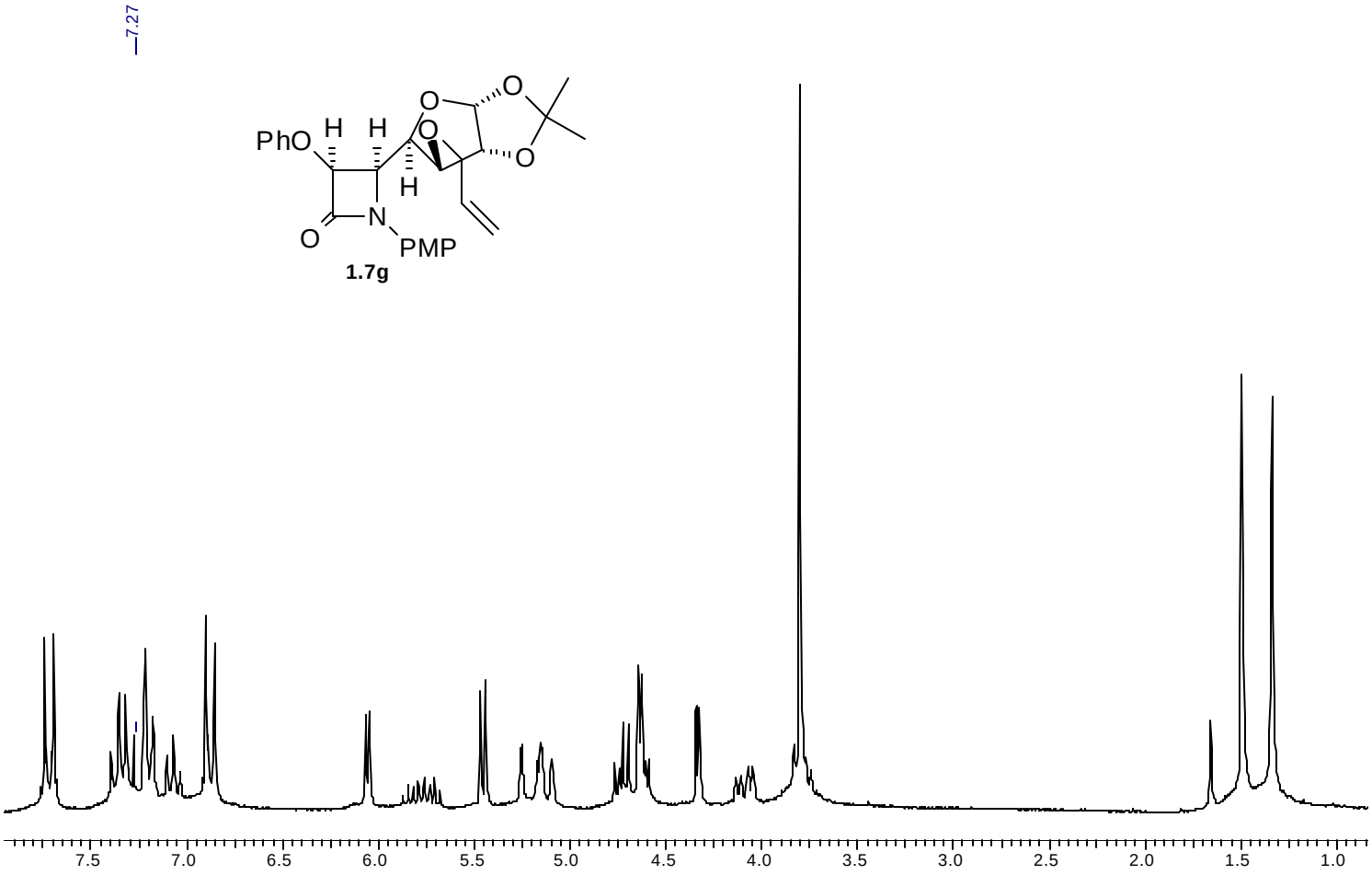

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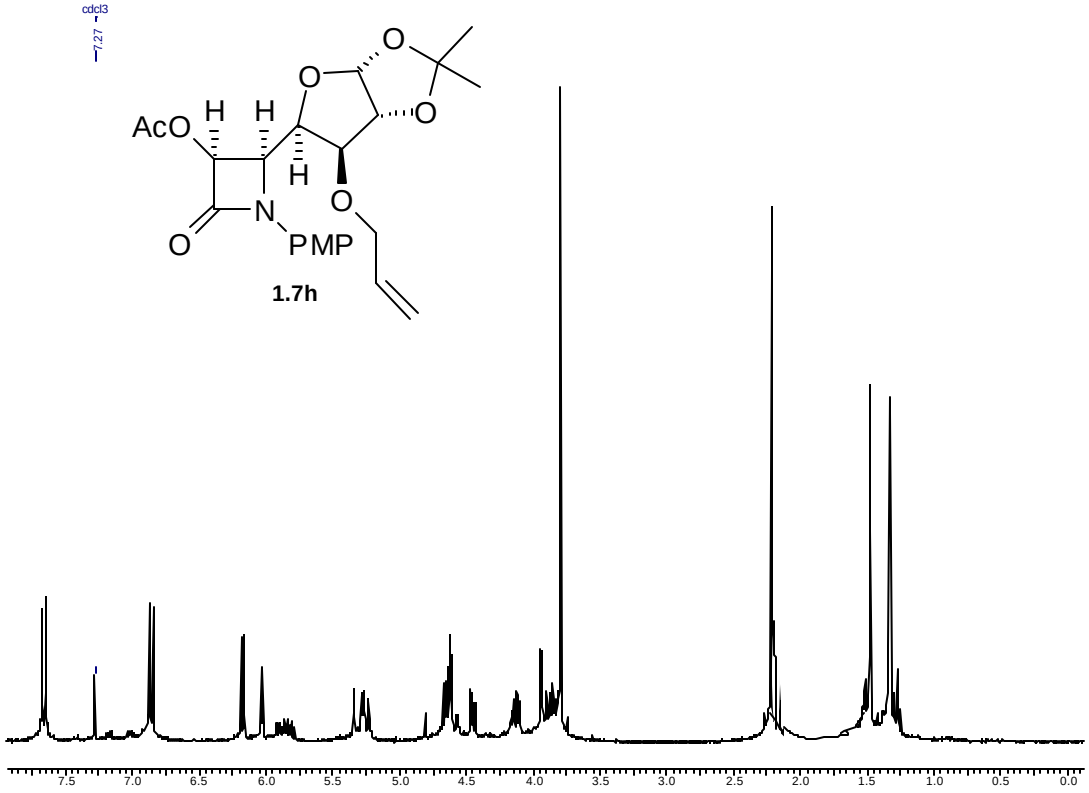
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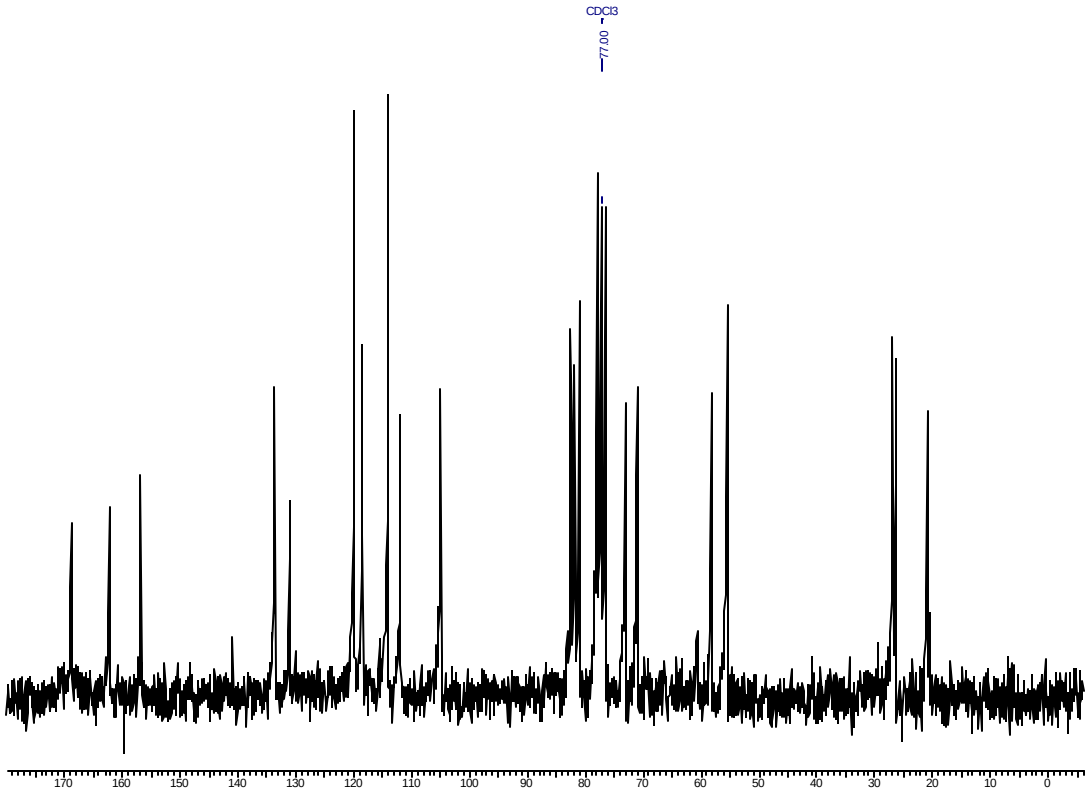
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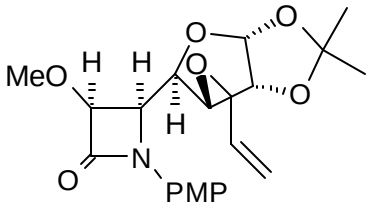
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1.7j

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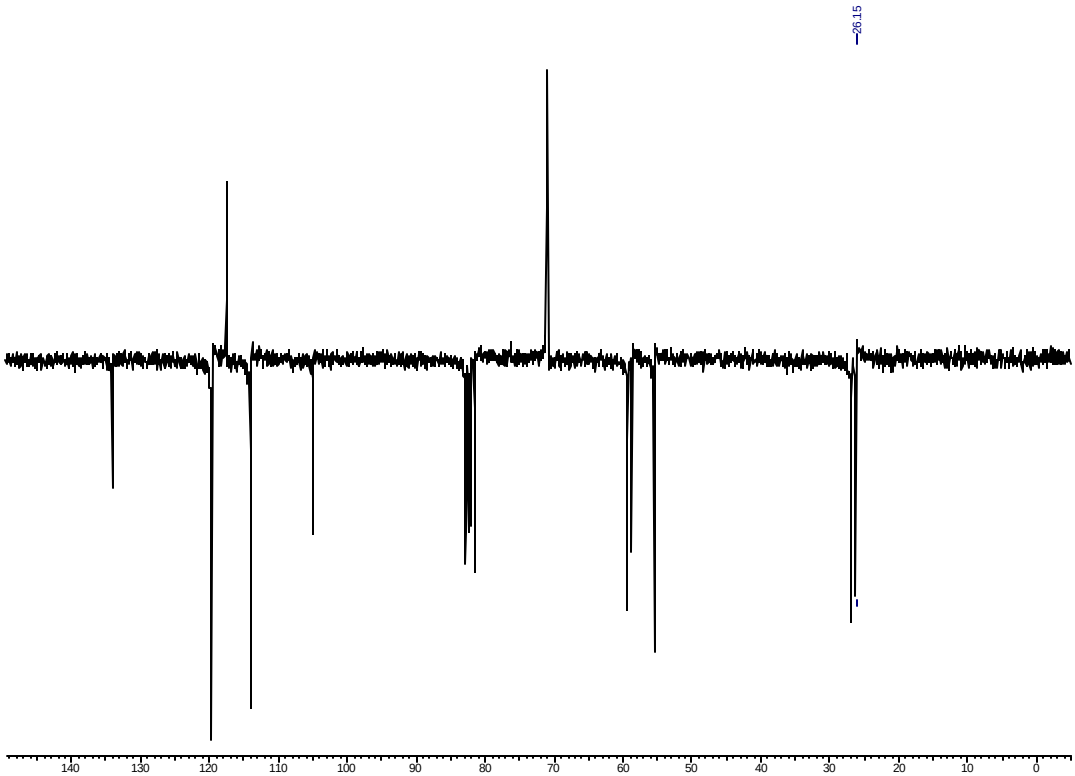
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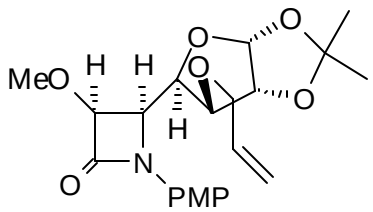

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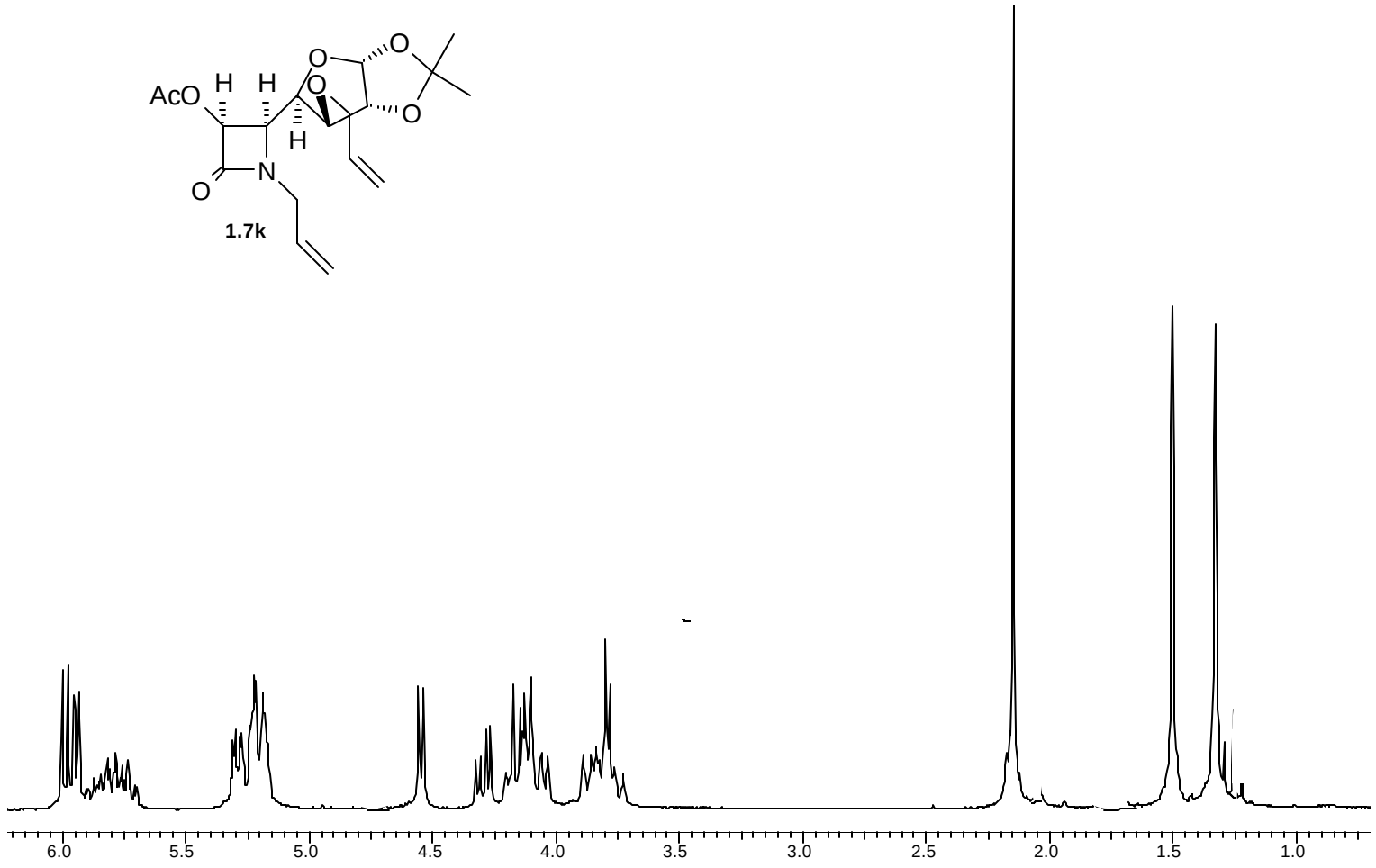

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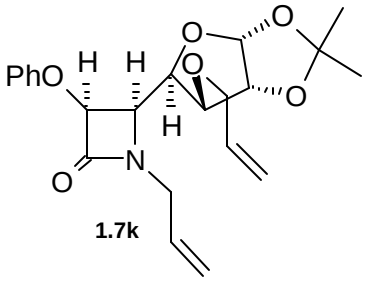
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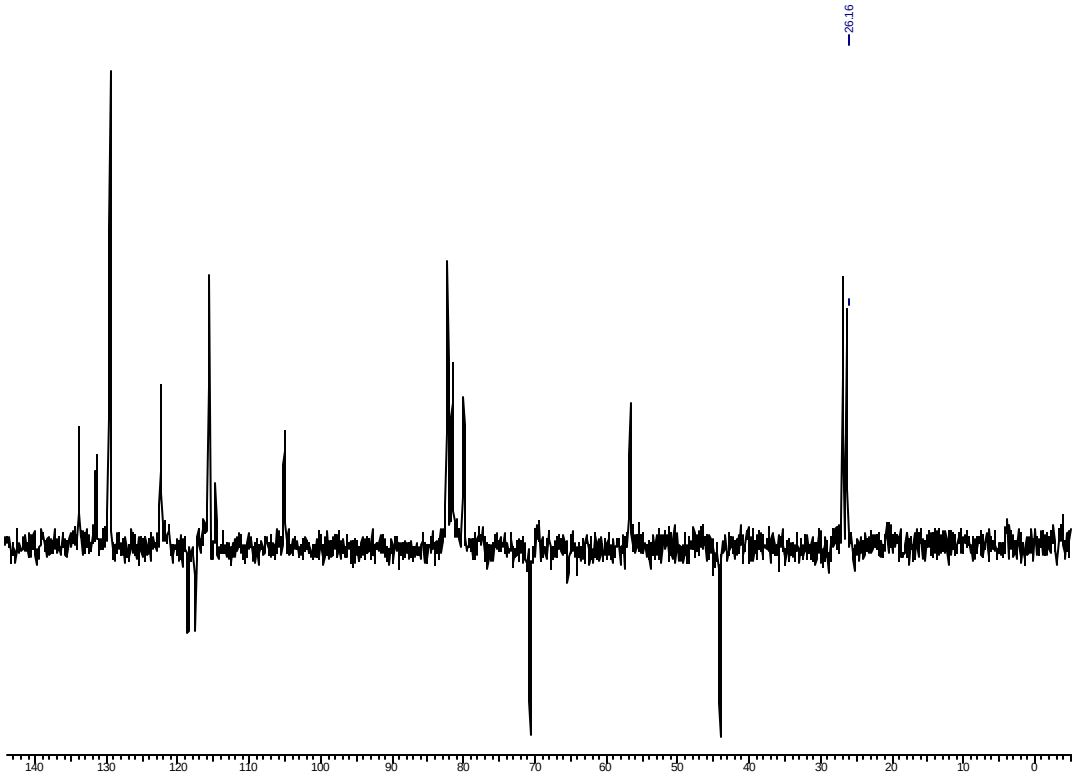
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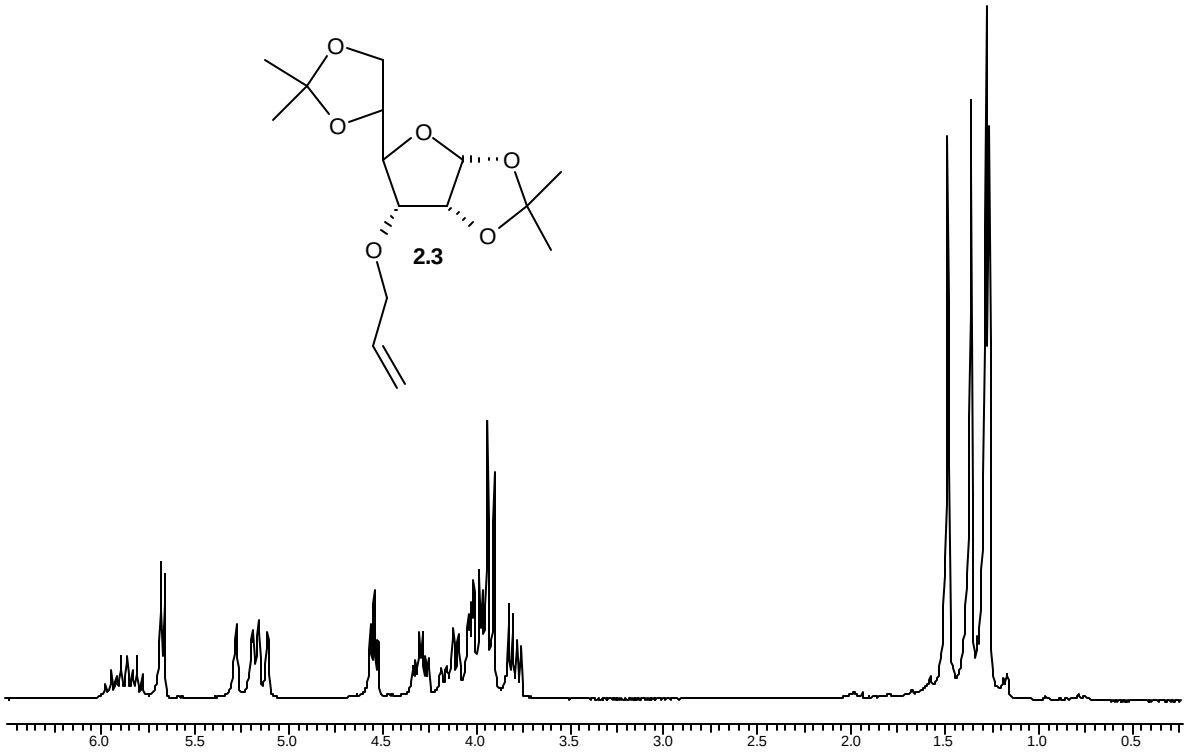
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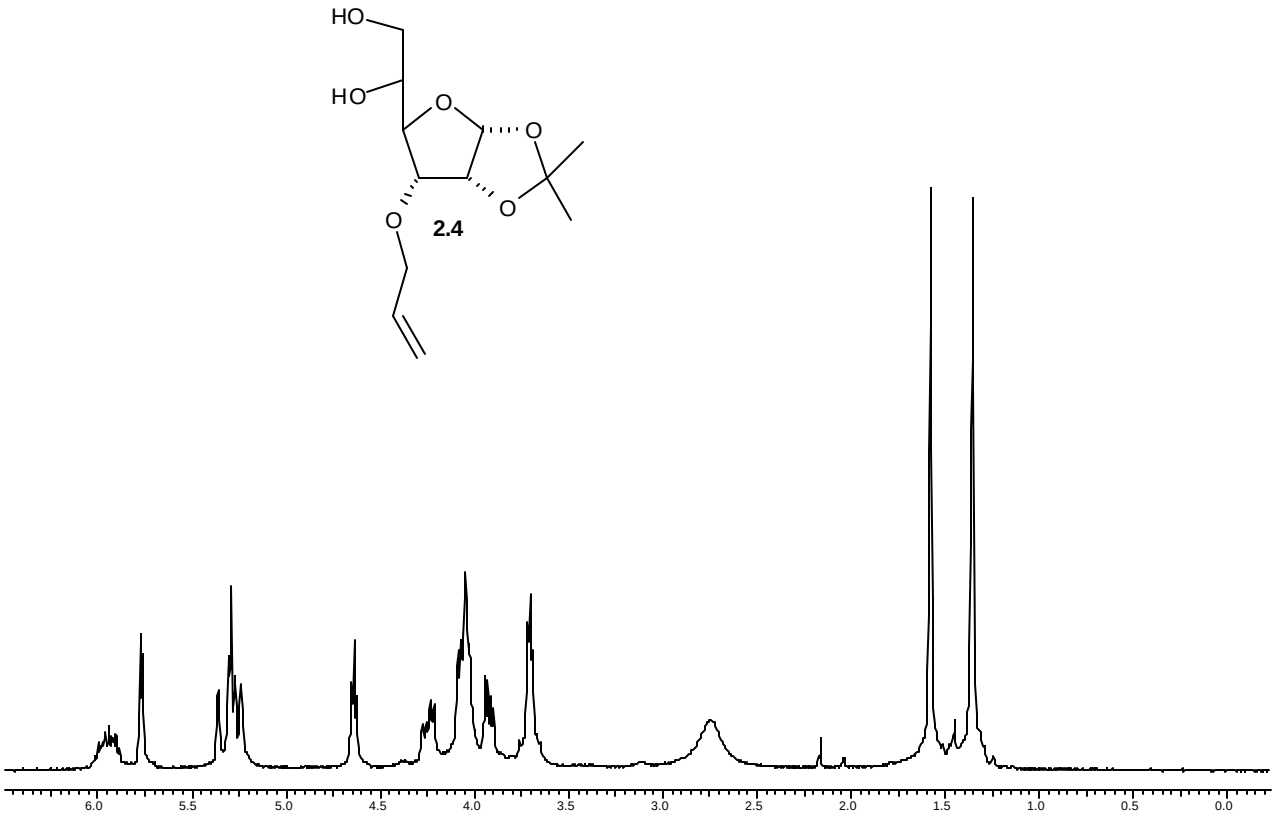
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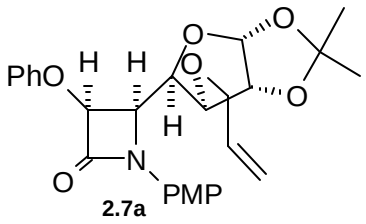
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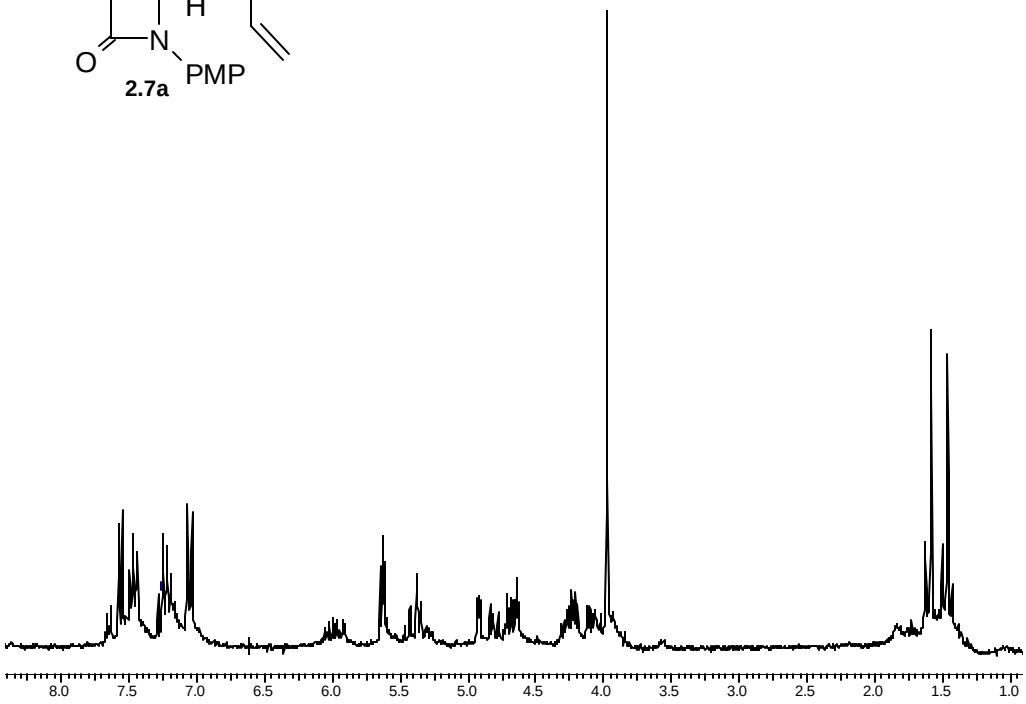
2.7a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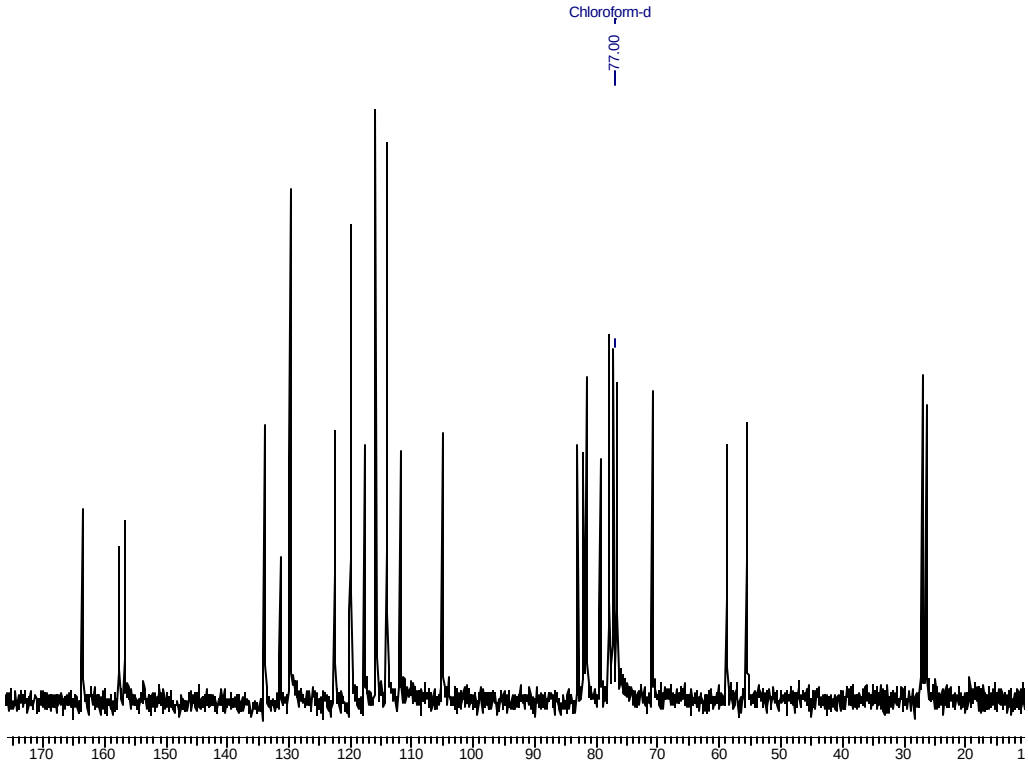
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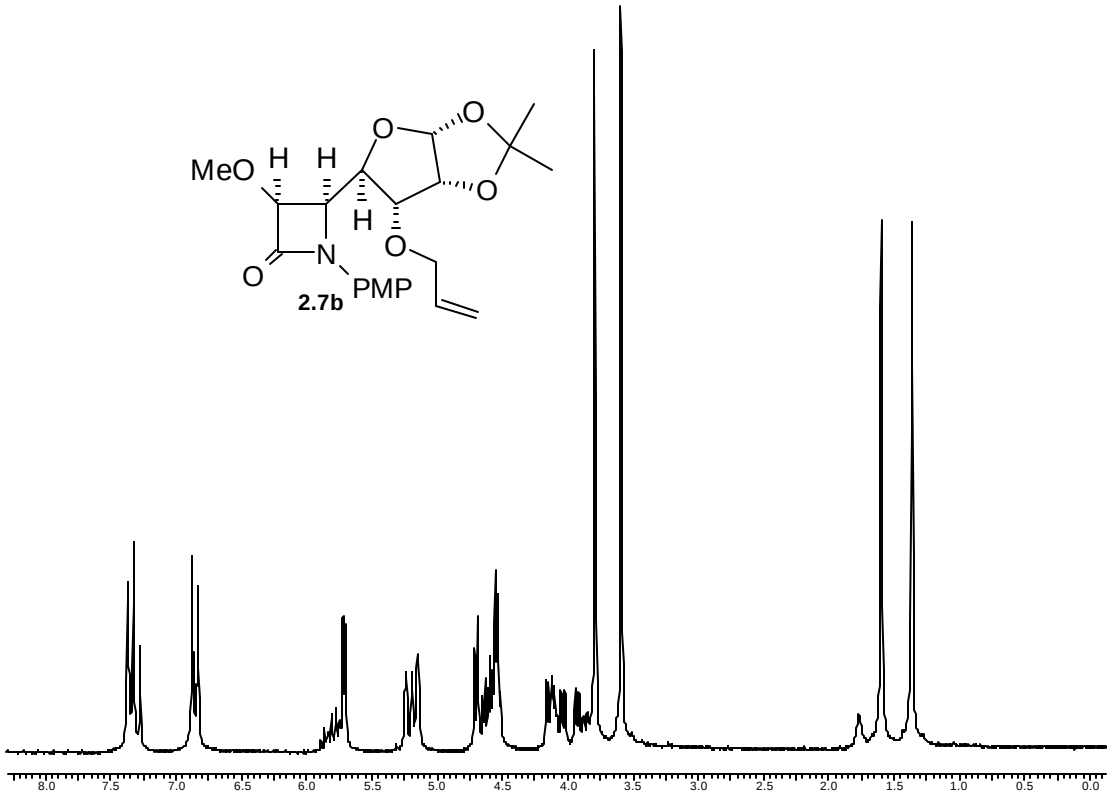
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PMP
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6.0
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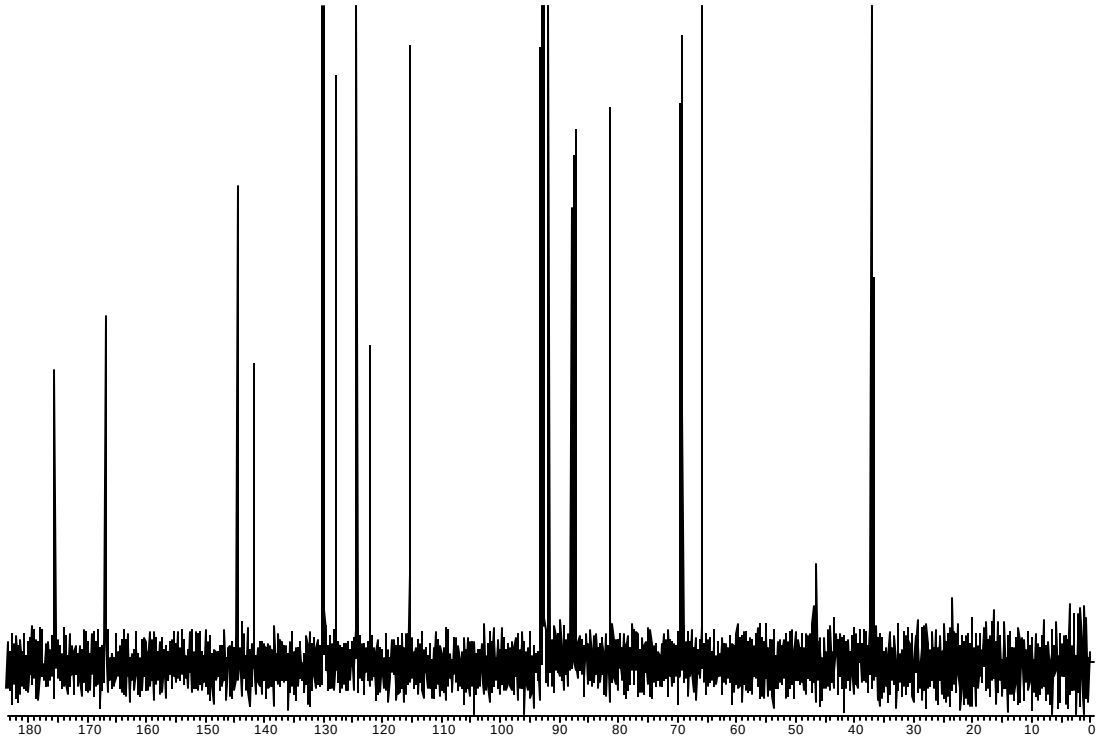
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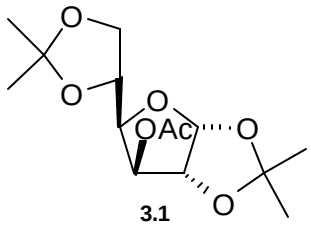
O
O
O
OAc
O
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3.1

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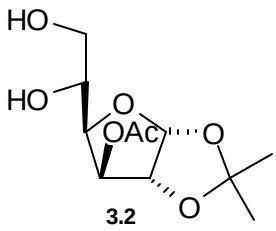
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HO
O
OAc
O
O

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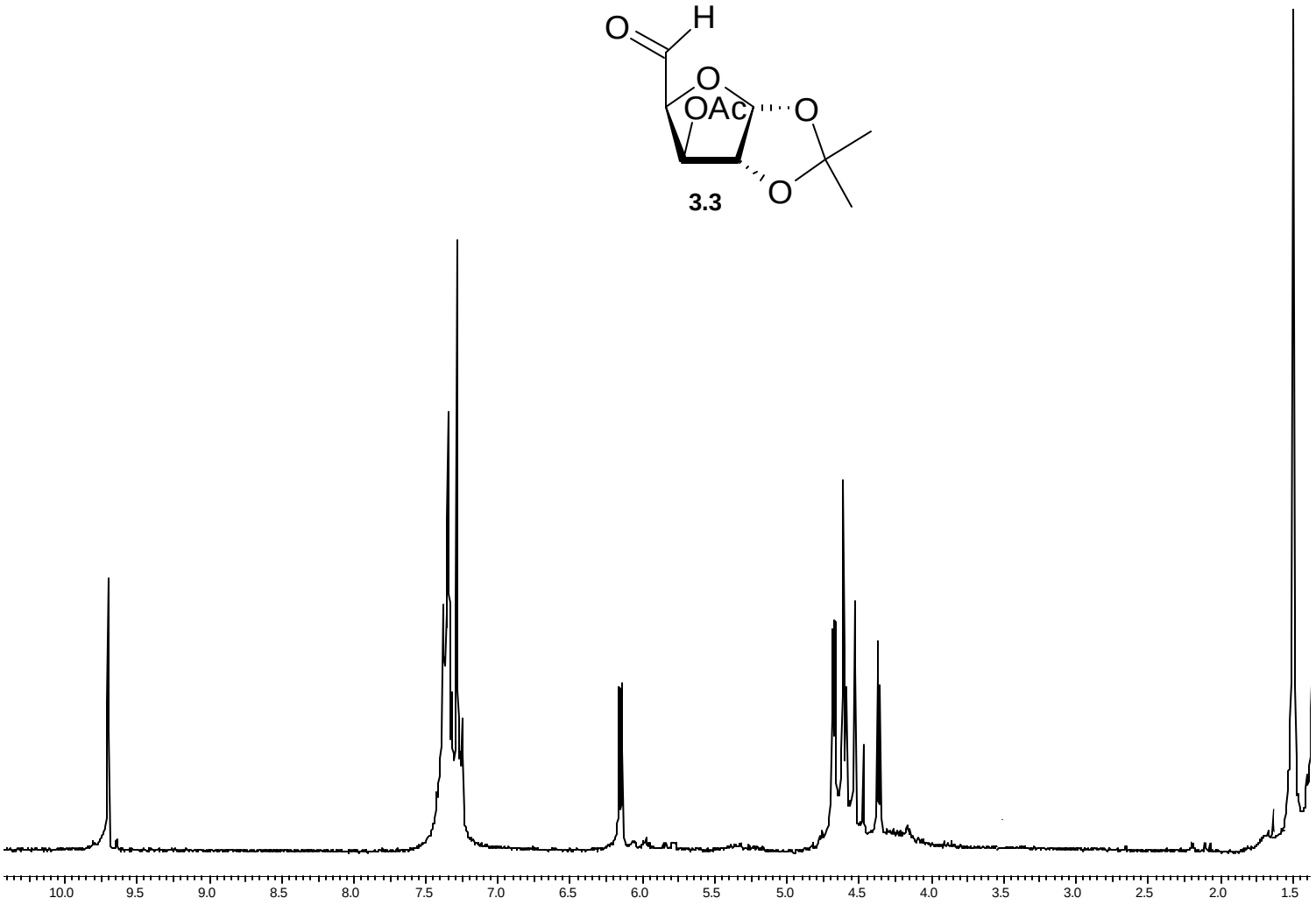

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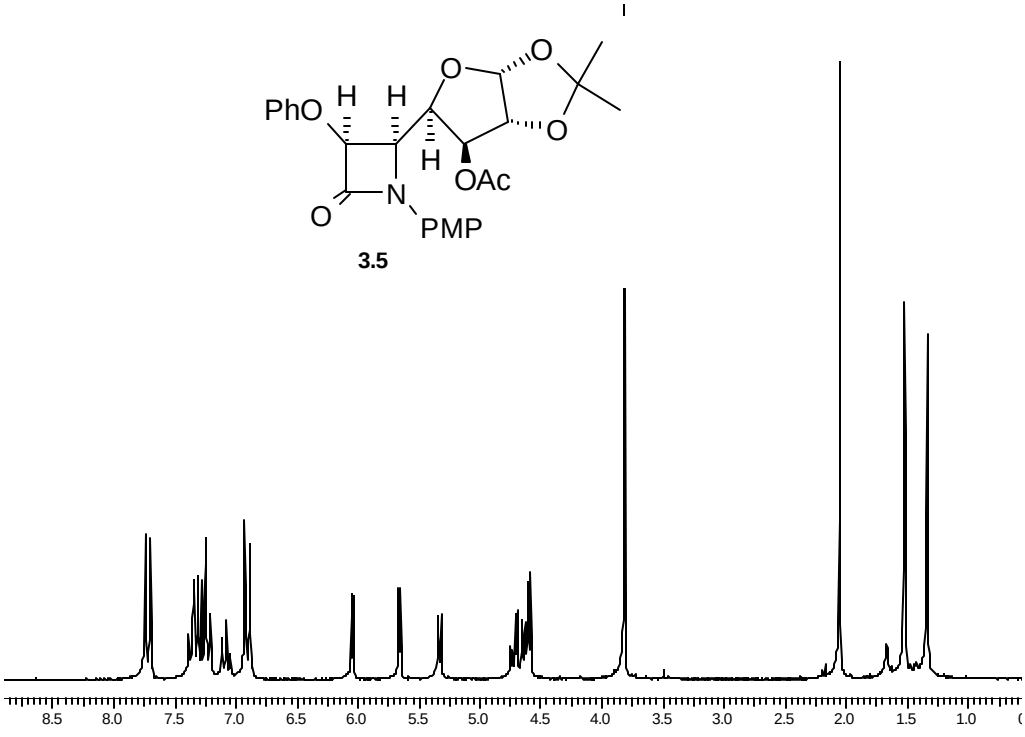
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OAc
N
O
PMP
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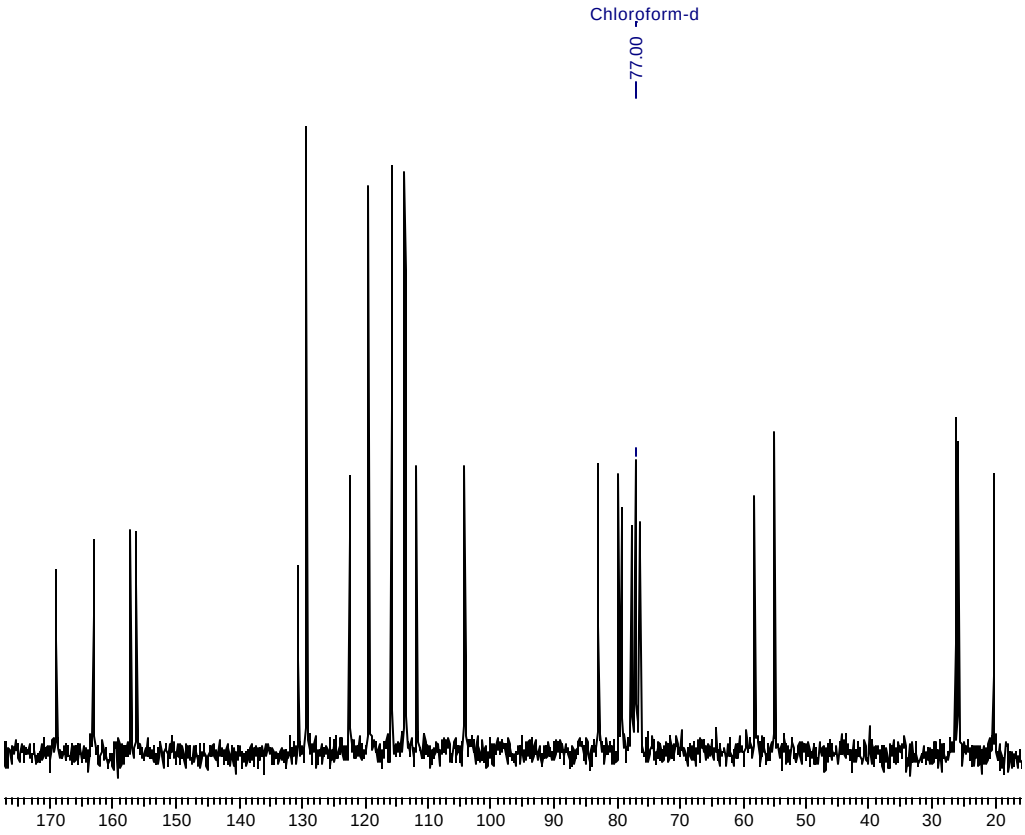
3.5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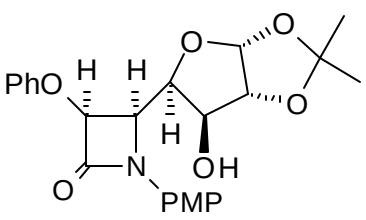
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H
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OH
O
PMP

3.6

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6.0
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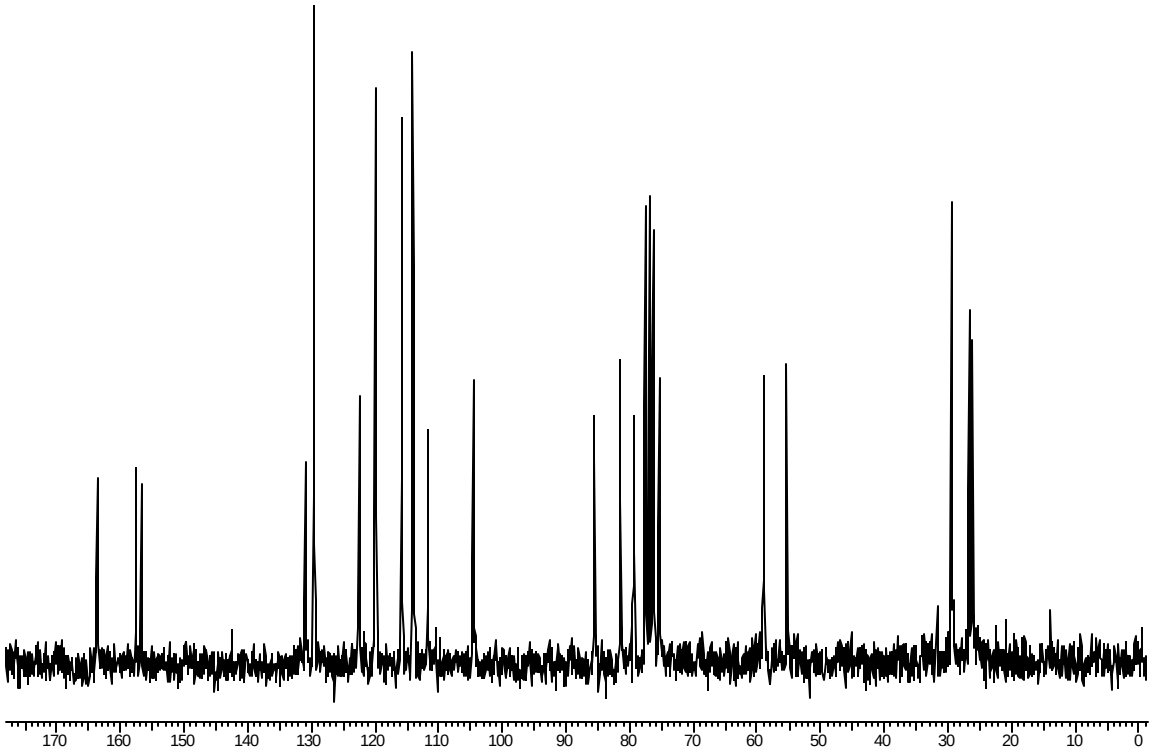
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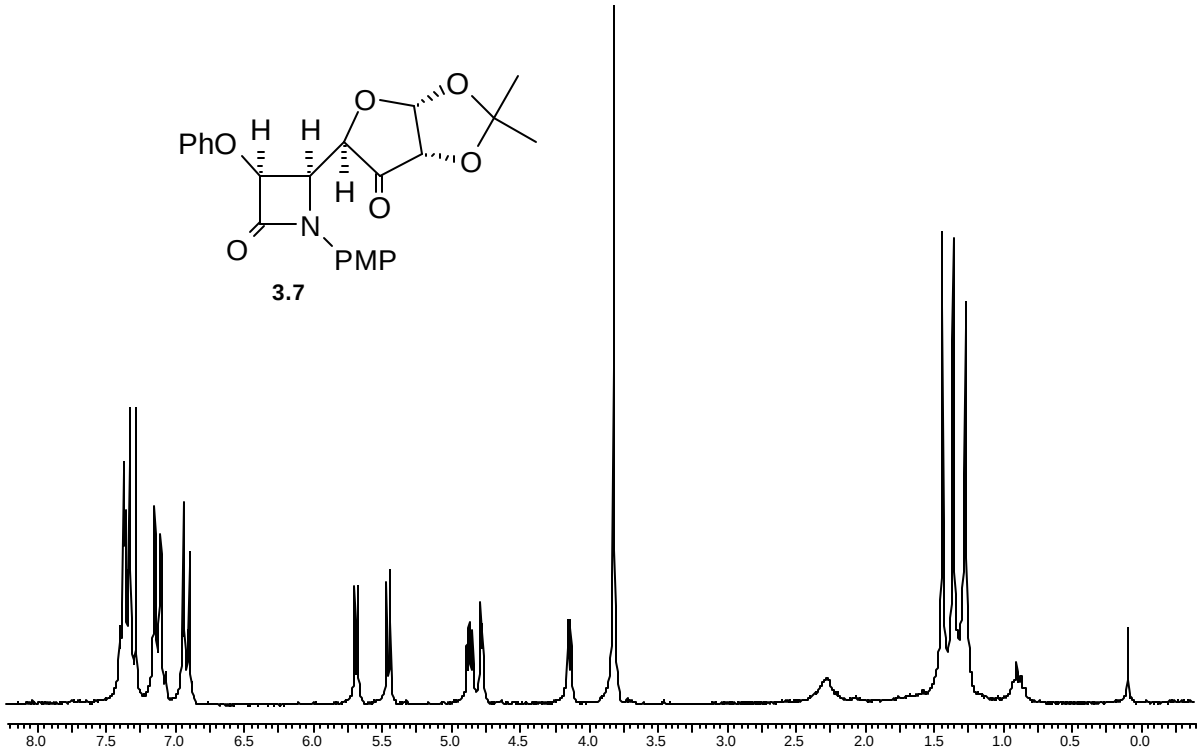
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O
N
O
PMP
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6.5
6.0
5.5
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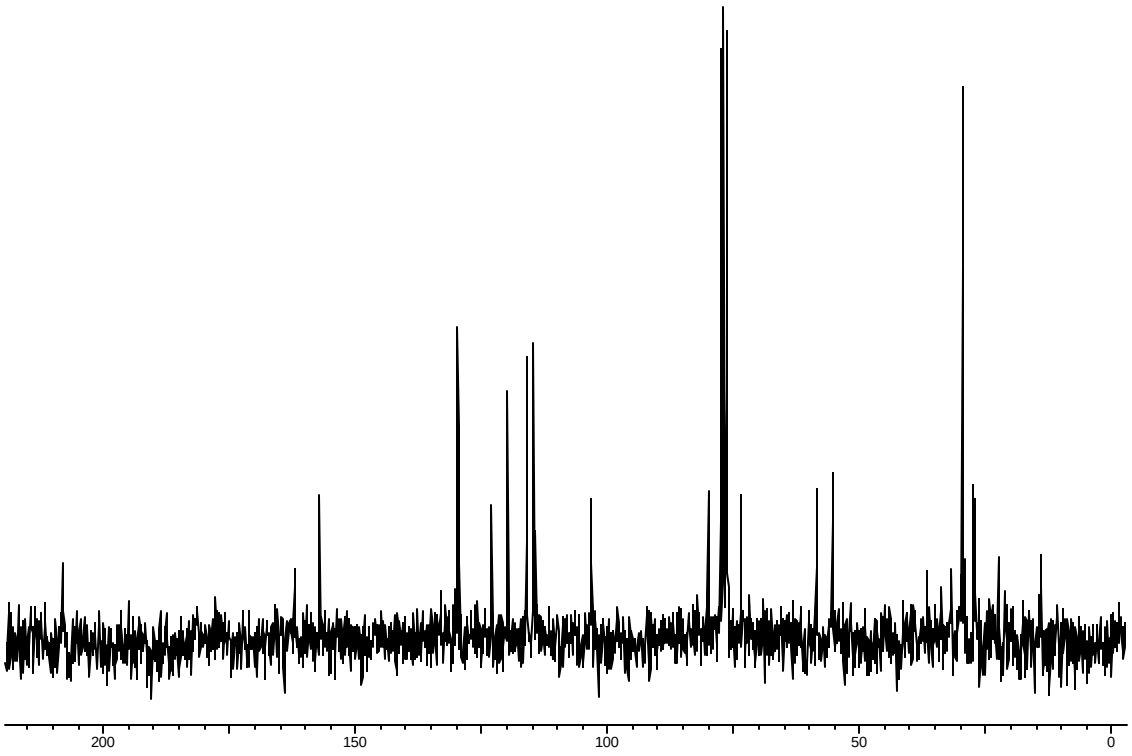
1.5
1.0
0.5
0.0

3.7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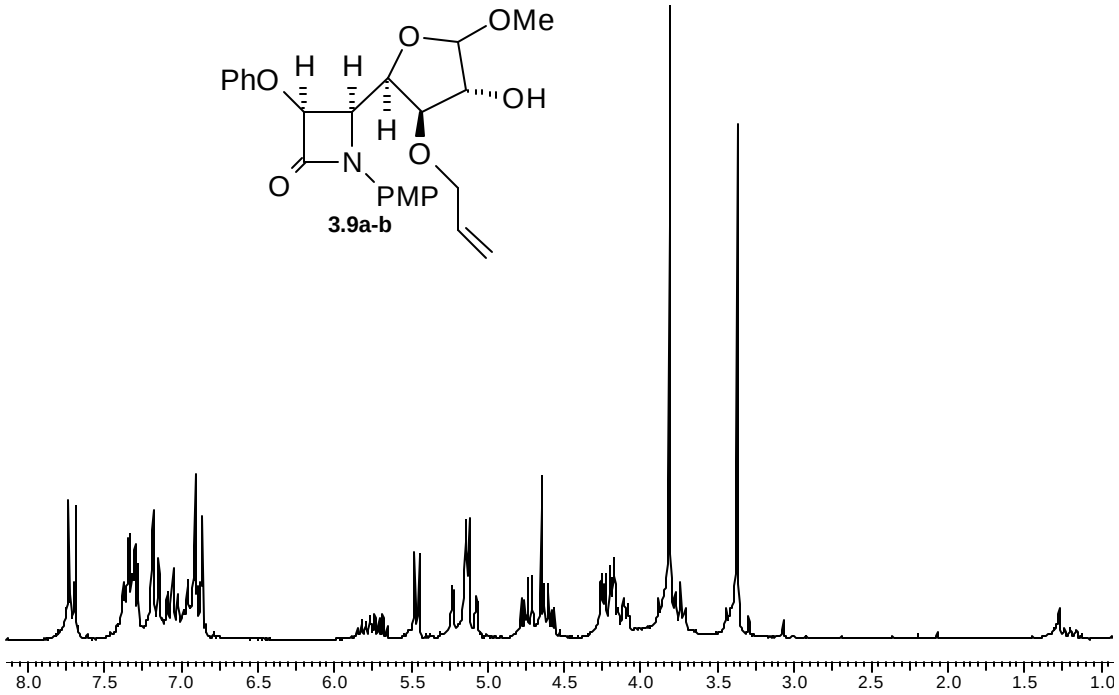
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PhO
H
H
OH
H
O
N
O
PMP
3.9a-b
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7.5
7.0
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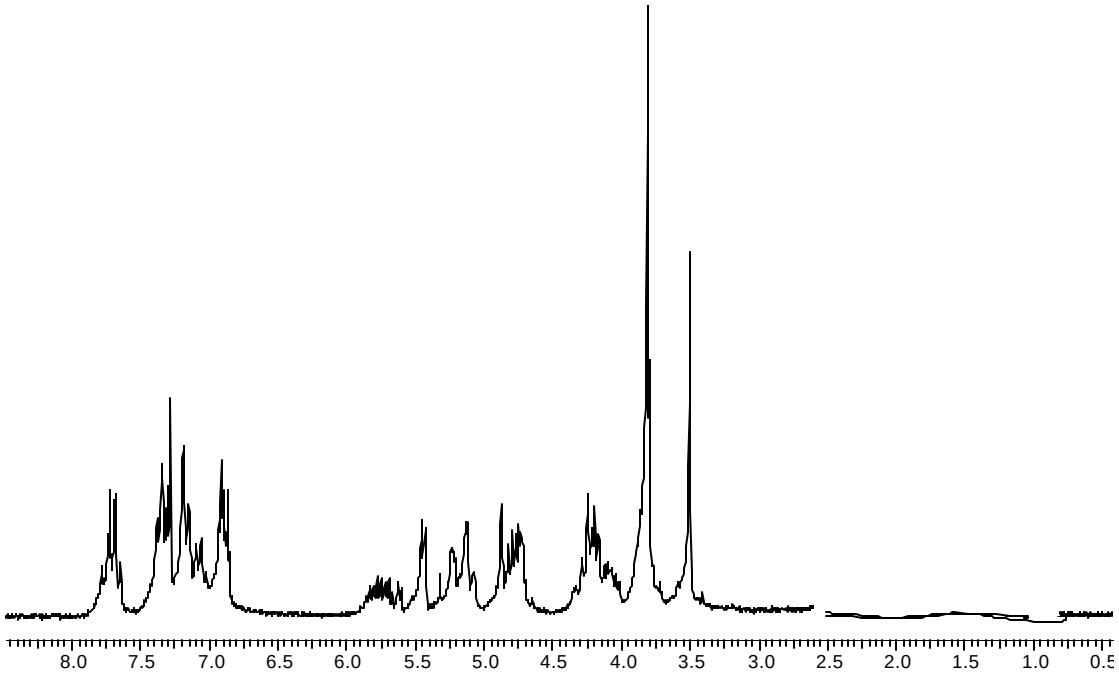
1.0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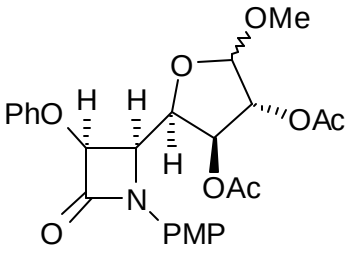
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PhO
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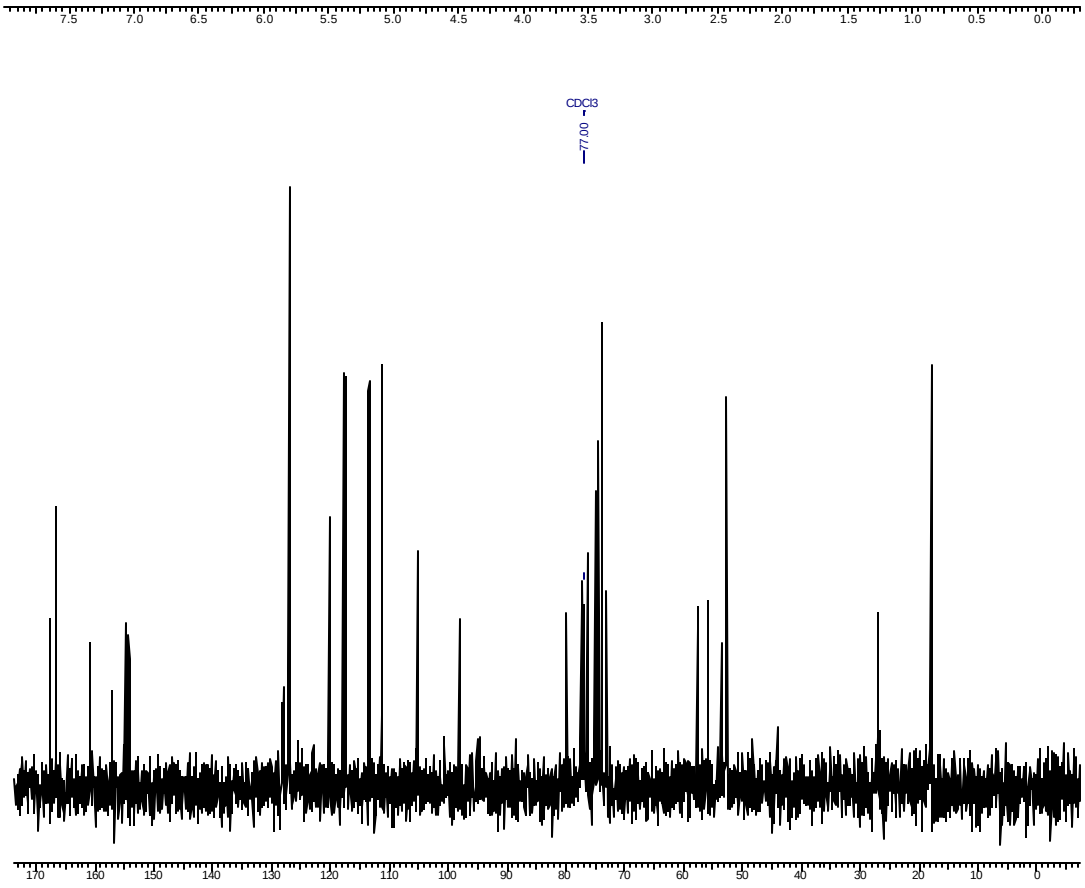
OAc
H
OAc
N
O
PMP

3.11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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CDCl3
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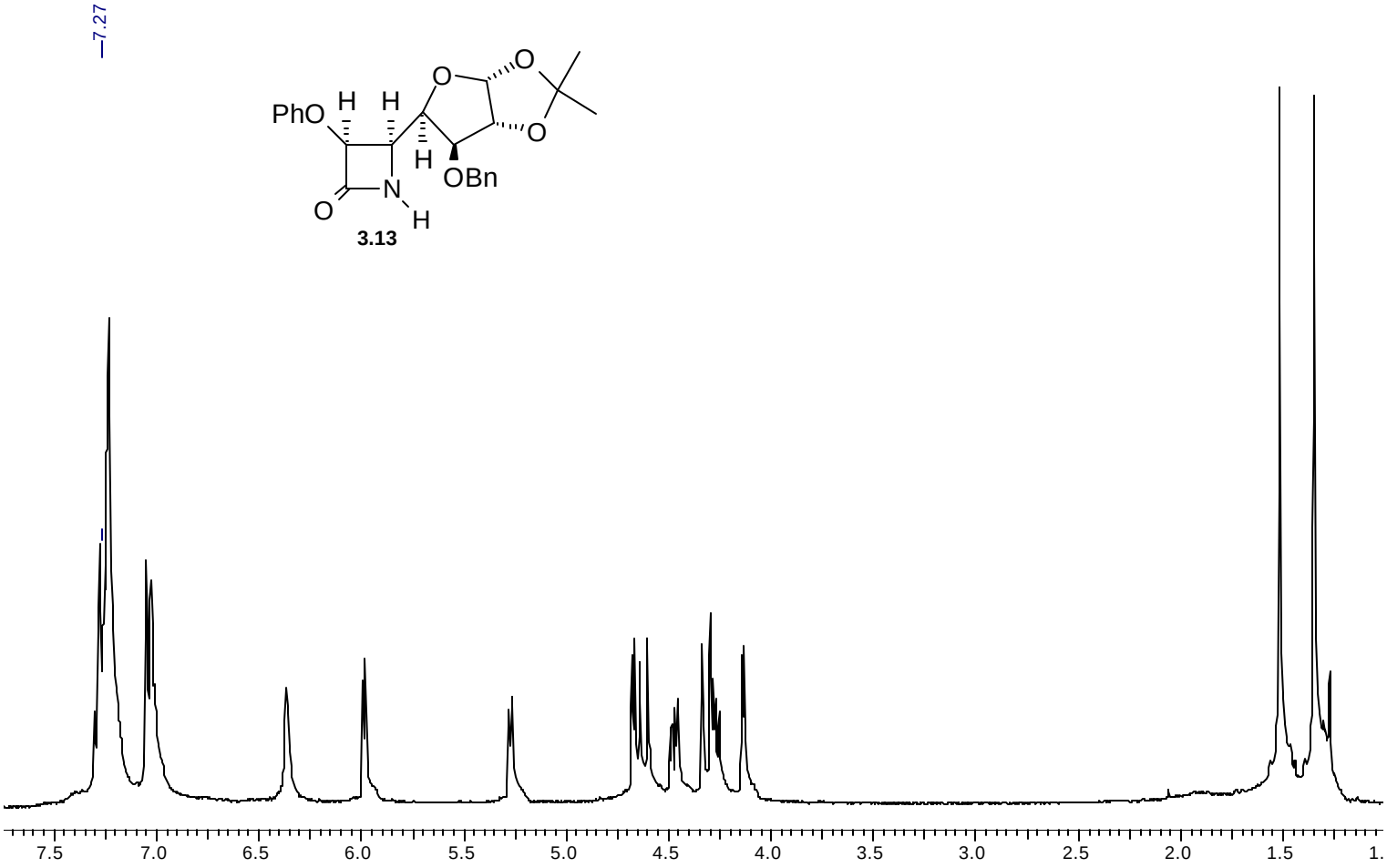
7.27
PhO
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H
O
O
O
H
OBn
N
H
O
3.13
7.5
7.0
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5.0
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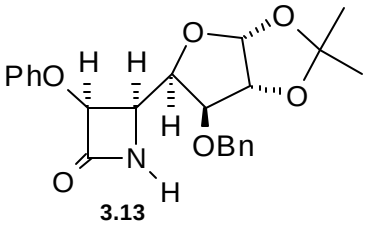
PhO
H
H
O
O
O
H
OBn
N
H
O

3.13

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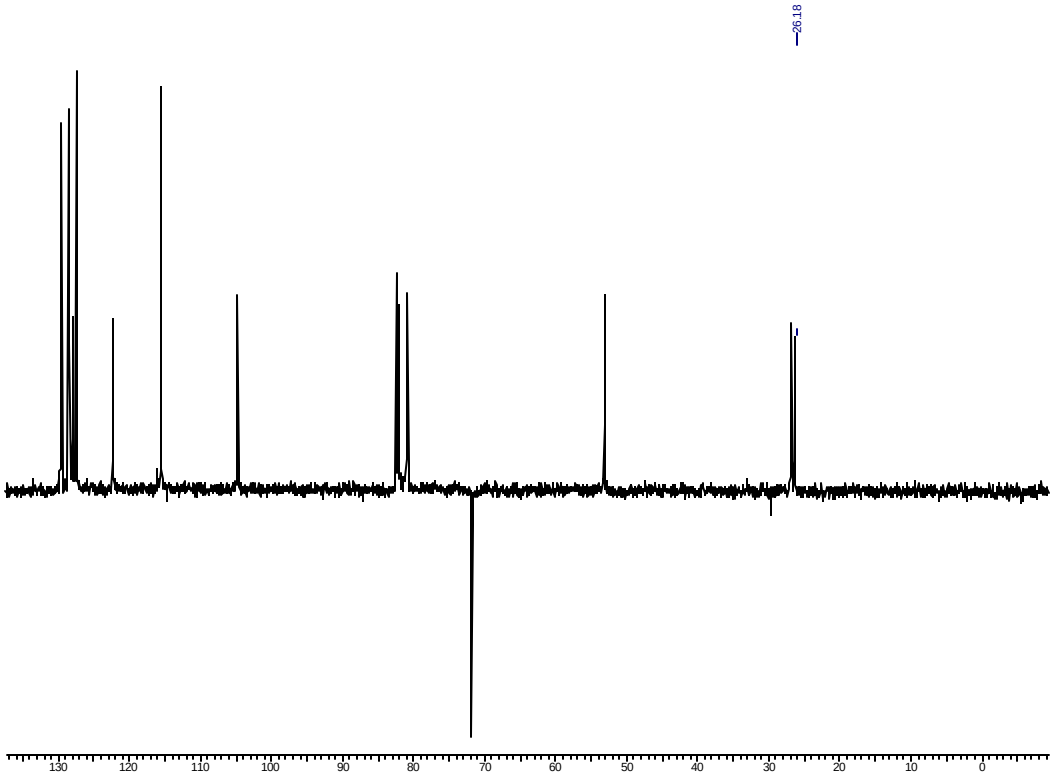
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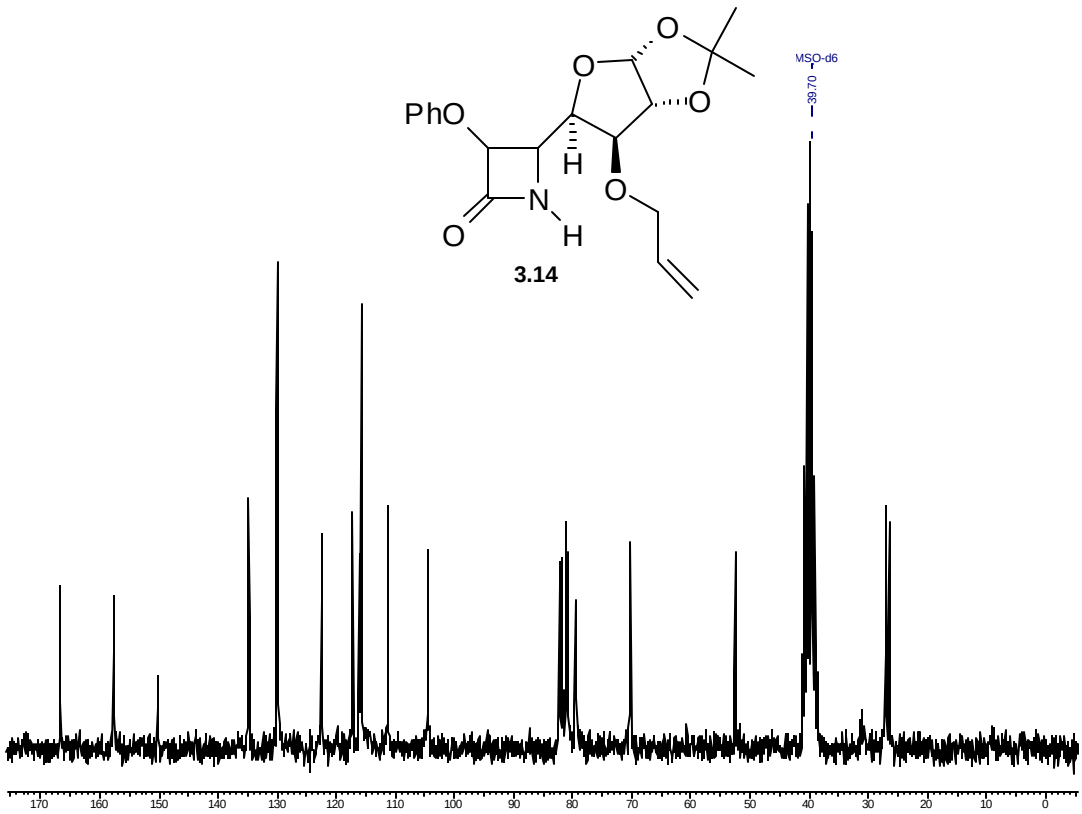
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O
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O
O
H
N
H
O
3.14
DMSO-d6
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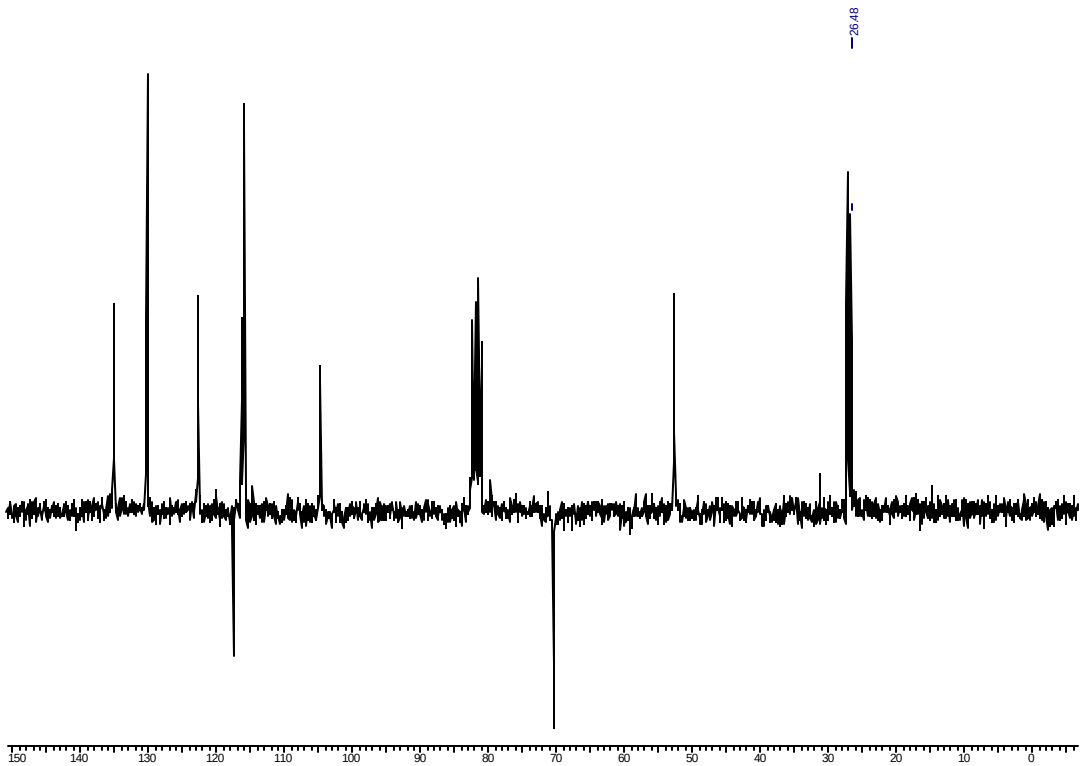
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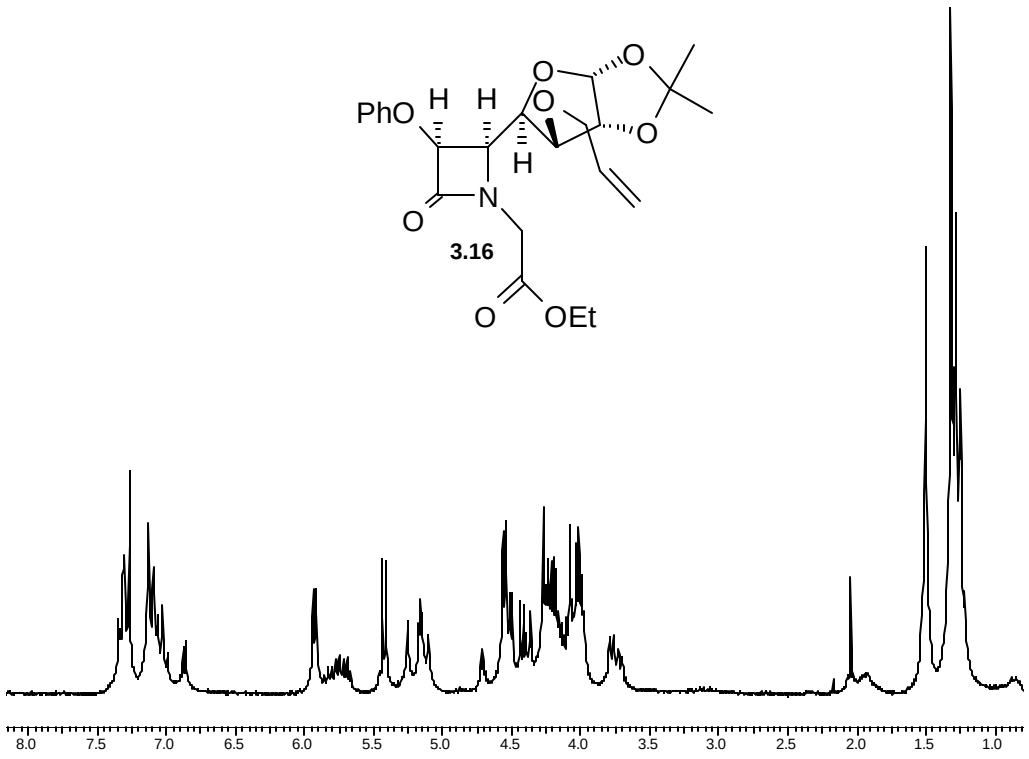
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N
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O
OEt
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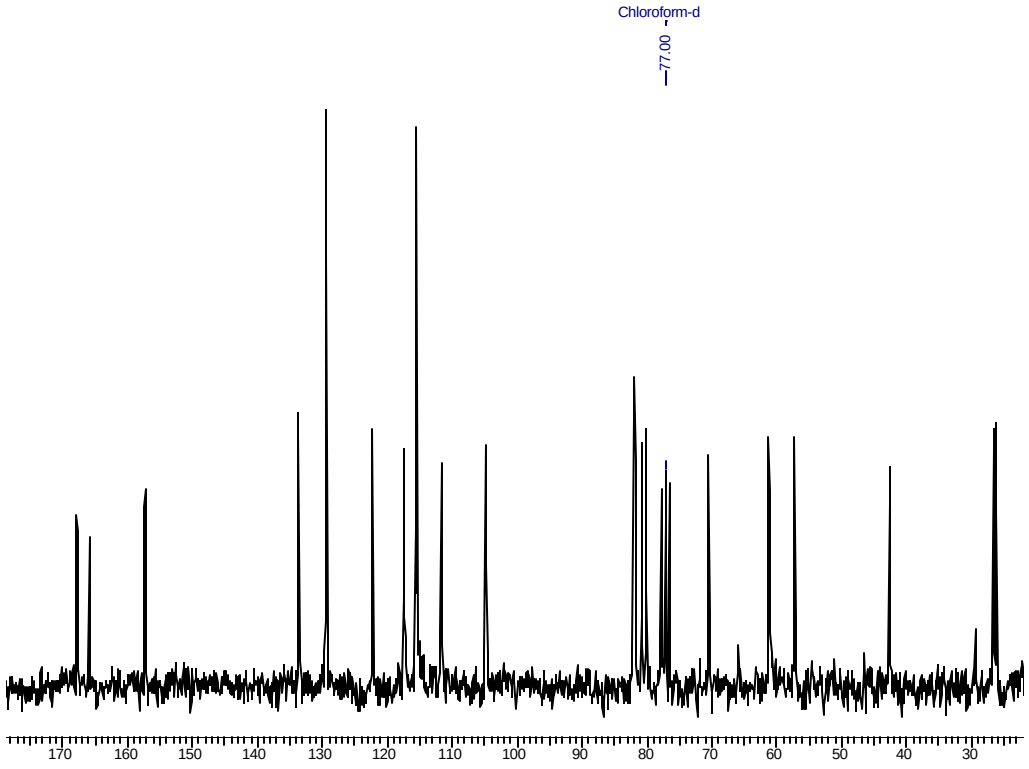
1.0


Chloroform-d
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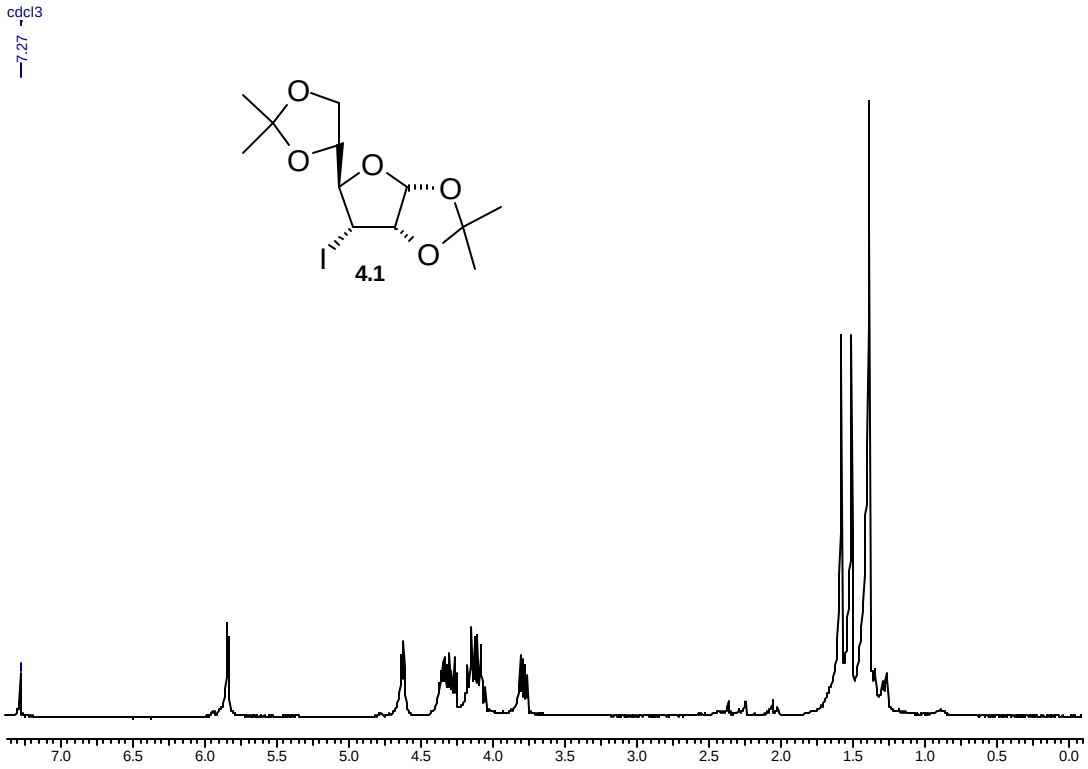
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7.27
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O
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O
O
I
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6.0
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1.5
1.0
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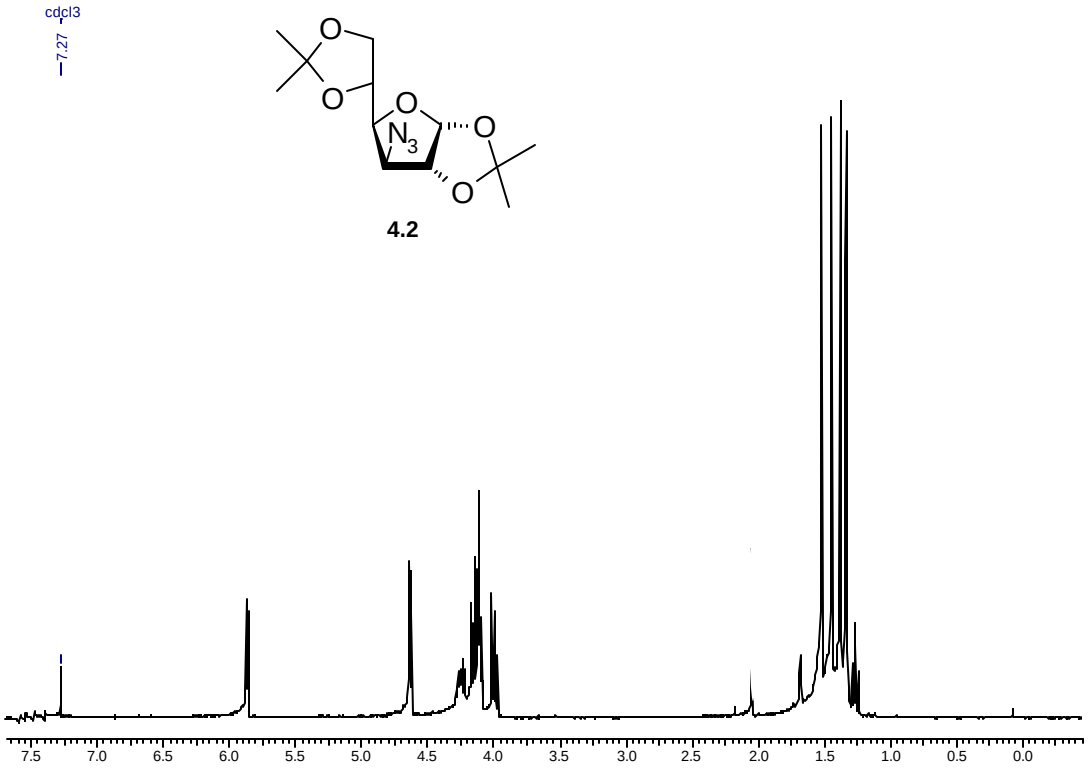
0.0

4.1


cdcl3
7.27
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O
O
N3
O
O
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6.0
5.5
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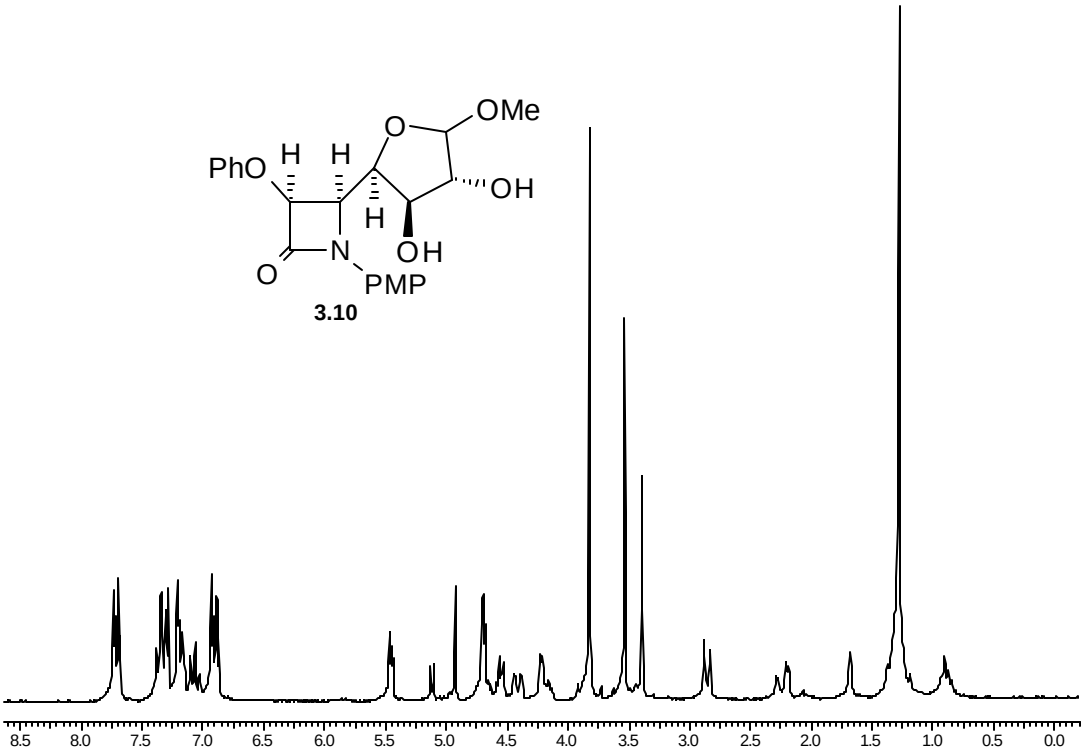
0.0

4.2


OMe
O
PhO
H
H
OH
H
N
OH
O
PMP
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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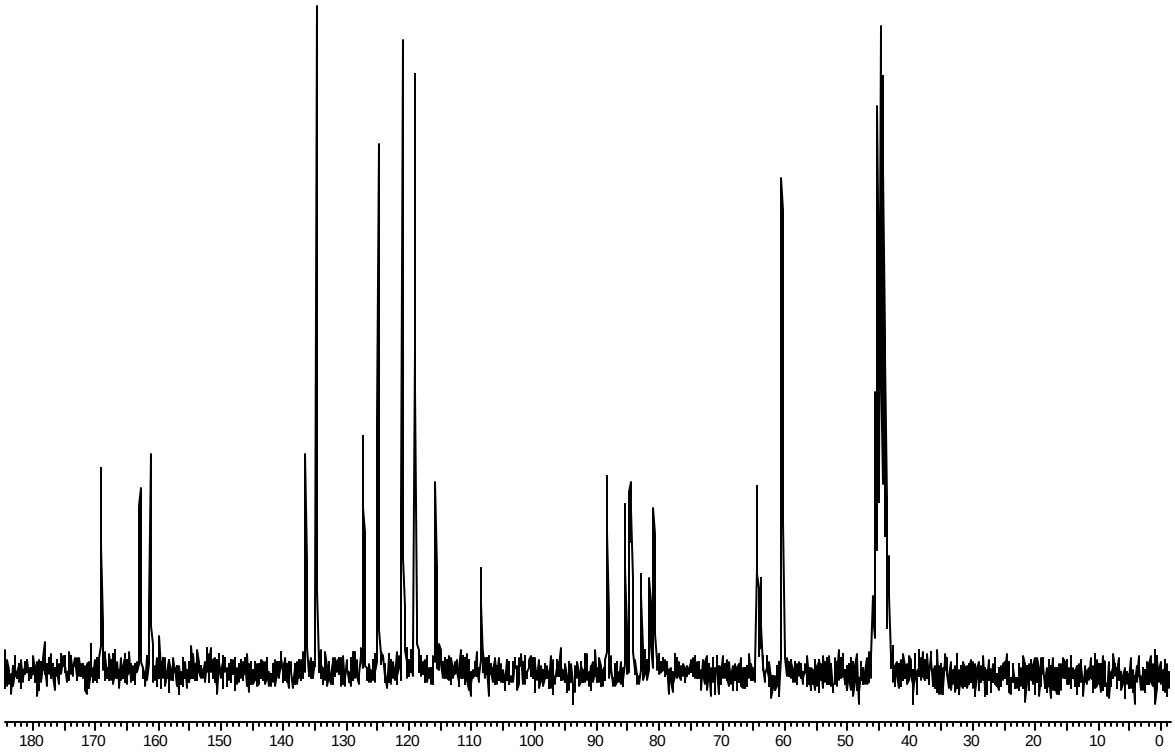
3.10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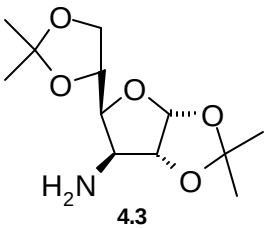

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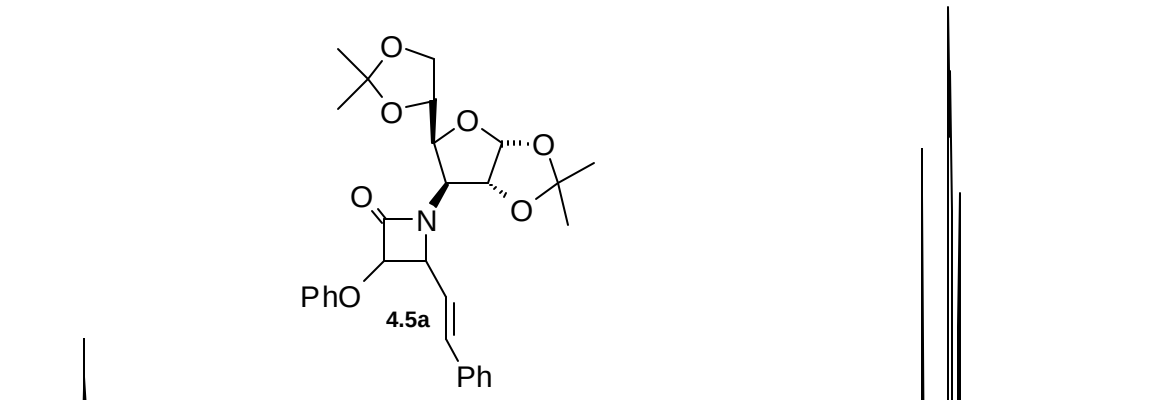
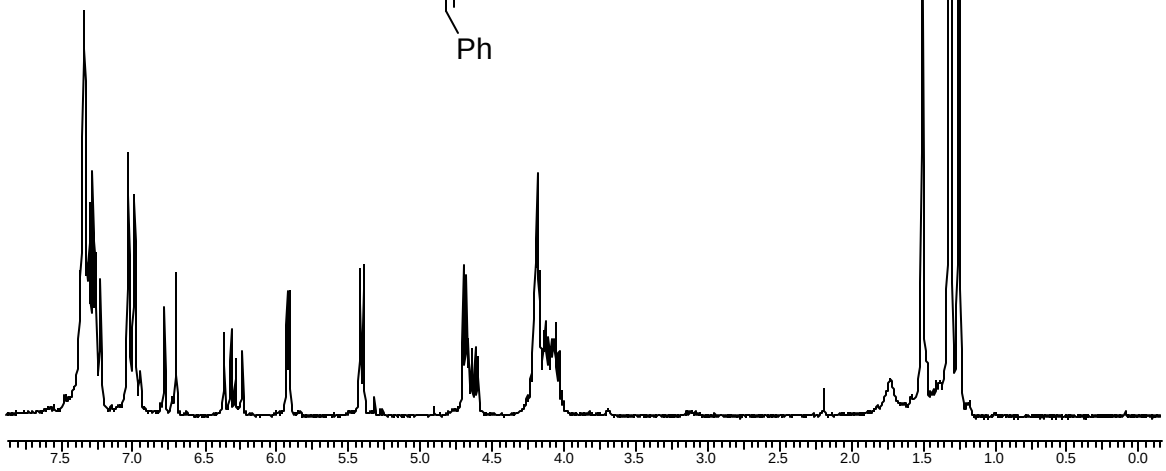

O
O
O
O
O
O
N
PhO
Ph

4.5a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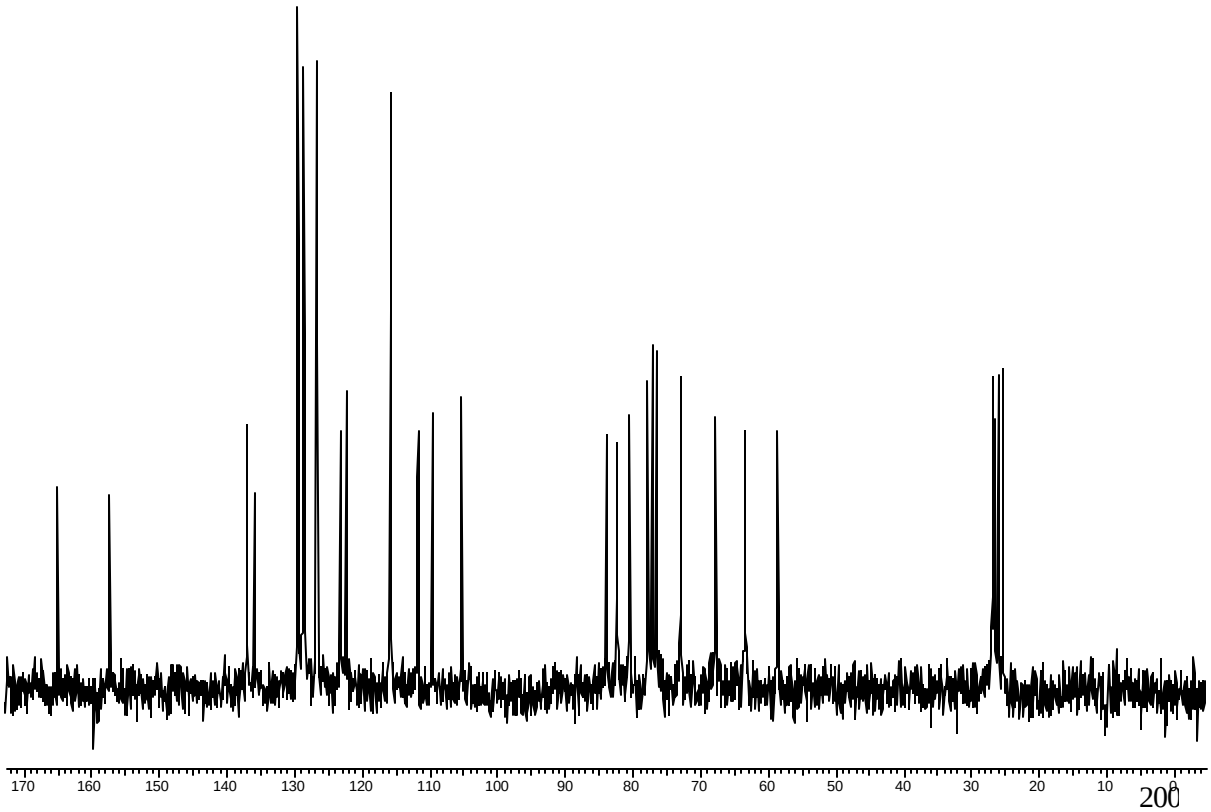
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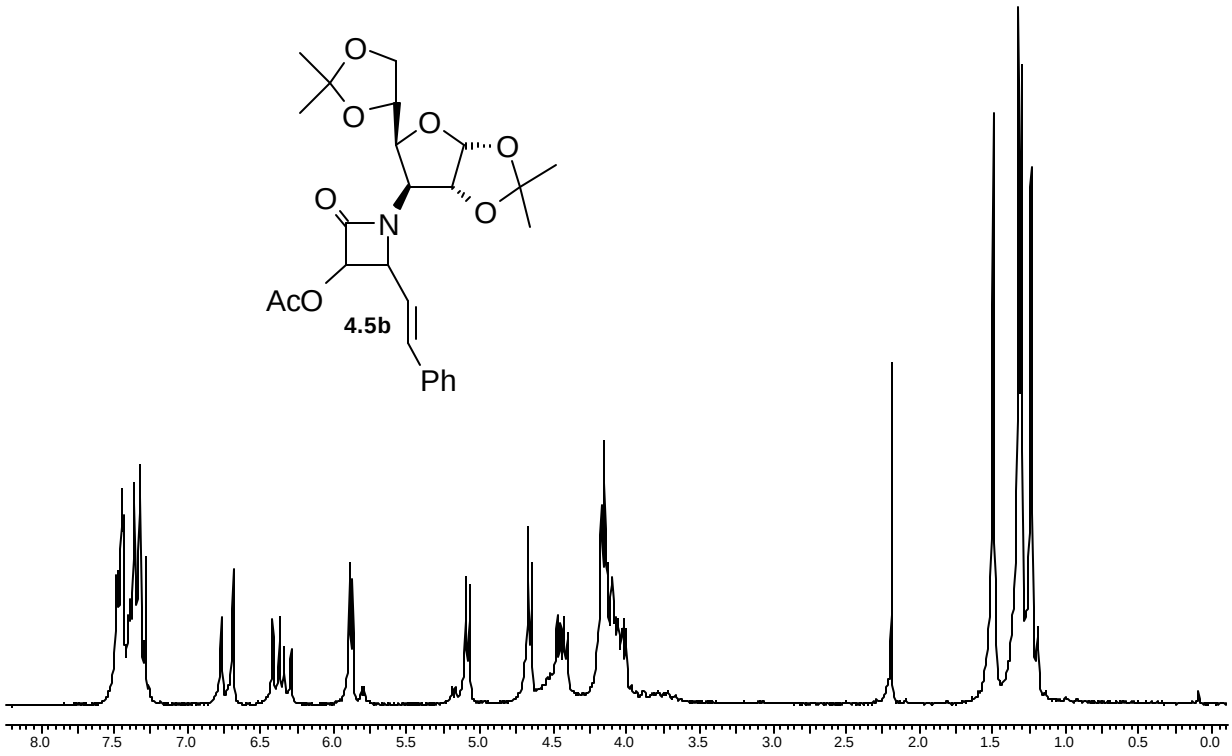
O
O
O
O
O
O
N
AcO
Ph
4.5b
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
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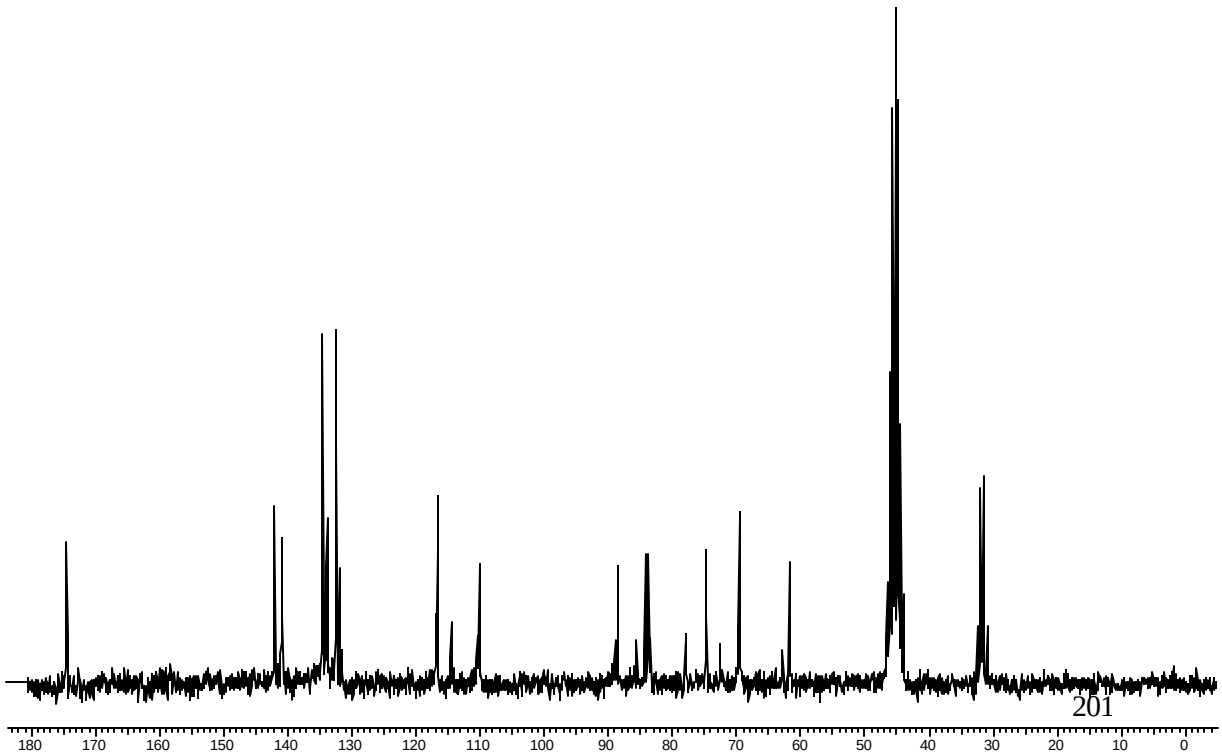
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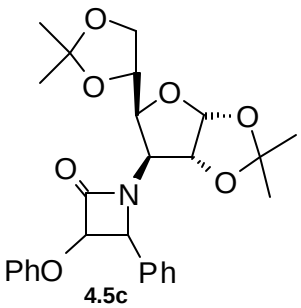
O
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O
O
N
PhO
Ph

4.5c

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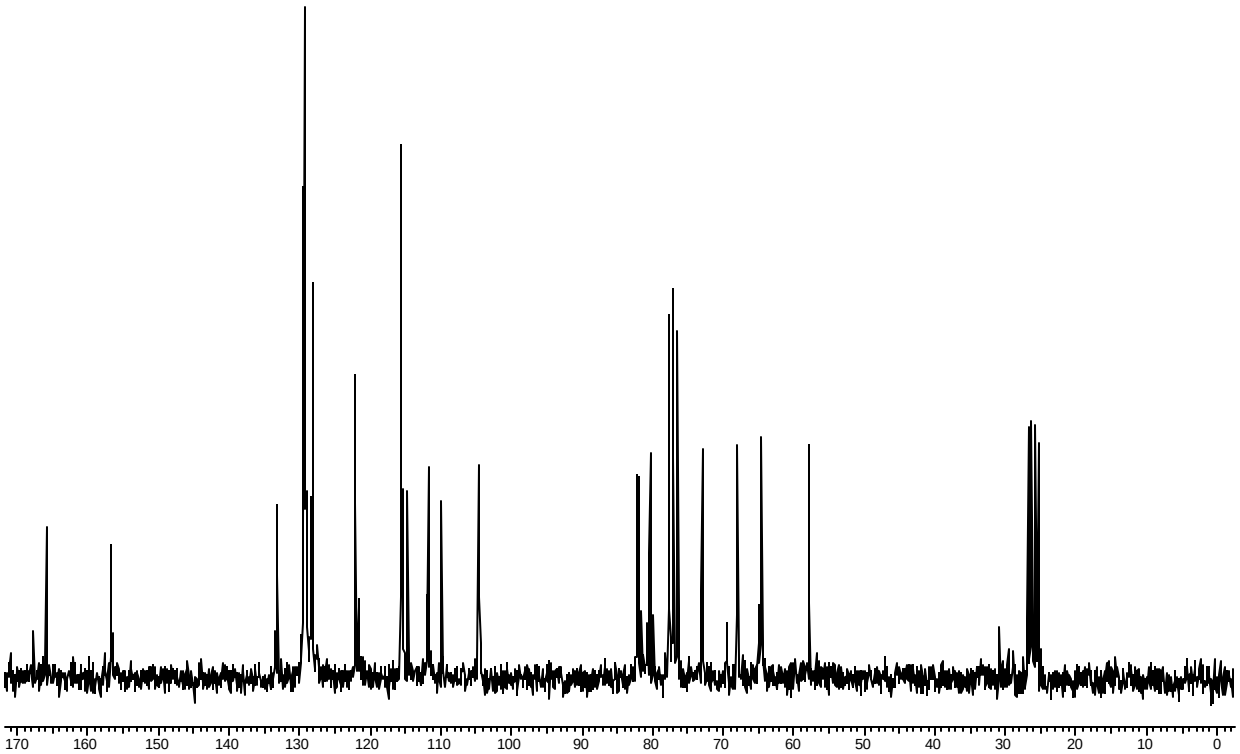
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