STUDIES IN POLYCYCLIC β-LACTAM SYNTHESIS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

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DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

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PUNE - 411 008

DECLARATION

I hereby declare that the work incorporated in the thesis entitled "**Studies in polycyclic β-lactam synthesis**" submitted for the degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. A. R. A. S. Deshmukh. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other university.

Date: .06.2005

National Chemical Laboratory
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A. Jayanthi
Research Student

Dedicated to my family

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Finally I thank the Almighty for giving me the strength and the determination to keep going with my chin up whenever I was faced with hardships in my life.

A. Jayanthi

Abstract of the thesis

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

Name of student: **A. Jayanthi**

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

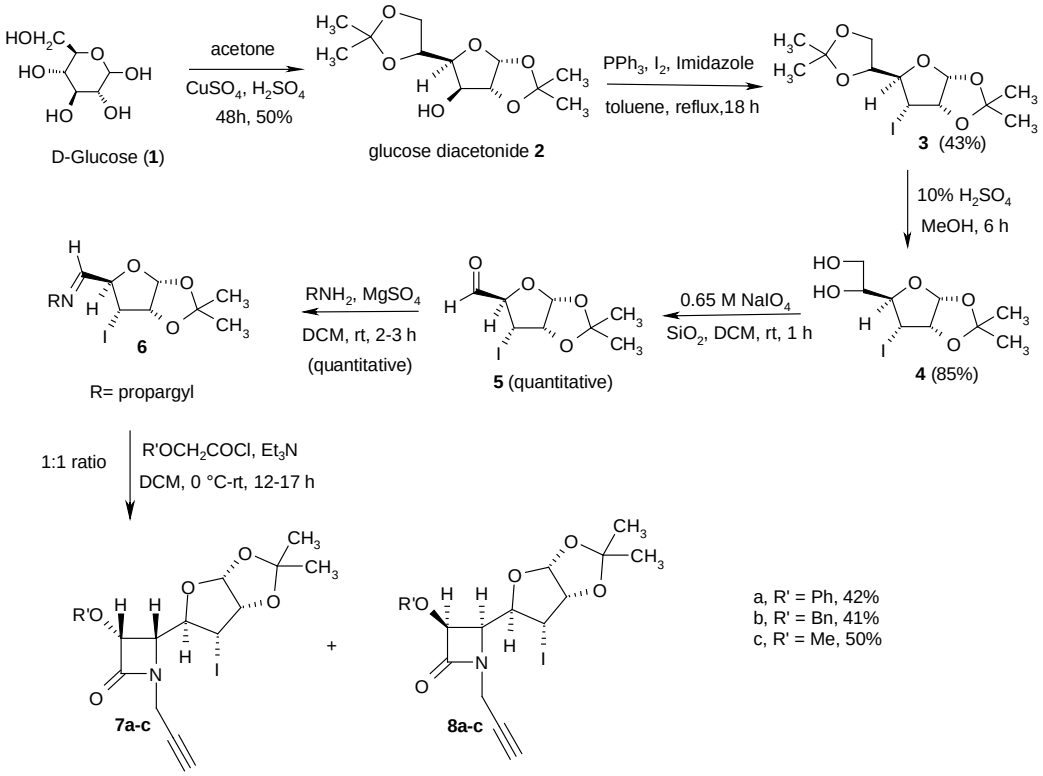
Abstract of thesis entitled: **"Studies in polycyclic β-lactam synthesis"**

Part – A

Synthesis of polycyclic β-lactams from glucose derived chiral template *via* intramolecular radical cyclization:

The extensive use of classical drugs such as penicillin and cephalosporin in antibiotherapy for several years resulted in increasing bacterial resistance through mutation and β-lactamase gene transfer. Much attention, therefore, has been focused on the synthesis of new non-classical polycyclic β-lactams to overcome the defense mechanism of bacteria and thus enabling improved treatment of bacterial infections. Considering the sensitivity of β-lactams towards nucleophilic reagents, several groups have, therefore, employed an intramolecular radical cyclization approach towards such azetidin-2-ones bearing appropriate appendages to synthesize polycyclic β-lactams with high regio- and stereoselectivity. Following suit, our work too has focused on construction of various polycyclic β-lactams using radical cyclization.

Scheme 1

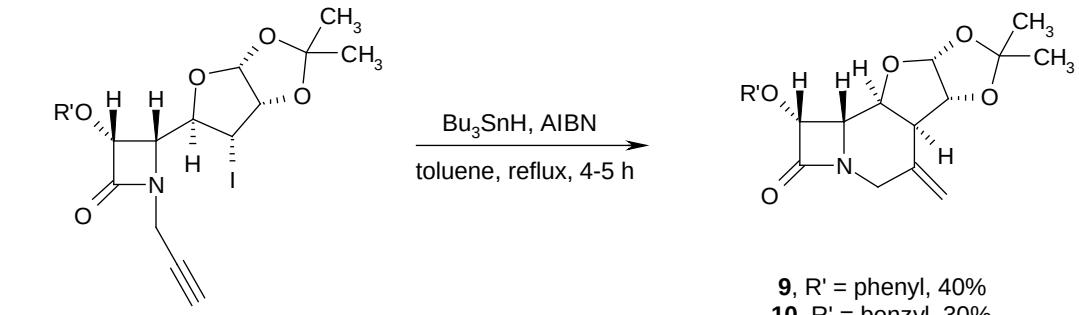


We planned our work for the construction of polycyclic β-lactams starting from D-glucose since they were known to show high levels of diastereoselectivity in the asymmetric Staudinger reaction for the β-lactam synthesis. Commercially available D-glucose (**1**) was converted into chiral iodo aldehyde **5** by known reaction sequences as shown in Scheme 1. The chiral imine **6** derived from iodo aldehyde and propargyl amine was then subjected to Staudinger reaction with various acid chlorides (benzyloxy, phenoxy and methoxy) in the presence of excess Et_3N to afford a 1:1 diastereomeric mixture of *N*-propargyl substituted β-lactams **7a-c** and **8a-c** in moderate yield (40-50 %). The diastereomers were separable either by flash column chromatography or by crystallization from methanol. The absolute stereochemistry at C-3 and C-4 carbons was assigned as 3*R*, 4*S* from the single crystal X-ray analysis of **7a**.

Equipped with an efficient synthesis of N-propargyl β-lactams, intramolecular radical cyclization was performed with the isolated diastereomers. Thus, when beta diastereomers **7a-b** were treated with tributyltin hydride in the presence of AIBN in

refluxing toluene (Scheme 2), *exo-dig* mode of cyclization operated and proceeded to furnish tetracyclic β-lactams **9-10** in 30-40 % yield.

Scheme 2

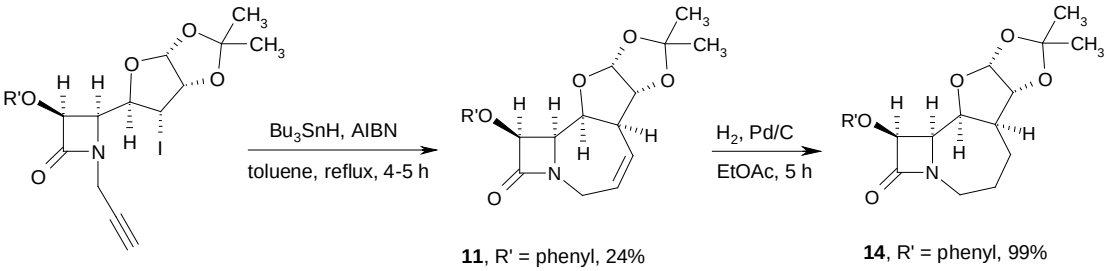


7a, R' = phenyl; **7b**, R' = benzyl

9, R' = phenyl, 40%
10, R' = benzyl, 30%

In the case of alpha diastereomers **8a-c**, the cyclization proceeded through *endo-dig* mode to afford polycyclic β-lactams **11-13** (Scheme 3). The regioselectivity of radical cyclization could be attributed to the steric effect imposed by the acetonide moiety.

Scheme 3

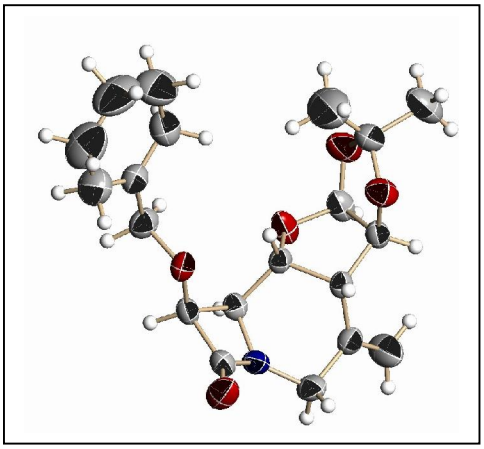


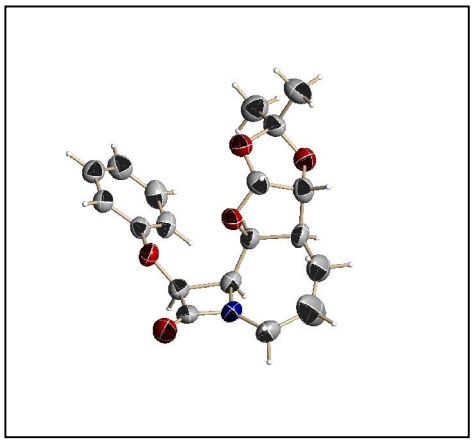
8a, R' = phenyl; **8b**, R' = benzyl;
8c, R' = methyl

11, R' = phenyl, 24%
12, R' = benzyl, 27%
13, R' = methyl , 37%

14, R' = phenyl, 99%

The structure and absolute stereochemistry of *exo-* and *endo-dig* cyclized products were confirmed by 2D NMR studies and single crystal X-ray analysis of **10** and **14.**

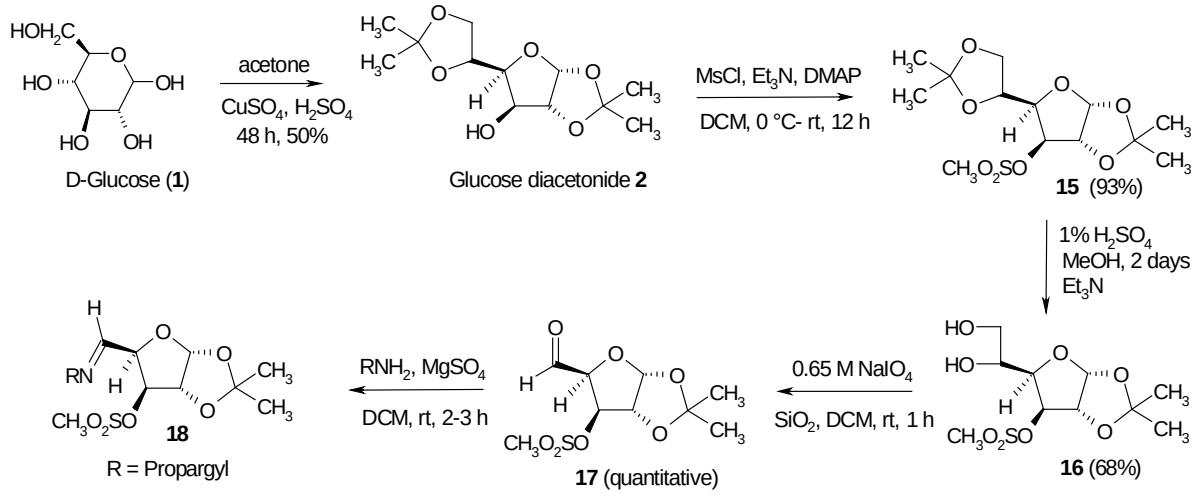


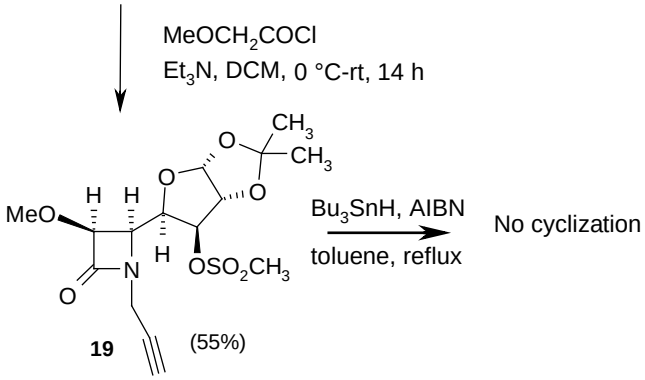


Crystal structure of 10 *Crystal structure of 14*

Consequent to the absence of diastereoselectivity with iodoaldehyde **5**, we prepared the mesylate derivative **15** of glucose diacetonide, which was then converted to the propargyl imine **18** employing identical transformations as for the iodo derivative. This propargyl imine **18** on Staudinger cycloaddition with methoxy acetyl chloride in the presence of Et_3N yielded a single diastereomer **19** exclusively. Unfortunately, attempted radical cyclization of **19** using tributyltin hydride proved to be unrewarding and resulted in recovery of starting material.

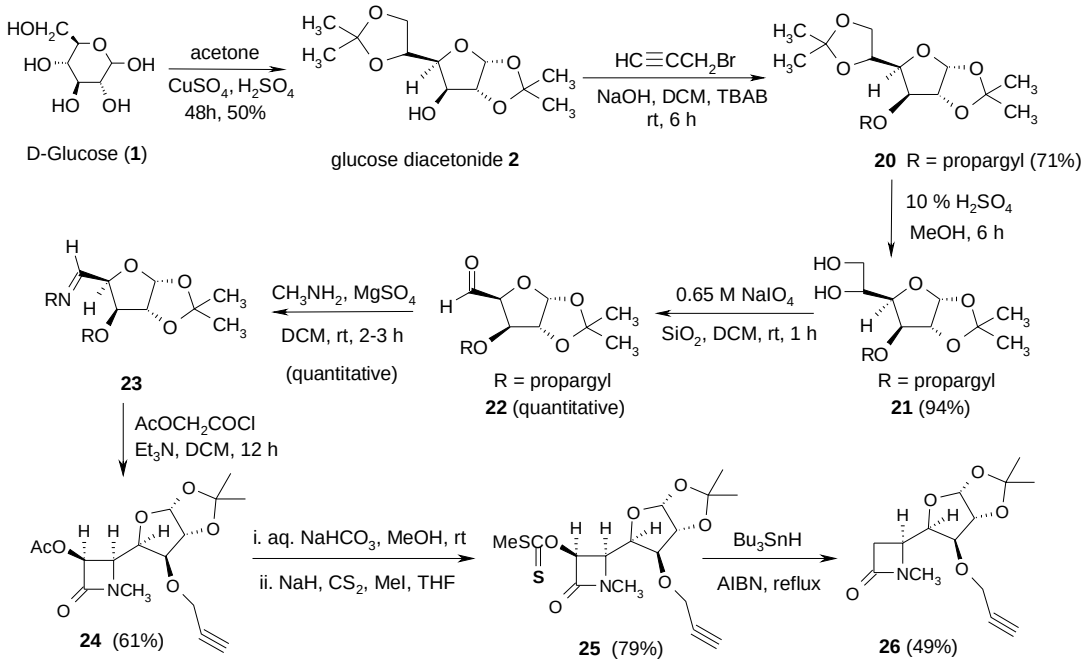
Scheme 4





We then designed an alternate strategy in which we envisaged the desired cyclization through a radical generated at the C-3 position of the β-lactam as against our earlier study wherein we had the radical generator on the carbohydrate moiety that was anchored to the C-4 position. Towards this, 3-acetoxy β-lactam **24** was prepared stereospecifically as shown in Scheme 5. Hydrolysis of the acetoxy functional group followed by treatment with carbon disulphide and methyl iodide in the presence of NaH gave the corresponding xanthate ester **25**. But our attempts at radical cyclization of the xanthate ester **25** resulted in the formation of the reduced product **26** instead of the desired cyclized one.

Scheme 5



Part – B

Allyl azides from allyl alcohols using triphosgene as an alcohol activator and their application in the synthesis of mono and polycyclic β-lactams:

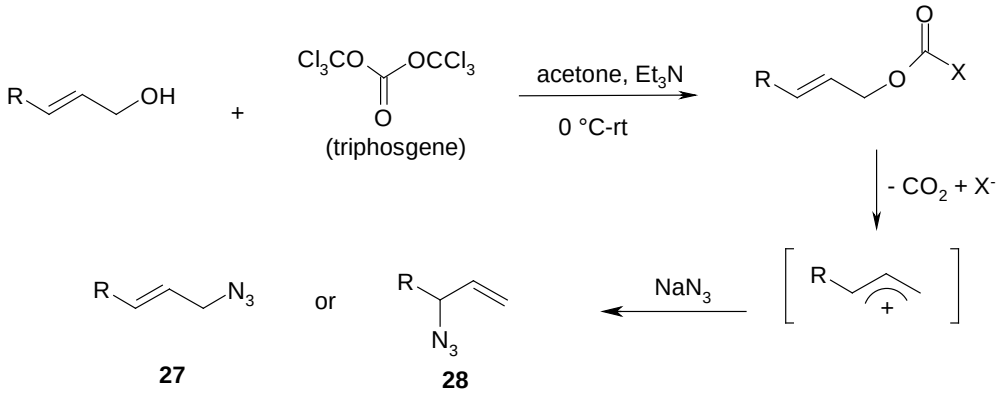
Allyl azides are important synthetic intermediates used in 1,3-dipolar cycloaddition, as precursor of nitrenes and particularly for conversion to allyl amines. In spite of their synthetic significance, only a few methods are known in the literature for the synthesis of allyl azides. They include transition metal catalyzed reactions using Pd, Mo catalysts and by direct conversion of allylic alcohols into the corresponding azides using NaN_3 in the presence of BF_3/Et_2O, PPh_3/CCl_4 and $TMSCl/NaI/H_2O$ to name a few. We have herein developed a simple new methodology for the one-pot synthesis of allyl azides from allyl alcohols using triphosgene and NaN_3 in excellent yields compared to earlier methods and utilized the thus prepared azides for the preparation of N_1-cinnamyl β-lactams and further to construct polycyclic β-lactams.

i. Synthesis of allyl azides from allyl alcohols:

A mixture of allyl alcohol and triethylamine was treated with triphosgene in acetone or acetonitrile at 0 °C and stirred at room temperature for 3 - 4 hours followed by addition of

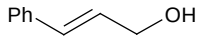
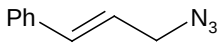
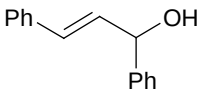
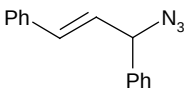
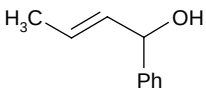
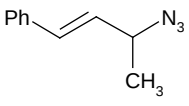
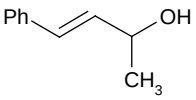
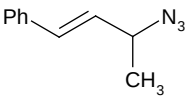
sodium azide to yield the corresponding allyl azide **27**/**28** in good to moderate yield (Scheme 6, table 1).

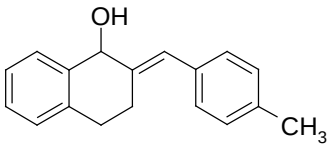
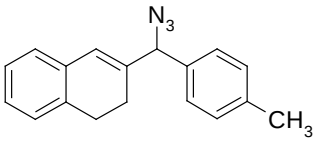
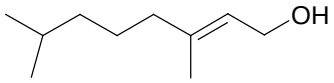
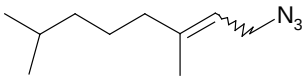
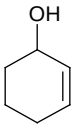
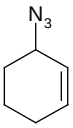
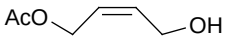
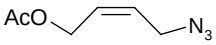
Scheme 6



Geraniol gave an E/Z mixture (55:45) of geranyl azides in 66 % along with a small amount of linanyl azide. Several azides were prepared by this method as shown in Table 1. 1-Phenyl-but-2-en-1-ol and 4-Phenyl-but-3-en-2-ol gave the same allyl azide through an identical carbocation intermediate (entry 3 and 4 in Table 1). Phenyl substituted allyl alcohols gave excellent yields compared to methyl substituted alcohols, while low yields of azides were obtained in the case of lower allylic alcohols. The mechanism of formation of allylic azides could be proposedly through a nucleophilic attack of azide on the allyl carbocation, which in turn is generated from allyl chloroformate through evolution of carbon dioxide.

Table 1: **Preparation of allyl azides using triphosgene and sodium azide**

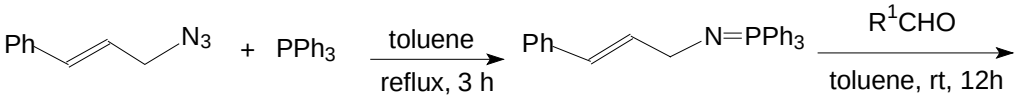
S. No.	Substrate	Product	Yield (%)
1			80
2			90
3			66
4			60

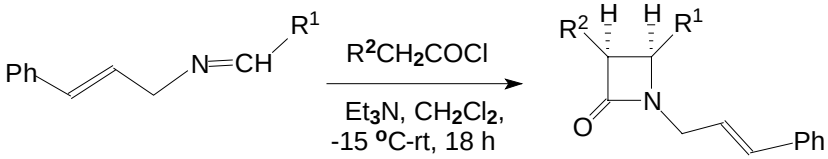
5			91
6			66
7			46 GC yield
8			63
9	$PhCH_2OH$	$PhCH_2N_3$	64

ii. Synthesis of *N*1-cinnamyl β-lactams:

It is well documented that iminophosphoranes derived from azides can be used as precursors to generate imines and thereby for the synthesis of β-lactams through Staudinger cycloaddition with ketenes. Cinnamyl azide was chosen as an example and its iminophosphorane on treatment with aldehyde gave imine **29**, which was then used as such without further purification.

Scheme 7



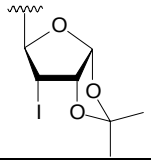
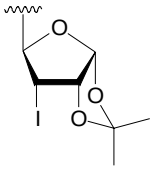


29 **30a-i**

The cycloaddition reaction of imine **29** with ketenes, generated from acid chlorides and Et_3N, afforded *cis*-*N*1-cinnamyl β-lactams **30a–i** (Scheme 2, Table 2). The chiral aldehyde derived from D-glucose gave the corresponding chiral imine, which on further reaction with

ketene derived from benzyloxy and phenoxyacetyl chloride yielded a 1:1 diastereomeric mixture of *cis*-β-lactams **30h-i** in good yield (entry 7 and 8 in Table 2).

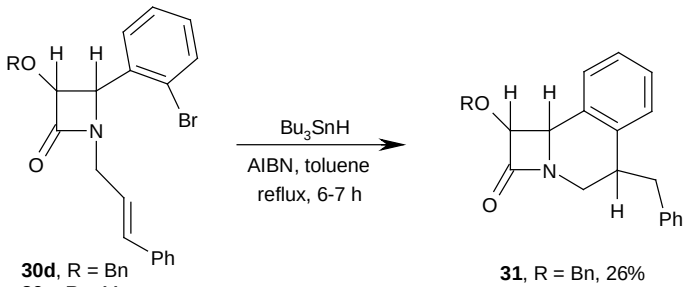
Table 2: Synthesis of *N*1-cinnamyl azetidin-2-ones

S. No.	Compound	R^1	R^2	Yield (%)
1	**30a**	Ph	-OCH_2Ph	74
2	**30b**	Ph	-OPh	84
3	**30c**	Ph	-OMe	84
4	**30d**	2-BrPh	-OCH_2Ph	72
5	**30e**	2-BrPh	-OMe	82
5	**30f**	4-MeOPh	-OMe	61
6	**30g**	4-MeOPh	-OCH_2Ph	78
7	**30h**		-OPh	72 (1:1 ratio)
8	**30i**		-OBn	76 (1:1 ratio)

iii. Synthesis of polycyclic β-lactams:

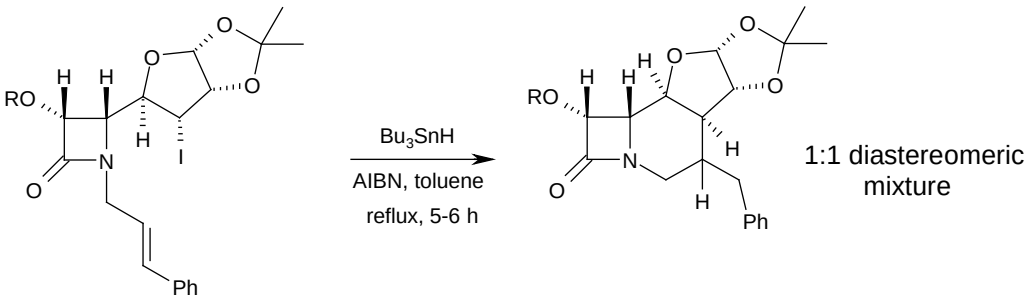
Considering their importance because of the carbapenam-like structure, azetidin-2-ones prepared from 2-bromobenzaldehyde and iodo substituted glucose aldehyde are suitable substrates to study intramolecular radical cyclization for the synthesis of polycyclic β-lactams (Scheme 8).

Scheme 8



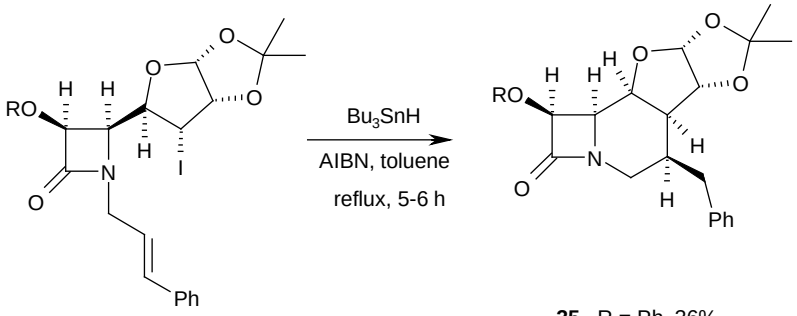
30d, R = Bn
30e, R = Me

31, R = Bn, 26%
32, R = Me, 28%



30h (beta isomer), R = Ph
30i (beta isomer), R = Bn

33, R = Ph, 64%
34, R = Bn, 56%



30h (alpha isomer), R = Ph
30i (alpha isomer), R = Bn

35, R = Ph, 36%
36, R = Bn, 28%

β-lactams **30d-e** on treatment with Bu_3SnH in the presence of catalytic amount of AIBN gave tricyclic benzocarbapenam type of compounds **31-32** *via exo-trig* cyclization. Similarly, glucose derived β-lactams **30h-i** also underwent smooth radical cyclization adopting an *exo-trig* cyclization pathway. Interestingly, a mixture of diastereomers **33-34** was obtained with the β-diastereomers while the α-diastereomers furnished a single isomer of the carbapenam like cyclized products **35-36** with excellent diastereospecificity.

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as Nujol mull or in Chloroform or neat, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattason, UK, Model-RS-1 FT-IR, using sodium chloride optics. IR bands are expressed in frequency cm^{-1}.
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker MSL-300, Bruker AC-200 and DRX-500. Chemical shifts were recorded in parts per million (δ). Abbreviations, viz., s= singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300 and Bruker DRX-500 instrument operating at 50 MHz, 75 MHz and 125 MHz.
5. Elemental analysis (C, H, N) was obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Optical rotation was measured on a JASCO-181 digital Polarimeter, JASCO P-1020 Polarimeter and ADP-220 Polarimeter using sodium D line (5893 Å). Concentration is expressed in g/100 mL)
7. EI Mass spectra were recorded on a Finnigan Mat-1020 spectrometer with a direct inlet system and electron spray ionization method (EI).
8. The progress of the reaction was monitored by analytical thin layer chromatography plates pre-coated with silica gel 60 F_{254} (Merck). Column purification of diastereomeric mixture of β-lactams and radical cyclized compounds was carried out with silica gel obtained from Merck (230-400 mesh, 9385 grade and 100-200 mesh) under nitrogen pressure.
9. ^{1}H NMR and ^{13}C NMR spectra of the compounds are attached at the end of the corresponding parts. For all the samples containing methylene and quaternary

carbons DEPT spectrum was scanned after scanning ^{13}C NMR spectrum and then the assignment of the peaks in ^{13}C NMR was done.

10. Known compounds were characterized by IR and proton NMR spectroscopy.
11. Petroleum ether refers to the fraction boiling between 60-80 °C.
12. Solvents for chromatography were distilled at their respective constant boiling points.
13. All reactions requiring anhydrous conditions were performed under a positive pressure of Argon using oven-dried glassware (120 °C), which was cooled under nitrogen.
14. Dichloromethane was dried over anhydrous P_2O_5 and stored over 4Å molecular sieves. Ether, THF and dioxane were distilled over sodium benzophenone ketyl.
15. All other solvents were dried following the procedure given in the book "Purification of Laboratory Chemicals" by Armarego and Perin (third edition).
16. Compounds have been named based on nomenclature provided by Chem Draw software.

CONTENTS

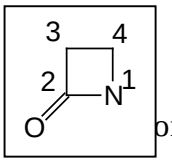
PART A

Synthesis of polycyclic β-lactams from glucose derived chiral template via intramolecular radical cyclization

This work has been published in *Synlett* **2004**, 1249 and *Synthesis* **2004**, *18*, 2965

Introduction:

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



(β-Lactam ring)

Figure 1

Until 1970, penicillin and cephalosporins[4] were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7-α-methoxycephalosporins[5] from "*Streptomyces*" in 1971 stimulated the search for novel antibiotics. The β-lactam antibiotics can be classified into several groups based on their structures (Figure 2).

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

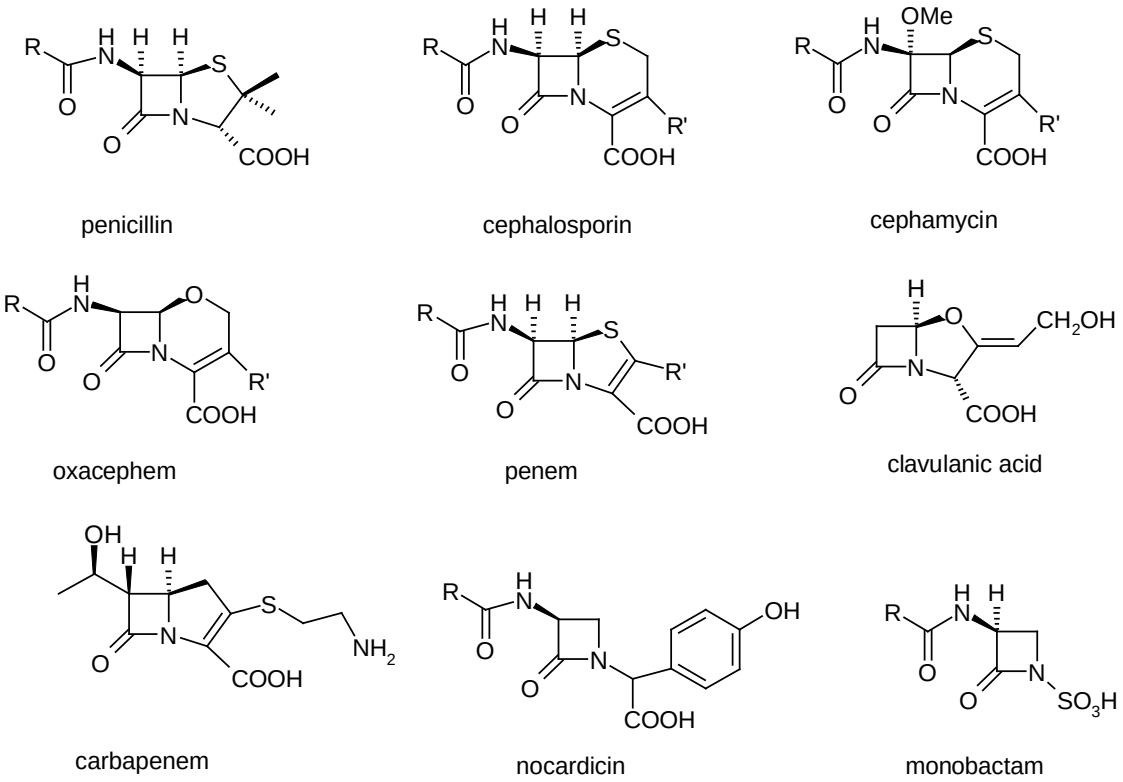
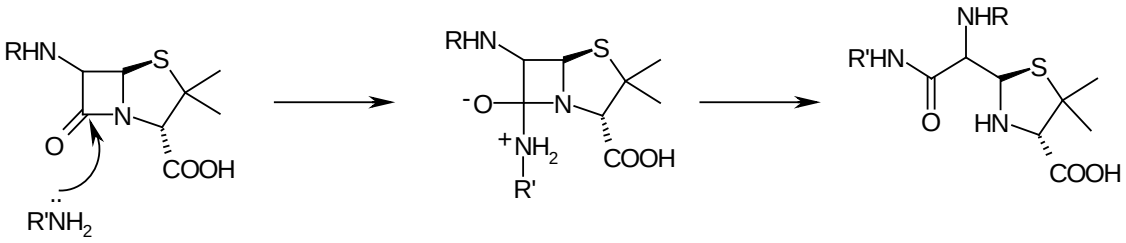


Figure 2. Classification of β-lactam antibiotics based on core structure

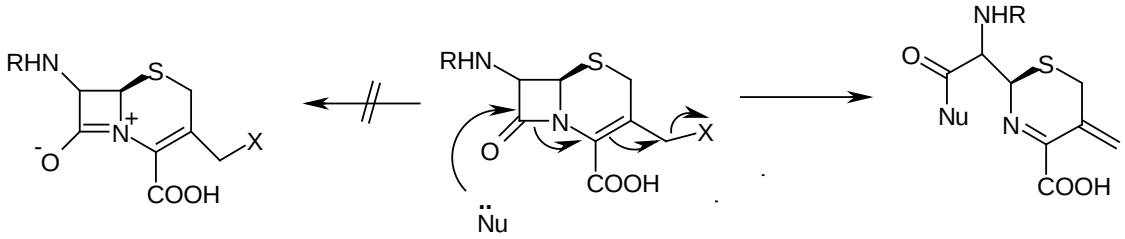
Mode of action of penicillin:

The biological activity of these antibiotics is mainly due to the presence of β-lactam ring. The SAR (structure activity relationship) studies[6] have shown that the essential requirement for an antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in an active form to the target site. Penicillin binds to the so-called 'penicillin-binding proteins (PCBs) which are specific molecules on the inner membrane of the cell wall. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[7] The schematic representation of this phenomenon in the case of penicillin and cephalosporin is shown below.

Biological activity of penicillin:[8]



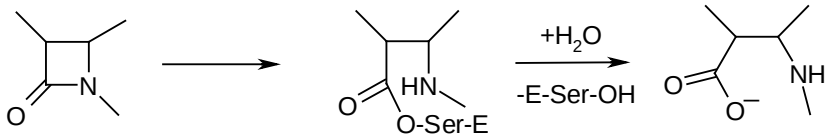
***Biological activity of cephalosporin*:[9]**



β-lactamases and β-lactamase inhibitors:

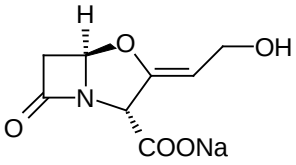
β-lactamases[10] are bacterial enzymes majorly responsible for resistance against β-lactam antibiotics. They present a serious and growing threat to the efficacy of antibacterial chemotherapy and thus pose a major challenge to human health. These defensive enzymes, prevalent in nearly every pathogenic bacterial strain, hydrolyze the β-lactam ring and release the cleaved, inactive antibiotics as amino acids.

There are four different classes of β-lactamase enzymes and they have been divided into two categories according to their catalytic active site. Class A, class C and class D enzymes, named as serine enzyme lactamases, possess serine in their active site and act by covalent acyl enzyme mechanism as shown below.[10] Class B enzymes on the other hand, called as Zinc enzyme lactamases, possess Zn metal ion in their active site and act via a non ionic intermediate mechanism.

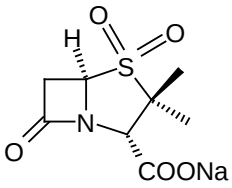


The problem of bacterial resistance to commercial antibiotics has opened a gateway to develop novel β-lactam antibiotics as β-lactamase inhibitors.[11-12] These β-lactamase inhibitors are compounds which are structural variants of natural antibiotics with a modified β-lactam skeleton. These compounds may not themselves possess antibiotic activity and hence would have to be used in combination with biologically active antibiotics. More specifically, they associate themselves with the lactamases, preventing prior interaction of β-lactamase with the β-lactam antibiotics and thereby safeguarding the antibiotic activity of the β-lactams.

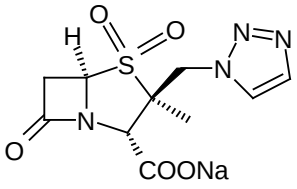
Clavulanic acid in combination with amoxicillin or ticarcillin, sulbactam in combination with ampicillin and tazobactam in combination with piperacillin are a few examples of clinically used β-lactamase inhibitors.



Clavulanate

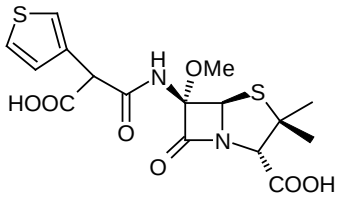


Sulbactam

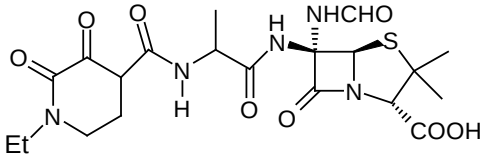


Tazobactam

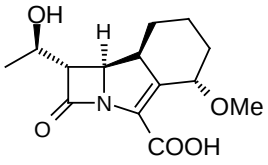
Temocillin, Formidacillin[12] and tricyclic tribactams[13] are other examples of effective β-lactamase inhibitors.



Temocillin



Formidacillin



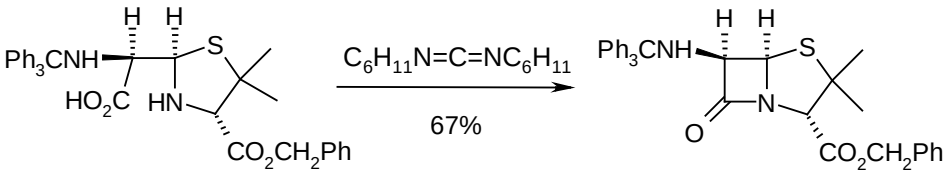
GV104326-Tribactams

Methods for constructing β-lactam ring:

There are several approaches available to construct these β-lactam building blocks and a few important methods will be discussed here.

Formation of the amide N1-C2 bond:

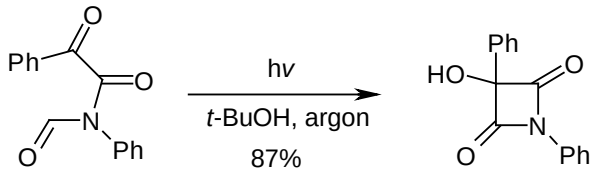
The simplest approach to the synthesis of azetidinone structures is via dehydration of β-amino acids. This method has been used in the landmark synthesis of penicillin by Sheehan et al. using dicyclohexylcarbodiimide as a condensing agent.[14]



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

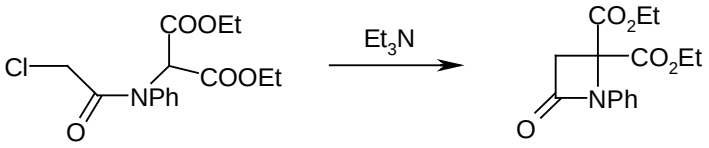
Formation of C2-C3 bond:

The formation of carbon-carbon bond at C2-C3 position is inherently more difficult compared to the N1-C2 amide bond formation. Maruyama et al. have achieved it via a photochemical approach to synthesize 4-keto-β-lactam.[15]



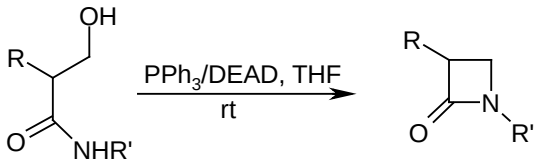
Formation of C3-C4 bond:

The simplest method for the formation of C3-C4 bond is to generate the nucleophilic center at C3 and an electrophilic center at C4, or vice versa. Sheehan and Bose have first reported azetidinone formation via an intramolecular nucleophilic displacement reaction using malonate anions and halides as the nucleophilic and electrophilic components respectively.[16]



Formation of C4-N1 bond:

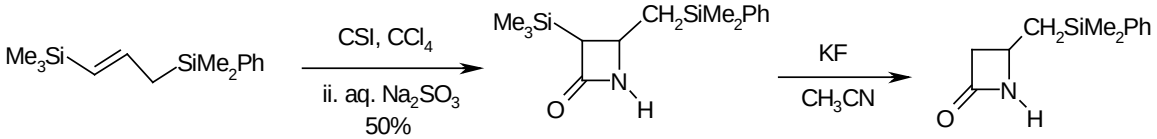
This methodology involves an S_N2 displacement of a good leaving group attached at β-carbon amide by an intramolecular amide nitrogen under basic conditions. Miller has reported the synthesis of β-lactams by the cyclization of β-hydroxy amides under Mitsunobu reaction conditions.[17]



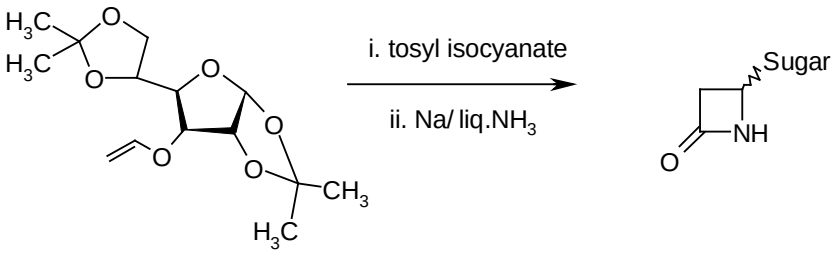
Multiple bond forming reactions:

Olefin-isocyanate cycloaddition reaction:

The addition of chlorosulfonyl isocyanate to olefins is a well-known method for the construction of β-lactams.[18] Colvin et al.[19] have reported the addition of chlorosulfonyl isocyante to various allyl and allenyl silanes to give functionalized β-lactams, which were then converted into synthetically important 3-unsubstituted *NH*-β-lactams by removal of the chlorosulfonyl group followed by silyl deprotection.

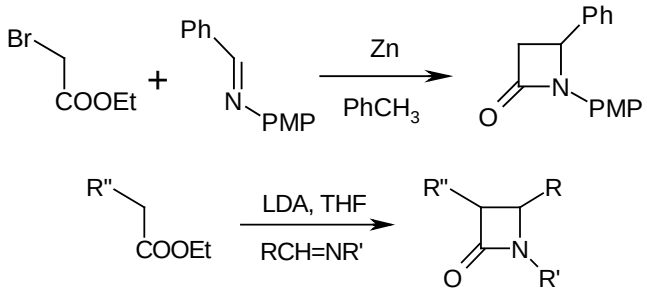


Chmielewski and co-workers have used this cycloaddition reaction between tosyl isocyanate and sugar derived vinyl ethers to obtain good diastereoselectivities in β-lactam formation.[20]



Enolate-imine condensation:

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



Staudinger reaction:

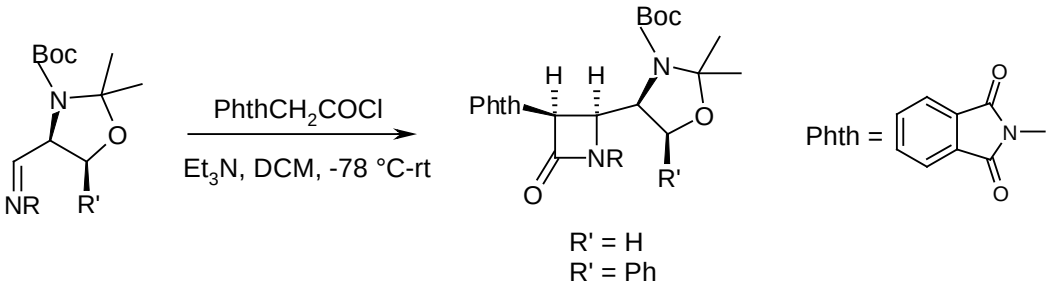
The first synthesis of a β-lactam was achieved by Staudinger[1] in 1907 by the [2+2] cycloaddition of ketene and imine. This reaction is called as Staudinger or ketene-imine cycloaddition reaction. In the modified Staudinger reaction, acid chlorides or activated carboxylic acids were used in the presence of a base as a ketene precursor. It is an excellent and well adopted method in the literature for the construction of β-lactam rings.

Asymmetric synthesis of β-lactams using Staudinger reaction:

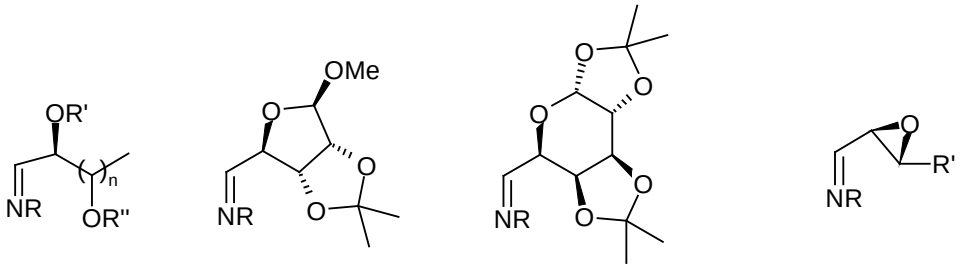
Better understanding of the mechanistic aspects of the β-lactams' biological activity and their inhibition and the chemical exploitation of β-lactams as synthetic intermediates in

organic chemistry have led to profound development in this field. In this regard, the accessibility of enantiopure β-lactams is an important requirement considering their pharmaceutical importance. The asymmetric Staudinger reaction is the most attractive and widely used method for this purpose because of its simplicity and predictability of stereo chemical outcome of the reaction. Asymmetry can be induced by using either chiral ketenes derived from acid precursors or chiral imines (derived from either chiral aldehydes or amines).

Chiral imines, derived from chiral aldehydes and achiral amines are the most effective for introducing asymmetry in the asymmetric Staudinger reaction. Generally, these imines give a very high level of diastereoselectivity in the cycloaddition reaction. Among the useful chiral imines, the *N*, *O*-protected aldimines are the most efficient ones.[22]

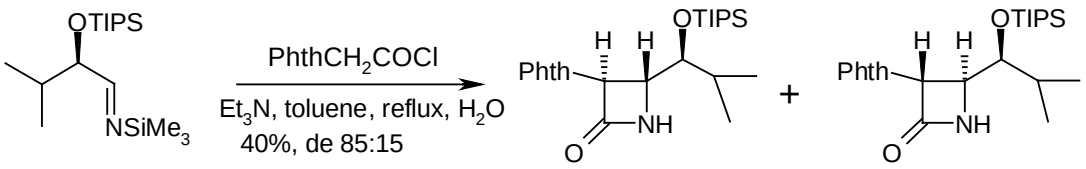


The most common approaches in the Staudinger reaction involve the use of α-oxyaldehyde derived imines, sugar derived imines and α, β-epoxyimines.[23]



Formation of *cis* isomer is generally favoured in all these cases with the observed ratios being as high as 90:10 in favour of the *cis* diastereomer.

Recently, Panunzio and co-workers have reported a case of *trans*-selectivity preference in cycloaddition reaction. The method involves the reaction of phthalimidoacetyl chloride with *N*-trimethylsilyl imines and triethylamine in refluxing toluene.[24]

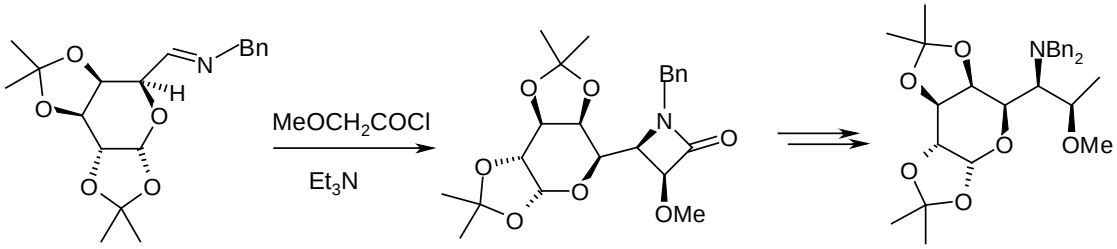


Carbohydrate derived chiral imines:

Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[25] The use of carbohydrates in the asymmetric synthesis of β-lactams has become well established and considerable amount of work has been done on sugar derived imines for β-lactam ring construction.

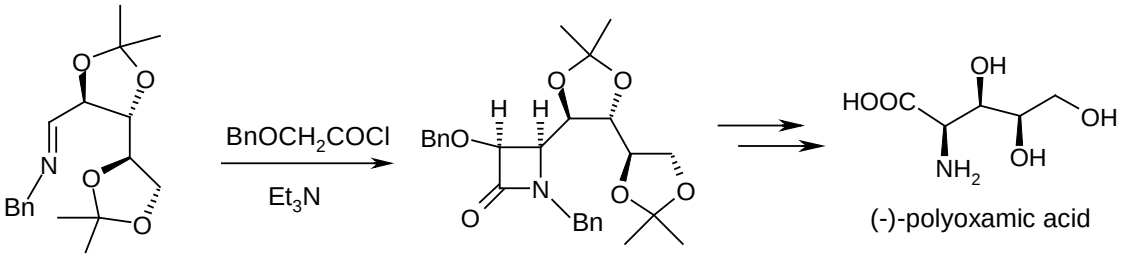
Bose and Manhas[26] have reported successful utilization of chiral imines derived from carbohydrates in the asymmetric Staudinger reaction. They synthesized different chiral auxiliaries derived from sugars and employed them as chiral imine components. These chiral imines proved to be very efficient, providing a high level of diastereoselectivity (de >90%) in all cases. They have mainly used these β-lactams as chiral synthons rather than as a chiral pool and have utilized the carbohydrate skeleton for the synthesis of important natural products.

A single *cis*-diastereomer was obtained from the reaction of D-galactopyranose derived chiral imine and methoxy-ketene. On further synthetic transformation this isomer was converted into 6-*epi*-lincosamine.[27]

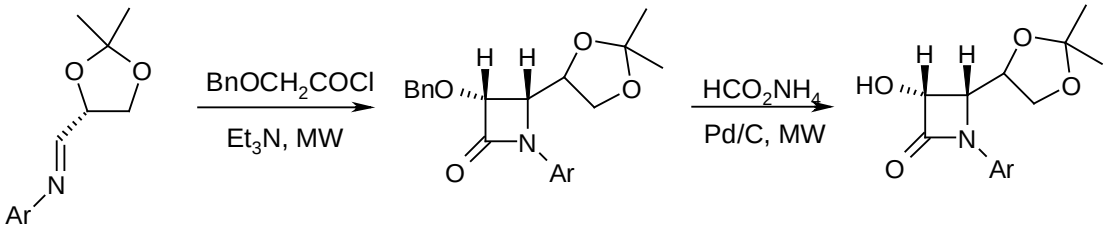


6-*epi*-lincosamine

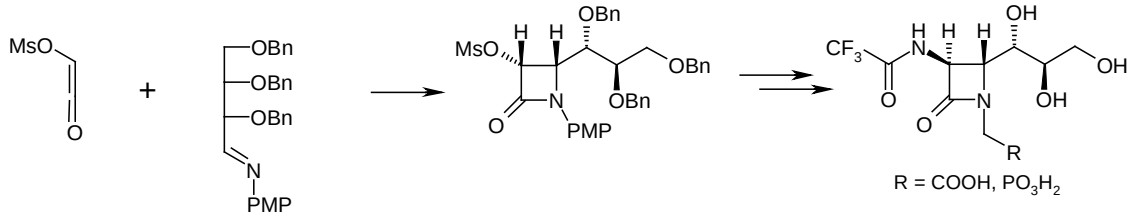
Similarly, the cycloaddition reaction of benzyloxyketene with the imine provided *cis*-β-lactams with complete control of diastereoselectivity. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, an antipode of natural (+)-polyoxamic acid.[28]



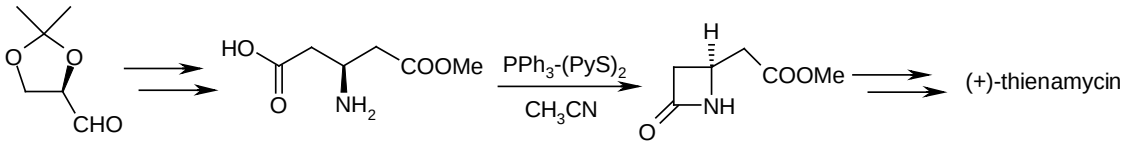
Bose and Manhas have recently reported the enantiospecific synthesis of α-hydroxy-β-lactams using Schiff's bases derived from D-glyceraldehyde under microwave irradiation.[29]



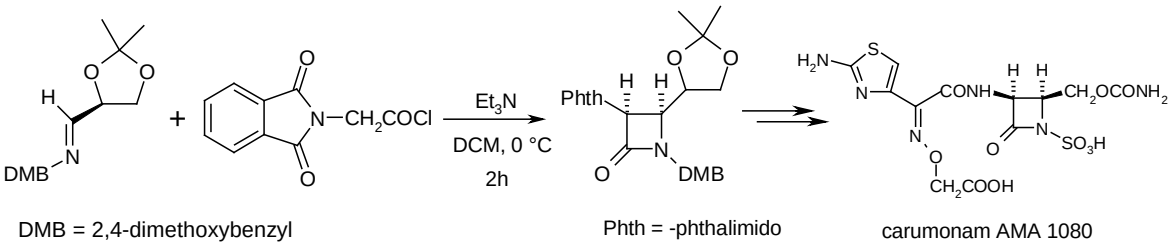
Recently, Stortz et al. have reported the use of D-erythrose derived imines for the synthesis of 2,3-dideoxy-D-mannonic acid derivatives.[30]



The (R)-glyceraldehyde acetonide prepared from D-mannitol has been converted into a β-amino ester, which on cyclization with 2,2'-dipyridyl disulphide and triphenylphosphine gave 3-unsubstituted β-lactam. This β-lactam has been converted into (+)-thienamycin antibiotic in several steps.[31]

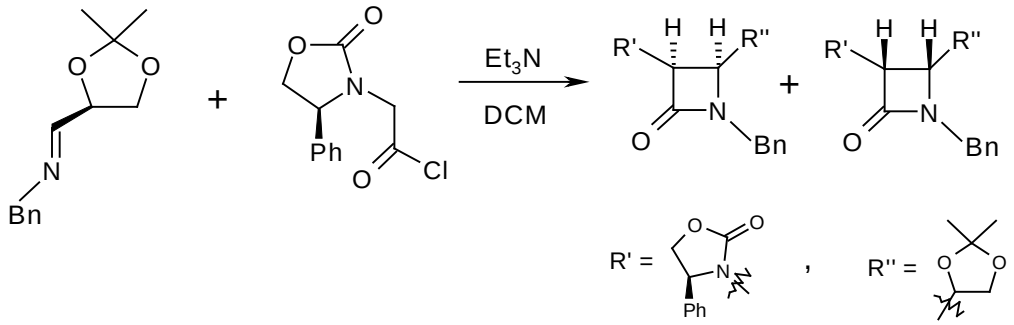


The imine derived from L-(-)-glyceraldehyde and 2,4-dimethoxybenzylamine underwent Staudinger reaction with phthalimidoacetyl chloride to afford the corresponding 3-Phth substituted β-lactam, which is a key intermediate in the synthesis of carumonam antibiotics.[32]

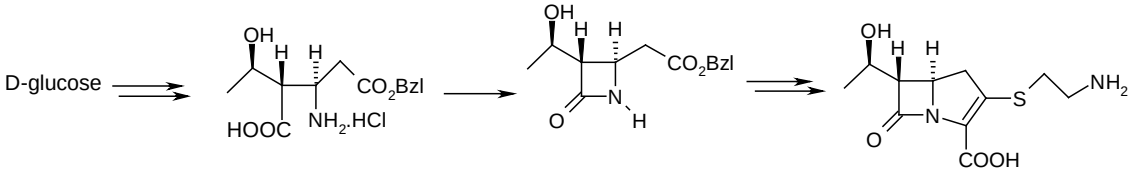


DMB = 2,4-dimethoxybenzyl Phth = -phthalimido carumonam AMA 1080

Palomo et al. have treated the imine derived from L-(-)-glyceraldehyde and benzylamine with oxazolidinone derived acid chloride to give *cis*-β-lactams in good yield with 40:60 diastereomeric ratio.[33]

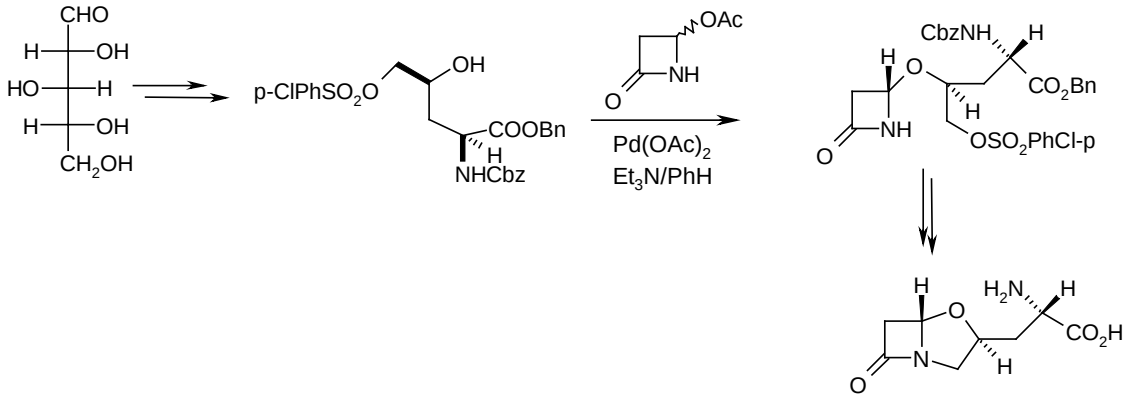


The β-amino acid derived from D-glucose, on cyclization in the presence of DCC gave β-lactam, which was further converted into (+)-thienamycin antibiotic in several steps.[34]



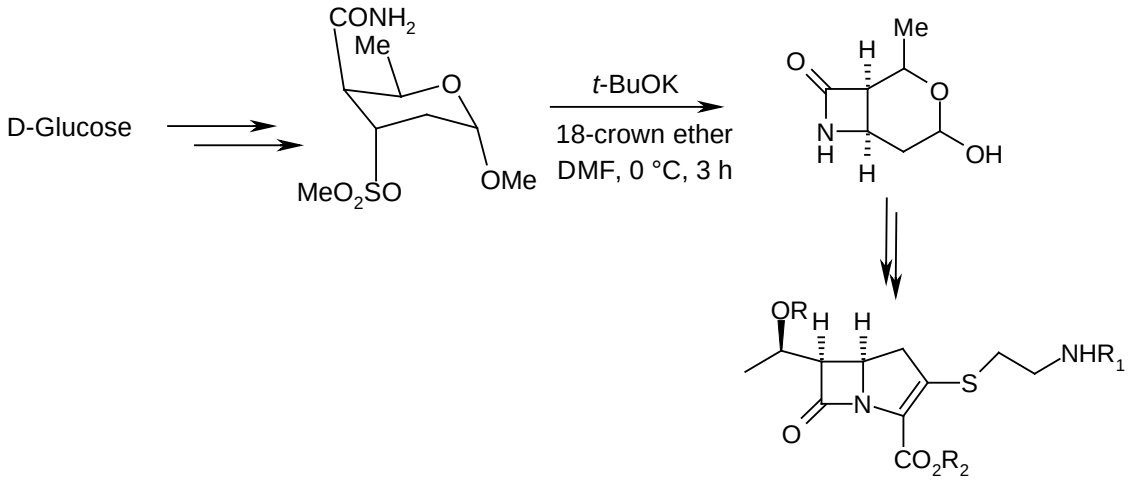
(+)-thienamycin

A chiral amino alcohol derived from D-xylose was coupled with racemic 4-acetyloxy-*N*-unsubstiuted-β-lactam in the presence of palladium acetate–Et_3N to give diastereomeric 70:30 mixture of β-lactams in 65% yield. The major isomer has been converted to the antibiotic clavamine Ro 22-5417.[35]



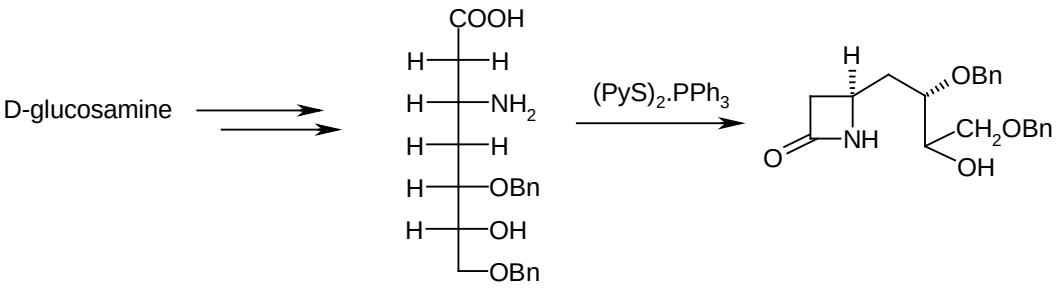
clavamine Ro 22-5417

The amide derived from D-glucose has been cyclized in the presence of potassium *tert*-butoxide, to give bicyclic β-lactams in 45% yield. This bicyclic β-lactam has been transformed into 6-*epi*thienamycin in a multi-step process.[36]



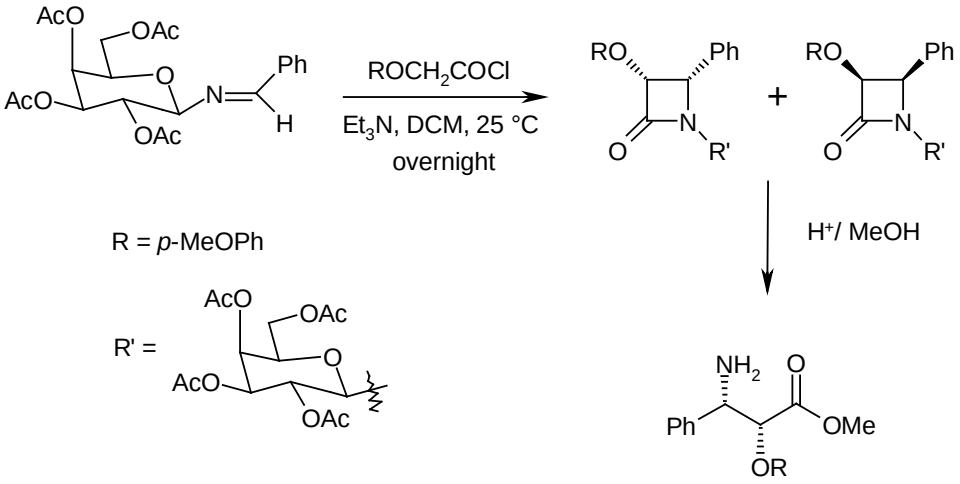
6-*epi*thienamycin

The β-amino acid derived from D-glucosamine has been cyclized to *N*-unsubstituted β-lactam in the presence of 2,2'-dipyridyl disulfide and triphenylphosphine. This *N*-unsubstituted β-lactam serves as an intermediate for the synthesis of (+)-thienamycin antibiotic.[37]

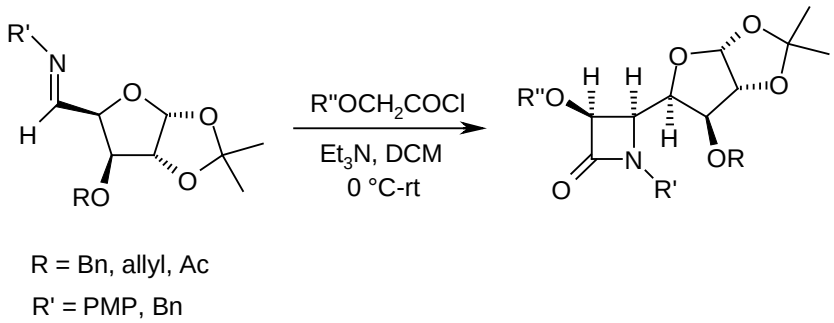


Georg et al. have used the chiral imine derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactose amine for disatereoselective synthesis of β-lactams. They obtained a 60:40

diastereomeric mixture of β-lactams in 90% yield. The α-isomer is transformed to β-amino ester, which is used as a building block for the synthesis of side chain of anticancer agent taxol.[38]



Recently Arun et al. have employed a D-glucose derived chiral aldehyde for the diastereospecific synthesis of *cis*-β-lactams in good yield using asymmetric Staudinger reaction.[39]



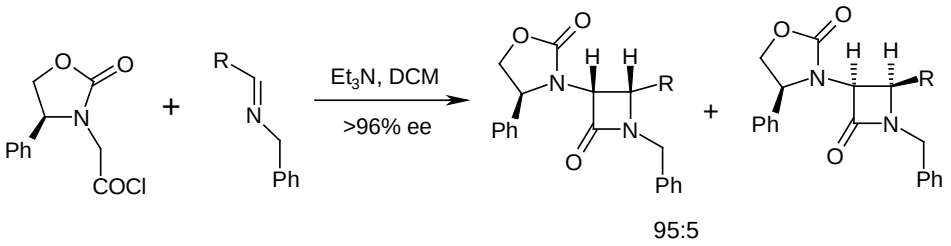
R = Bn, allyl, Ac

R' = PMP, Bn

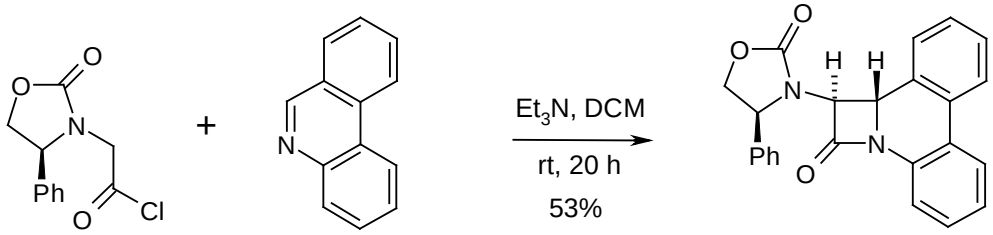
Chiral Ketenes:

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

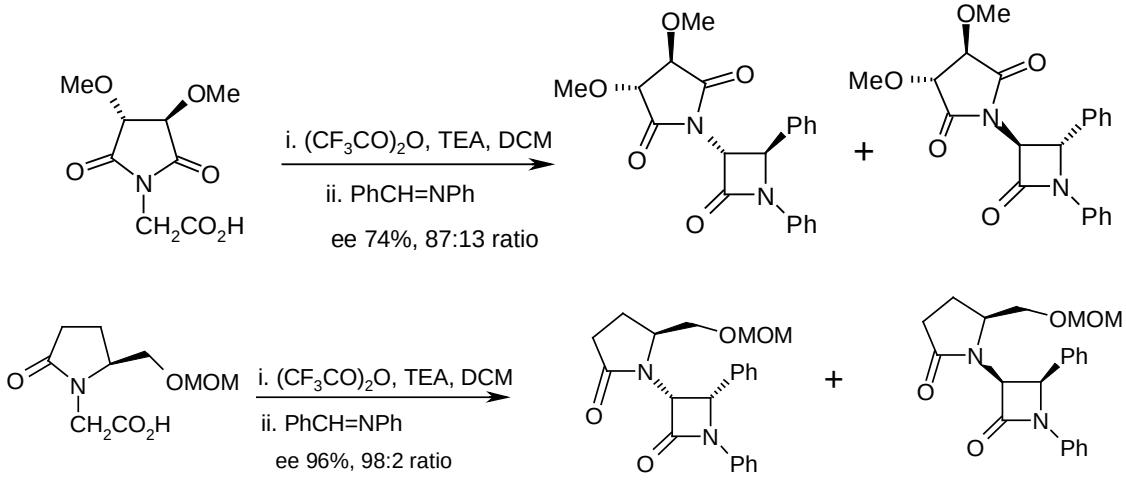
The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides and triethylamine, with achiral imines afforded optically active β-lactams with high levels of asymmetric induction, typically greater than 96% ee.[40]

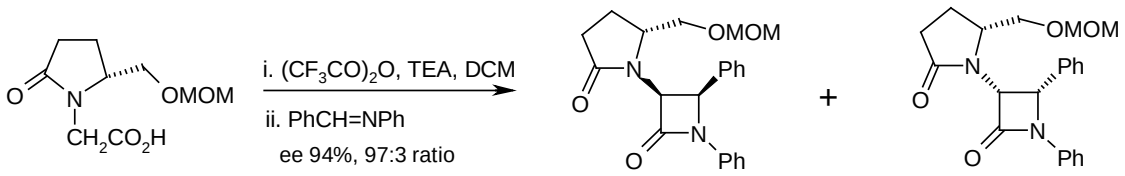


Recently, phenanthridine has been reported to give exclusively *trans* β-lactam with Evans-Sjogren chiral ketene.[41]

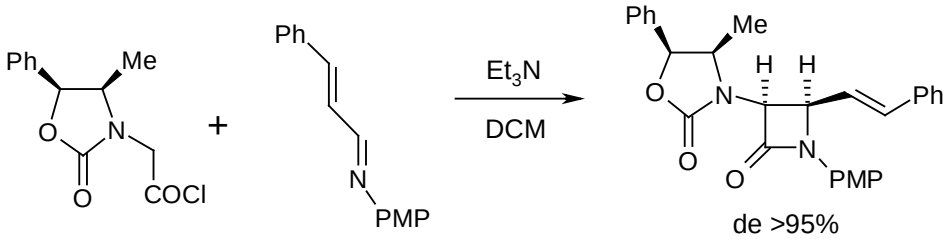


Ikota, in a series of papers, has reported a highly stereoselective β-lactam formation by asymmetric cyclo-condensation employing chiral heterocycles derived from L-(+)-tartaric acid, (*S*)-glutamic acid and (*S*)-serine as ketene precursors. Ikota used these acids in the presence of trifluoroacetic anhydride and a base to achieve high levels of diastereoselectivity.[42a-b]

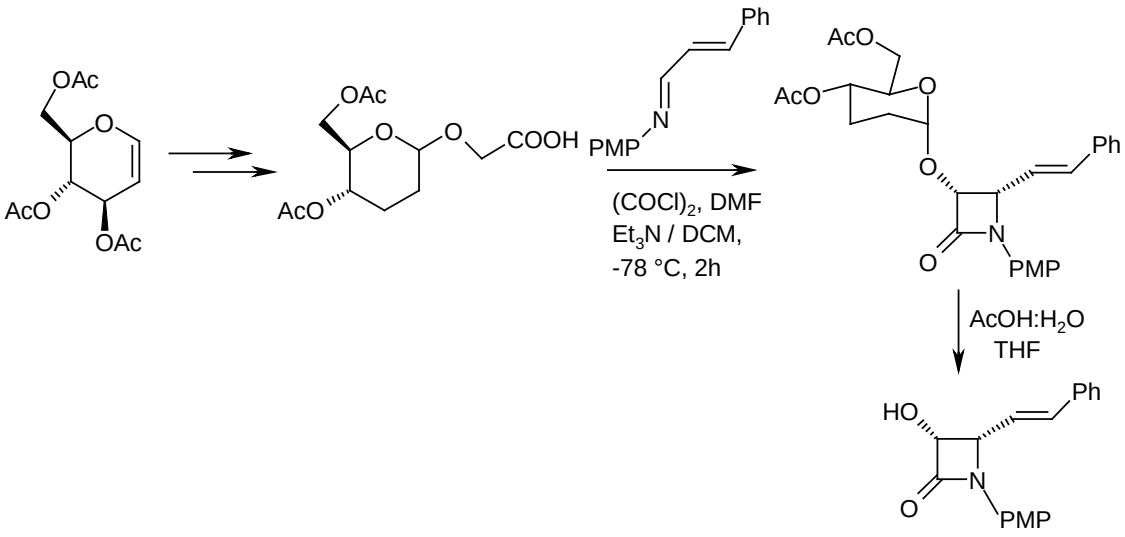




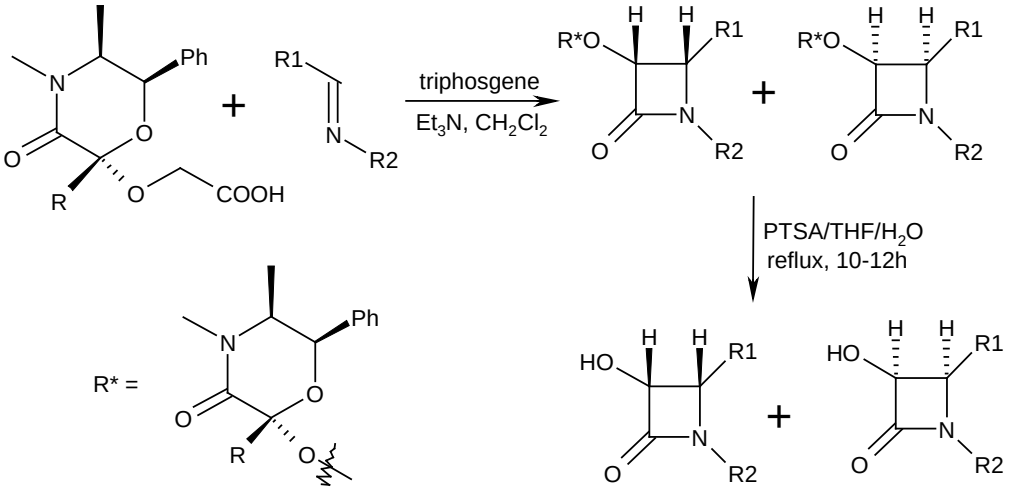
Cooper et al. used a norephedrine derived oxazolidinone derivative as the chiral ketene and achieved >95% diastereoselectivity in the β-lactam formation.[43]



Borer et al. have employed tri-*O*-acetyl-D-glucal derived chiral acid as ketene precursor for disatereoselective synthesis of β-lactams and obtained a diastereoselectivity of 70:30 in this reaction. The sugar moiety was deprotected upon treatment with acetic acid/water to generate 3-hydroxy-β-lactam, which may be used in the synthesis of taxol side chain.[42c]



Shinkre et al. have reported the ephedrine derived chiral acid for the asymmetric Staudinger reaction with various imines in the presence of triphosgene as an acid activator to afford a diastereomeric mixture of cis β-lactams in good yields. The chiral auxiliary, ephedrine, was removed under acidic hydrolysis and furnished both the enantiomers of 3-hydroxy-4-aryl β-lactams. One of these hydroxy β-lactams (β isomer) is an advanced intermediate for the synthesis of taxol side chain.[42d]



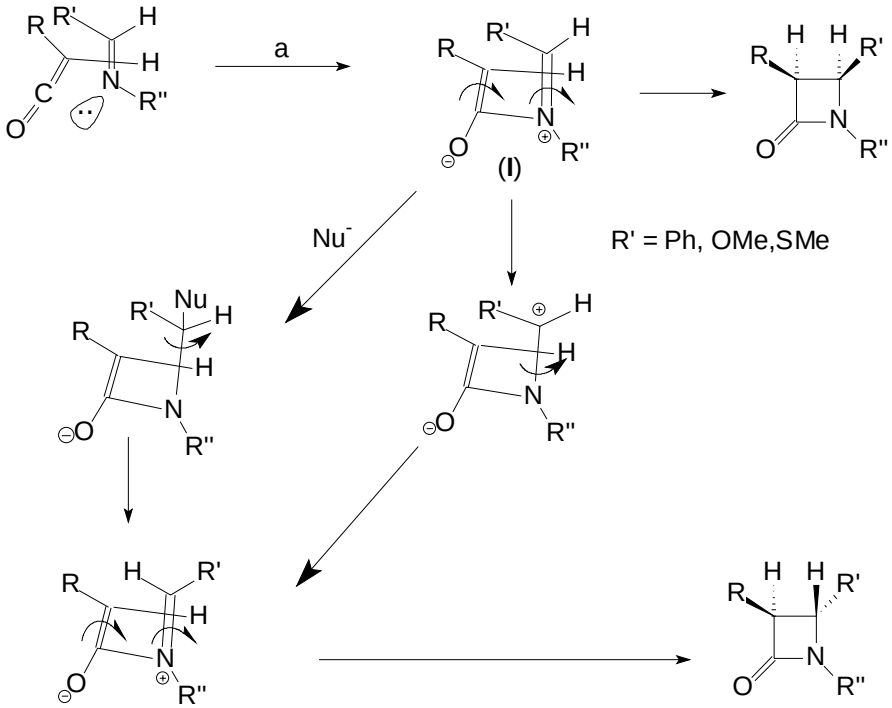
Mechanism:

Although the ketene-imine cycloaddition (Staudinger reaction) has been known for over nine decades, the mechanism and the stereochemical course of this reaction are still obscure. Recent efforts in this aspect have resulted in a series of papers by various groups.[44] Based on these results, a two-step zwitterionic mechanism has been preferred to a concerted [2+2] cycloaddition.

The involvement of a zwitterionic intermediate has been proved by various spectroscopic methods and zwitterion trapping experiments.[45] That the zwitterion intermediate was indeed formed from a ketene precursor was proved by results from Lynch's group[46] wherein, treatment of the acid chloride with diisopropylamine in an FT-IR cell displayed a strong band at 2120, which was assigned to the ketene.

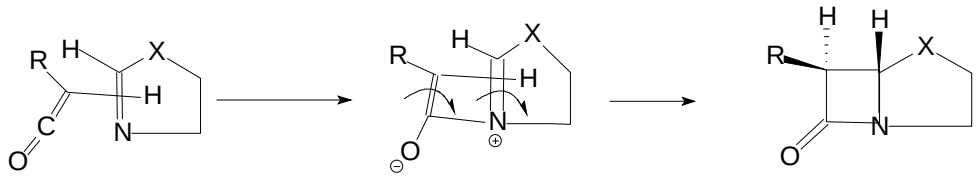
It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, that is, in a plane perpendicular to the substituents of the ketene, resulting in the formation of the zwitterionic intermediate (I).[47] This hypothesis was supported by semi empirical molecular orbital calculations (MNDO) of a transition intermediate in the reaction between methyl ketene and *N*-methyl-2-methylimine. [43]

It is further believed that the attack of the imine occurs from the less hindered side of the ketene while forming the zwitterionic intermediate (I). Rotation of the imine into the plane of the ketene followed by a *con*-rotatory ring closure produces the thermodynamically less stable β-lactam in which the smaller group on the imine (hydrogen) and the smaller substituent on the ketene are *cis* to each other. The *con*-rotatory ring closure can occur only in a clockwise direction since ring closure in other direction (anticlockwise) would necessitate the imine and ketene substituent to pass through each other. These stereochemical explanations are in good agreement with the results obtained from many acyclic imines and ketenes.



When the substituent R′ on the sp^2 carbon can stabilize a positive charge (e.g. Ph, OMe, or SMe), the zwitterionic intermediate may undergo isomerization from the more stable imine geometry to the *syn* imine geometry, before cyclization, producing the thermodynamically more stable *trans* β-lactam. This is the case with imidates, thioimidates and in some cases with benzaldimines. If the amino substituent R′ is large, this isomerization can be suppressed.

Isomerization of the zwitterionic intermediate can also occur by addition of nucleophiles to the zwitterion followed by rotation and elimination. The relative rate of each of these processes determines the stereochemical outcome of the reaction. In the case of cyclic imines one should always get a *trans* β-lactam since the imine substituents are held in *syn* geometry and the same has been observed in most cases.



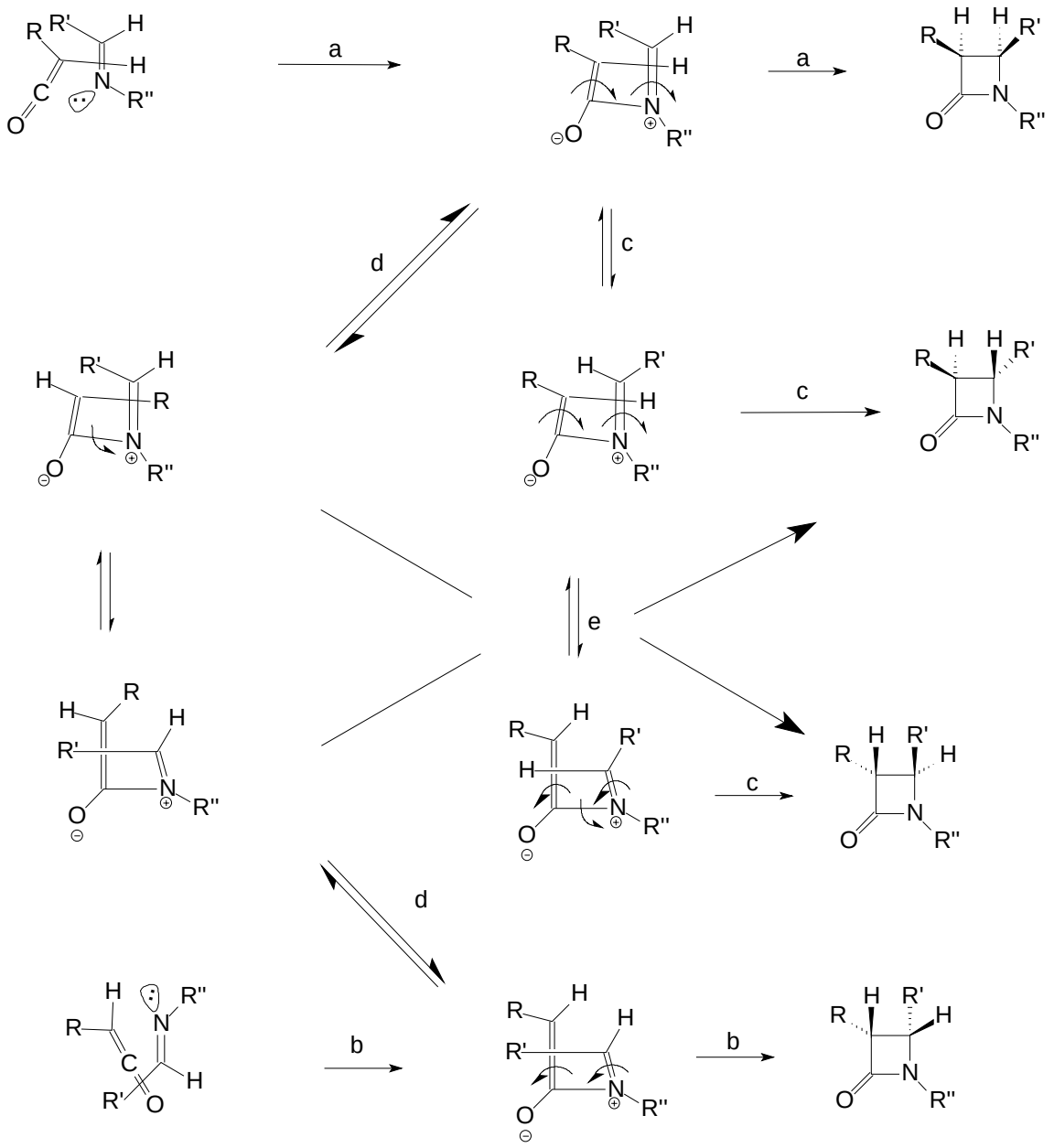
Asymmetric Induction:

Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene; attack of the imine over the top face of the ketene followed by *con*-rotatory ring closure will produce one enantiomer, while the attack of the imine from the bottom face followed by *con*-rotatory ring closure will produce the other enantiomer. Since two new chiral centers are formed during β-lactam ring formation, four isomers are possible, i.e. a pair each of *cis* and *trans* isomers. Depending upon the reaction conditions and the different paths followed, the formation of a single or all four isomers are possible. The chart below explains the formation of all four isomers depending on the stereochemical course of the reaction.

The attack of the imine from the less hindered side of the ketene can occur with two different perpendicular orientations; as in *path a* or as in *path b*. For reactions exhibiting high diastereoselectivity in *cis* manifold, differentiation between these two must be high and cyclization of the zwitterions must be faster than any of the possible isomerizations. If reaction conditions or structural features in the ketene or imine slow down the cyclization

step or accelerate the isomerization or both, stereoselectivity may be drastically altered, even if the initial selectivity between *path a* and *b* is high.

The formation of the thermodynamically more stable *trans* β-lactam from a *trans* imine can only result from isomerization of either the iminium portion (*path c*) or the enolate portion *(path d)* of the zwitterions prior to cyclization. Isomerization should be promoted by substituents that stabilize positive charge on the iminium carbon and / or by substituents that stabilize the enolate, slowing cyclization relative to isomerization. If the cyclization of the initially formed zwitterions is very slow, all four diastereomeric β-lactams are then accessible from any single zwitterion by isomerization followed by rotation about the C-N single bond (*path e*).



Polycyclic β-lactams:

Members of the class of antibacterial agents, of which penicillin was the precursor, are known as β-lactams, as they contain a β-lactam ring that is vital to their activity.[48] These β-lactam based drugs destroy the bacteria by inhibiting bacterial cell wall synthesis but they tend to become inactive because of the hydrolysis of highly strained β-lactam ring due to β-lactamase enzymes produced by bacteria in defense.[49]

The global problem of increasing bacterial resistance towards these commercial drugs has motivated synthetic chemists to develop new methodologies to synthesize non-classical type of azetidin-2-ones, which can withstand these β-lactamases and could also be used as starting materials for the synthesis of various biologically important compounds.[50] Recently, tricyclic β-lactams, generally referred as trinems, were found to show excellent enzyme inhibition towards class C β-lactamases as well as dehydropeptidases and thus sparked the evolution of novel bi- and polycyclic β-lactams.[51]

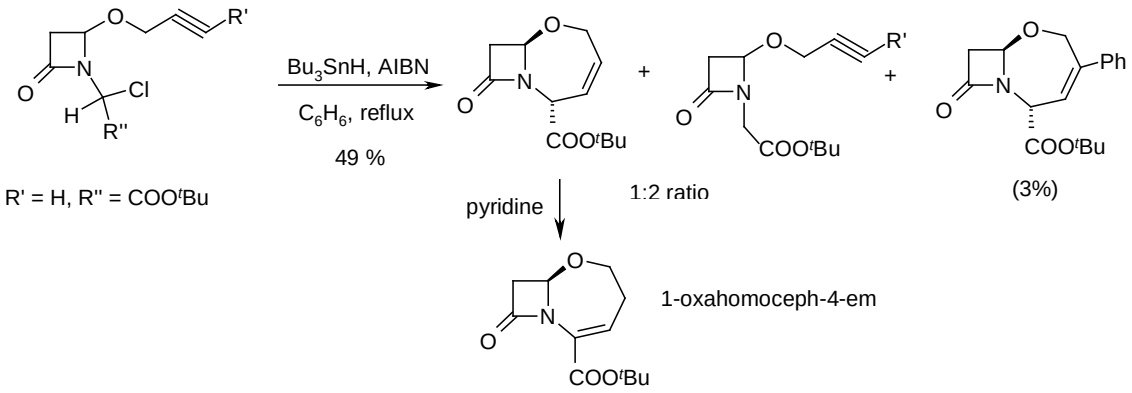
Several methods have been reported on the synthesis of polycyclic β-lactams involving intramolecular radical cyclization, ring closing metathesis, Diels-Alder reaction, Pauson Khand cyclization, Heck reaction and 1,3-dipolar cycloaddition of nitrones and alkenes. These methods are described here briefly.

Intramolecular radical cyclization:

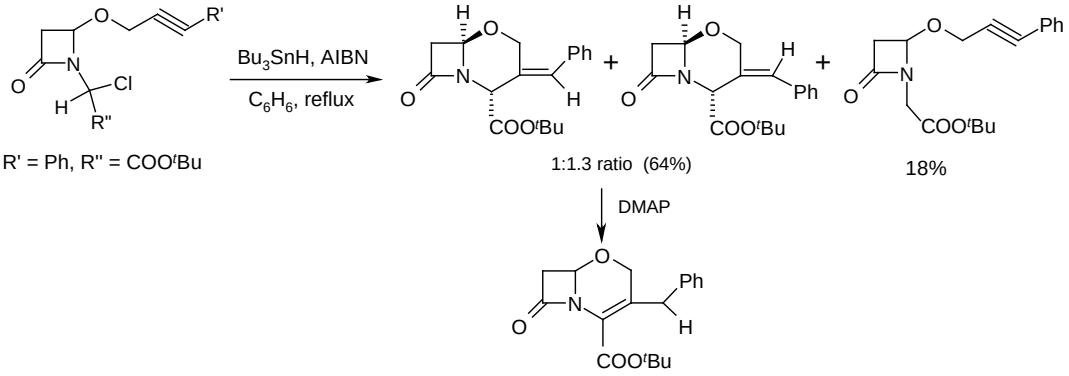
The stereoselective synthesis of heterocycles and carbocycles mediated through radical cyclization has been accepted as an efficient methodology in organic chemistry because of their operational simplicity, tolerance to functionalization and high regio- and stereoselectivity.[52] The tactic of radical cyclization has also been utilized in the construction of non-classical fused β-lactams by keeping in mind the sensitivity of the β-lactam ring towards nucleophilic reagents.

Bachi has opened this gateway in β-lactam chemistry to synthesize a new family of synthetic antibiotics oxacephem and 1-oxahomocephem derivatives wherein the β-lactam ring is fused with an unsaturated six or seven membered ring as in cephalosporins.[53] He has used *N*-chloromethyl azetidin-2-ones as substrates for cyclization with the chloro substituent serving as a radical generator and the acetylenic triple bond acting as a radical acceptor.

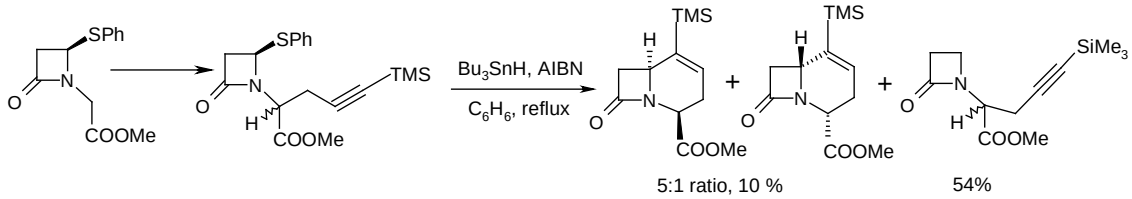
The intramolecular radical annulation of the acetylenic chloro compound proceeded smoothly and gave 1-oxahomoceph-3-em via *7-endo* mode of addition along with reduced product (2:1 mixture, 49%). The 1-oxahomoceph-3-em was then gently isomerized by treatment with pyridine to the required 1-oxahomoceph-4-em in which the carboxylate group is in conjugation with the lactam nitrogen and the double bond.



Phenyl substituted acetylenic chloro derivative yielded a *E*/*Z* mixture of 6-*exo* annulated oxacephem compounds as a result of formation of a stable benzylic radical intermediate. In order to obtain skeleton resembling cephalosporins, the *E*/*Z* mixture was treated with DMAP so as to effect migration of the double bond from the exocyclic poisition into conjugation with the ester group to yield 1-oxaceph-3-em derivatives. Under this condition, only the *Z*-isomer underwent migration whereas the *E*-isomer remained intact.

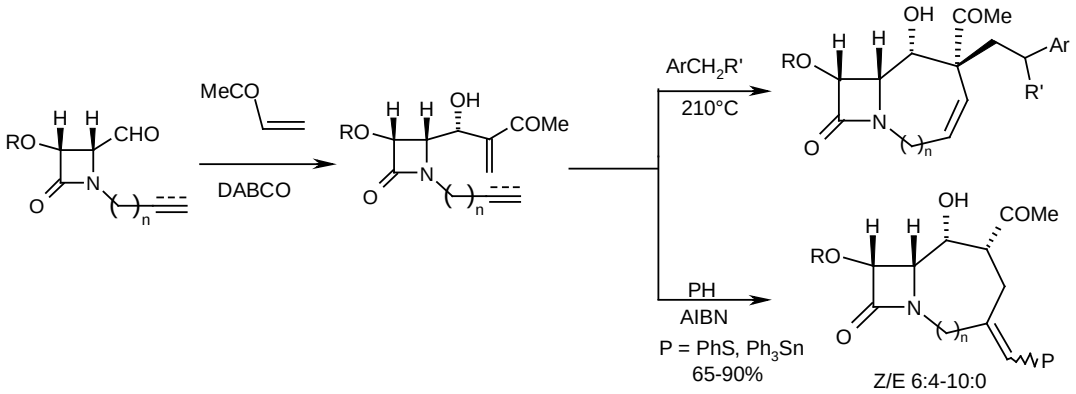


The carbodethia analogues of cephem are called as carbacephems. Kametani et al. have synthesized these ring systems from acetylenic substituted 4-phenylthio azetidin-2-ones. The *6-exo* mode of addition of the generated radical to the triple bond gave an inseparable mixture of cabacephemes in 10% yield, affording the desulfurized compound as the major product in 54% yield. The low yield of cyclized product was attributed to the linearity of the carbon-carbon triple bond.[54]

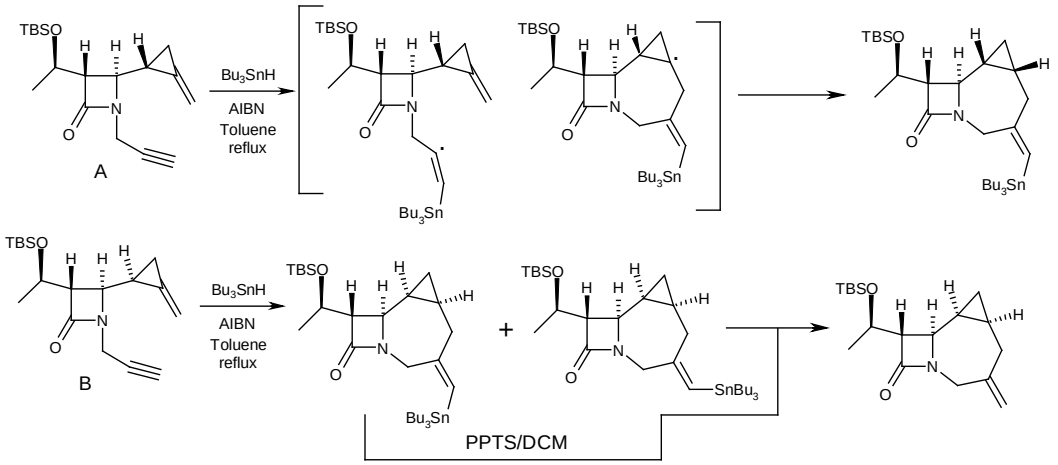


Alcaide and co-workers[55] have reported the formation of bicyclic β-lactams fused to medium-sized heterocycles by employing Baylis-Hillman reaction on 4-oxoazetidine-2-carbaldehydes followed by intramolecular radical cyclization. The more nucleophilic benzyl radical first attacks the electron deficient alkene and the thus generated radical cyclizes in *endo* fashion to give benzylic substituted carbocycles, whereas, in the case of

electrophilic thiyl and stannyl radical, the addition of these radicals to the double bond is faster thus providing *exo* methylenic bicyclic β-lactams.



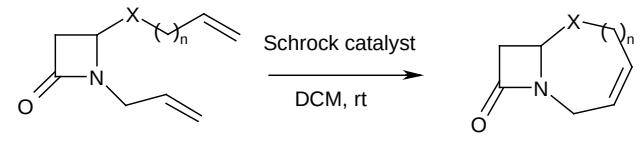
Penford et al.[56] reported the synthesis of novel *N*-fused β-lactams using a radical cascade sequence in azetidin-2-ones bearing a methylenecyclopropane unit. The radical cyclization of β-lactam A in the presence of tributyltin hydride and AIBN gave tricyclic vinylstannane as a single diastereomer. On the other hand, cyclization of azetidin-2-one B under similar reaction conditions provided *Z* and *E* isomers of tricyclic compounds in 73 and 11% yields respectively. In all these cases the reaction proceeded via *7-endo* cyclization.



(A detailed report on radical cyclization in β-lactam chemistry is described in Part B)

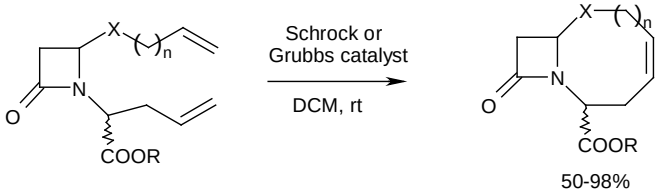
Ring closing metathesis:

Olefin metathesis has been a great boon for organic chemists and found its application in the synthesis of many physiologically important macrolactones, macrolactams, fine chemicals and various natural products like epothilones and roseophillin etc.[57] Polyfunctional β-lactam dienes are excellent substrates to perform ring closing metathesis reactions. Barett and co-workers have reported the ring closing metathesis of 1,4-bis(ene)-substituted azetidin-2-ones to construct potentially biologically active bicyclic β-lactam arrays. This is the first report of ring closing metathesis on polycyclic β-lactams.[58]

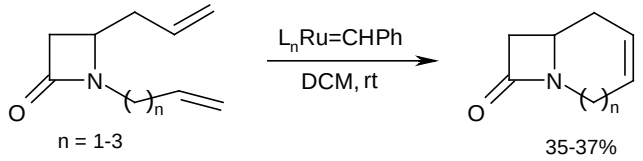


The seven-membered oxahomocephem derivative was obtained in 84% yield in the presence of Schrock molybdenum catalyst. The eight-, nine- and ten-membered fused β-lactams were formed in 76%, 23% and 10% yields respectively under high dilution condition and a higher catalyst loading of 20 mol%.[58]

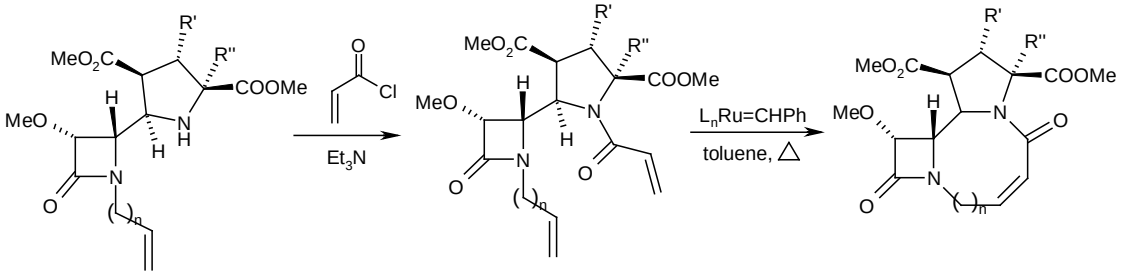
Later, they have introduced a carboxylic acid theme adjacent to the β-lactam nitrogen atom in order to develop biologically useful bicyclic β-lactams. The ring closing metathesis of monocyclic dienes bearing a carboxylate ester gave cephalosporin like bicyclic β-lactams when treated with Schrock or Grubbs′ catalyst under mild reaction conditions.[59]



Apart from the synthesis of oxygen, nitrogen, and sulfur containing heterocycles fused with β-lactams, this methodology can also be used in the fusion of 6-8 membered carbocycles onto the β-lactam ring system.[60]

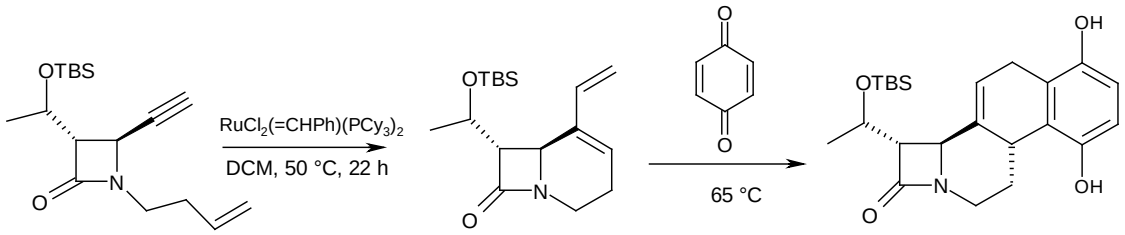


A combination of [2+2] or [3+2] cycloaddition and ring-closing metathesis sequence was reported as a useful synthetic tool for the asymmetric synthesis of unusual tricyclic 2-azetidinones bearing a fused medium sized heterocycle and two bridgehead nitrogen atoms related to conformationally restricted peptidomimetics.[61] Treatment of dienes in the presence of Grubbs second-generation catalyst in dichloromethane failed to yield the cyclized product. However, in refluxing toluene, tricyclic pyrrolidinyl β-lactams fused to eight, nine and ten membered rings were obtained.



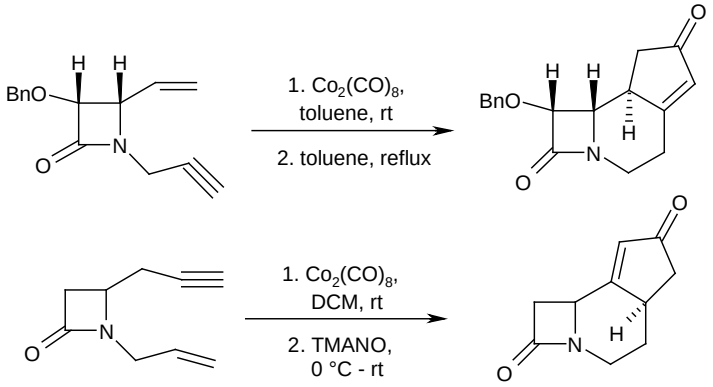
Desroy et al. have recently reported an efficient one-pot synthesis of tricyclic and tetracyclic β-lactams by employing ring-closing metathesis and Diels-Alder reactions. The enyne substituted azetidin-2-ones on treatment with Grubbs catalyst gave the bicyclic

compound in 87% yield, which upon Diels-Alder cycloaddition with various dienophiles provided tricyclic compounds in excellent yields.[62]

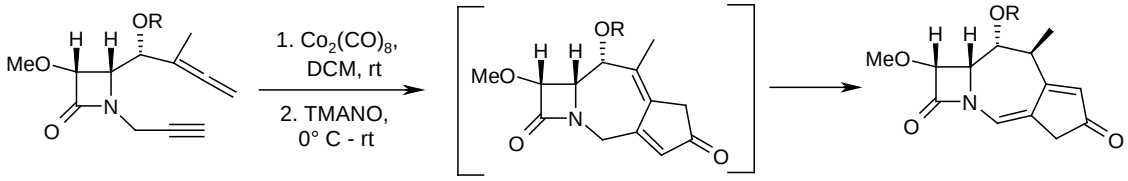


Pauson - Khand reaction:

A straightforward approach to access tricyclic β-lactams is the Pauson-Khand cycloaddition reaction, wherein, two of the three rings of the tricyclic azetidin-2-ones could be generated simultaneously on a preformed monocyclic β-lactam precursor. Alcaide et al. have reported the Pauson-Khand cyclization of enyne azetidin-2-ones using a stoichiometric amount of $Co_2(CO)_8$. The alkyne-$Co_2(CO)_6$ complexes formed initially, cyclized to give tricyclic compounds as a single diastereomer. Wet silica gel, TMANO (trimethylamine N-oxide) or boiling toluene was employed as a promoter for this cyclization.[63]



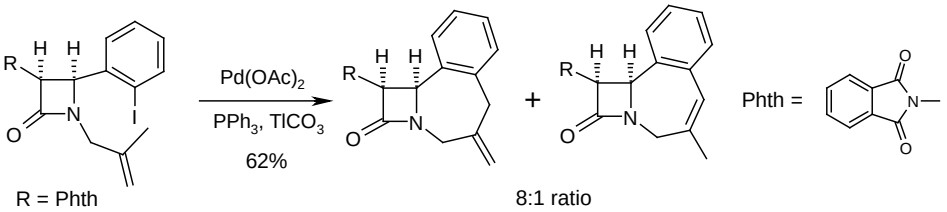
However, the synthesis of tricyclic β-lactams bearing central ring larger than six, by employing the above methodology was unsuccessful. Consequently, Alcaide et al. have synthesized these tricyclic azetidin-2-ones fused to seven-membered rings from allenyne monocyclic β-lactams via a [2+2+1] cycloaddition reaction in the presence of $Co_2(CO)_8$ under mild reaction conditions with good diastereoselectivity. The initially formed cyclo adducts isomerized to the more stable tricyclic compounds having the dienone moiety in conjugation with the lone pair on nitrogen.[64]



Heck Reaction:

The construction of nitrogen heterocycles is an important task in organic synthesis because of their abundance in natural and pharmaceutical products.[65] The process of heteroannulation involving an unsaturated functionality and Pd catalysts is one of the best methods for the synthesis of such compounds.

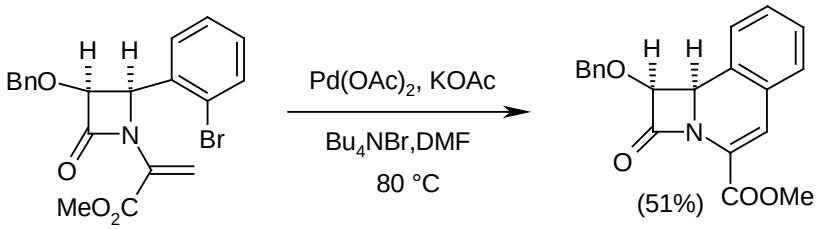
Grigg and co-workers have carried out palladium catalyzed intramolecular cyclization of iodoaryl β-lactams using 10 mol% $Pd(OAc)_2$, 20mol% PPh_3 and $TlCO_3$ (2 mol%) under Heck reaction conditions. The methallyl substituted iodoaryl β-lactam was annulated in a fashion favouring the *7-endo-trig* mode to afford an 8:1 mixture of structural (*exo-endo*) isomers.[66]



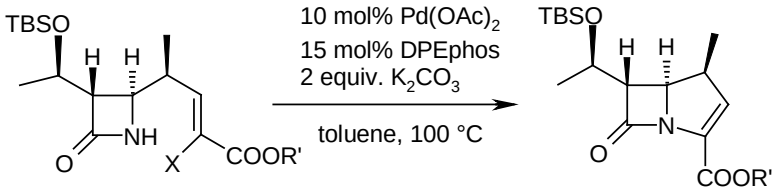
R = Phth

8:1 ratio

In another example, the less reactive bromoaryl β-lactam was efficiently converted into the fused dihydropyridine using Heck coupling reaction in good yield.[67]

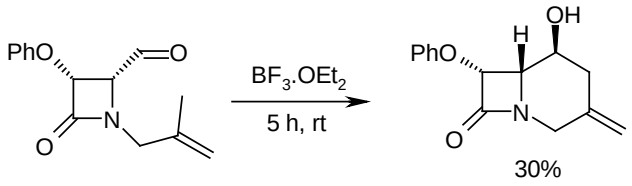


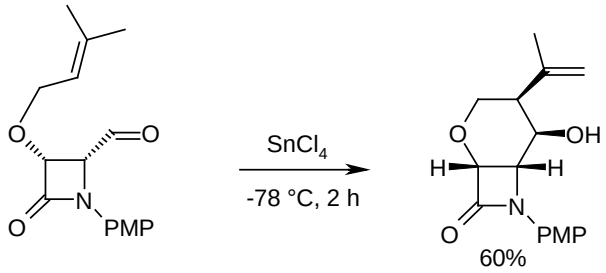
Kozawa et al. have described an efficient synthesis of 3-alkoxycarbonyl-1β-methylcarbapenem antibiotic by using the Buckwald method of palladium catalyzed C-N bond-formation between a vinyl halide and β-lactam nitrogen in the presence of $Pd(OAc)_2$, DPEphos and K_2CO_3 base. The time of addition of base played an important role because initial addition of base along with catalyst inhibited the effective coordination of phosphine ligand to Pd(0) and gave reduced yield of bicyclic compounds.[68]



Ene reaction:

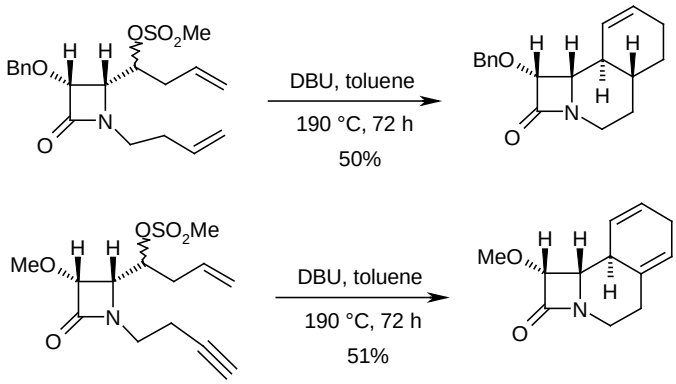
The Lewis acid catalyzed intramolecular ene cyclization of unsaturated carbonyl compounds is considered to be an efficient method for the stereoselective synthesis of functionalized cyclic products because of its operational simplicity, high levels of regio and stereocontrol. Alcaide has used azetidin-2-one-tethered alkenyl aldehydes possessing an activated alkenyl group at *N*1 or C-3 position of the β-lactam as substrates for ene cyclization to provide fused piperidine- or tetrahydropyran-β-lactams.[69]





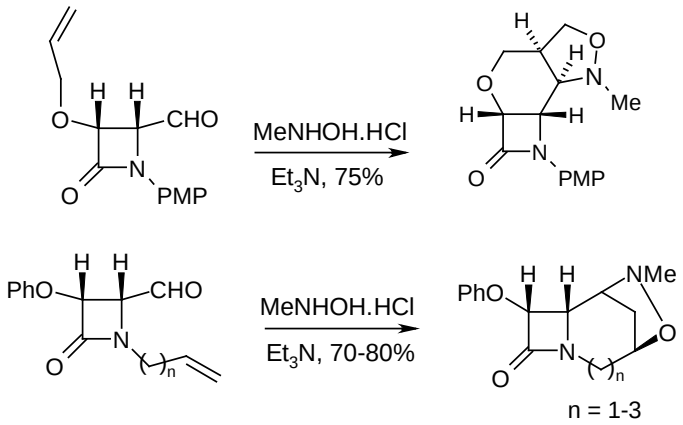
Diels-Alder reaction:

The intramolecular Diels-Alder reaction is a simple and efficient method to obtain tricyclic 2-azetidinones with a six-membered heterocyclic ring fused to the β-lactam nucleus.[70] The mesylates of homoallylic alcohols, prepared via the addition of propenylmetal reagents to the 4-oxoazetidine-2-carbaldehydes. Upon heating in a sealed tube with one equivalent of DBU in toluene, the mesylate underwent a tandem elimination-intramolecular Diels-Alder reaction to give the corresponding cycloadducts with considerable levels of stereoselectivity.

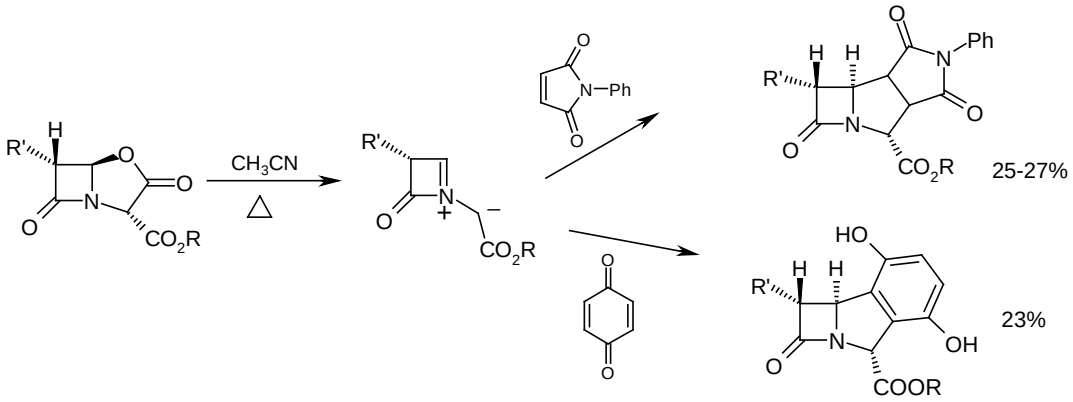


1,3-dipolar-cycloaddition reaction:

Alcaide and co-workers have shown the applicability of intramolecular nitrone-alkene cycloaddition reaction on 2-azetidinone-tethered alkenyl(alkynyl)aldehydes to prepare fused tricyclic β-lactams.[71] The regioselectivity of the cycloaddition was dependant on the position of the alkene(alkyne) substituent in the starting 4-azetidin-2-one carbaldehydes and gave bridged or fused tricyclic compounds. The formation of bridged ring products was interesting because intramolecular nitrone-alkene cycloaddition reactions are generally known to produce fused-ring products.



Gallagher and co-workers have synthesized these tricyclic fused β-lactams by employing 1,3-dipolar cycloaddition of azomethine ylide generated by decarboxylation of a bicyclic β-lactam. The azomethine ylide underwent cycloaddition with dipolaraphiles such as *N*-phenylmaleimide and 1,4-benzoquinone to give tricycles in modest yield.[72]



Present Work:

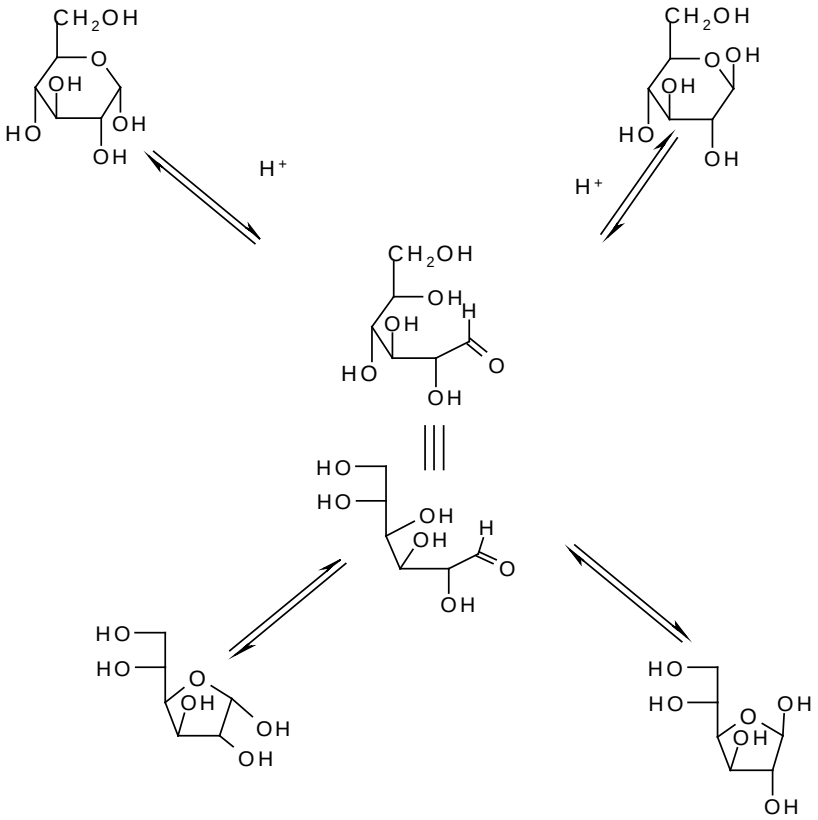
The use of carbohydrate derived chiral auxillaries in the asymmetric β-lactam synthesis is well established. Though several sugar derived chiral aldehydes have been employed in the formation of optically pure azetidin-2-ones, the use of a D-glucose derived chiral aldehyde, as a chiral imine precursor has not been explored extensively.

We therefore, decided to take this interesting proposition up for further research and focused our attention on using D-glucose derived chiral aldehyde as a chiral source for our study. We were interested in studying the stereocontrol that the steric disposition of the glucose acetonide might impose on the β-lactam ring formation. We also planned to synthesize polycyclic β-lactams via intramolecular radical cyclization of the carbohydrate derived azetidin-2-ones bearing suitable appendages to generate a radical and a radical acceptor.

Synthesis of Chiral Iodoaldehyde:

Our scheme started with the cheaply available D-glucose (**1**), which was converted to the corresponding glucose diacetonide derivative **2** on treatment with anhydrous $CuSO_4$

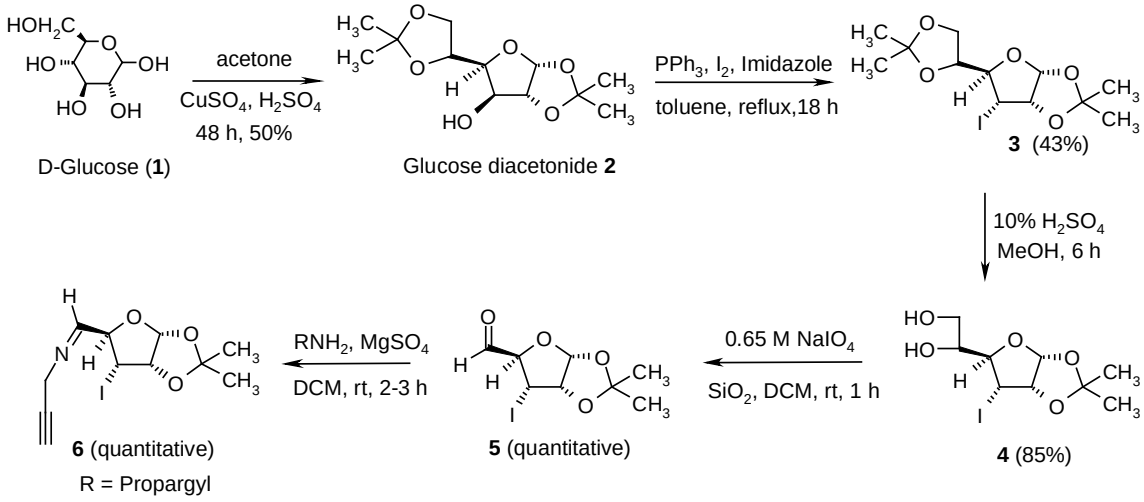
and catalytic amount of sulphuric acid in dry acetone. The diacetonide formation could lead to the formation of two products, namely, the five-membered furanose and the six-membered pyranose. Formation of the former is favoured because in the furanoid form, glucose offers two suitably disposed vicinal diols for condensation. Also, fusion of a five membered acetal to a furanoid ring causes less strain as against a similar fusion to a pyranoid ring. The β-forms can be eliminated due to the *anti* conformation of the two-hydroxyl groups.



Commercially available D-glucose (**1**) was treated with anhydrous cupric sulphate in the presence of anhydrous acetone and a catalytic amount of H_2SO_4 to give glucose diacetonide **2** in 50% yield according to the known literature method.[73] This was then converted to iodo glucose diacetonide **3** with iodine, triphenylphosphine and imidazole in 43% yield.[74] Selective deprotection of the primary acetonide moiety using 10% H_2SO_4 and methanol followed by oxidative cleavage of diol **4** with 0.65 M aqueous solution of $NaIO_4$

and silica gel[75] gave the desired iodo substituted aldehyde **5** in quantitative yield (Scheme 1).

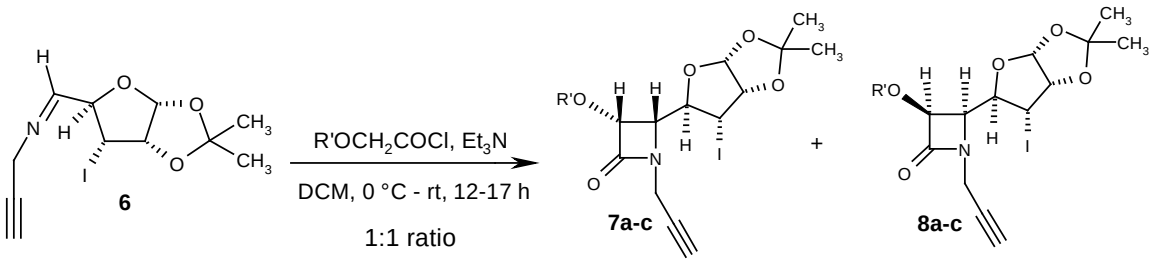
Scheme 1



Synthesis of N-propargyl substituted β-lactams:

The iodo aldehyde **5** thus prepared was treated with propargyl amine in the presence of anhydrous $MgSO_4$ to give the corresponding chiral imine **6**, which was used as such for the Staudinger reaction with substituted acid chlorides in the presence of excess Et_3N (Scheme 2) to afford *N*-propargyl substituted β-lactams **7a-c** & **8a-c**. The crude NMR showed the formation of both alpha and beta diastereomers in a 1:1 ratio (no diastereoselectivity). Diastereomers were separable by flash chromatography or crystallization from methanol except in the case of methoxy substituted β-lactams. The yield was moderate in all the cases (40-50%).

Scheme 2

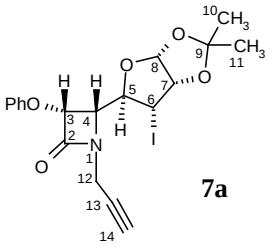


a: R' = Ph, 42%
b: R' = Bn, 41%
c: R' = Me, 50%

The structure and stereochemistry of **7a** was studied by COSY and NOESY 2D NMR techniques and single crystal X-ray crystallography. The IR spectrum of **7a** showed a strong absorption at 1770 cm^{-1} indicating the presence of carbonyl group of the β-lactam ring.

In the ^{1}H NMR spectrum, the acetonide methyl groups appeared as singlets at 1.41 and 1.58 ppm. The acetylenic proton H-14 was seen as a triplet at 2.37 ppm (J = 2.4 Hz). The methylene protons attached to nitrogen (H-12) gave two doublet of doublets at 4.02 and 4.46 ppm (J = 2.5 & 17.9 Hz, 3.0 & 18.1 Hz).

The anomeric proton H-8 showed a doublet at 5.88 ppm (J 3.5 Hz) and the proton H-7 adjacent to the anomeric carbon appeare as a triplet at 4.65 ppm with a coupling constant value of 3.9 Hz. Th proton H-6 was seen as a doublet of doublet at 4.13 ppm (J = 3.6, 4. Hz) and another doublet of doublet at 4.74 ppm (J = 3.6, 3.9 Hz) wa assigned to the H-5 proton.



7a

The β-lactam protons H-4 and H-3 appeared as a triplet at 4.30 ppm (J = 4.8, 3.9 Hz) and a doublet at 5.34 ppm (J = 4.8 Hz) respectively. A coupling constant value of 4.8 Hz indicated that H-3 and H-4 are *cis* to each other (*trans*: J = 1-2.5 Hz). Aromatic protons appeared in the region of 7.02-7.37 ppm.

In the ^{13}C NMR spectrum, C-6 carbon bearing iodo substituent appeared at 19.4 ppm. The acetonide methyl carbons C-10 and C-11 appeared at 26.8 and 26.9 ppm respectively. The *N*-CH_2 carbon C-12 was seen at 30.9 ppm, which was identified from the ^{13}C-DEPT experiment. The β-lactam C-4 and C-3 carbons appeared at 56.3 and 80.1 ppm respectively. The acetylenic carbons C-14 and C-13 were seen at 74.0 ppm and 75.8 ppm correspondingly.

The other carbohydrate carbons C-5, C-7 and C-8 appeared at 80.8, 81.7 and 103.4 ppm respectively, while the C-9 carbon showed a peak at 112.4 ppm. The aromatic carbons appeared in the region of 115.9-157.5 ppm and the β-lactam carbonyl carbon C-2 appeared at 165.6 ppm.

COSY experiment was carried out for **7a** to further confirm the bond connectivities (Figure 3). The anomeric proton H-8 showed a strong interaction with H-7, which in turn was in connection with H-6. The H-6 proton further showed interaction with H-5 proton. β-

lactam proton H-3 showed a strong coupling with H-4, which was further connected to H-5. The *N*-CH_2 protons also showed strong interactions.

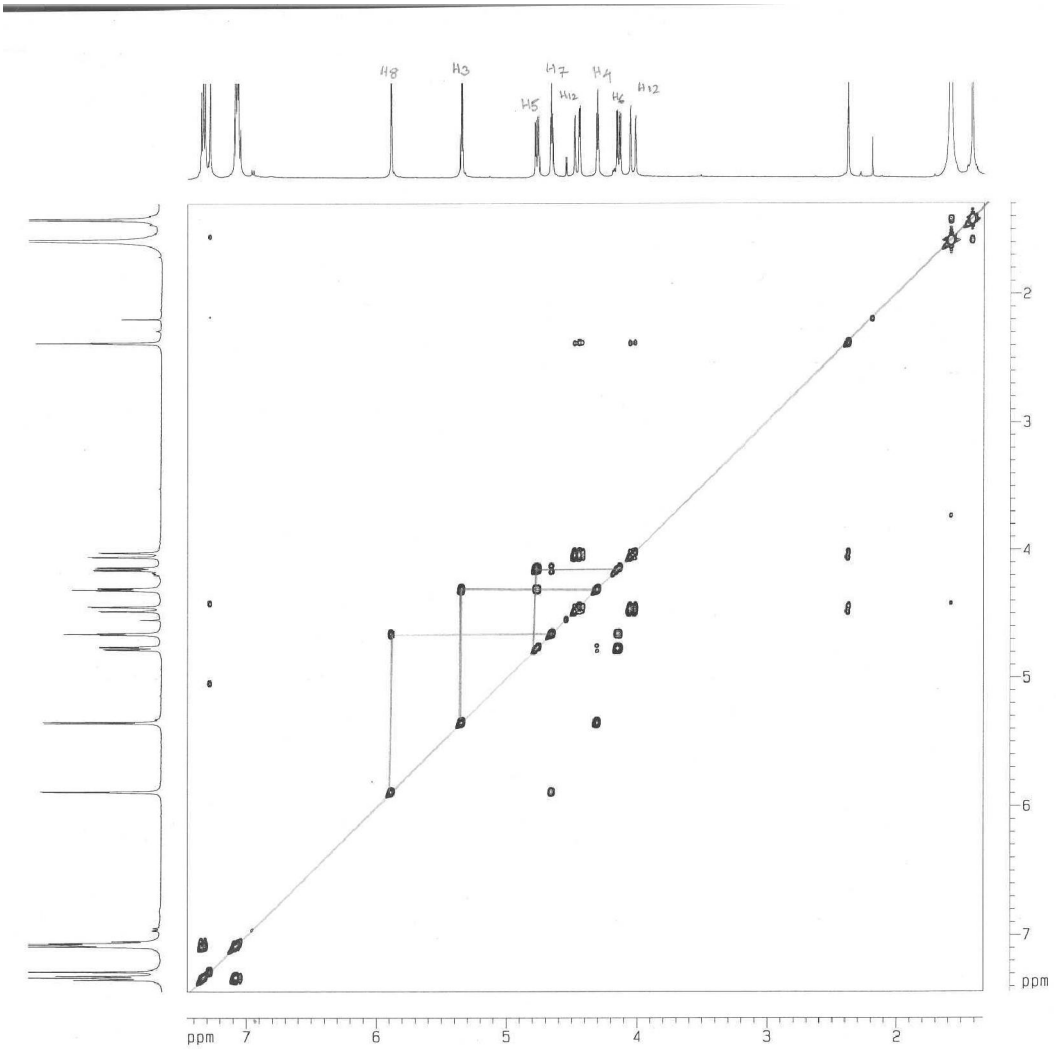


Figure 3. COSY 2D NMR spectrum of **7a**

proton	ppm	*J*	^{1}H-^{1}H connectivity

H-8	5.88 (d)	3.5 Hz	H-7
H-7	4.65 (t)	3.9 Hz	H-8, H-6
H-6	4.13 (dd)	3.6, 4.4 Hz	H-7, H-5
H-5	4.74 (dd)	3.6, 3.9 Hz	H-6, H-4
H-4	4.30 (t)	4.8, 3.9 Hz	H-3, H-5
H-3	5.34 (d)	4.8 Hz	H-4

The NOSEY spectrum of **7a** gave an idea about the stereo alignment of the newly generated β-lactam protons (Figure 4). The orientation of H-8 and H-7 protons was known to be beta. In the spectrum, the H-7 proton showed spatial interaction with H-4, which further showed connectivity with H-3 proton, revealing that H-8, H-7, H-3 and H-4 are all on the same side i.e. in β-orientation. The mass spectrum of **7a** gave M+1 peak at *m/z* 470, also supporting the structure of the compound.

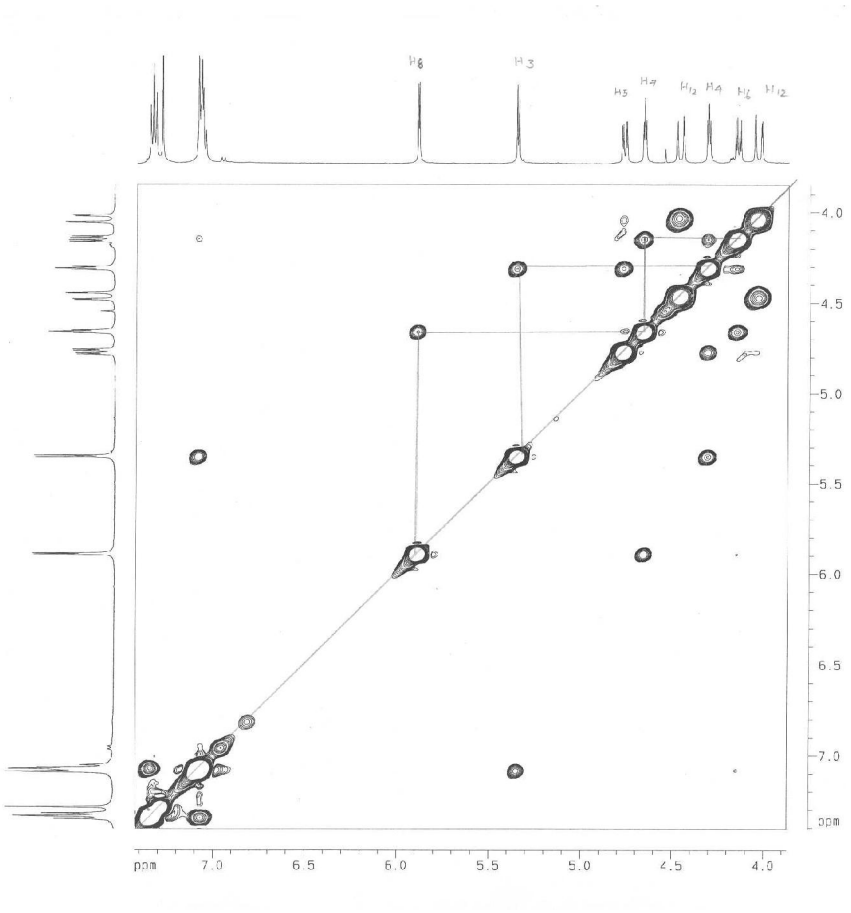


Figure 4. NOESY spectrum of **7a**

X-ray crystal structure of 7a:

Finally the structure of β-lactam and stereochemistry of newly formed centers C-3 and C-4 of the *N*-propargyl substituted azetidin-2-one **7a** were ascertained from the single crystal X-ray crystallography analysis. X-ray quality crystals of **7a** were obtained as colourless crystals by careful crystallization from isopropanol. Crystal dimensions, 0.43 x 0.21 x 0.14 mm; crystal system, orthorhombic; space group $P2_12_12_1$; a = 8.104(2), b = 9.166(2), c = 26.351(6) Å; V = 1957.4(8) $Å^3$; Z = 4; D_c = 1.592 g/cm^3; μ (Mo Kα) (λ = 0.7107 Å) = 1.664 mm^{-1}; F(000) = 936; θ =1.55 to 23.27°; T = 293(2) K; Max. and min. transmission = 0.8041 and 0.5320; Reflections collected/unique = 8515/2801 [R (int) = 0.0181]; Completeness to θ = 23.27 99.6 %; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 2801/0/240; Goodness-of-fit on F^2 = 1.156; Final R indices [I>2σ(I)] = R1 = 0.0196, wR2 = 0.0497; R indices (all data) = R1 = 0.0203, wR2 = 0.0501.

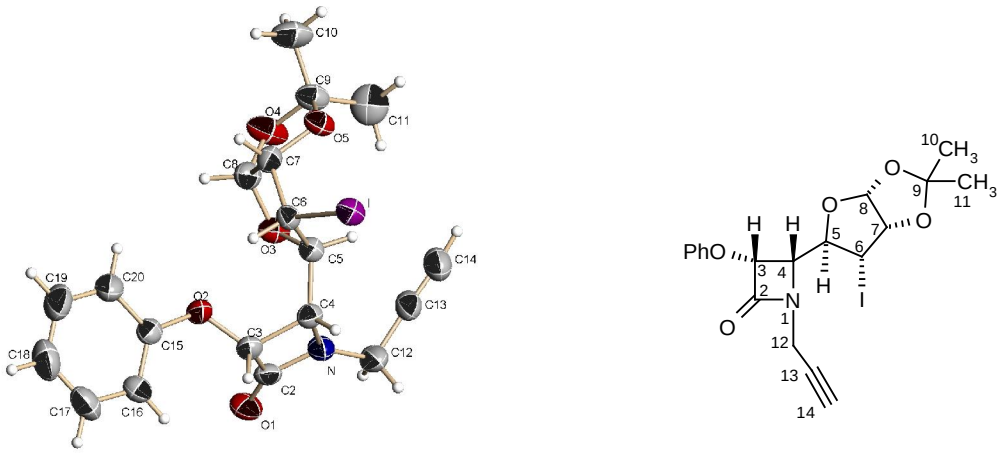


Figure 5. ORTEP Diagram of **7a**

The 3*R*, 4*S* absolute stereochemistry was established for β-lactam ring protons of **7a** on the known absolute stereochemistry of carbohydrate residue by the single crystal X-ray analysis of **7a (**Figure 5). The same stereochemistry was assigned to the other derivative **7b**. Since the stereochemistry of newly generated C-3 and C-4 centers was confirmed as 3*R*, 4*S* by NOESY and single crystal X-ray analysis, we have assigned the opposite stereochemistry for the other diastereomer **8a.**

In the case of benzyloxy substituted *N*-propargyl β-lactams **7b** and **8b**, we could separate only the β-isomer **7b**, while the corresponding α-isomer **8b** was obtained as a mixture along with benzyloxy substituted propargyl amide. This α-isomer **8b** and amide mixture was used as such for further intramolecular radical cyclization. The methoxy derivatives of *N*-propargyl β-lactams **7c** and **8c** were obtained as an inseparable mixture and used without isolation later.

Thus, the Staudinger reaction of glucose derived propargyl imine with ketenes was highly stereoselective and gave only *cis* β-lactams recognized from the coupling constant value of J = 3-5 Hz but with no diastereoselectivity. The reason for the lack of diastereoselectivity may be due to the *anti* orientation of the imine appendage on carbon C-

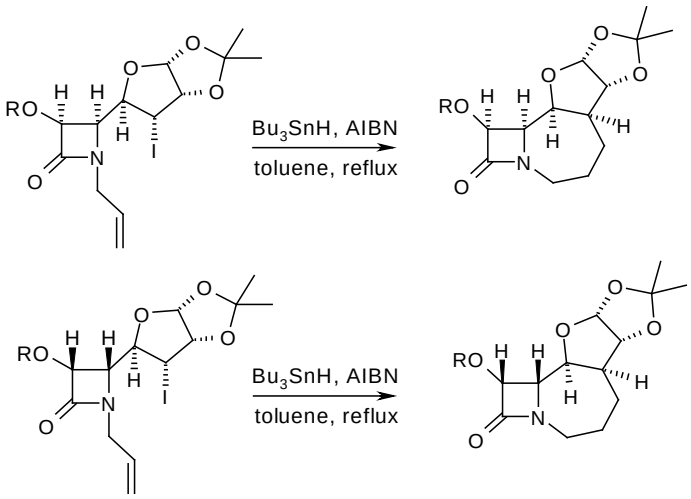
5 and the iodo substituent on carbon C-6 thus directing the attack of imine on ketene from both sides and leading to the formation of a 1:1 diastereomeric mixture of β-lactams **7** & **8**.

Intramolecular radical cyclization of N-propargyl substituted azetidin-2-ones:

Hexenyl radical cyclization is very efficient and well studied for mechanistic as well as synthetic applications.[76] The stereochemical outcome of such kind of cyclizations can be predicted by Beckwith's transition state model.[77] According to this model and Baldwin's rules, *5-exo* cyclization is more common than *6-endo* cyclization. In case of heptenyl and heptynyl radical cyclizations too, examples of *6-exo* cyclizations are well known,[78] while *7-endo* cyclizations are very rare.[79]

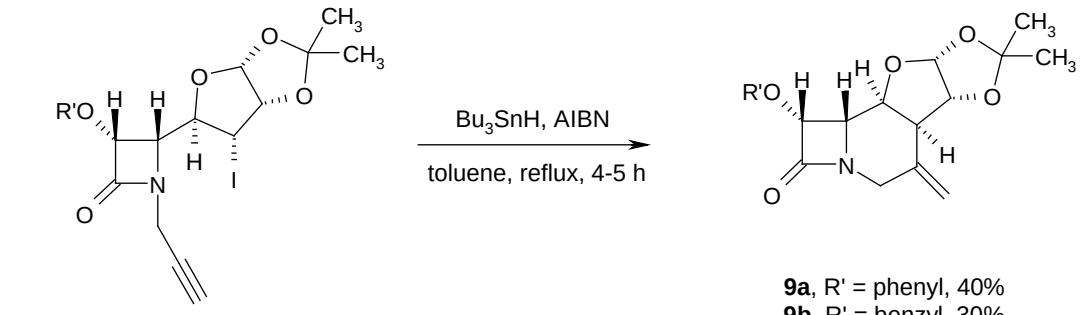
We have hence chosen the above synthesized *N*-propargyl substituted β-lactams as substrates to study the mode of intramolecular radical annulation and in particular to construct highly strained and stable polycyclic β-lactams. The results of previous studies from our group on *N*-allyl systems revealed that the generated heptenyl radical cyclized in *7-endo* fashion to afford tricyclic compounds irrespective of the stereochemistry of β-lactam hydrogens (Scheme 3).[80]

Scheme 3



In our present study, the *N*-propargyl substituted azetidin-2-one **7a** was treated with a solution of tributyltin hydride and a catalytic amount of AIBN in refluxing toluene. The generated heptynyl radical, in the usual fashion, attacked the triple bond in *exo dig* mode to generate a new six membered ring providing the fused tetracyclic β-lactam **9a** bearing an *exo* methylene group, exclusively in 40% yield (Scheme 4). The product **9a** was purified by flash column chromatography and characterized by spectral studies.

Scheme 4

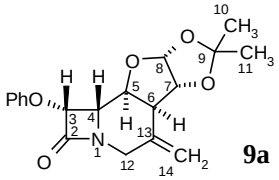


7a, R' = phenyl; **7b**, R' = benzyl

9a, R' = phenyl, 40%
9b, R' = benzyl, 30%

The IR spectrum of **9a** showed a strong band at 1765 cm^{-1} indicating the presence of carbonyl group of β-lactam ring. The ^{1}H NMR spectrum of the cyclized product gave two sharp singlets at 1.31 and 1.32 ppm for the acetonide methyl protons. One of the bridgehead protons, H-6 appeared as a doublet at 2.89 ppm (J = 4.4 Hz). The two doublets at 3.72 (J = 14.7 Hz) and 4.34 ppm (J = 15.1 Hz) correspond to the N-CH_2 protons (H-12). The β-lactam protons H-4 and H-3 appeared as a triplet at 3.89 ppm (J = 3.9, 3.4 Hz) and a doublet at 5.37 ppm (J = 3.9 Hz) respectively.

The anomeric proton H-8 appeared as a doublet at 5.87 ppm (J = 3.9 Hz) while the adjacent proton H-7 was seen as a multiplet at 4.87-4.98 ppm along with *exo* methylene protons (H-14). The H-5 proton gave a singlet at 5.24 ppm and the aromatic protons appeared as a multiplet in the region of 7.00-7.36 ppm.



9a

The COSY spectrum of **9a** supported the above NMR assignments but the NOESY spectrum did not give any evidence regarding the spatial connectivity of newly generated chiral centers C-5 and C-6 protons.

The ^{13}C NMR of **9a** showed a peak at 26.4 ppm for the acetonide methyl carbons. The *N*CH_2 and C-6 carbons were seen at 45.4 and 47.7 ppm correspondingly. The β-lactam carbons C-4 and C-3 appeared at 54.9 and 75.1 ppm respectively while the other chiral centers C-7, C-5 and C-8 appeared at 80.5, 81.8 and 104.6 ppm correspondingly. The quaternary carbon of acetonide C-9 was seen at 111.6 ppm. The *exo* methylenic carbon C-

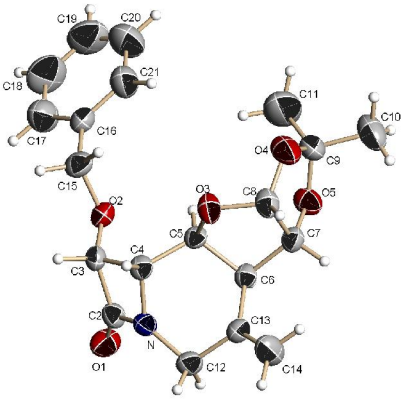
14 appeared at 113.5 ppm and C-13 appeared at 115.5 ppm. The aromatic carbons were seen in the region of 122.6-156.9 ppm and the β-lactam carbonyl appeared at 166.3 ppm.

In the ^{13}C-DEPT experiment, two peaks below at 45.4 and 113.5 ppm evidenced the presence of two methylene carbons and confirmed the *exo-dig* mode of cyclization of beta diastereomer **7a**.

X-ray crystallographic studies of 9b:

To further confirm the orientation of H-5 and H-6 protons and also to assign the stereochemistry at C-6 centre, the benzyloxy substituted *N*-propargyl β-lactam **7b** was subjected to radical cyclization under similar reaction conditions to give a pale yellow crystalline solid **9b** in 30% yield.

The tricyclic β-lactam **9b** was crystallized as pale yellow crystals from isopropanol. Crystal dimensions, 0.21 x 0.19 x 0.06 mm; crystal system, monoclinic, space group $P2_1$; a = 9.839(15), b = 8.148(12), c = 11.946(18) Å; V = 945.6(2) Å^3; Z = 2; D_c = 1.255 g/cm^3; μ (Mo Kα) (λ = 0.7107 Å) = 0.090 mm^{-1}; F(000) = 380; θ = 1.73 to 24.99°; T = 293(2) K; Max. and min. transmission = 0.9943 and 0.9813; Reflections collected/unique = 9089/3324 [R(int) = 0.0320]; Completeness to θ = 24.99 99.8%; Refinement method = Full-matrix least-squares on F^2; Data/restraints/parameters = 3324/1/237; Goodness-of-fit on F^2 = 1.071; Final R indices [I>2σ(I)] = R1 = 0.0497, wR2 = 0.1024; R indices (all data) = R1 = 0.0584, wR2 = 0.1065.



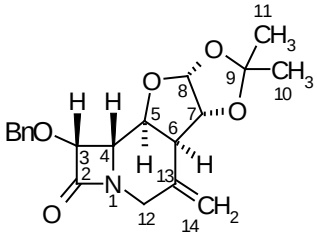
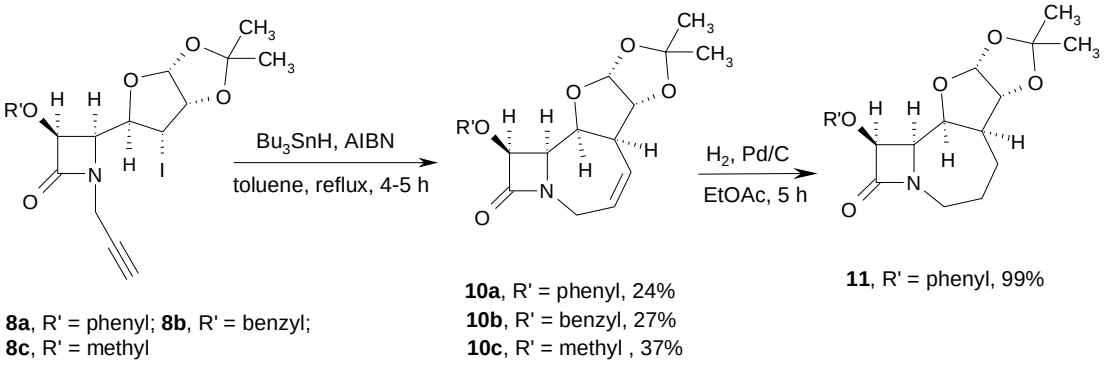


Figure 6: ORTEP Diagram of **9b**

The presence of an *exo* methylenic group formed via *6-exo-dig* addition is clearly evidenced from the ORTEP diagram of tetracyclic compound **9b** (Figure 6). Both the bridgehead protons are stereoaligned in alpha form and are *cis* to each other. The absolute stereochemistry of C-3, C-4 and C-6 centers was determined to be *3R*, *4S* and *6S* from the known absolute stereochemistry of *7R* and *8R* of the sugar moiety.

Similarly, the alpha diastereomer **8a** was treated with a solution of tributyltin hydride and a catalytic amount of AIBN in toluene under identical reaction conditions (Scheme 5). The radical generated from the iodo substituent gets trapped with the terminal carbon of acetylenic bond via unusual 1,7-bond coupling and afforded 7-*endo-dig* annulated product **10a** in 24% yield.

Scheme 5

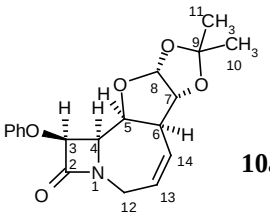


8a, R' = phenyl; **8b**, R' = benzyl;
8c, R' = methyl

10a, R' = phenyl, 24%
10b, R' = benzyl, 27%
10c, R' = methyl , 37%

11, R' = phenyl, 99%

The tricyclic β-lactam **10a** was likewise characterized by spectral studies. IR spectrum of **10a** showed a strong band at 176[illegible] cm^{-1} corresponding to the carbonyl group of the β-lactam ring. I the ^1H NMR spectrum, the acetonide methyl protons appeared a singlets at 1.14 and 1.27 ppm. The H-6 proton gave a broad singl at 2.99 ppm and a doublet at 3.86 ppm (J = 19.0 Hz) corresponds t one of the NCH_2 protons.



10a

A multiplet at 4.27-4.44 ppm integrating for four protons was assigned to H-5, H-7, H-4 and H-12. Another multiplet at 5.32-5.57 ppm integrating for three protons was assigned to H-13, H-14 and H-3 protons. The anomeric proton appeared as a doublet at 5.82 ppm (J = 3.0 Hz) while the aromatic protons appeared in the region of 6.95-7.32 ppm.

In the COSY spectrum of cyclized product **10a** (Figure 7), the anomeric proton H-8 showed a strong interaction with H-7, which in turn showed a strong coupling with H-6 proton. The H-6 proton further connected with H-14 proton. The H-14 showed a strong interaction with H-13 proton, which was further connected with H-12 protons. The β-lactam H-3 gave a strong coupling with H-4.

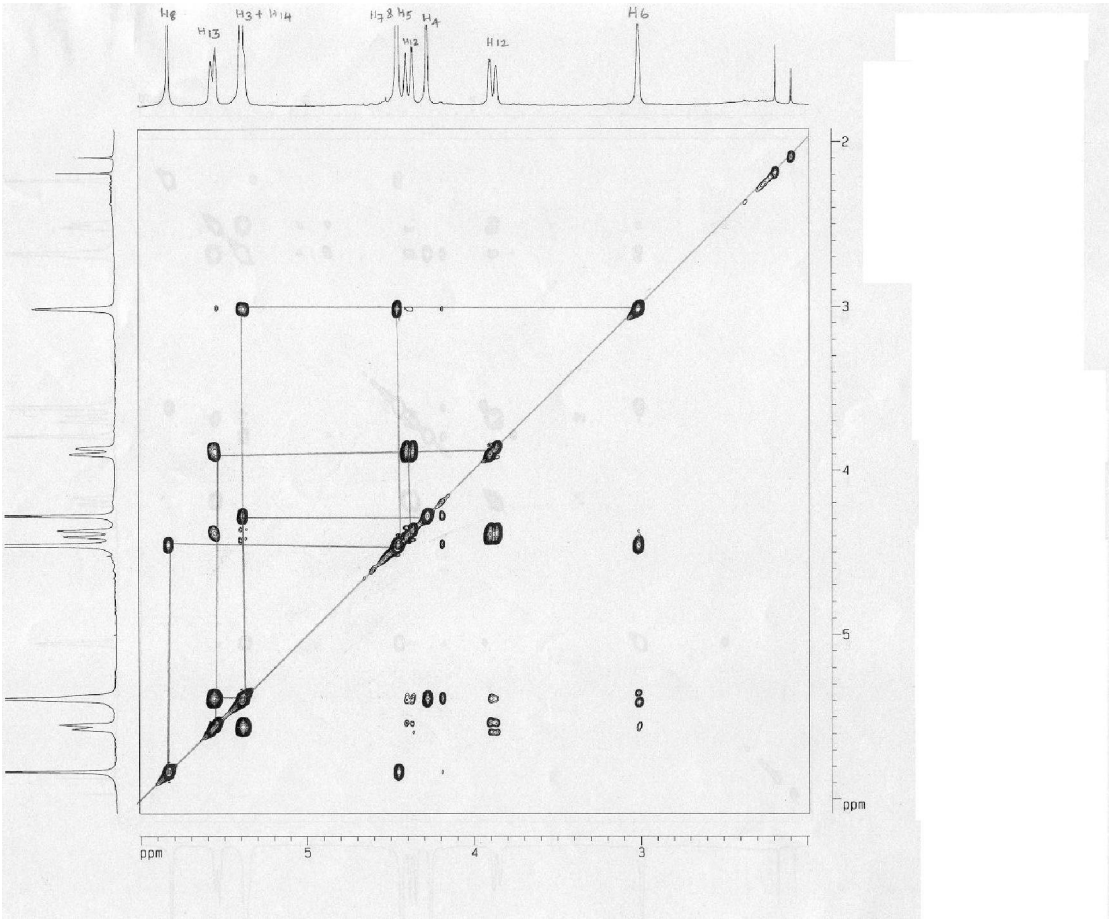


Figure 7**. COSY Spectrum of** 10a

Proton	δ (ppm)	***J* (Hz)**	^{1}H-^{1}H connectivity
H-8	5.82 (d)	3.0 Hz	H-7
H-7	4.27-4.44 (m)	-	H-6, H-8
H-6	2.99 (s)	-	H-14, H-5, H-7
H-13	5.32-5.57 (m)	-	H-14 & H-12

H-3	5.32-5.57 (m)	-	H-4

In the NOSEY spectrum of 10a **(Figure 8), H-3 proton showed spatial connectivity with H-6 protons and also with H-5 proton revealing that H-3, H-6 and H-5 protons are all on the same side i.e. in alpha orientation. This confirmed that the geometry of bridgehead protons is *cis* with respect to each other.**

In the ^{13}C-DEPT experiment, only one peak appeared below at 41.7 ppm corresponding to the N-CH_2 carbon providing an evidence for the formation of *endo-dig* cyclized product. In addition, the double bond present in the *endo-dig* cyclized product 10a **was hydrogenated using Pd/C as a catalyst to furnish** 11 **in quantitative yield. The spectral and X-ray crystal structure of** 11 **matched perfectly with the authentic material obtained via intramolecular radical cyclization of *N*-allyl systems. This study further confirmed the structure of *7-endo-dig* compound** 10a**.**

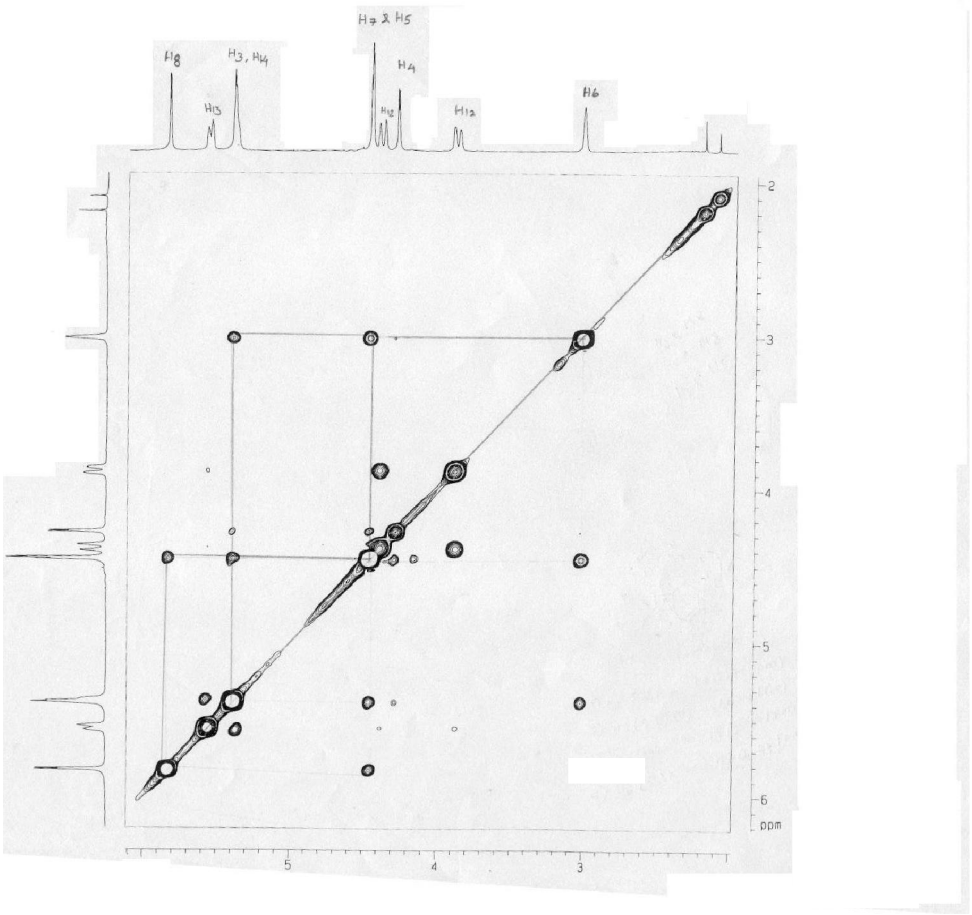


Figure 8**. NOESY spectrum of** 10a

The benzyloxy and methoxy derivatives 8b **and** 8c **also underwent smooth radical cyclization and gave 7-membered fused polycyclic β-lactams** 10b **and** 10c **in 27% and 37% yield respectively (Scheme 5). The linearity of the triple bond distances the acceptor from the radical, thus leading to poor yields of cyclized products in all cases.**

In case of both alpha and beta diastereomers of *N*-propargyl substituted β-lactams, the radical cyclization was highly stereospecific and gave either *6-exo-dig* or *7-endo-dig* products depending upon the stereochemistry of the β-lactam ring. The

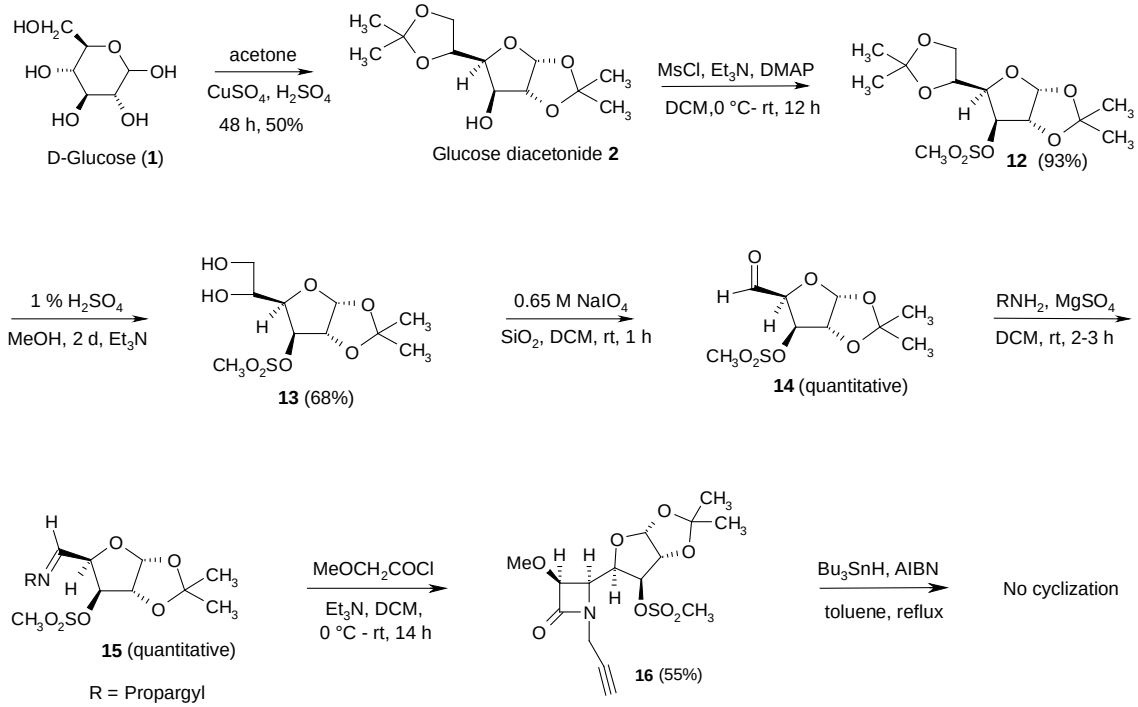
reason for the change in the mode of cyclization could possibly be attributed to the steric bulk of acetonide moiety.

Diastereospecific synthesis of N-propargyl substituted azetidin-2-ones:

Consequent to the absence of diastereoselectivity with iodoaldehyde 5**, we prepared the mesylate derivative** 12 **of glucose diacetonide by treating the glucose diacetonide** 2 **with methane sulfonyl chloride and Et_3N in the presence of a catalytic amount of DMAP in dichloromethane at room temperature. The mesylated glucose diacetonide** 12 **was then subjected to selective primary acetonide deprotection with 1% H_2SO_4 and methanol followed by oxidative cleavage with aqueous sodium periodate solution to furnish the aldehyde** 14 **in quantitative yield. The chiral aldehyde** 14 **was then condensed with propargyl amine to give the corresponding propargyl chiral imine** 15 **(Scheme 6).**

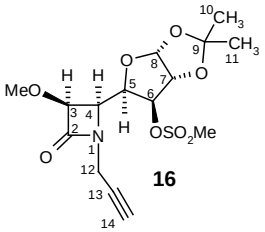
This propargyl imine 15 **on Staudinger cycloaddition with methoxy acetyl chloride in the presence of Et_3N afforded β-lactam** 16 **as a single diastereomer (Scheme 6). The compound** 16 **was characterized by IR and ^1H NMR spectral studies.**

Scheme 6



The IR spectrum of the compound 16 **showed a strong absorption band at 1763 cm^{-1} corresponding to the carbonyl group of the β-lactam ring. In the ^{1}H NMR spectrum, the acetonide methyl protons and mesylate methyl protons appeared as singlets at 1.33, 1.51 and 3.09 ppm. The acetylenic proton H-14 was seen as a triplet at 2.25 ppm (*J* = 2.4 Hz). The singlet at 3.61 ppm was assigned to methoxy group of β-lactam ring while a doublet of doublet at 3.86 ppm (*J* = 2.9, 4.8 Hz) and another at 4.08 ppm (*J* = 4.8, 5.4 Hz) were assigned for the H-5 proton and the β-lactam proton H-4 respectively.**

The nitrogen attached methylene protons appeared as a multiplet. The two doublets at 4.57 (*J* = 5.4 Hz) and 4.76 ppm (*J* = 3.4 Hz) were assigned to H-3 and H-7 protons whereas the H-6 and H-8 protons appeared as



doublets at 5.19 (*J* = 2.9 Hz) and 6.02 (*J* = 3.4 Hz) ppm respectively. The M+1 peak at *m/z* 376 confirmed the structure of mesylate β-lactam 16**.**

Unfortunately, attempted radical cyclization of 16 **using tributyltin hydride proved to be unrewarding and resulted in recovery of starting material.**

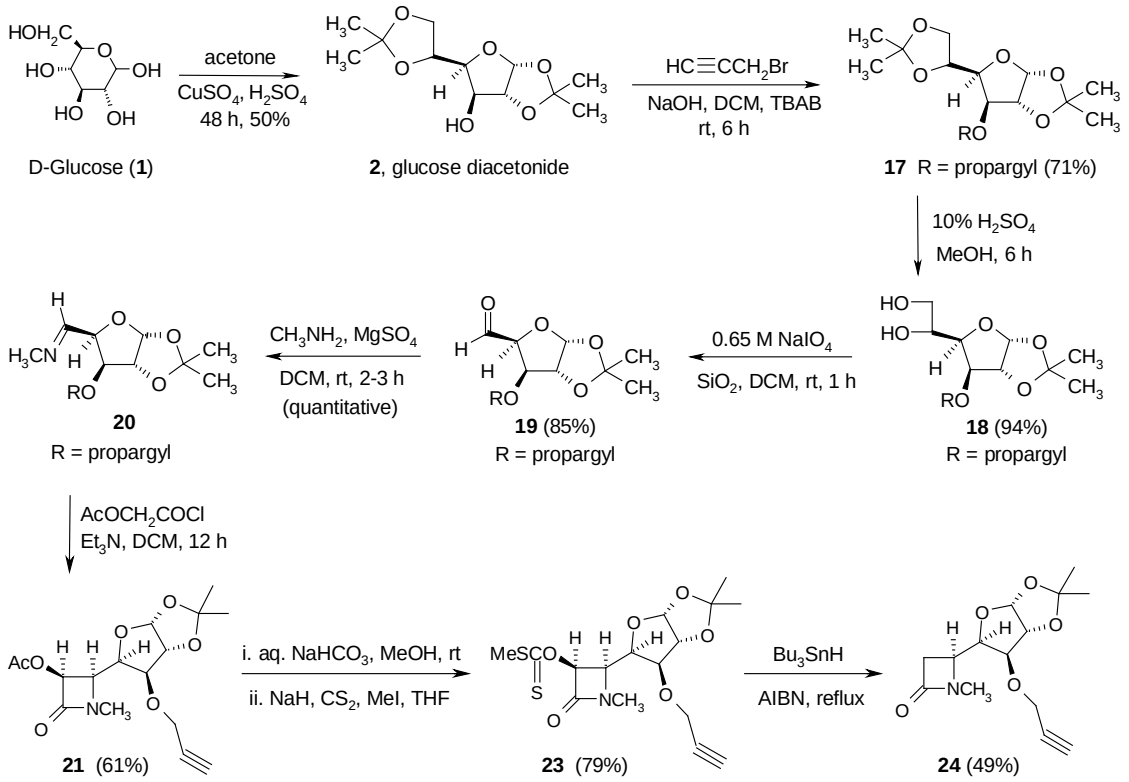
Diastereospecific synthesis of O-propargyl β*-lactam:*

We then designed an alternate strategy in which we envisaged the desired cyclization through a radical generated at the C-3 position of the β**-lactam as against our earlier study wherein we had the radical generator on the carbohydrate moiety that was anchored to the C-4 position. Towards this, 3-acetoxy-**β**-lactam** 21 **was prepared stereospecifically as shown in Scheme 7.**

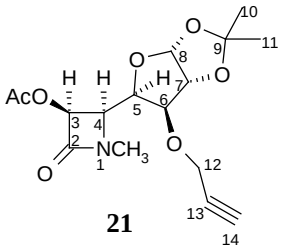
Glucose diacetonide 2 **was treated with a solution of 50% aqueous NaOH followed by reaction with propargyl bromide in the presence of a catalytic amount of tetrabutylammonium bromide in dichloromethane to provide propargyl protected glucose diacetonide derivative** 17 **in 71% yield.**

The selective primary acetonide deprotection followed by cleavage of the obtained diol 18 **provided us the required aldehyde** 19 **in quantitative yield. Chiral aldehyde** 19 **was reacted with 40% aqueous methylamine solution to furnish the imine** 20**, which on Staudinger reaction with acetoxyacetyl chloride in the presence of excess triethylamine furnished β-lactam derivative** 21 **in 61% yield as a single diastereomer.**

Scheme 7



A strong absorption band at 1769 cm^{-1}, 1751 cm^{-1} and 2121 cm^{-1} in the IR spectrum of the compound β-lactam 21 **correspond to carbonyl group of the β-lactam ring, acetoxy group and acetylenic carbon-carbon triple bond. In the ^1H NMR spectrum, the acetonide methyl protons, acetoxy and N-CH_3 methyl protons appeared as singlets at 1.32, 1.50, 2.14 and 2.92 ppm respectively. The acetylenic proton H-14 gave a triplet at 2.45 ppm (J = 2.5 Hz). A multiplet integrating for four protons at 4.00-4.18 ppm was assigned to nitrogen attached methylene protons (H-12), H-6 and the β-lactam proton H-4.**



21

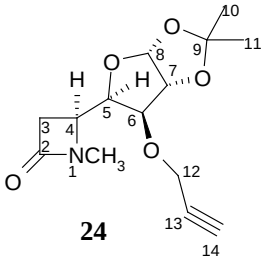
The H-5 proton was seen as a doublet of doublet at 4.28 ppm (*J* = 3.2, 8.3 Hz) and H-7 appeared as a doublet at 4.62 ppm (*J* = 3.5 Hz). A doublet at 5.93 ppm (*J* = 4.3 Hz) integrating for two protons was assigned to H-3 and H-8 protons. In the ^{13}C-NMR spectrum, the acetoxy and the β-lactam carbonyl carbons appeared at 164.4 and 168.7 ppm correspondingly. The M+1 peak at *m/z* 340 confirmed the structure of β-lactam 21**.**

The acetoxy azetidin-2-one 21 **was then hydrolyzed with a saturated solution of sodium bicarbonate in methanolic medium under mild conditions at room temperature to give the hydroxy β-lactam** 22 **obtained as a gummy solid in 84% yield. The hydroxy β -lactam** 22 **was then converted into the corresponding xanthate ester** 23 **by treatment with sodium hydride followed by subsequent addition of carbon disulphide and methyl iodide (Scheme 7).**

Intramolecular radical cyclization of xanthate ester 23 **was attempted with tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing toluene. Unfortunately, the generated radical preferred to abstract a hydrogen radical giving the reduced product** 24 **instead of the desired cyclized one. The reduced product** 24 **was obtained as a white solid in 49% yield.**

The IR spectrum of the reduced product 24 **showed a strong band at 1743 cm^{-1} corresponding to the carbonyl group of the β-lactam ring. In the ^{1}H NMR spectrum, three singlets at 1.23, 1.40 and 2.78 ppm were assigned to acetonide methyl and nitrogen attached methyl protons respectively. A triplet at 2.45 ppm was assigned for the acetylenic proton, whereas the methylene H-3 protons appeared as doublet at 2.51 ppm (*J* = 14.9 Hz) and doublet of doublet at 2.98 ppm (*J* = 5.1, 14.5 Hz).**

The H-4 proton was seen as a multiplet in the range 3.64-3.71 ppm. A multiplet at 4.01-4.14 ppm integrating for four protons was assigned for OCH_2, H-5 and H-6 protons. The H-7 proton gave a doublet at 4.49 ppm (*J* = 3.9 Hz) and the anomeric proton H-8 also appeared as a doublet at 5.86 ppm (*J* = 3.5 Hz). In the ^{13}C-Dept experiment, two methylene peaks below at 39.2 and 57.0 ppm indicated clearly the formation of reduced product. The M+1 peak at *m/z* 282 further supported the above.



24

The failure of the cyclization with the *O*-propargyl substrate could be attributed to the large distance between the radical and radical acceptor, while the linearity of the acetylenic bond could also be seen as a detrimental factor.

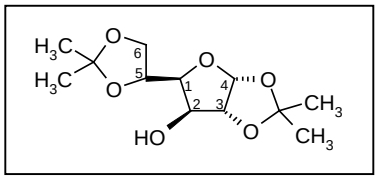
Conclusion:

In conclusion, iodoaldehyde derived from cheap and inexpensive D-glucose was employed as a chiral source for the asymmetric Staudinger reaction to yield the *N*-propargyl substituted diastereomeric azetidin-2-ones (1:1 ratio) stereoselectively. The intramolecular radical cyclization of these β-lactams gave either 6-*exo*-*dig* or 7-*endo*-*dig* cyclized tetracyclic β-lactams depending upon the stereochemistry of the β-lactam protons. The structure and stereochemistry of these polycyclic β-lactams were established by spectral studies and single crystal X-ray analysis. The mesylate and propargyl derivatives of glucose diacetonide led to the formation of a single diastereomer stereospecifically. But the attempted radical cyclization of these β-lactams met with failure. In the case of mesylate, this could possibly be due to stability

towards radical reaction conditions. On the other hand, for the propargyl derivative, the failure could be attributed to the remoteness of the xanthate derived radical from the site of the radical acceptor, i.e. the triple bond of the propargyl group.

EXPERIMENTAL SECTION

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



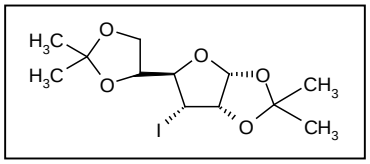
A suspension of anhydrous D-glucose (**1**) (28.0 g, 155.40 mmol)**,** anhydrous cupric sulphate (28.2 g, 176.70 mmol) and conc. H_2SO_4 (2 mL) in dry acetone (600 mL) was stirred at room temperature for 48 h. The reaction mixture was then neutralized with potassium carbonate (200 g) and stirred overnight. The reaction mixture was filtered through a Buchner funnel and the acetone layer was dried over sodium sulphate and evaporated *in vacuo*. The resulting solid was recrystallized from hot cyclohexane to give pure white crystalline glucose diacetonide **2** in 50% yield (20 g).

white solid; mp 109-110 °C

IR ($CHCl_3$): ν_{max} 3429 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3H, C*H*$_3$), 1.32 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.79 (bs, 1H, O*H*), 4.01-4.40 (m, 5H, *H-1*, *H-2*, *H-5* & *H-6*), 4.54 (d, *J* 3.4 Hz, 1H, *H-3*), 5.95 (d, *J* 3.4 Hz, 1H, H-4)

3-deoxy-3-iodo-1, 2; 5, 6-di-O-diisopropylidene-α-D-allofuranose (3):

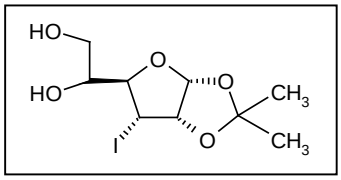


carbon numbering is same as in **2**

A mixture of hydroxy compound **2** (3.0 g, 11.52 mmol), triphenylphosphine (9.06 g, 34.54 mmol) and imidazole (2.35 g, 34.51 mmol) in toluene was heated under reflux for 10 minutes to make the solution homogeneous. Iodine (5.8 g, 23.04 mmol) was added to the solution and refluxed for a further 18 h with stirring. The reaction mixture was cooled and successively washed with saturated $NaHCO_3$ (75 mL), sodium metabisulphite (75 mL) solutions and water, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting mass was treated with diethyl ether to precipitate Ph_3PO. The ether filtrate was concentrated *in vacuo* and the residue was chromatographed (100-200 mesh, 2-3% acetone-petroleum ether) to afford 1.84 g (43%) of **3** as a thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 6H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 3.78 (dd, *J* 4.4, 4.4 Hz, 1H, *H-2*) 4.08-4.36 (m, 4H, *H-1*, *H-5* & *H-6*), 4.62 (t, *J* 3.4, 4.4 Hz, 1H, *H-3*), 5.84 (d, *J* 3.4 Hz, 1H, *H-4*)

***3-deoxy-3-iodo-1, 2-O-isopropylidene-α-D-allofuranose (4)**:*



carbon numbering is same as in **2**

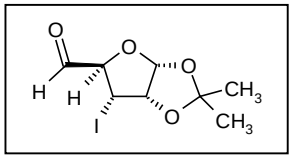
Glucose diacetonide **3** (2.9 g, 7.80 mmol) was dissolved in methanol (47 mL). Water (17 mL) and 10% H_2SO_4 (2.7 mL) were added and stirred at room temperature for 6 h. The reaction mixture was then neutralized with K_2CO_3 (pH 7) and the solvent was distilled off under reduced pressure. The residue was extracted with dichloromethane (2 x 50 mL), dried over Na_2SO_4 and concentrated to give a white crystalline solid of diol **4** in 85% yield (2.2 g) which was used as such without further purification for next reaction.

white solid; mp 118-119 °C

IR ($CHCl_3$): ν_{max} 3314, 3437 cm^{-1}

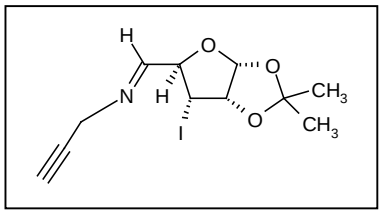
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.2 (dd, *J* 3.9, 7.8 Hz, 1H, *H*OCH$_2$), 2.63 (d, *J* 4.9 Hz, 1H, *H*OCH), 3.75-4.07 (m, 4H, *H-1*, *H-5* & *H-6*), 4.32 (dd, *J* 2.4, 2.9 Hz, 1H, *H-2*), 4.64 (t, *J* 2.9, 3.4 Hz, 1H, *H-3*), 5.83 (d, *J* 3.4 Hz, 1H, *H-4*)

***Synthesis of iodoaldehyde (5)**:*



To a vigorously stirred suspension of chromatographic grade silica gel (5.0 g) in dichloromethane (40 mL) in a 100 mL flask was added a 0.65 M aqueous solution of $NaIO_4$ (5 mL) dropwise with stirring. Diol **4** (0.8 g, 2.40 mmol) in CH_2Cl_2 (5 mL) was then added and the reaction was monitored by TLC until disappearance of the starting material (1 h). The mixture was filtered, washed with water, dried over Na_2SO_4 and concentrated to give pure iodoaldehyde **5** in quantitative yield (0.710 g, 99%), which was then used as such for imine formation.

***Synthesis of propargyl imine (6)**:*



To a solution of propargyl amine (0.1 mL, 1.43 mmol) in dichloromethane (10 mL), 4 equivalents of anhydrous $MgSO_4$ and a solution of iodo aldehyde **5** (0.429 g, 1.44 mmol) in dichloromethane (10 mL) were added at room temperature. The reaction mixture was stirred for 3 h and then filtered through a sintered glass crucible. The filtrate was concentrated and the resulting imine **6** (quantitative yield) was used as such for the β-lactam formation.

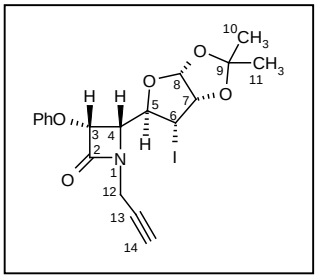
General procedure for the preparation of β-lactams 7 & 8:

A solution of the acid chloride (phenoxyacetyl chloride, benzyloxyacetyl chloride or methoxyacetyl chloride) (1.50 mmol) in dichloromethane (30 mL) was added to a solution of imine **6** (1.00 mmol) and triethylamine (4.50 mmol) in CH_2Cl_2 (20 mL) at 0 °C. It was then allowed to warm to room temperature and stirred for a further 15 h. The reaction mixture was washed with saturated sodium bicarbonate solution (10 mL) and saturated brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give a diastereomeric mixture (1:1) of β-lactams **7** & **8** in 40-50% yields. Both the diastereomers were separated by flash column chromatography or by recrystallization from methanol.

***Reaction of imine 6 with phenoxyacetyl chloride**:*

A mixture of β-lactams **7a** and **8a** were obtained from imine **6** (0.870 g, 2.59 mmol) on reaction with Et_3N (1.62 mL, 11.65 mmol) and phenoxy acetyl chloride (0.53 mL, 4.35 mmol) by following the above general procedure in 42% yield. The crude product was purified by flash column chromatography (10% acetone-petroleum ether) to get **8a** as a gummy material (0.270 g, 22%). However, the other diastereomer **7a** was obtained as a mixture along with the corresponding amide of phenoxyacetyl chloride and propargyl amine, which was then further purified by crystallization from methanol to get a white crystalline solid (0.240 g, 20%).

Compound 7a



white crystalline solid; mp 109-110 °C

$[\alpha]_D^{25}$ = +133.0 (*c* 0.93, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1770 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.37 (t, *J* 2.4 Hz, 1H, *H-14*), 4.02 (dd, *J* 2.5, 17.9 Hz, 1H, *H-12*), 4.13 (dd, *J* 3.6, 4.4 Hz, 1H, *H-6*), 4.30 (t, *J* 4.8, 3.9 Hz, 1H, *H-4*), 4.46 (dd, *J* 3.0, 18.1 Hz, 1H, *H-12*), 4.65 (t, *J* 3.9 Hz, 1H, *H-7*), 4.74 (dd, *J* 3.6, 3.9 Hz, 1H, *H-5*), 5.34 (d, *J* 4.8 Hz, 1H, *H-3*), 5.88 (d, *J* 3.5 Hz, 1H, *H-8*), 7.02-7.09 (m, 3H, *aromatic*), 7.29-7.37 (m, 2H, *aromatic*)

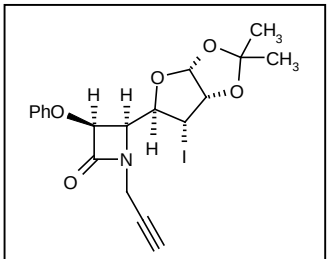
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.4, 26.8, 26.9, 30.9, 56.3, 74.0, 75.8, 80.1, 80.8, 81.7, 103.4, 112.4, 115.9, 122.7, 129.7, 157.5, 165.6

MS: *m/z* = 470 (M+1)

Anal. **Calcd** for **$C_{19}H_{20}NO_5I$**: C, 48.61 %; H, 4.30 %; N, 2.99 %

Found: C, 48.49 %; H, 4.27 %; N, 2.80 %

Compound 8a



carbon numbering is same as in **7a**

thick oil

$[\alpha]_D^{25}$ = -13.4 (*c* 1.08, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1769 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 2.40 (t, *J* 2.5 Hz, 1H, *H-14*), 3.87-4.02 (m, 2H, *H-12* & *H-6*), 4.36 (t, *J* 3.4, 4.9 Hz, 1H, *H-4*), 4.43-4.55 (m, 2H, *H-12* & *H-7*), 4.64 (t, *J* 3.4, 3.4 Hz, 1H, *H-5*), 5.37 (d, *J* 4.9 Hz, 1H, *H-3*), 5.81 (d, *J* 3.4 Hz, 1H, *H-8*), 7.03-7.12 (m, 2H, *aromatic*), 7.31-7.37 (m, 3H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 25.6, 25.9, 30.6, 55.2, 73.3, 75.4, 79.1, 79.9, 107.5, 111.2, 113.9, 114.8, 121.5, 128.8, 156.3, 164.1

MS: *m/z* = 470 (M+1)

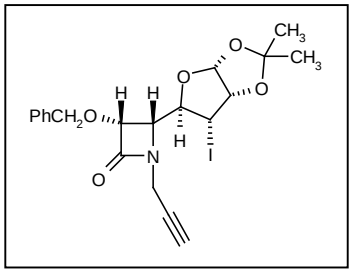
Anal. **Calcd** for **$C_{19}H_{20}NO_5I$**: C, 48.61 %; H, 4.30 %; N, 2.99 %

Found: C, 48.80 %; H, 4.11 %; N, 2.93 %

Reaction of imine 6 with benzyloxyacetyl chloride:

A mixture of β-lactams **7b** and **8b** were obtained from imine **6** (0.956 g, 2.85 mmol), when treated with triethylamine (1.78 mL, 12.80 mmol) and benzyloxyacetyl chloride (0.67 mL, 4.24 mmol) by following the general procedure in 41% overall yield. The mixture was separated by flash column chromatography (10% acetone-petroleum ether) to get pure **7b** as a gummy material (0.312 g, 23%). However, other diastereomer **8b** could not be obtained in pure form either by very careful chromatography or by crystallization. Therefore, this diastereomer was used as such for further reaction.

Compound 7b



carbon numbering is same as in **7a**

thick oil

$[\alpha]_D^{25}$ = +101.5 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1762 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 2.33 (t, *J* 2.5 Hz, 1H, *H-14*), 3.99-4.13 (m, 3H, *H-4* & *H-12*), 4.44 (dd, *J* 2.4, 2.4 Hz 1H, *H-6*), 4.70 (m, 5H, $C_6H_5CH_2O$, *H-3*, *H-7* & *H-5*), 5.77 (d, *J* 3.4 Hz, 1H, *H-8*), 7.36-7.38 (m, 5H, aromatic)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.0, 26.8, 31.3, 57.1, 73.3, 73.7, 75.9, 80.4, 81.7, 103.3, 112.2, 127.9, 128.4, 130.0, 136.8, 167.1

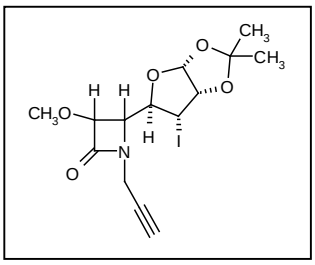
MS: *m/z* = 484 (M+1)

Anal. **Calcd**. for **$C_{20}H_{22}O_5NI$**: C, 49.70 %; H, 4.59 %; N, 2.30 %

Found: C, 49.86 %; H, 4.64 %; N, 2.48 %

Reaction of imine 6 with methoxyacetyl chloride:

To a solution of imine **6** (0.335 g, 1.00 mmol) and Et_3N (0.63 mL, 4.50 mmol) in dichloromethane (20 mL) was added slowly a solution of methoxyacetyl chloride (0.162 g, 1.50 mmol) in dichloromethane (10 mL) at 0 °C over a period of 30 minutes. The reaction mixture was then allowed to warm to room temperature and stirred for a further 15 h. The usual work up afforded an inseparable mixture (0.204 g, 50%) of diastereomers **7c** and **8c**.



carbon numbering is same as in **7a**

IR ($CHCl_3$): ν_{max} 1767 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 6H, C*H*$_3$), 1.58 (s, 6H, C*H*$_3$), 2.34-2.35 (m, 2H, *H-14*), 3.58 (s, 3H, OC*H*$_3$), 3.61 (s, 3H, OC*H*$_3$), 3.84 (d, *J* 2.5 Hz, 1H, *H-6*), 3.93 (d, *J* 2.5 Hz, 1H, *H-6*), 3.96-4.16 (m, 5H, *H-12* & *H-4*), 4.38 (d, *J* 2.5 Hz, 1H, *H-5*), 4.41-4.48 (m, 2H, *H-4* & *H-5*), 4.57-4.67 (m, 4H, *H-3* & *H-7*), 5.84 (d, *J* 3.4 Hz, 1H, *H-8*), 5.87 (d, *J* 3.4 Hz, 1H, *H-8*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8, 22.1, 26.6, 26.8, 31.0, 31.2, 56.0, 56.8, 59.5, 73.5, 73.7, 79.1, 80.3, 80.8, 81.7, 83.7, 84.0, 103.3, 112.0, 112.3, 166.6, 167.2

MS: *m/z* = 408 (M+1)

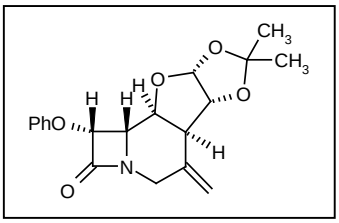
General procedure for radical cyclization of* β-*lactams 7a-b, 8a-c:

To a refluxing solution of β-lactam (1.00 mmol) in toluene (100 mL) was added a solution of Bu_3SnH (1.50 mmol) and AIBN (0.20 mmol) in toluene (50 mL) over a period of 3 h. The reaction mixture was refluxed for a further 2-3 h. After completion of the reaction (TLC), the solvent was distilled off under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica gel, petroleum ether / ethyl acetate) to give pure cyclized products 9-10**.**

Radical cyclization of 7a:

In accordance with the general procedure, to a refluxing solution of iodo β-lactam **7a** (0.180 g, 0.38 mmol) in toluene (36 mL), was added a solution of Bu_3SnH (0.16 mL, 0.60 mmol) and AIBN (13 mg, 0.08 mmol) in toluene (18 mL) for 3 h via a syringe pump and refluxed for an additional 3 h. The solvent was evaporated *in vacuo* and purification of the crude material upon flash column chromatography (10-20% EtOAc-petroleum ether) gave the *exo-dig* tetracyclic β-lactam **9a** in 40% yield (0.053 g).

Compound 9a



carbon numbering is same as in 7a

white crystalline solid; mp 109-110 °C

$[\alpha]_D^{25}$ = +42.07 (*c* 2.1, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1765 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31-1.32 (d, 6H, 2xCH_3), 2.89 (d, *J* 4.4 Hz, 1H, *H-6*), 3.72 (d, *J* 14.7 Hz, 1H, *H-12*), 3.89 (t, *J* 3.9, 3.4 Hz, 1H, *H-4*), 4.34 (d, *J* 15.1 Hz, 1H, *H-12*),

4.87-4.98 (m, 3H, *H-14* & *H-7*), 5.24 (s, 1H, *H-5*), 5.37 (d, *J* 3.9 Hz, 1H, *H-3*), 5.87 (d, *J* 3.9 Hz, 1H, *H-8*), 7.00-7.07 (m, 3H, *aromatic*), 7.29-7.36 (m, 2H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4, 45.4, 47.7, 54.9, 75.1, 80.5, 81.8, 104.6, 111.6, 113.5, 115.5, 122.6, 129.6, 137.1, 156.9, 166.3

MS: *m/z* = 344 **(**M+1)

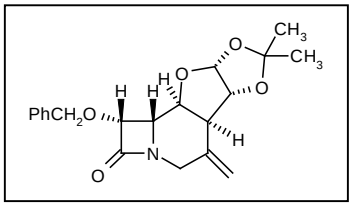
Anal. **Calcd** for **$C_{19}H_{21}NO_5$**: C, 66.45 %; H, 6.17 %; N, 4.08 %

Found: C, 66.33 %; H, 5.97 %; N, 4.24 %

***Radical cyclization of 7b**:*

Following the general procedure given above, treatment of iodo-β-lactam **7b** (0.102 g, 0.21 mmol) with Bu_3SnH (0.09 mL, 0.34 mmol) and AIBN (0.007 g, 0.04 mmol), provided the tetracyclic β-lactam **9b** as a pale yellow crystalline solid (0.023 g, 30% yield), upon flash column chromatographic purification using 10-30% EtOAc-petroleum ether.

Compound 9b



carbon numbering is same as in **7a**

pale yellow solid; mp 128 °C

$[\alpha]_D^{25}$ = +44.7 (*c* 1.06, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1759 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 2.89 (d, *J* 5.0 Hz, 1H, *H-6*), 3.70-3.63 (m, 2H, *H-4* & *H-12*), 4.28 (d, *J* 14.7, 1H, *H-12*), 4.72 (d, *J* 11.0 Hz, 1H, $C_6H_5CH_aH_bO$), 4.82-4.85 (m, 2H, $C_6H_5CH_aH_bO$ & *H-3*), 4.99-5.02 (m, 3H, *H-7* & *H-14*), 5.20 (s, 1H, *H-5*), 5.96 (d, *J* 3.2 Hz, 1H, *H-8*), 7.26-7.45 (m, 5H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.8, 45.4, 47.8, 54.7, 72.8, 75.4, 81.3, 81.8, 111.6, 113.4, 127.9, 128.5, 136.6, 137.5, 168.0

MS: *m/z* = 358 (M+1)

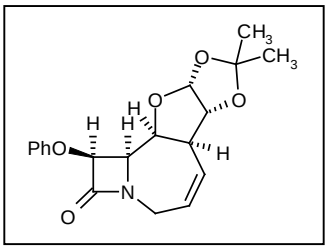
Anal. **Calcd** for **$C_{20}H_{23}NO_5$**: C, 67.20 %; H, 6.49 %; N, 3.92 %

Found: C, 67.05 %; H, 6.60 %; N, 4.02 %

***Radical cyclization of 8a**:*

Following the general procedure, a solution of Bu_3SnH (0.16 mL, 0.60 mmol) and AIBN (12.4 mg, 0.08 mmol) in toluene (18 mL) was added to a boiling solution of iodo β-lactam **8a** (0.178 g, 0.38 mmol) in toluene (36 mL) for 3 h via a syringe pump and refluxed for an additional 3 h. Usual work up and purification by flash column chromatography (10-20% EtOAc-petroleum ether) afforded the *endo-dig* tetracyclic compound **10a** (0.031 g, 24 %).

Compound 10a



carbon numbering is same as in **7a**

thick oil

$[\alpha]_D^{25}$ = +25.38 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1762 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 2.99 (br s, 1H, *H-6*), 3.86 (d, *J* 19.0 Hz, 1H, *H-12*), 4.27-4.44 (m, 4H, *H-5*, *H-7*, *H-4* & *H-12*), 5.32-5.57 (m, 3H, *H-13*, *H-14* & *H-3*), 5.82 (d, *J* 3.0 Hz, 1H, *H-8*), 6.95-7.05 (m, 3H, *aromatic*), 7.28-7.32 (m, 2H, *aromatic*)

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 41.7, 50.5, 57.5, 74.2, 79.6, 84.5, 104.9, 111.8, 115.5, 122.0, 124.8, 125.8, 129.5, 157.4

MS: *m/z* = 344 (M+1)

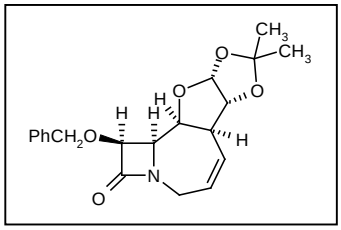
Anal. **Calcd**. for **$C_{19}H_{21}NO_5$**: C, 66.45 %; H, 6.17 %; N, 4.08 %

Found: C, 66.62 %; H, 6.28 %; N, 4.20 %

***Radical cyclization of 8b**:*

Adopting the general procedure, to a solution of mixture of β-lactam **8b** and amide (0.404 g containing 0.246 g of β-lactam, 0.51 mmol based on ^{1}H NMR) in toluene (48 mL) was added a solution of Bu_3SnH (0.2 mL, 0.75 mmol) and AIBN (0.017 g, 0.10 mmol) in toluene (24 mL) for 3.5 h and heated for a further 2.5 h. The solvent was evaporated *in vacuo* and the crude material was purified by flash column chromatography (10-50% EtOAc-petroleum ether) to yield the *endo-dig* product **10b** as a gummy liquid (0.049 g, 27% yield).

Compound 10b



carbon numbering is same as in **7a**

thick oil

$[\alpha]_D^{25}$ = -21.86 (*c* 0.58, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1756 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 3H, C*H*$_3$), 1.37 (s, 3H, C*H*$_3$), 2.86 (br s, 1H, *H-6*), 3.64 (d, *J* 17.6 Hz, 1H, *H-12*), 3.88 (d, *J* 4.4 Hz, 1H, *H-4*), 4.15 (d, *J* 18.3 Hz, 1H, *H-12*), 4.34 (d, *J* 3.6 Hz, 1H, *H-7*), 4.38 (d, *J* 4.4 Hz, 1H, *H-5*), 4.55 (d, *J* 11.7 Hz, 1H, $C_6H_5CH_aH_b$), 4.64 (d, *J* 4.4 Hz, 1H, *H-3*), 4.80 (d, *J* 11.7 Hz, 1H, $C_6H_5CH_aH_b$), 5.20-5.24 (br d, *J* 12.4 Hz, 1H, *H-13*), 5.37 (d, *J* 12.4 Hz, 1H, *H-14*), 5.72 (d, *J* 2.9 Hz, 1H, *H-8*), 7.17-7.30 (m, 5H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 26.9, 50.4, 41.4, 57.3, 72.9, 74.6, 81.1, 84.5, 104.9, 111.7, 124.7, 126.0, 128.3, 127.8, 137.6, 166.9

MS: *m/z* = 358 (M+1)

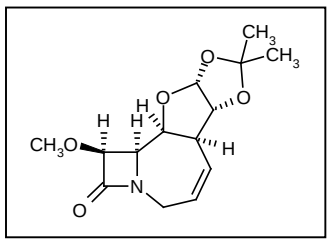
Anal. Calcd. for **$C_{20}H_{23}NO_5$**: C, 67.21 %; H, 6.49 %; N, 3.92 %

Found: C, 67.40 %; H, 6.62 %; N, 3.98 %

***Radical cyclization of 8c**:*

Following the general procedure, a diastereomeric mixture of methoxy β-lactam **7c** and **8c** (0.341 g, 0.84 mmol) on reaction with Bu_3SnH (0.34 mL, 1.27 mmol) and AIBN (28 mg, 0.16 mmol) gave the tetracyclic β-lactam **10c** in pure form upon purification by flash column chromatography (44 mg, 37%).

Compound 10c



carbon numbering is same as in **7a**

thick oil

$[\alpha]_D^{25}$ = -17.04 (*c* 0.68, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1758 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.52 (s, 3H, C*H*$_3$), 3.02 (br s, 1H, *H-6*), 3.59 (s, 3H, OC*H*$_3$), 3.79 (d, *J* 18.7 Hz, 1H, *H-12*), 4.06 (d, *J* 4.4 Hz, 1H, *H-4*), 4.27 (d, *J* 18.6 Hz, 1H, *H-12*), 4.46 (d, *J* 3.7 Hz, 1H, *H-5*), 4.56 (d, *J* 3.7 Hz, 1H, *H-7*), 4.58 (d, *J* 4.4 Hz, 1H, *H-3*), 5.38 (d, *J* 12.7 Hz, 1H, *H-13*), 5.53 (d, *J* 13.1 Hz, 1H, *H-14*), 5.83 (d, *J* 3.7 Hz, 1H, *H-8*)

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 26.9, 41.3, 50.5, 57.1, 59.3, 83.4, 84.5, 104.9, 111.6, 124.6, 126.0, 166. 8

MS: *m/z* = 282 (M+1)

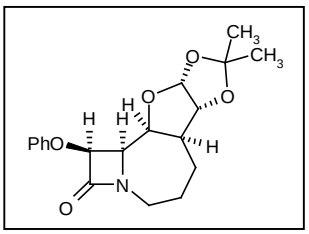
Anal. **Calcd** for **$C_{14}H_{19}NO_5$**: C, 59.76 %; H, 6.80 %; N, 4.98 %

Found: C, 59.90 %; H, 6.96 %; N, 5.10 %

***Hydrogenation of 10a**:*

Tricyclic β-lactam **10a** (13 mg, 0.04 mmol) was hydrogenated at 60psi pressure of H_2 for 7 h at room temperature using Pd/C (10%, 50 mg) as a catalyst. The reaction mixture was filtered though a short bed of celite and the solvent was distilled off under reduced pressure to get **11** as a white crystalline solid (13 mg, 99%), which was further purified by column chromatography (60% EtOAc-petroleum ether).

Compound 11



carbon numbering is same as in **7a**

white crystalline solid; mp 144-145 °C

$[\alpha]^{25}_D$ = +1.88 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1760 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): 1.16 (s, 3H, C*H*$_3$), 1.26 (s, 3H, C*H*$_3$), 1.58-1.68 (m, 4H, CHC*H*$_2$C*H*$_2$), 2.35-2.37 (m, 1H, *H-6*), 3.12-3.16 (m, 1H, *H-12*), 3.73-3.77 (m, 1H, *H-12*), 4.12 (d, *J* 4.3 Hz, 1H, *H-4*), 4.32 (dd, *J* 4.4, 3.6 Hz, 2H, *H-5 & H-7*), 5.38 (d, *J* 4.3 Hz, 1H,

H-3), 5.86 (d, *J* 3.6 Hz, 1H, *H-8*), 6.98-7.06 (m, 3H, *aromatic*), 7.28-7.30 (m, 2H, *aromatic*)

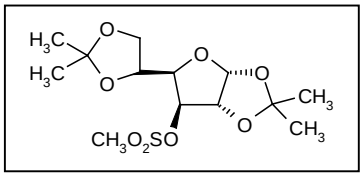
^{13}C NMR (125 MHz, $CDCl_3$): 23.7, 26.4, 26.5, 27.9, 43.0, 48.5, 57.8, 75.2, 85.4, 104.8, 111.1, 115.5, 121.9, 129.4, 157.4, 164.8

MS: m/z = 346 (M+1)

Anal. Calcd. for **$C_{19}H_{23}NO_5$**: C, 66.06 %; H, 6.72 %; N, 4.06 %

Found: C, 66.17 %; H, 6.81 %; N, 4.24 %

***Synthesis of mesylate derivative (12) of glucose diacetonide**:*

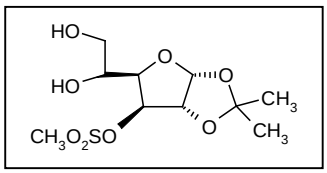


carbon numbering is same as in **2**

Alcohol **2** (3.0 g, 11.50 mmol) was dissolved in dry DCM (50 mL) followed by addition of Et_3N (1.6 mL, 11.50 mmol) and DMAP (0.421 g, 3.45 mmol)) at 0 °C for 30 minutes. Methane sulfonyl chloride (1.08 mL, 13.90 mmol) was then added at 0 °C over a period of 10 minutes and the reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with H_2O (2 x 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. A white solid of **12** was obtained in 93% yield (3.63 g) after purification by column chromatography using (100-200 mesh silica gel, 5-7% acetone-petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6H, 2xCH_3), 1.43 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.11 (s, 3H, SO_2CH_3), 4.02 (dd, *J* 3.4, 3.9 Hz, 1H, *H-1*), 4.14-4.21 (m, 3H, *H-5* & *H-6*), 4.80 (d, *J* 3.9 Hz, 1H, *H-3*), 4.98 (d, *J* 2.0 Hz, 1H, *H-2*), 5.96 (d, *J* 3.4 Hz, 1H, *H-4*)

***Mesylate diol (13)**:*



carbon numbering is same as in **2**

Mesylate derivative **12** of glucose diacetonide (2.0 g, 5.91 mmol) was dissolved in methanol (20 mL) followed by addition of 1% H_2SO_4 (2.1 mL) and the methanolic solution was stirred at room temperature for 2 days. The reaction mixture was then treated with Et_3N

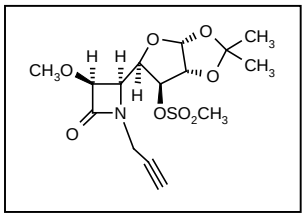
(2.1 mL) and the solvent was evaporated *in vacuo* to get the crude diol, which was then purified by column chromatography (100-200 mesh, 70-80% EtOAc-petroleum ether) to afford a thick liquid of mesylate diol **13** (1.2 g, 68%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.69 (br s, 2H, O*H*), 3.16 (s, 3H, SO_2CH_3), 3.75-3.92 (m, 3H, H-5 & H-6), 4.23 (dd, *J* 2.5, 2.5 Hz, 1H, *H-1*), 4.77 (d, *J* 3.4 Hz, 1H, H-3), 5.14 (d, *J* 2.4 Hz, 1H, *H-2*), 5.96 (d, *J* 3.4 Hz, 1H, *H-4*).

Reaction of mesylate imine 15 with methoxyacetyl chloride:

Mesylate diol **13** was cleaved to the corresponding aldehyde **14** and then to imine **15** according to the procedure given for iodo diol **4**. To a solution of imine **15** (0.794 g, 2.62 mmol) in DCM (30 mL), Et_3N (1.66 mL, 11.57 mmol) and a solution of methoxyacetyl chloride (0.36 mL, 3.95 mmol) in DCM were added at 0 °C over a period of 30 minutes and stirred at room temperature for 15 h. Usual work up and purification by flash column chromatography (15% EtOAc-petroleum ether) gave a single isomer of β-lactam **16** in 55% yield (0.540 g).

Compound 16



carbon numbering is same as in **7a**

pale yellow solid; mp 96-98 °C

IR ($CHCl_3$): ν_{max} 1763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.25 (t, *J* 2.4 Hz, 1H, H-14), 3.09 (s, 3H, SO_2CH_3), 3.61 (s, 3H, OCH_3), 3.86 (dd, *J* 2.9, 4.8 Hz, 1H, *H-5*), 4.08 (dd, *J* 4.8, 5.4 Hz, 1H, *H-4*), 4.31-4.44 (m, 2H, *H-12*), 4.57 (d, *J* 5.4 Hz, 1H, *H-3*), 4.76 (d, *J* 3.4 Hz, 1H, *H-7*), 5.19 (d, *J* 2.9 Hz, 1H, *H-6*), 6.02 (d, *J* 3.4 Hz, 1H, *H-8*)

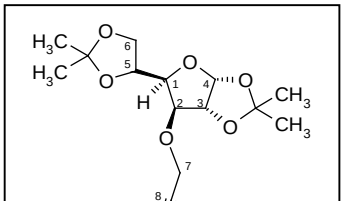
^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.6, 30.5, 38.3, 55.6, 59.3, 72.2, 79.8, 81.7, 83.3, 83.5, 104.7, 112.7, 121.7, 166.4

MS: (m/z) = 376 (M+1)

Anal. Calcd. for **$C_{15}H_{21}NO_8S$**: C, 47.99 %; H, 5.64 %; N, 3.73 %; S, 8.52 %

Found: C, 47.87 %; H, 5.59 %; N, 3.72 %; S, 8.44 %

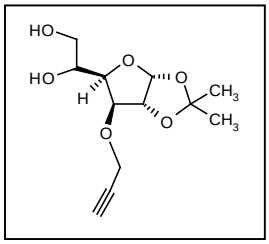
O-propargyl substituted glucose diacetonide (17):



Alcohol **2** (1.5 g, 5.76 mmol) was dissolved in dichloromethane (40 mL) and to this solution was added a 50% sodium hydroxide (8 mL) slowly at 0 °C. A solution of propargyl bromide (0.76 mL, 8.53 mmol) in dichloromethane (5 mL) and a catalytic amount of TBAB (0.644 g) were then added and the reaction mixture was stirred at room temperature for 6 h. The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was chromatographed (100-200 mesh, 3-4% acetone-petroleum ether) to afford *O*-propargyl derivative **17** of glucose diacetonide as a colorless liquid in 71% yield (1.2 g).

^{1}H NMR (200 MHz, $CDCl_3/CCl_4$ mixture 3:2 ratio): δ 1.31 (s, 3H, C*H*$_3$), 1.35 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 1.5, (s, 3H, C*H*$_3$), 2.48 (t, *J* 2.5 Hz, *H-9*), 3.99-4.30 (m, 7H, *H-1*, *H-2*, *H-5*, *H-6* & *H-7*), 4.64 (d, *J* 3.9 Hz, 1H, *H-3*), 5.89 (d, *J* 3.9 Hz, 1H, *H-4*)

Preparation of O-propargyl substituted diol (18):



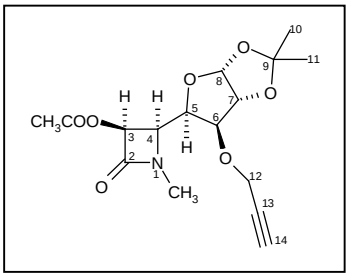
carbon numbering is same as in **17**

O-propargyl protected diacetonide **17** (1.2 g, 4.02 mmol) was dissolved in methanol (24 mL) followed by addition of H_2O (9 mL) and 10% H_2SO_4 (1.4 mL) and the reaction mixture was stirred at room temperature for 6.5 h. The reaction mixture was then neutralized with saturated K_2CO_3 solution and the solvent was concentrated *in vacuo*. It was then extracted with dichloromethane (2 x 30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to obtain diol **18** (0.98 g, 94%), which was sufficiently pure to be used as such for further reaction.

IR ($CHCl_3$): ν_{max} 3441, 3283 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, C*H*$_3$), 1.49 (s, 3H, C*H*$_3$), 2.39 (s, 2H, O*H*), 2.53 (t, *J* 2.3 Hz, 1H, *H-9*), 3.71-4.32 (m, 7H, *H-1*, *H-2*, *H-5*, *H-6* & *H-7*), 4.60 (d, *J* 3.9 Hz, 1H, *H-3*), 5.91 (d, *J* 3.5 Hz, 1H, *H-4*).

O-propargyl substituted* β-*lactam (21):



O-propargyl aldehyde **19** was prepared from the corresponding diol **18** using the procedure given for iodo aldehyde **5**. To a solution of *O*-propargyl aldehyde **19** (0.733 g, 3.24 mmol) over anhydrous $MgSO_4$ in DCM (20 mL) was added a 40% aqueous solution of methyl amine (0.4 mL) and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then filtered through celite and the dichloromethane was distilled off to yield *O*-propargyl substituted imine **20** in quantitative yield. *O*-propargyl substituted imine **20** was dissolved in DCM (30 mL) followed by addition of dry triethylamine (1.93 mL, 13.90 mmol) and kept at 0 °C. A solution of acetoxyacetyl chloride (0.5 mL, 4.64 mmol) in dichloromethane (10 mL) was then added slowly at the same temperature dropwise and the reaction mixture was stirred overnight at room temperature. The reaction mixture was treated with saturated sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo*. Column purification of the crude material gave a single isomer of white crystalline *O*-propargyl substituted β-lactam **21** in 61% yield (0.635 g).

crystalline white solid; mp 110-111 °C

$[\alpha]^D$ = -111.3 (*c* 1.33, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1769, 1751, 2121 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 2.14 (s, 3H, COC*H*$_3$), 2.45 (t, *J* 2.5 Hz, 1H, *H-14*), 2.92 (s, 3H, NC*H*$_3$), 4.00-4.18 (m, 4H, *H-12*, *H-6* & *H-4*), 4.28 (dd, *J* 3.2, 8.3 Hz, 1H, *H-5*), 4.62 (d, *J* 3.5 Hz, 1H, *H-7*), 5.93 (d, *J* 4.3 Hz, 2H, *H-3* & *H-8*)

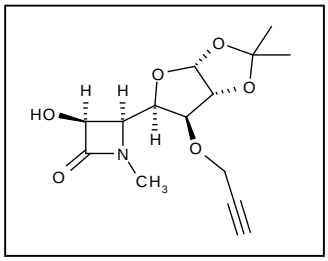
^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 26.0, 26.5, 28.1, 57.0, 74.2, 75.2, 78.5, 79.9, 81.5, 81.6, 104.7, 111.7, 164.4, 168.7

Anal. **Calcd**. for **$C_{16}H_{21}O_7N$**: C, 56.62 %; H, 6.24 %; N, 4.13 %

Found: C, 56.44 %; H, 6.25 %; N, 4.10 %

MS: *m/z* = 340 (M+1)

***Hydroxy* β-*lactam (22)*:**



carbon numbering is same as in **21**

Acetoxy β-lactam **21** (0.583 g, 1.72 mmol) was dissolved in methanol (8 mL) followed by addition of saturated sodium bicarbonate solution (3 mL) and stirred at room temperature for 8 h. The solvent was distilled off and the crude material was extracted with dichloromethane (2 x 30 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (100-200 mesh, 20-30% acetone-petroleum ether) to furnish hydroxy β-lactam **22** in 84% yield (0.428 g).

thick oil

$[\alpha]^D$ = -99.25 (*c* 0.80, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 3392, 1737, 2121 cm^{-1}

^{1}H NMR (200 MHz. $CDCl_3$): δ 1.24 (s, 3H, C*H*$_3$), 1.41 (s, 3H, C*H*$_3$), 2.56 (t, *J* 2.4 Hz, 1H, *H-14*), 2.80 (s, 3H, NC*H*$_3$), 3,86 (dd, *J* 4.7, 8.6 Hz, 1H, *H-4*), 4.17 (d, *J* 2.4 Hz, OC*H*$_2$), 4.24 (d, *J* 3.5 Hz, 1H, *H-6*), 4.31 (dd, *J* 3.5, 8.6 Hz, 1H, *H-5*), 4.31 (d, *J* 3.9 Hz, 1H, *H-7*), 4.86 (d, *J* 4.7 Hz, 1H, *H-3*), 5.86 (d, *J* 3.9 Hz, 1H, *H-8*)

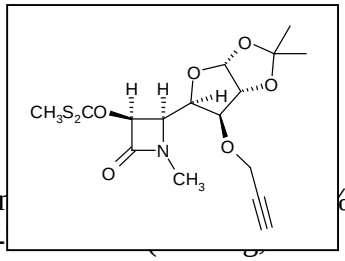
^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.7, 27.9, 57.6, 75.2, 75.4, 76.4, 79.1, 80.9, 82.2, 82.5, 104.9, 111.8, 170.2

Anal. **Calcd**. for **$C_{14}H_{19}NO_6$**: C, 56.54 %; H, 6.45 %; N, 4.71 %

Found: C, 56.41 %; H, 6.56 %; N, 4.59 %

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

Xanthate Ester (23):



carbon numbering is same as in **21**

To a suspension % suspension) in THF at 0 °C was added a solution of hydroxy β- mmol) in THF (20 mL) and the reaction mixture was stirred at room temperature for 30 minutes. A solution of carbon disulphide (0.41 mL in 5 mL THF) was then added slowly to the hydroxy β-lactam suspension and the reaction mixture was stirred at room temperature. After 2 h, methyl iodide (056 mL in 5 mL THF) solution was added very slowly at 0 °C and stirring was continued for 7 h at room temperature. The reaction mixture was quenched with water, extracted with dichloromethane, concentrated *in vacuo* and the residue was purified by column chromatography using 10-15% acetone-petroleum ether on 100-200 mesh silica gel to obtain xanthate ester **23** (0.441 g, 79%).
thick oil

$[\alpha]^{D}$ = -64.3 (*c* 0.20, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 2118, 1767 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, C*H*$_3$), 1.51 (s, 3H, C*H*$_3$), 2.45 (t, *J* 2.4 Hz, 1H, *H-14*), 2.60 (s, 3H, C*H*$_3$), 2.96 (s, 3H, NC*H*$_3$), 3.99 (d, *J* 3.5 Hz, 1H, *H-6*), 4.10-4.17 (m, 3H, OC*H*$_2$, *H-4*), 4.31 (dd, *J* 3.5, 7.8 Hz, 1H, *H-5*), 4.67 (d, *J* 3.5 Hz, 1H, *H-7*), 5.95 (d, *J* 3.5 Hz, 1H, *H-8*), 6.75 (d, *J* 4.7 Hz, 1H, *H-3*)

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 26.2, 26.6, 28.4, 57.4, 75.3, 78.5, 79.6, 80.5, 81.7, 82.3, 104.9, 111.9, 163.6, 214.0

Anal. **Calcd**. for **$C_{16}H_{21}S_2NO_6$**: C, 49.60 %; H, 5.47 %; N: 3.62 %; S, 16.52 %

Found: C, 49.54 %; H, 5.67 %; N, 3.80 %; S, 16.40 %

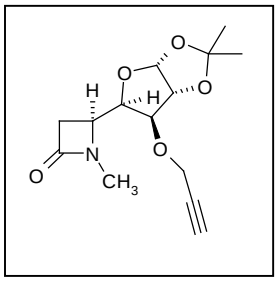
MS: *m/z* = 388.07 (M+1)

Radical cyclization of xanthate ester of O-propargyl β-lactam (23)*:*

Xanthate ester **23** (0.391 g, 1.01 mmol) was dissolved in dry toluene (80 mL), degassed and heated under reflux for 30 minutes. A solution of tributyltin hydride (0.4 mL, 1.5 mmol) and AIBN (16 mg, 0.1 mmol) in toluene (20 mL) was added through a syringe pump over a period of 4 h to the xanthate ester under reflux condition for overnight. The

solvent was distilled off *in vacuo* and the reduced product **24** (0.138 g, 49%) was obtained as a white crystalline solid upon flash column chromatography (20% EtOAc - petroleum ether).

Compound 24



carbon numbering is same as in **21**

white solid; mp 102-103 °C

$[\alpha]^{D}$ = -74.4 (*c* 0.63, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1743 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (s, 3H, C*H*$_3$), 1.40 (s, 3H, C*H*$_3$), 2.45 (t, *J* 2.4 Hz, 1H, *H-14*), 2.51 (d, *J* 14.9 Hz, 1H, *H-3*), 2.78 (s, 3H, NC*H*$_3$), 2.98 (dd, *J* 5.1, 14.5 Hz, 1H, *H-3*), 3.64-3.71(m, 1H, *H-4*), 4.01-4.14 (m, 4H, OCH_2, *H-5* & *H-6*), 4.49 (d, *J* 3.9 Hz, 1H, *H-7*), 5.86 (d, *J* 3.5 Hz, 1H, *H-8*)

^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.6, 28.3, 39.2, 51.1, 57.0, 75.4, 78.4, 81.4, 83.3, 105.6, 111.8, 166.5

Anal. **Calcd**. for **$C_{14}H_{19}NO_5$**: C, 59.76 %; H, 6.81 %; N, 4.98 %

Found: C, 59.60 %; H, 6.86 %; N, 5.14 %

MS: *m/z* = 282.14 (M+1)

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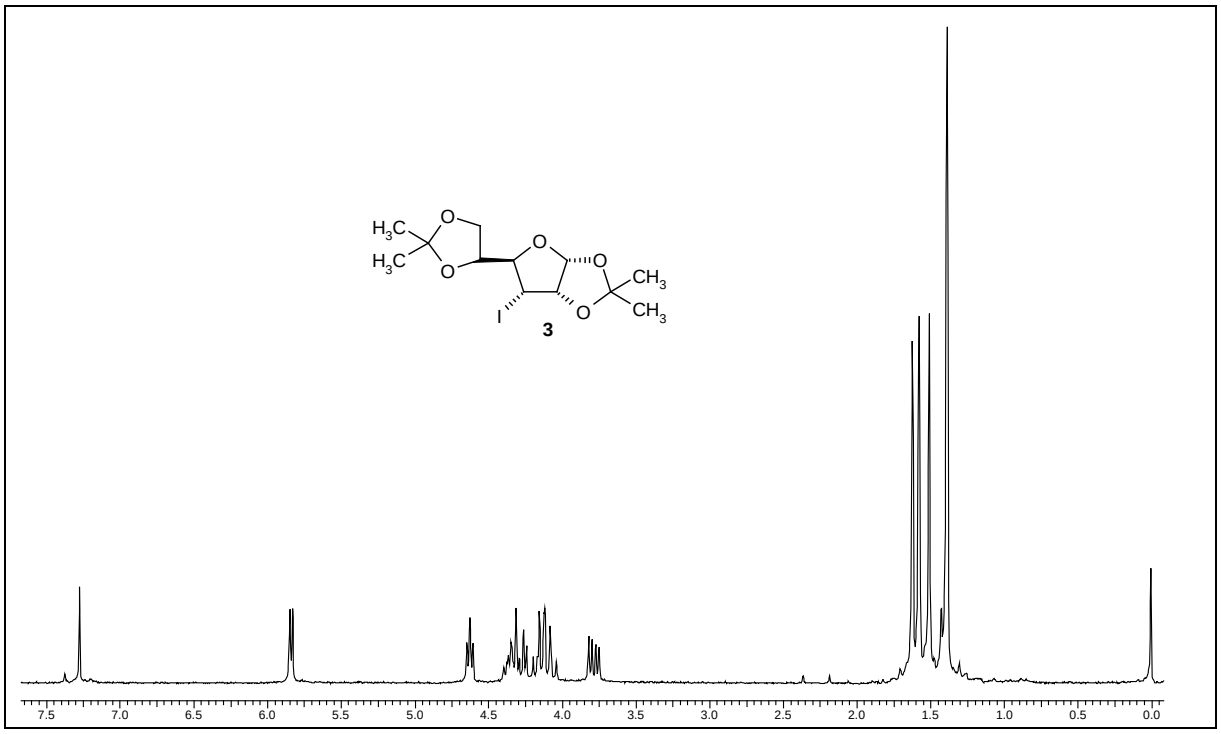
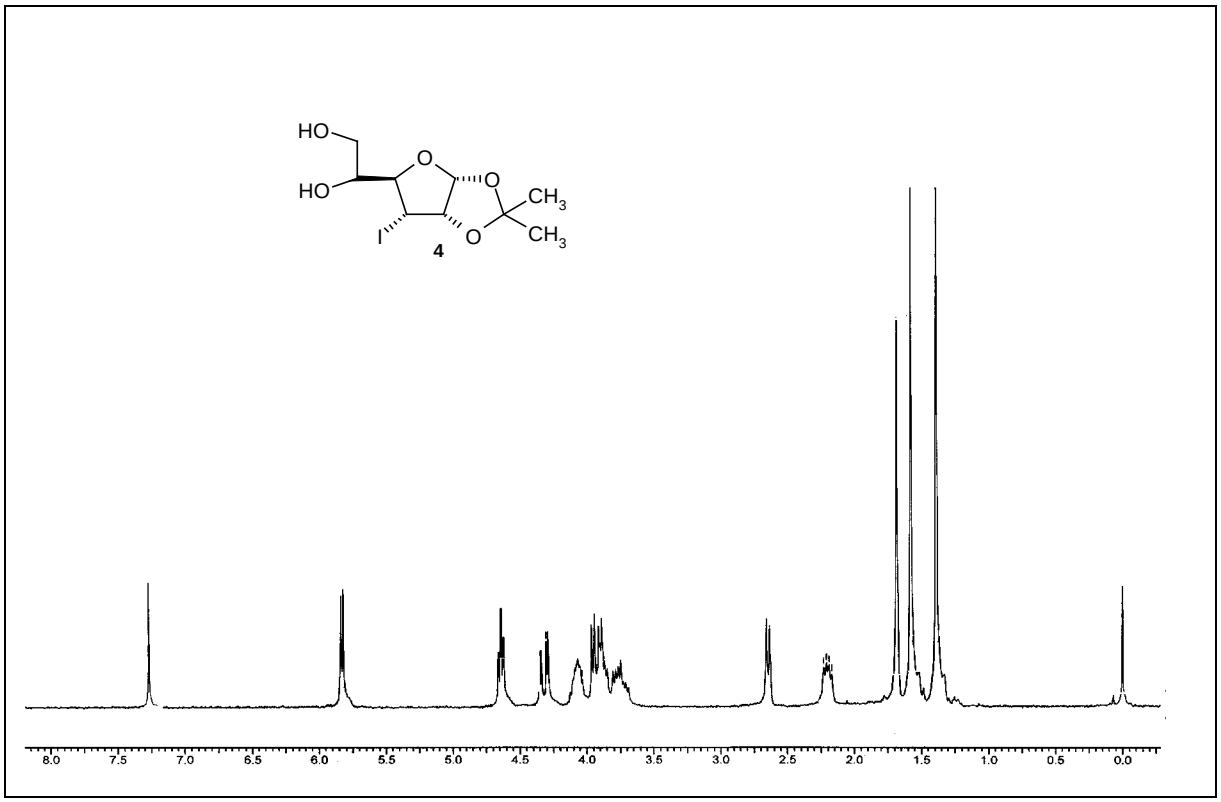
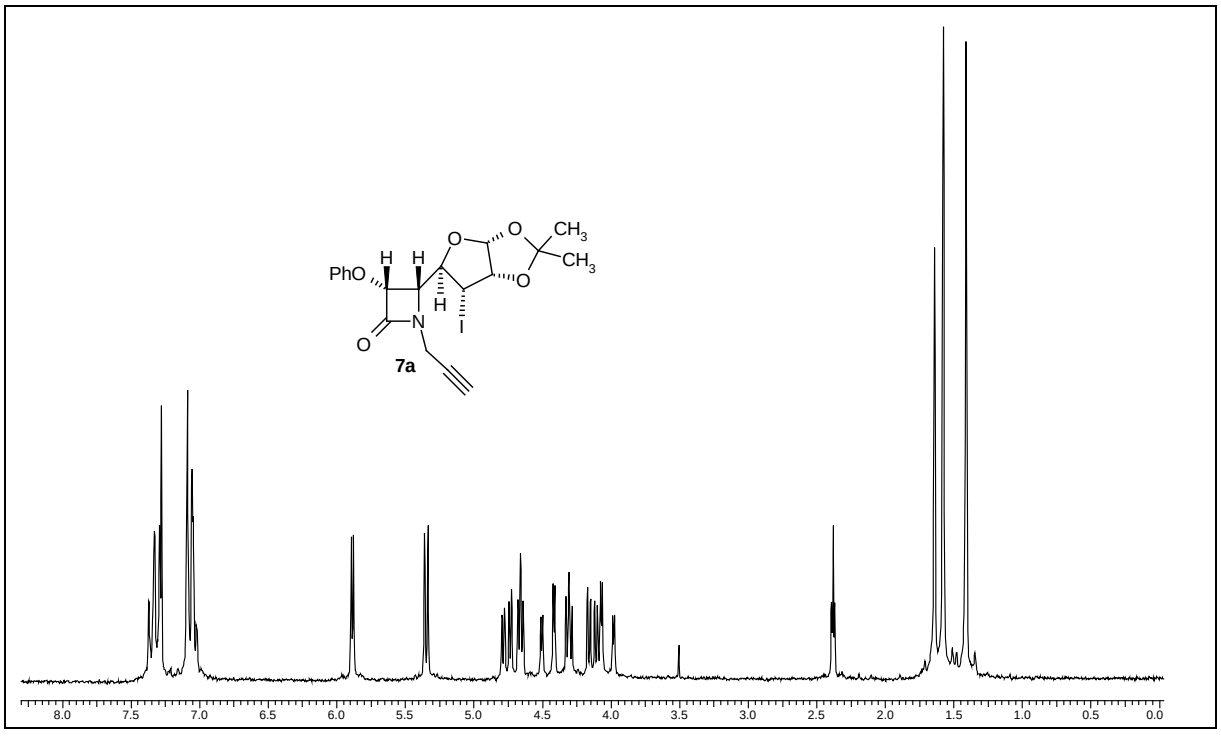
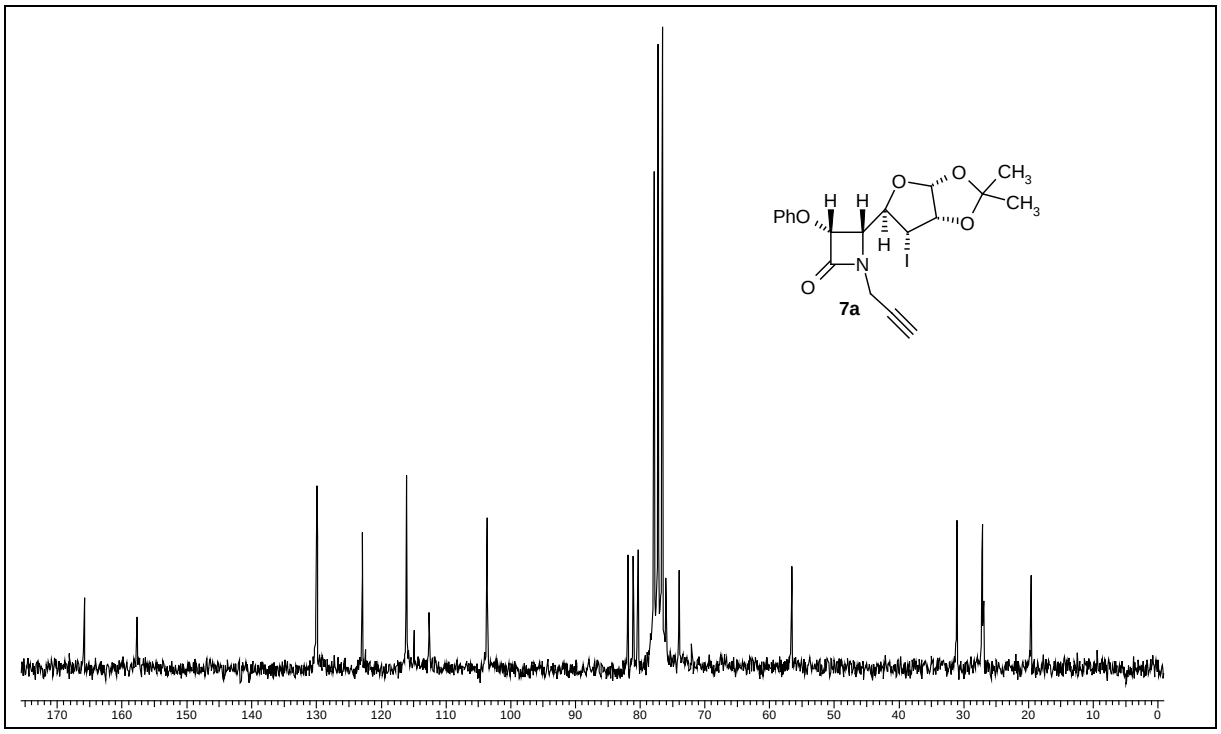
Part A

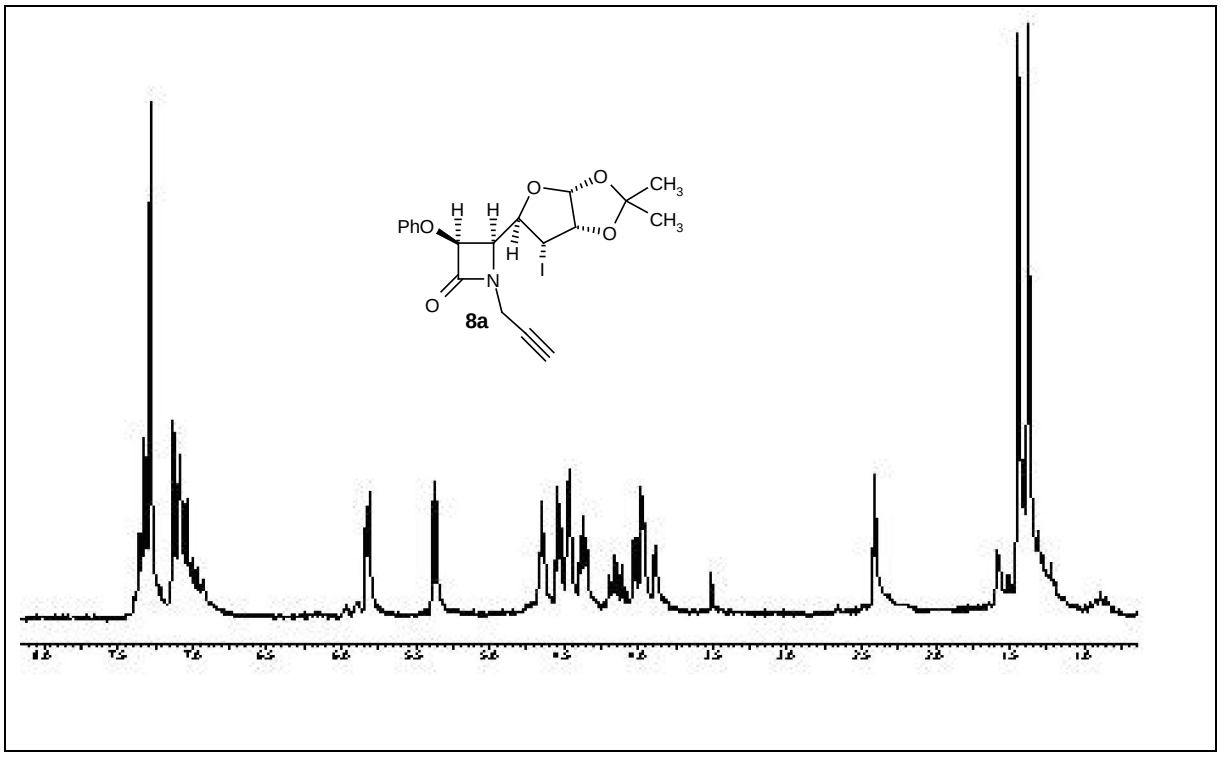
Spectra

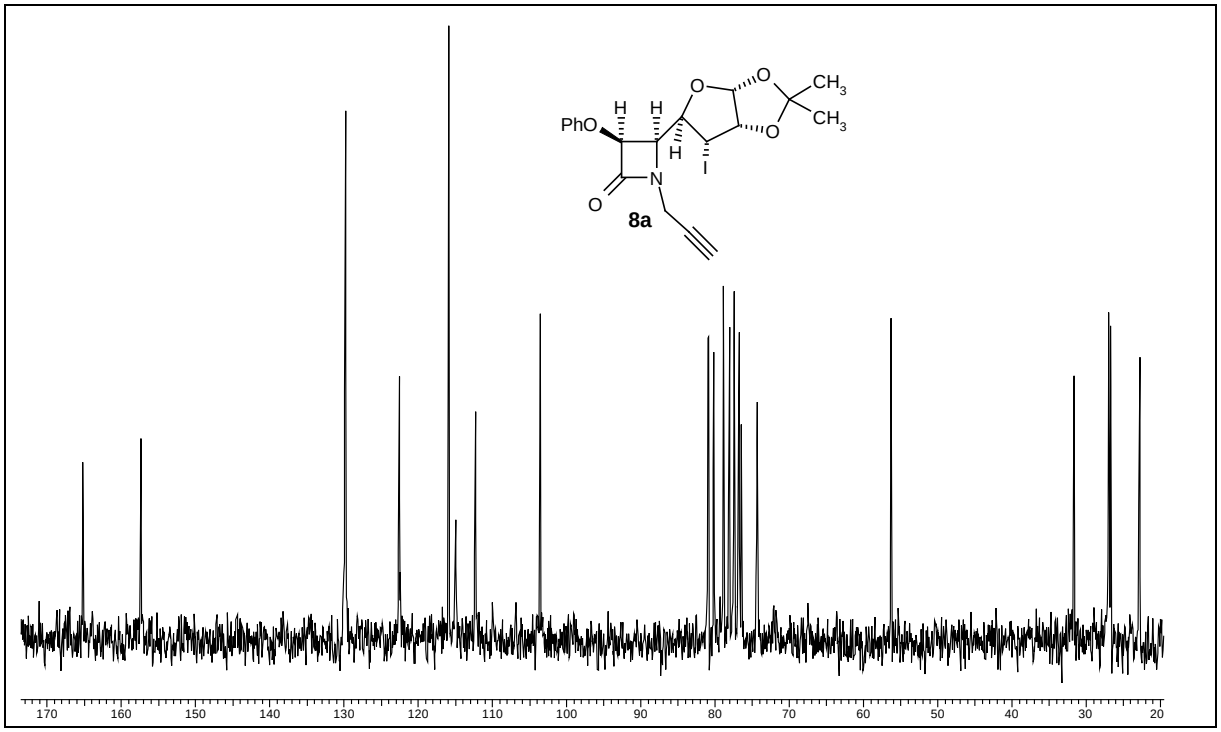


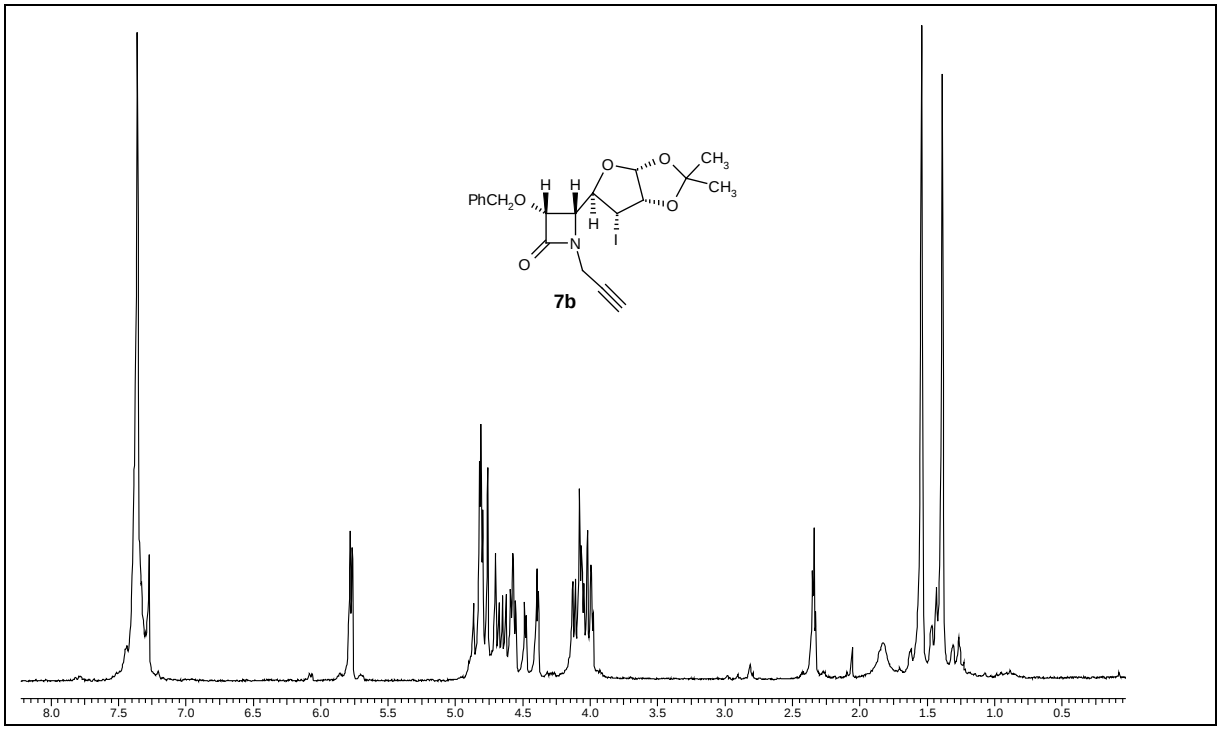


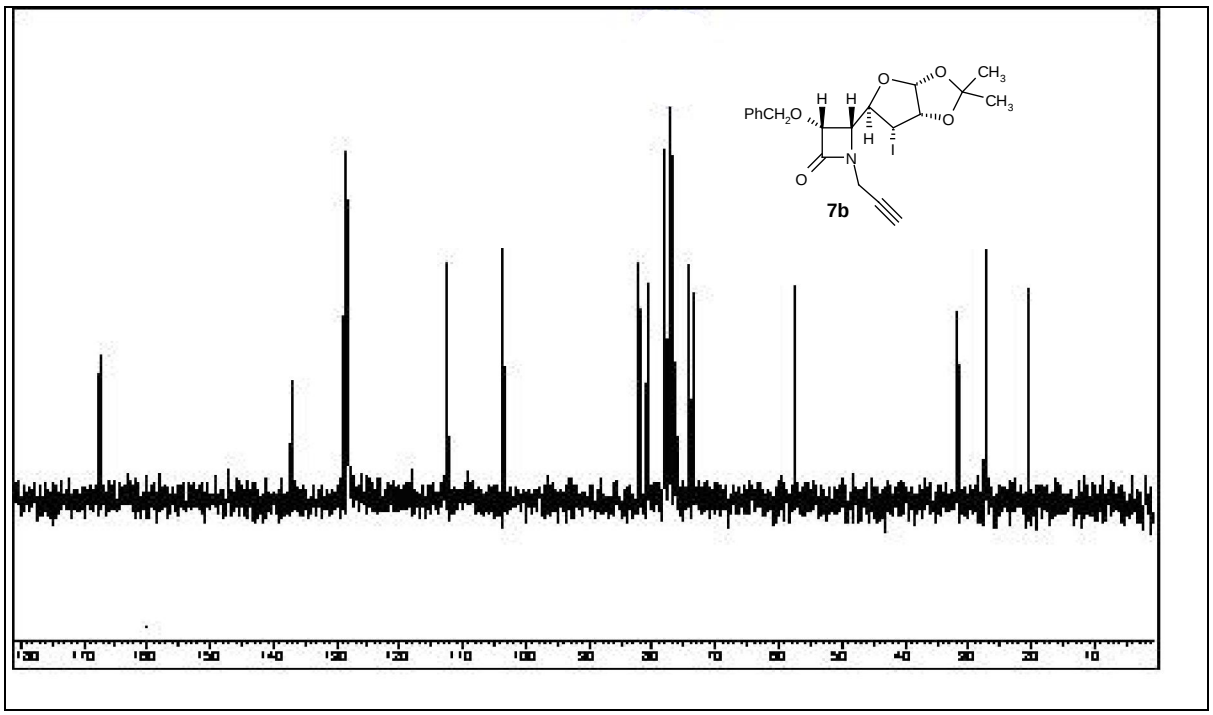


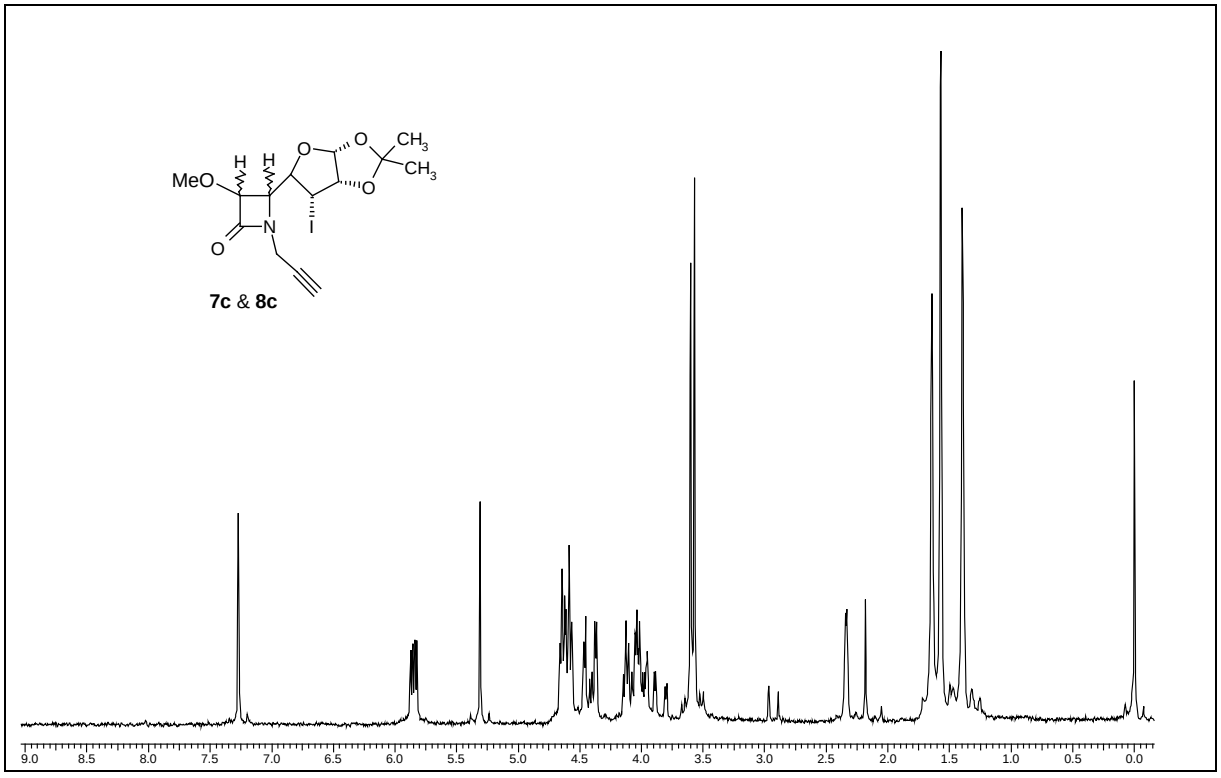












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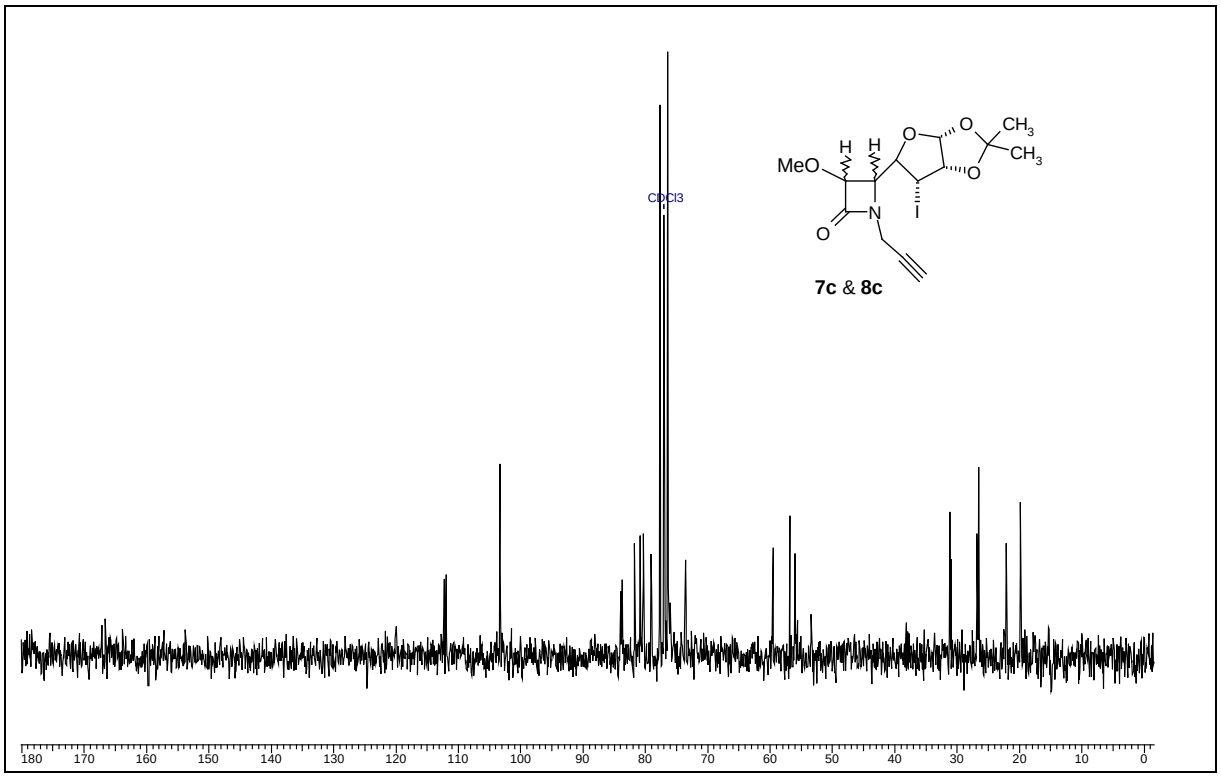

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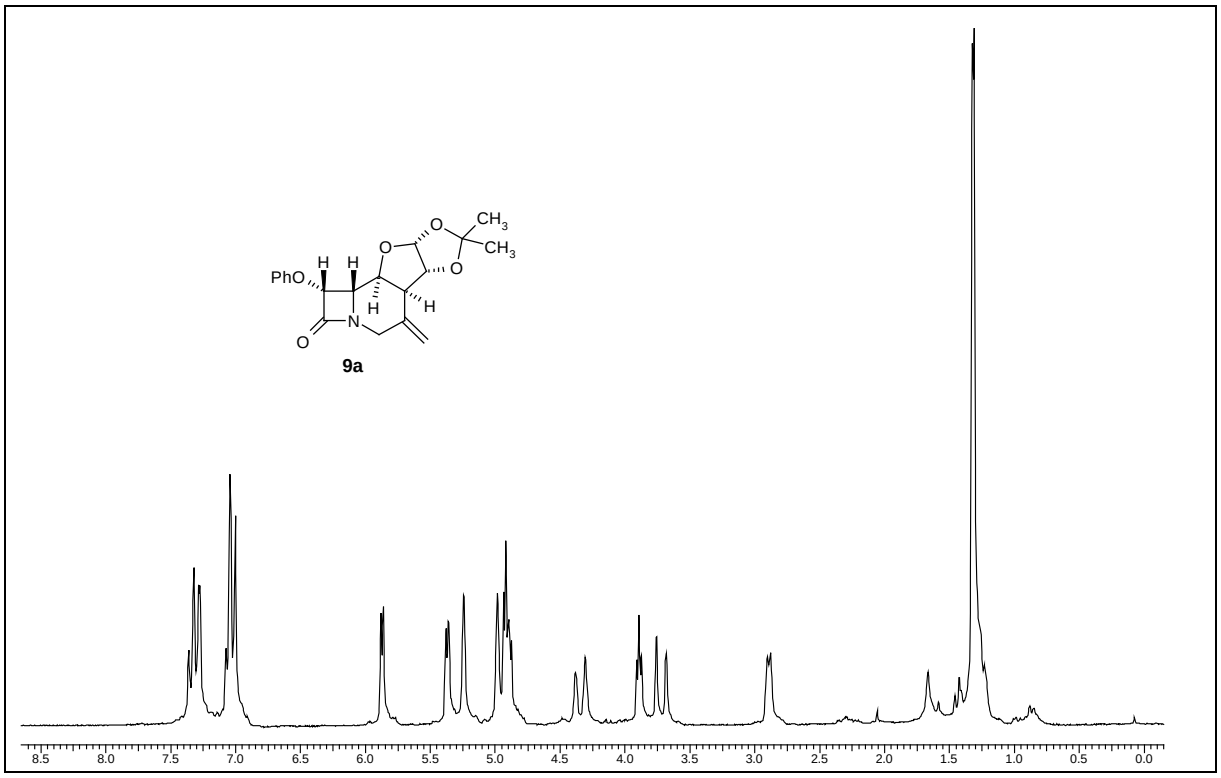

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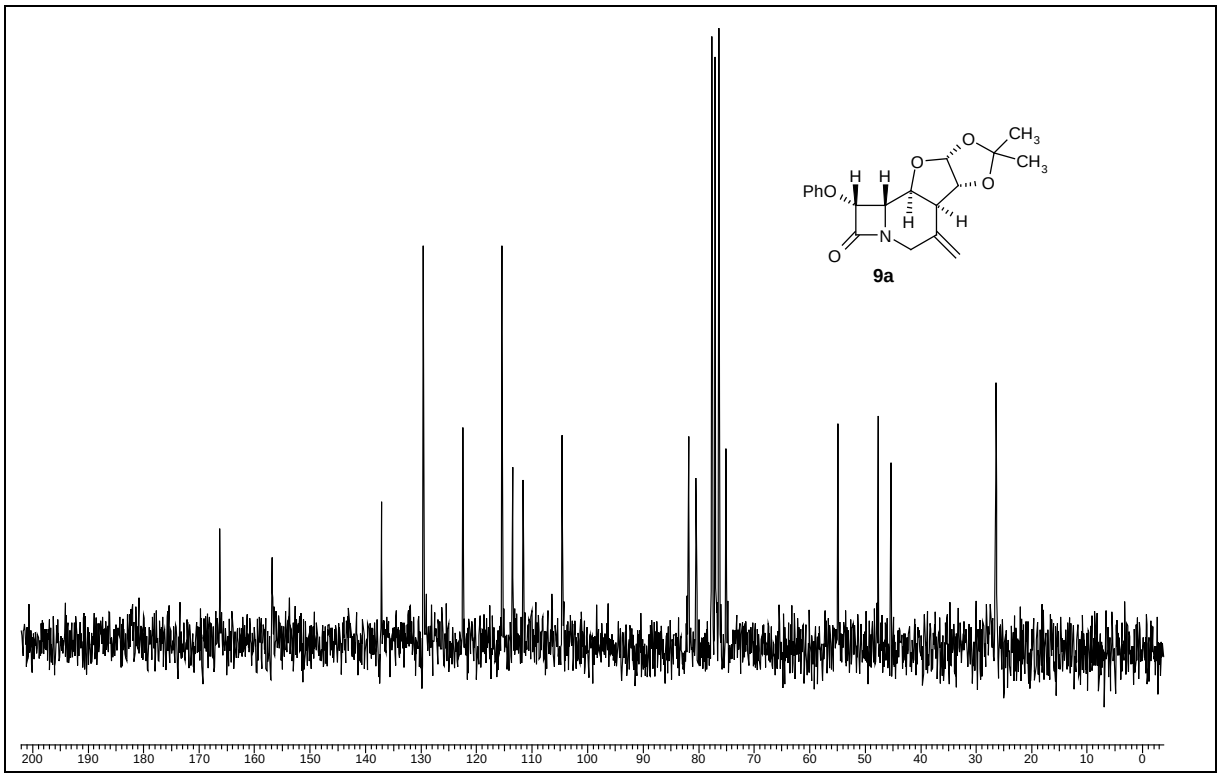

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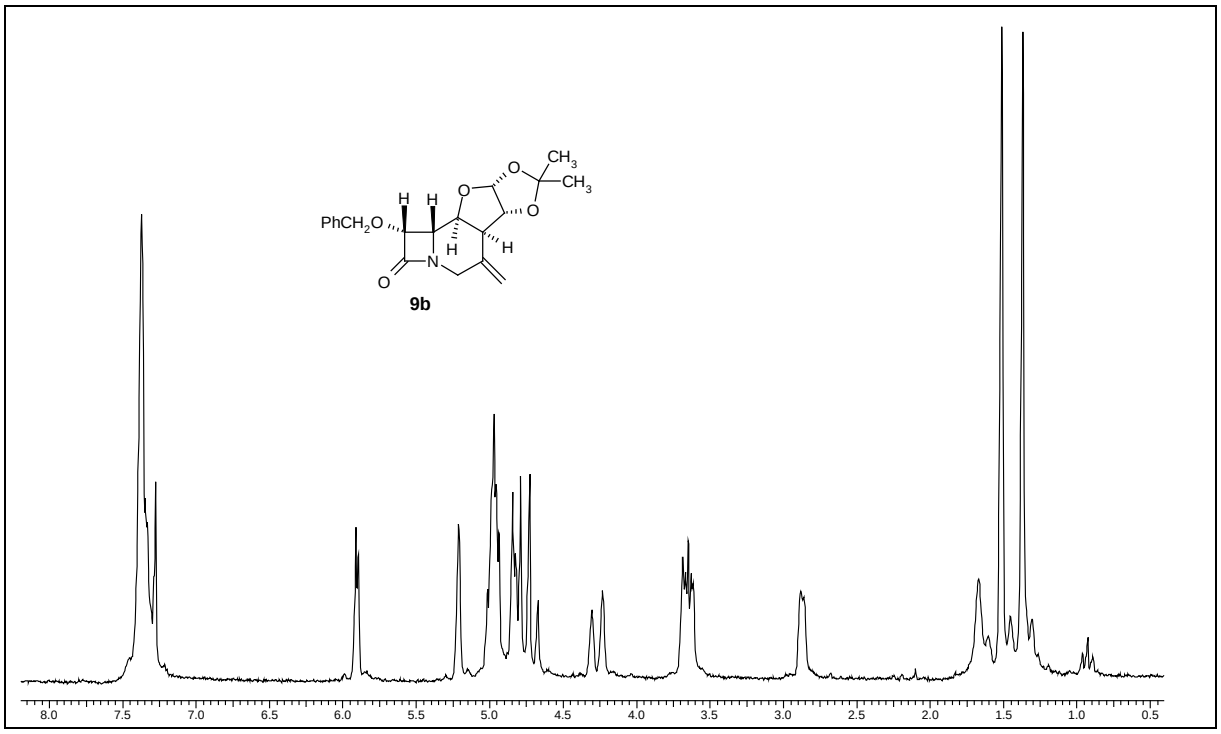

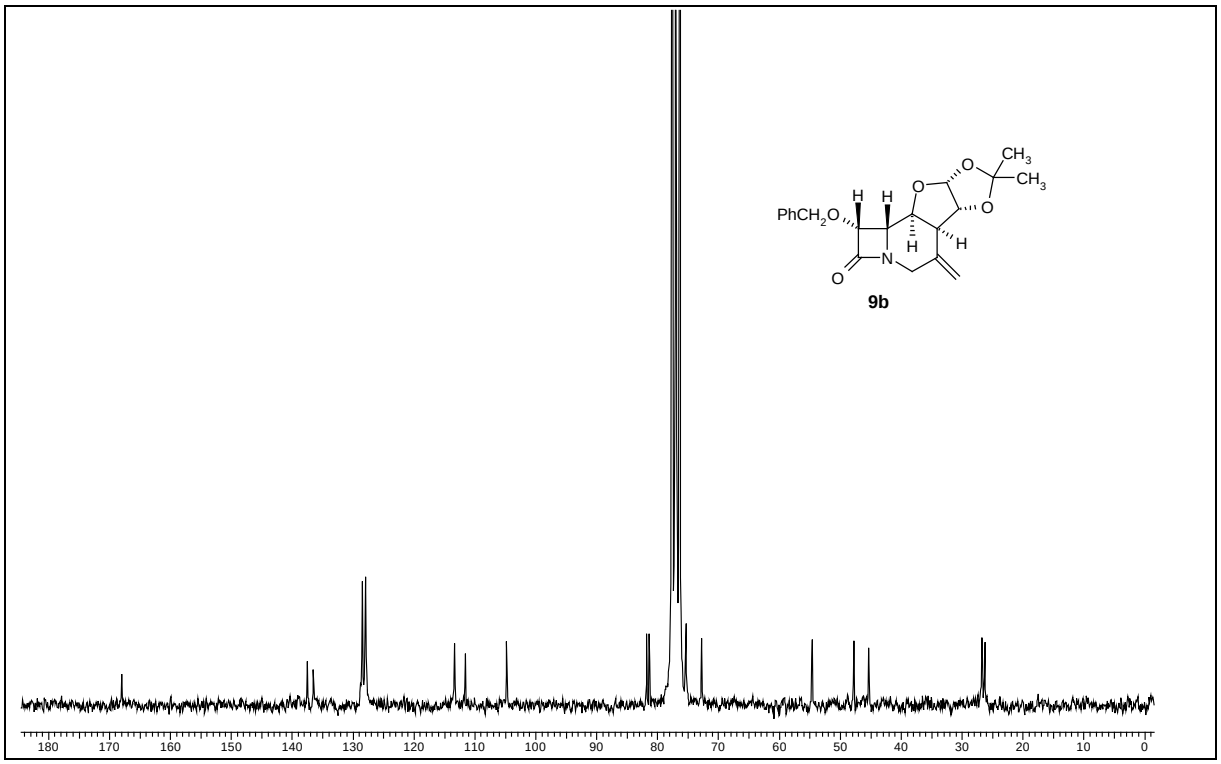

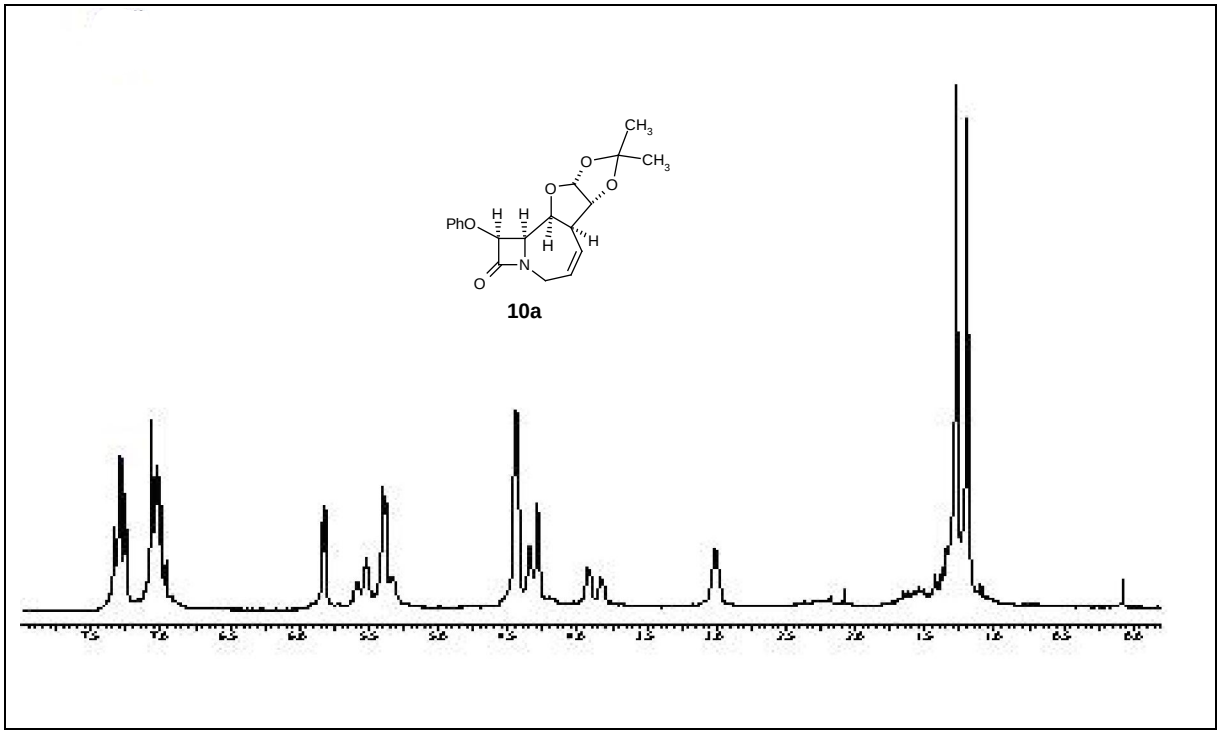

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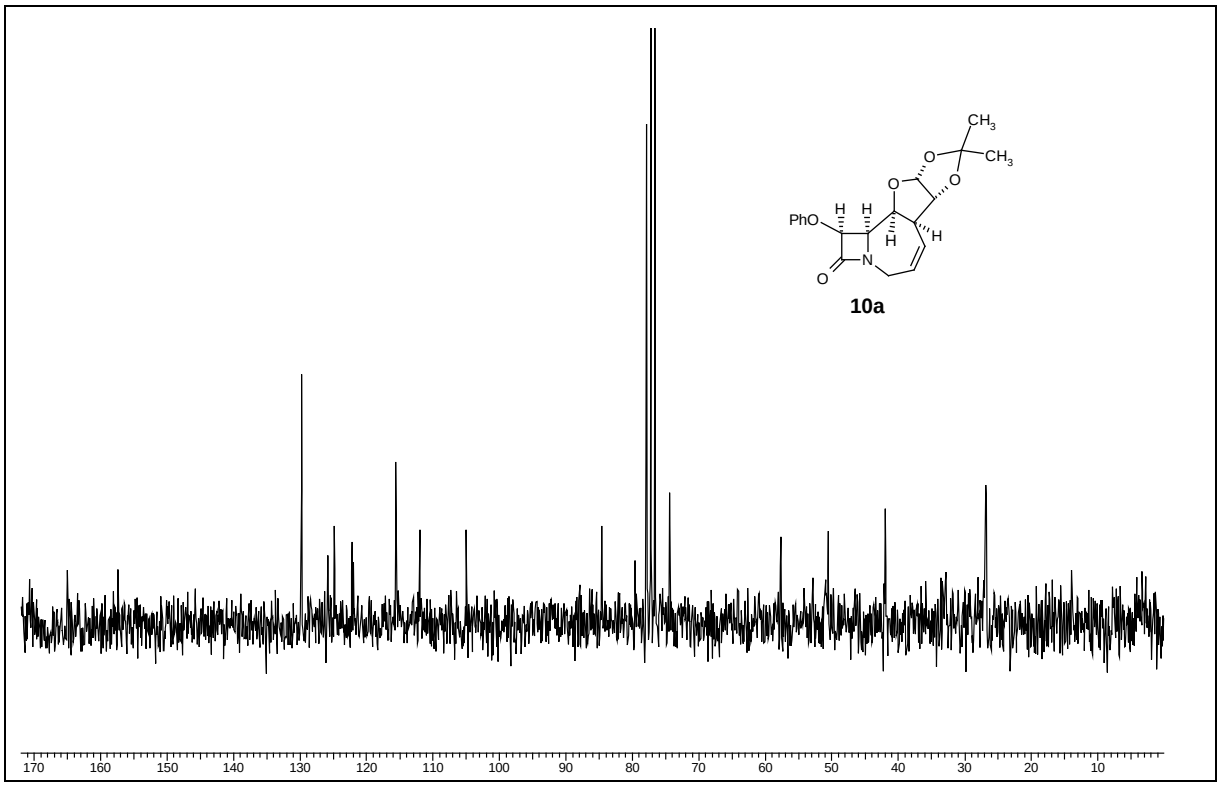

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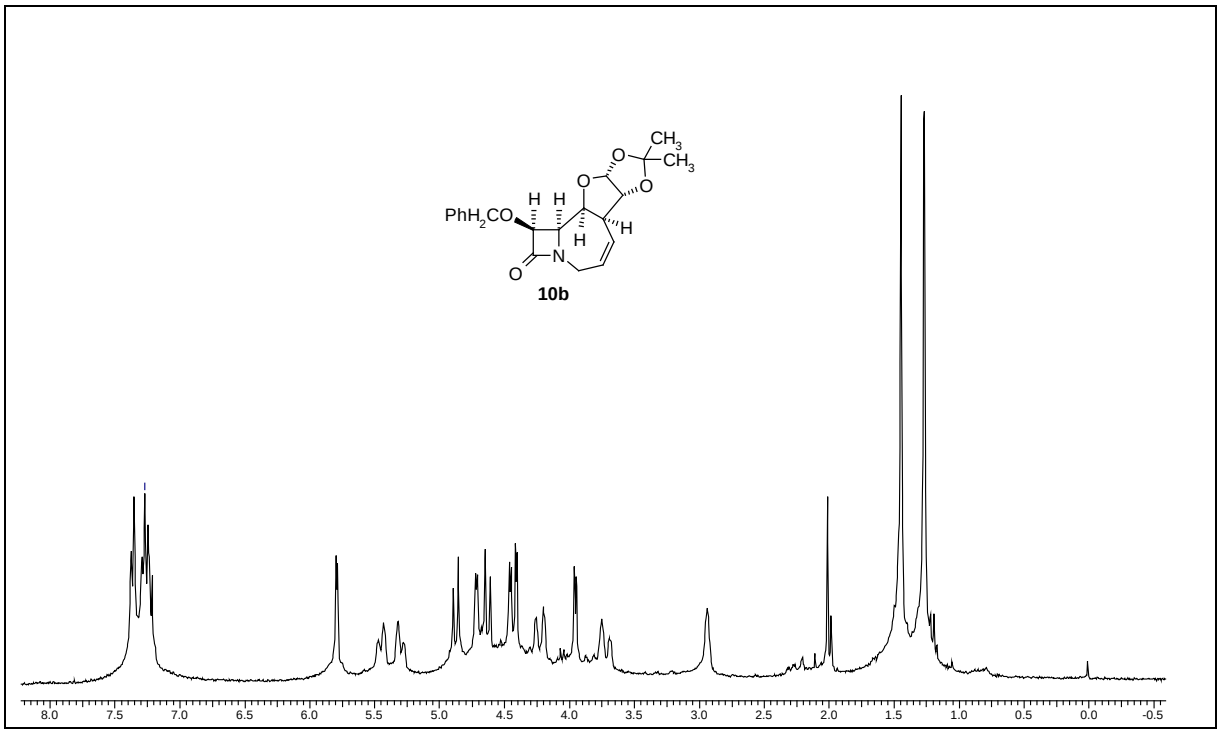

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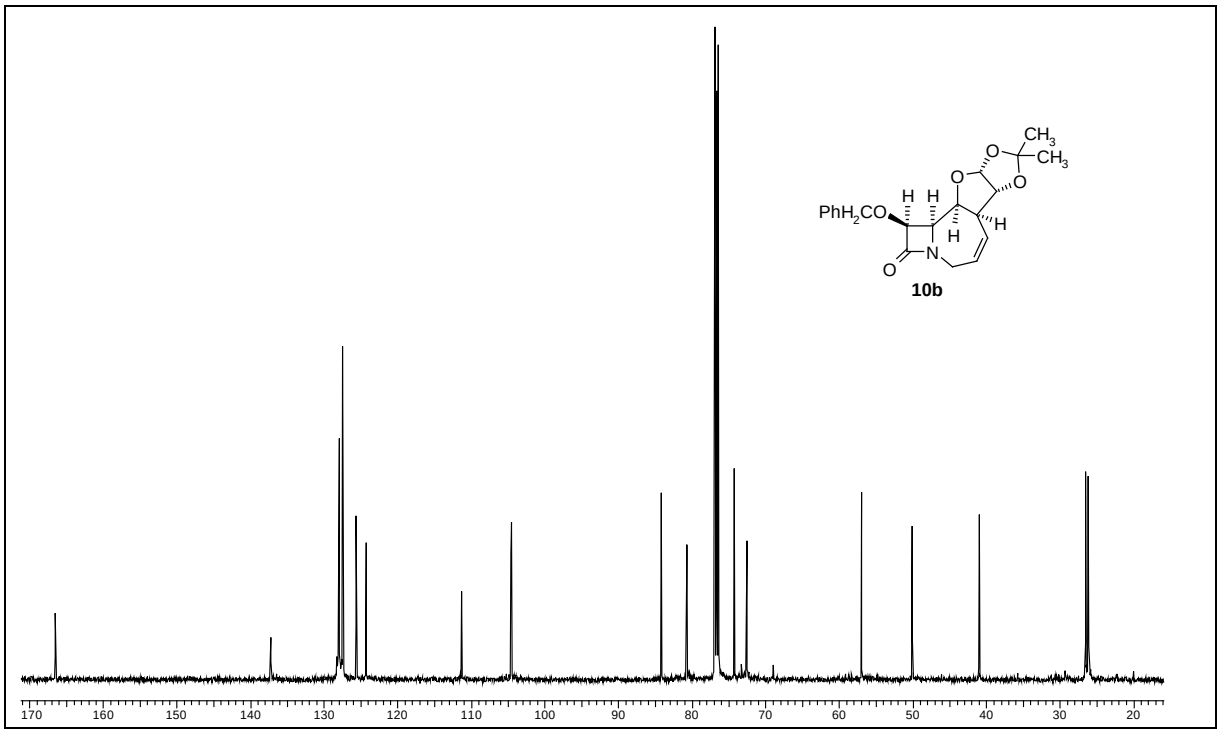

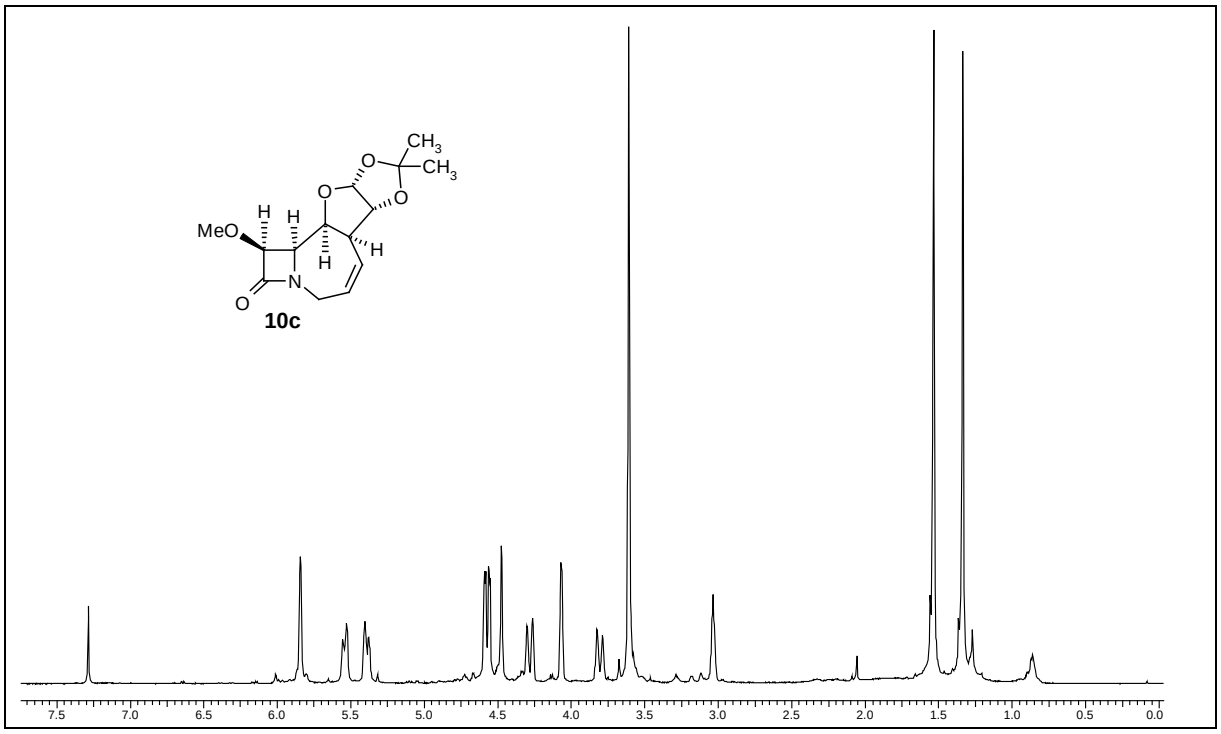

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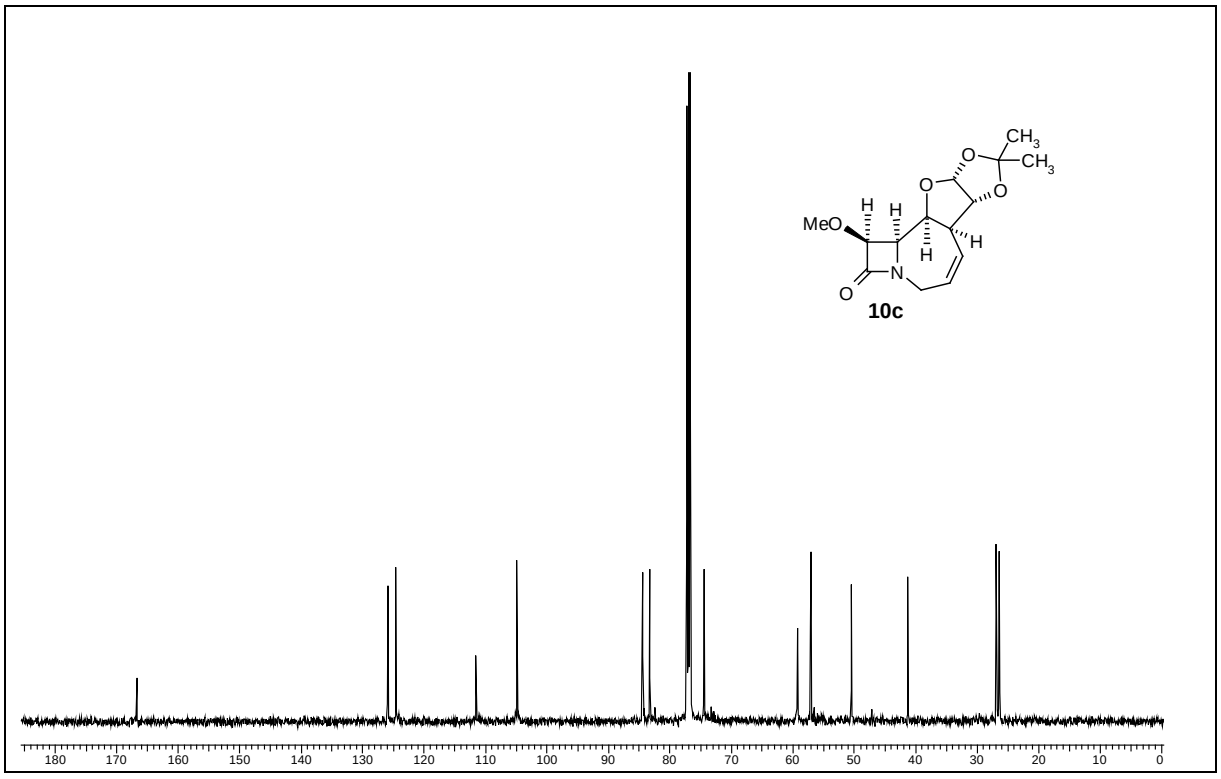

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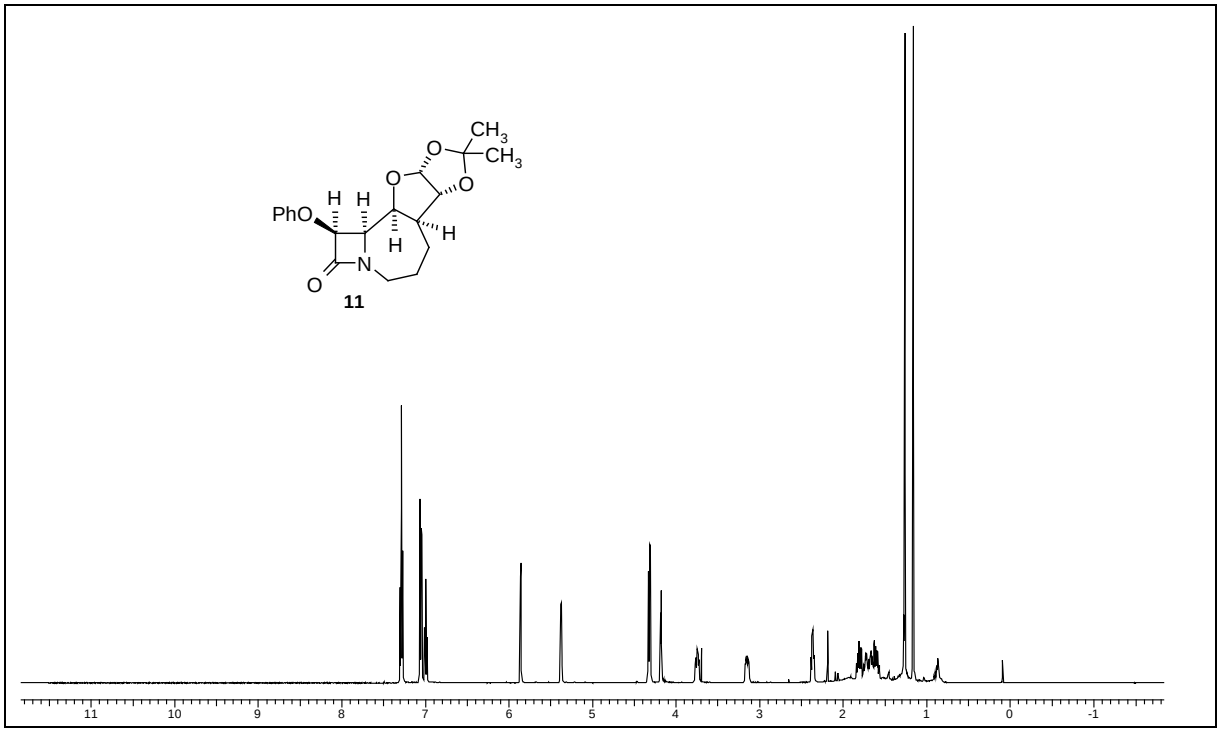
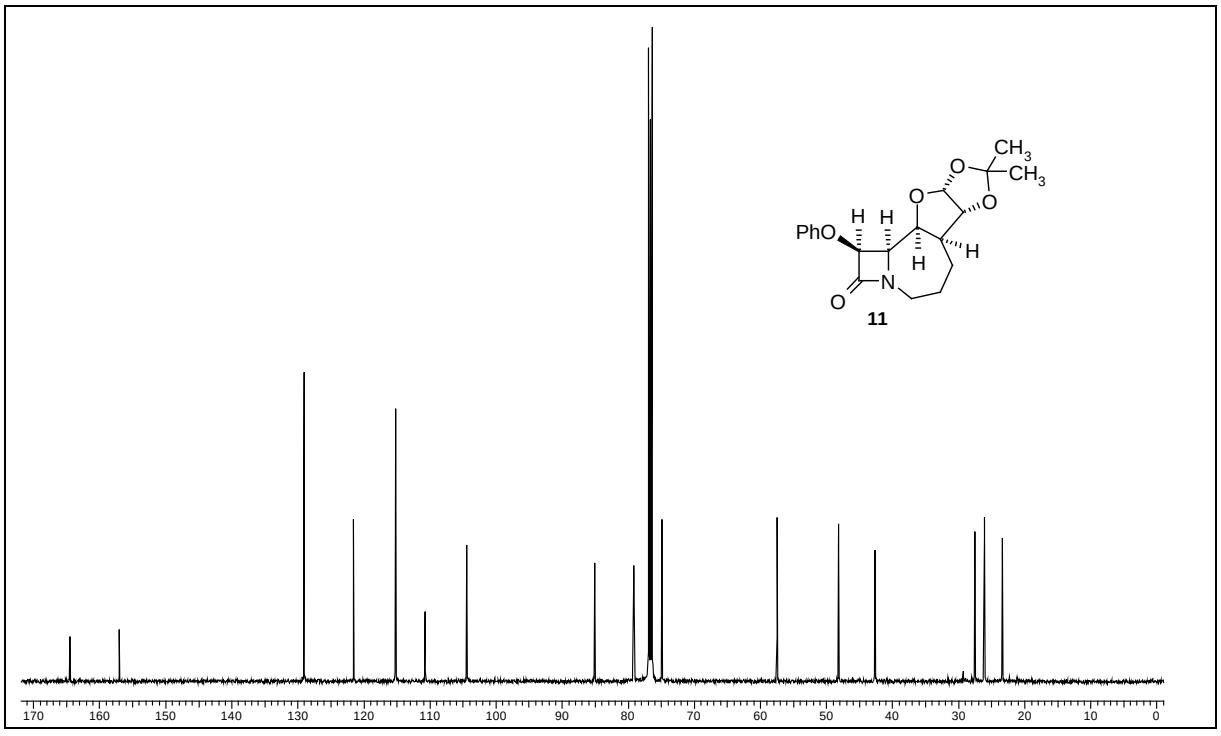
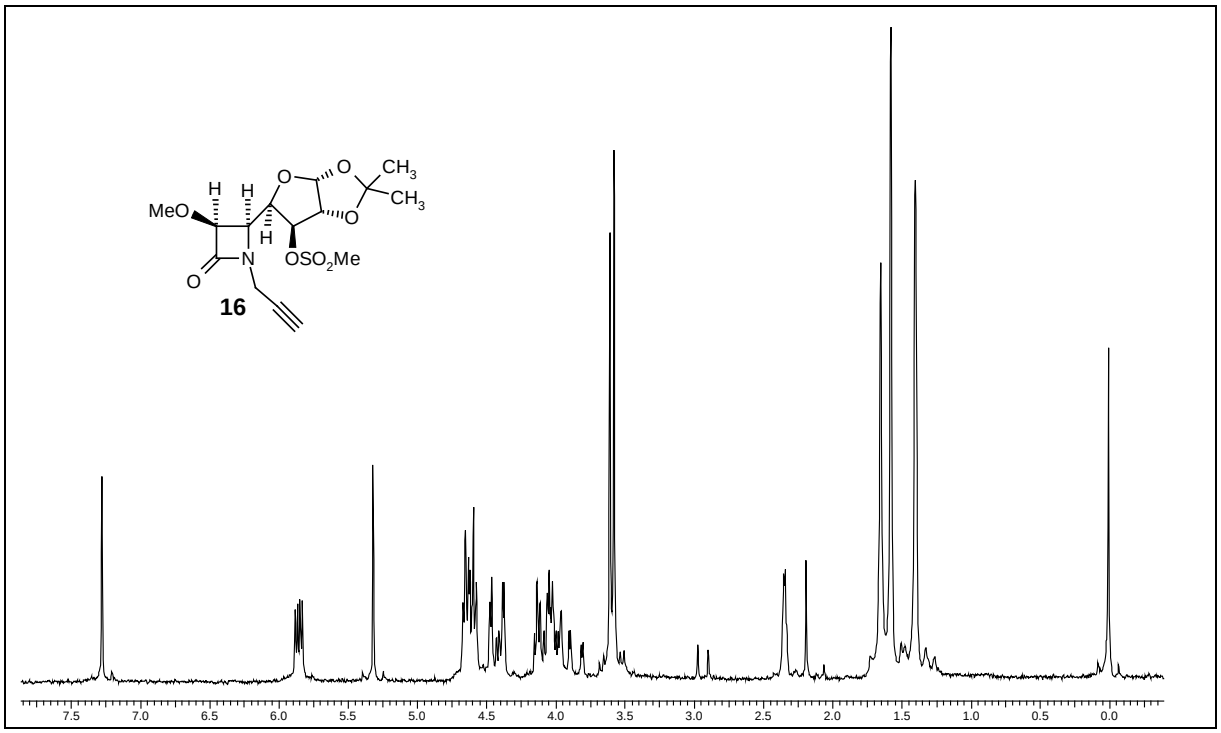
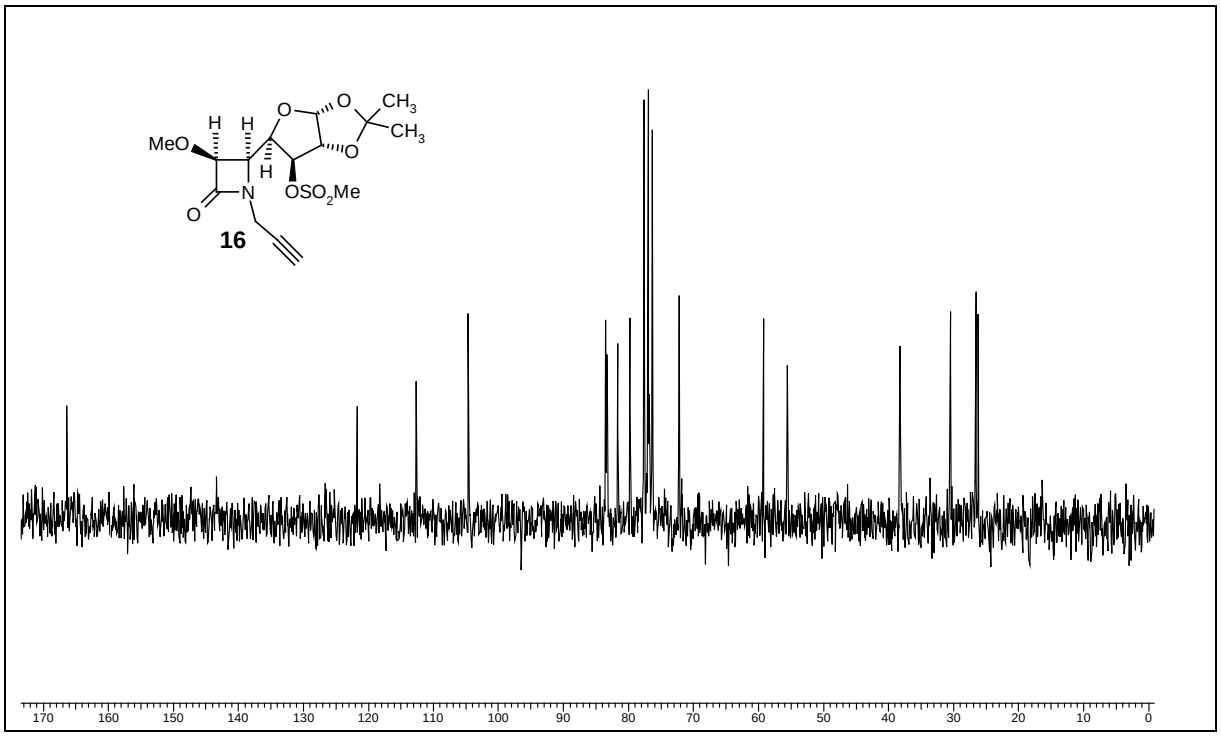
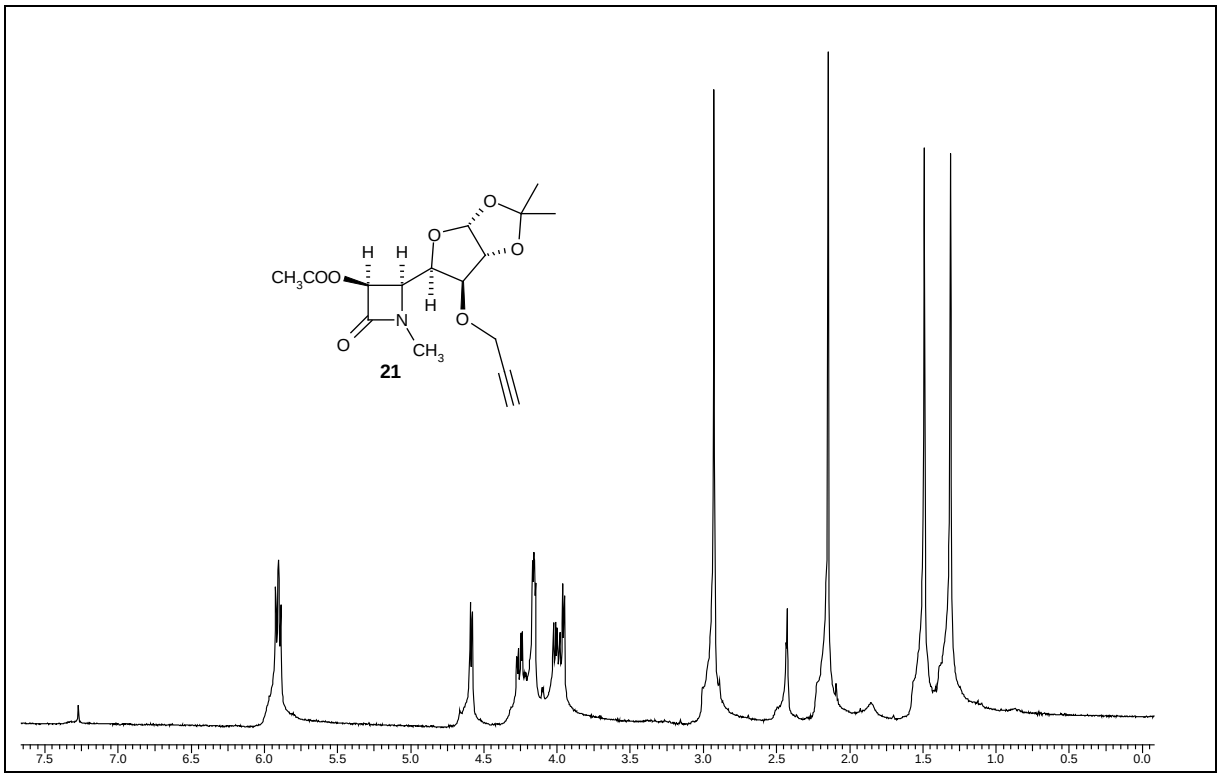
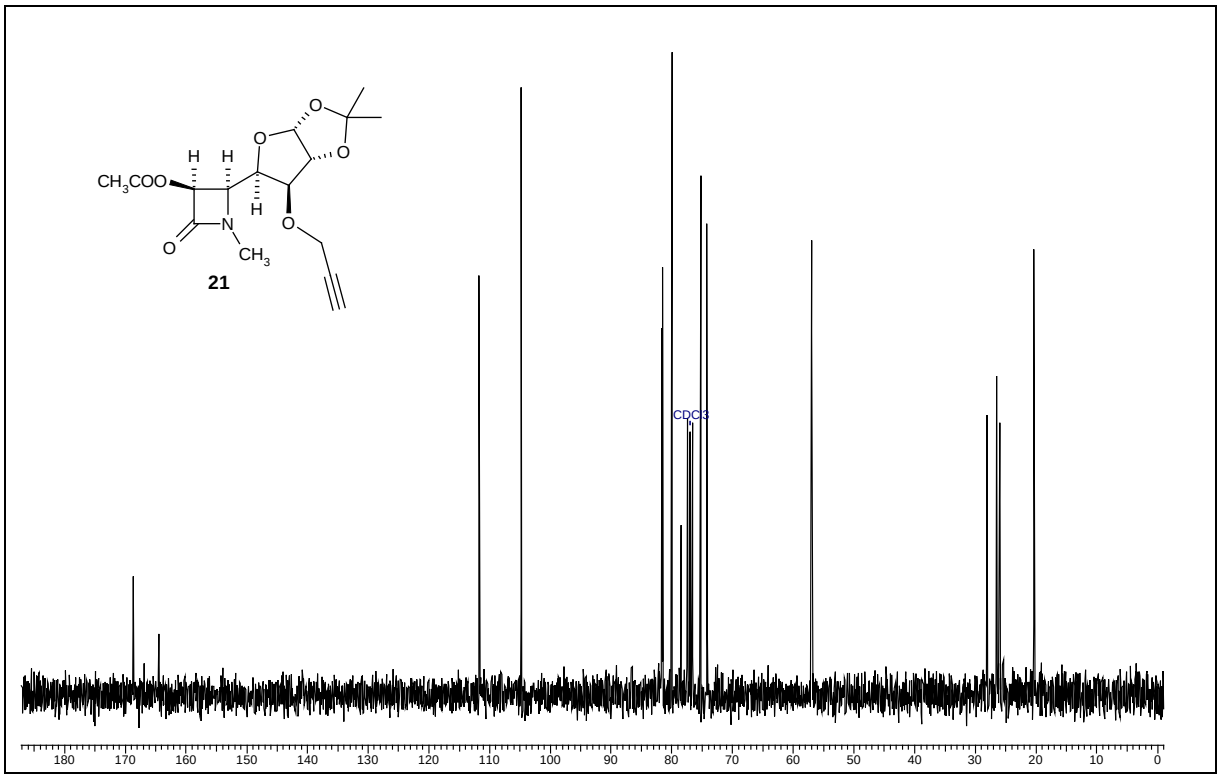


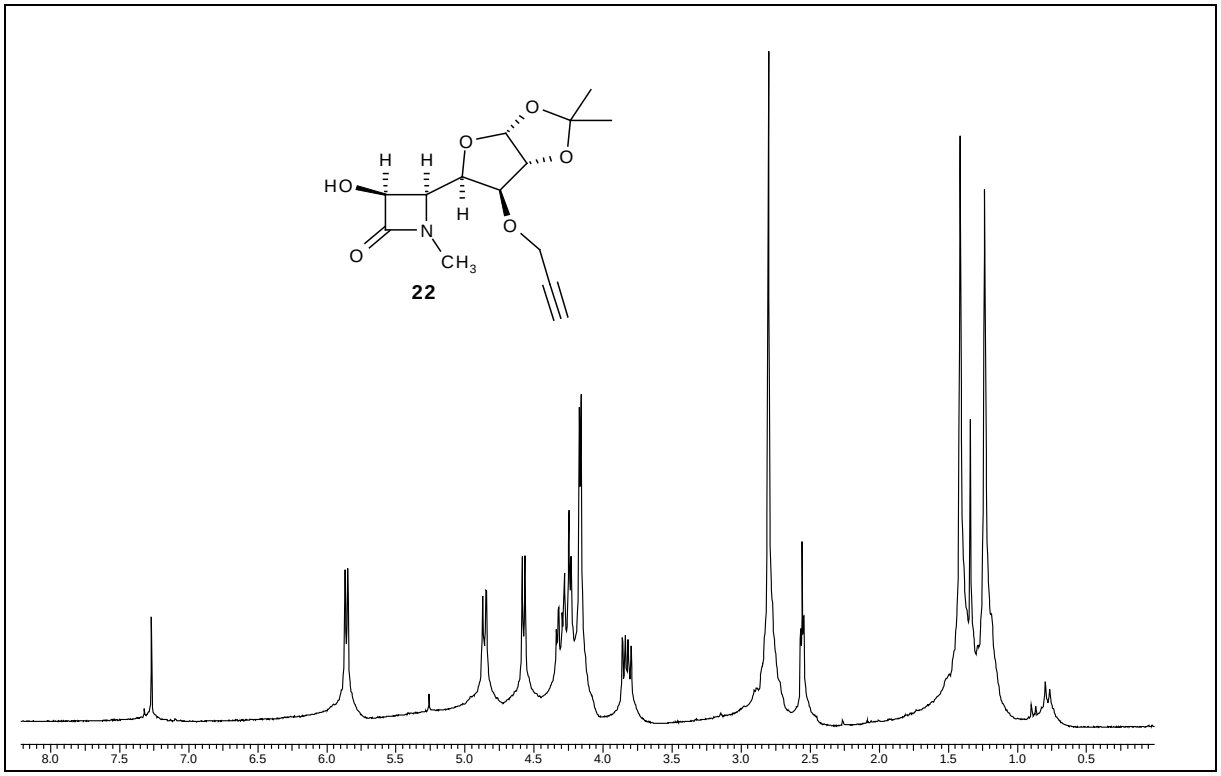


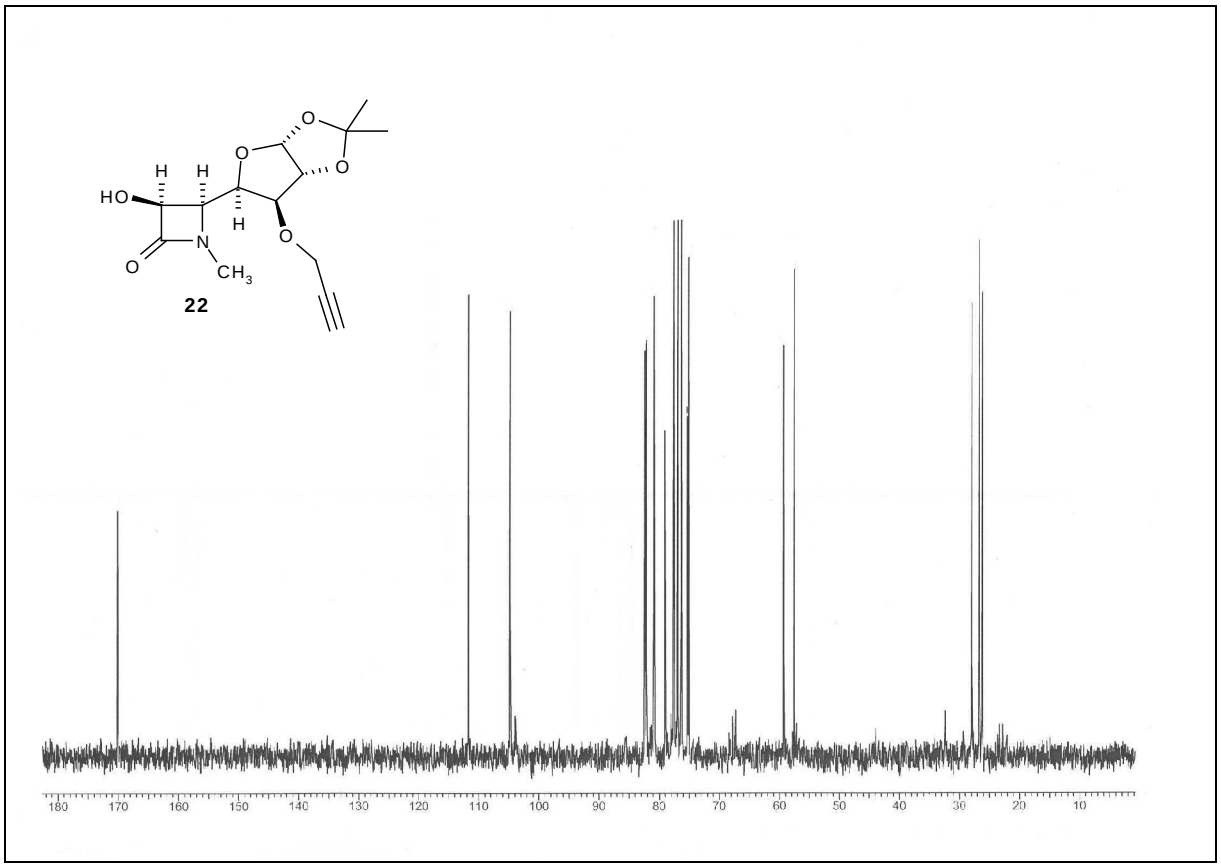


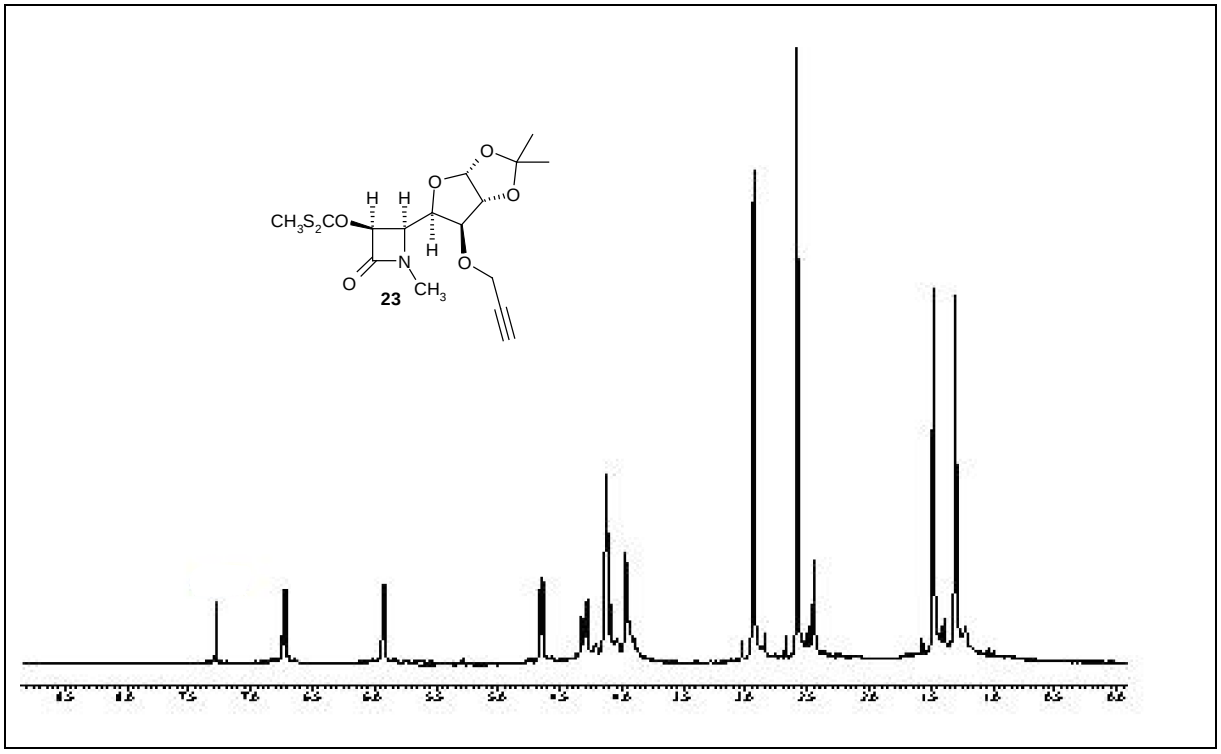


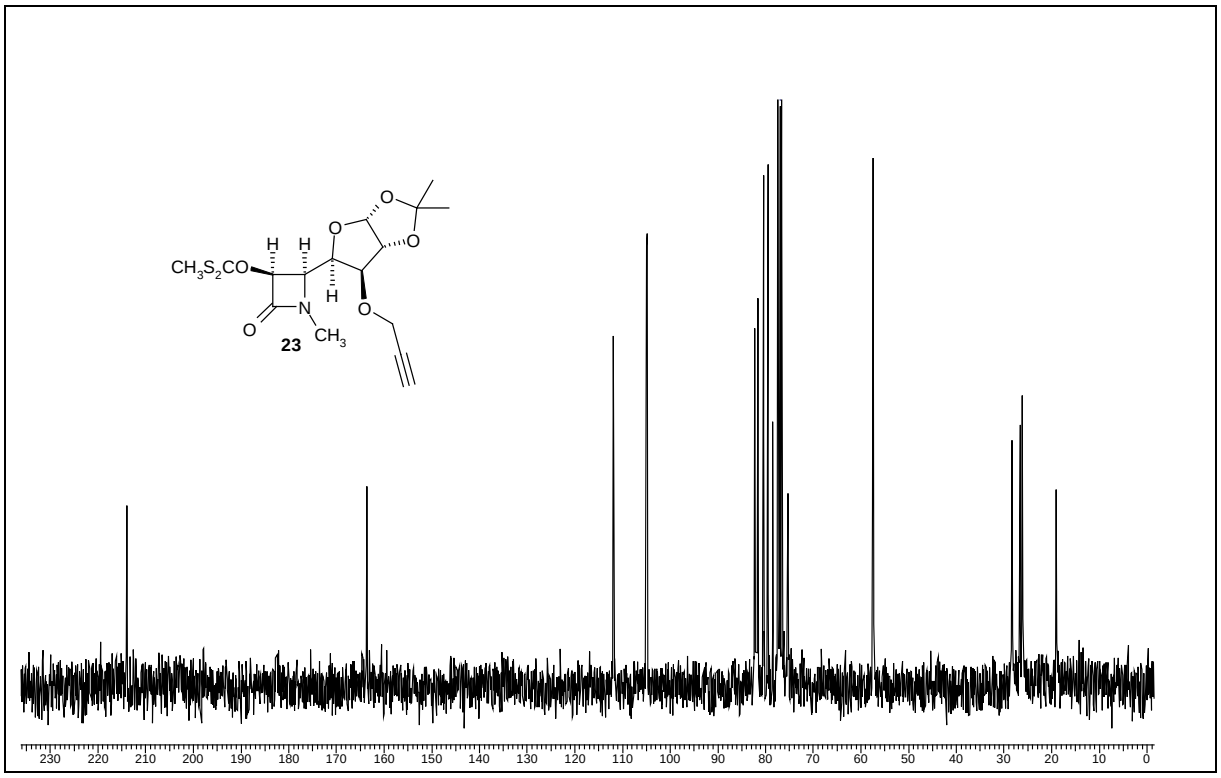


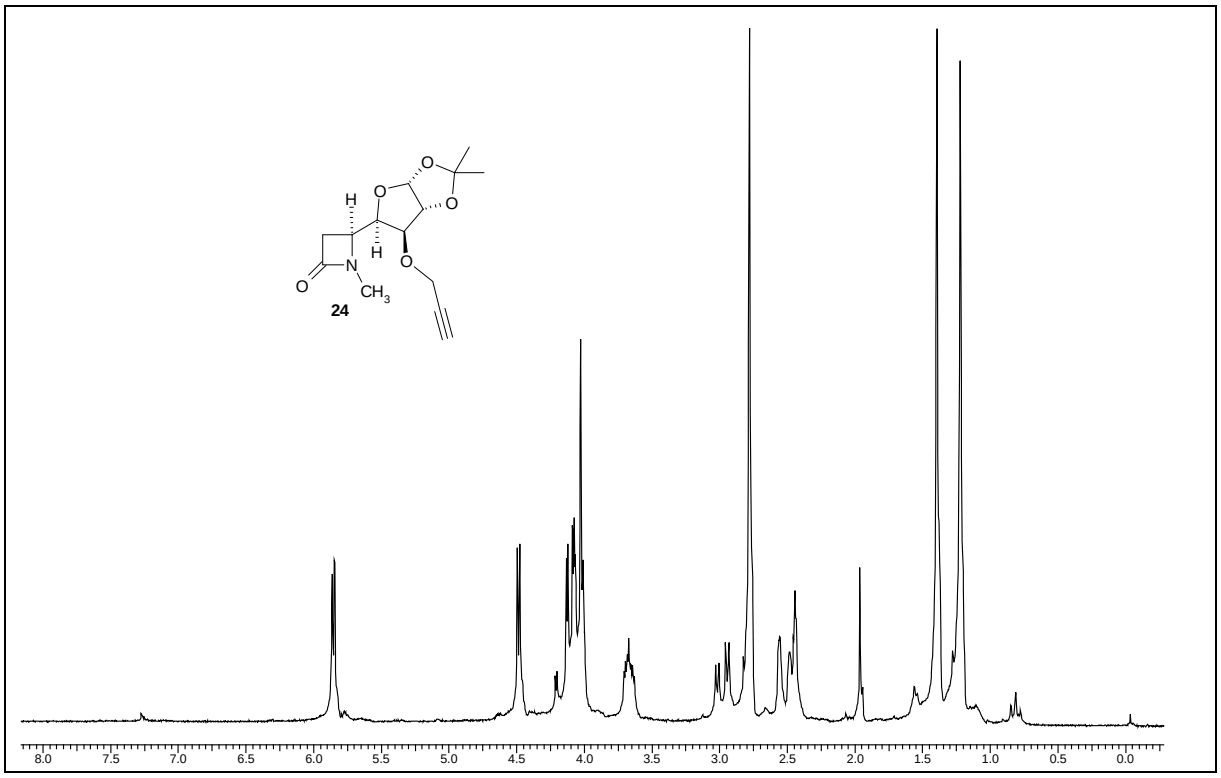


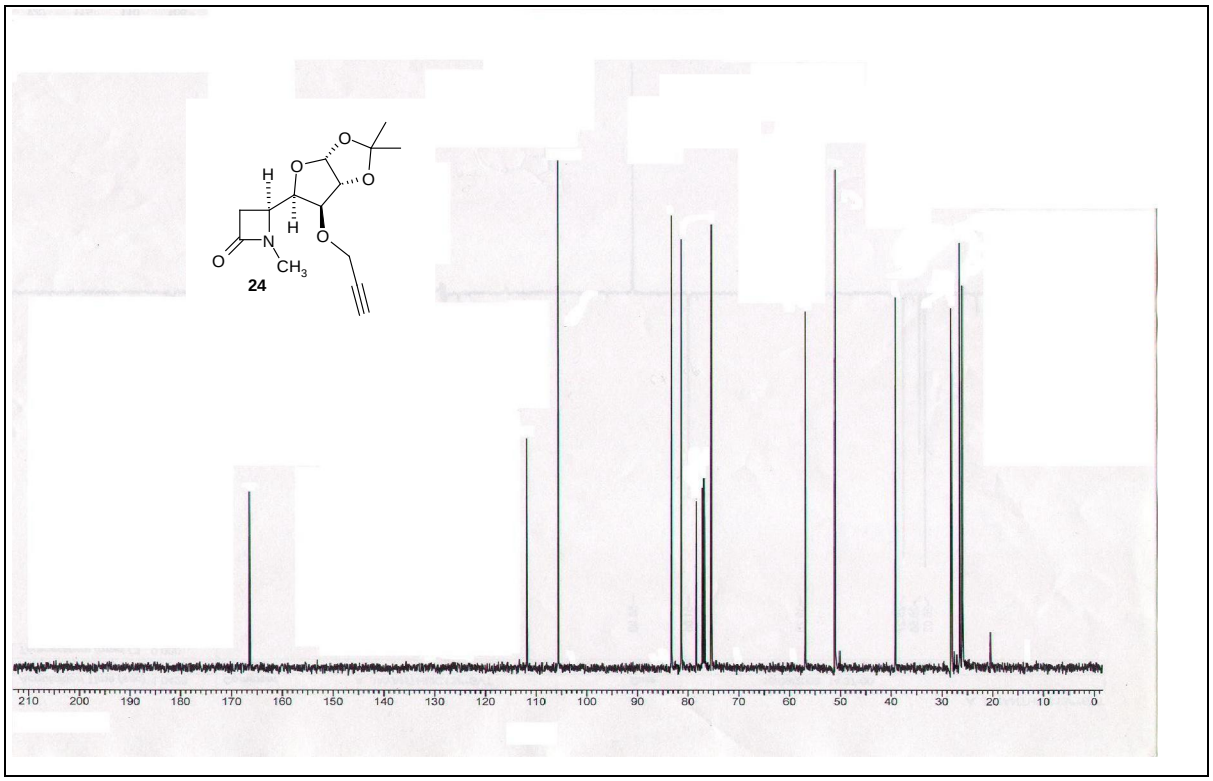












PART B

Allyl azides from allyl alcohols using triphosgene as an alcohol activator and their application in the synthesis of mono and polycyclic β-lactams

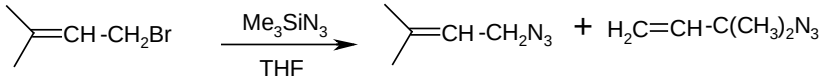
This work has been published in *Synlett* **2004**, 979 and *Synthesis* **2004**, *18*, 2965

Synthesis of allyl azides:

Allyl azides are a versatile class of compounds[1] used frequently in 1,3-dipolar cycloaddition reactions,[2] as precursors of nitrenes[3] and especially for conversion to allyl amines,[4] which are important synthetic intermediates of many natural products[5] and enzyme inhibitors.[6-8] The iminophosphorane derived from allyl azides can be transformed into various nitrogen containing compounds such as secondary amines,[9] amides,[10] imines,[11] nitro compounds,[12] nitriles[13] and primary allyl amines.[4a] The most common approaches for the synthesis of these azides involve i) the direct nucleophilic substitution of organic halides with azide ii) conversion of allyl alcohols to acetates or carbonates followed by transition metal catalyzed nucleophilic substitution reaction with azide anion. A few other methods are also known in literature and will be discussed briefly below.

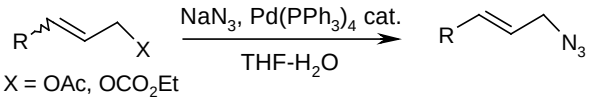
Methods available for the synthesis of allylic azides:

1. The substitution reaction of organic halides such as benzyl and allyl halides with trimethylsilyl azide under homogeneous and neutral conditions in a non-aqueous solvent gave the corresponding azides in moderate yield.[14]



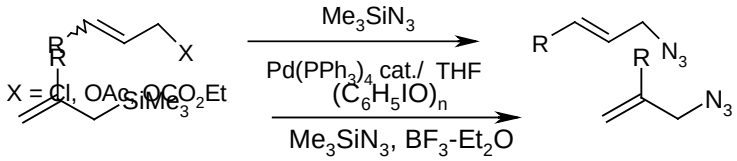
2. Murahashi et al. have reported the palladium-catalyzed azidation of allylic acetates and carbonates with aqueous NaN_3 to give the corresponding allyl azides. The reaction is performed under aqueous condition and is hence unsuccessful with water sensitive substrates.[15]

3. Safi and co-workers designed a method to overcome the problem posed by moisture sensitive substrates wherein they used trimethylsilyl azide under anhydrous



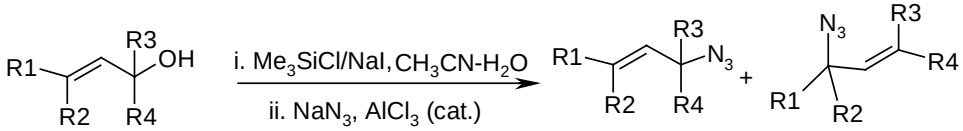
conditions to obtain (*E*)-allyl azides in good yield irrespective of the stereochemistry of starting material.[16]

4. A novel system, iodosylbenzene-trimethylsilyl azide-$BF_3.Et_2O$ was developed by Arimoto et al. to effect the direct conversion of allyl silanes to azides.[17]

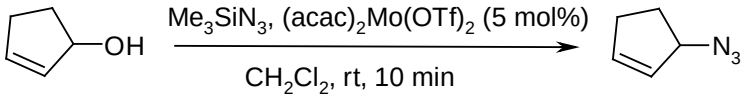


5. Kanai et al. have reported a convenient one-pot protocol for the synthesis of allyl azides wherein an allyl alcohol was transformed into the iodide by HI, generated in situ from TMSCl/NaI/H_2O, followed by nucleophilic substitution with NaN_3 in the presence of $AlCl_3$ as a catalyst.[18]

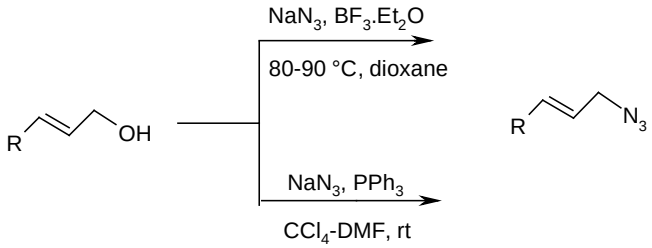
6. Malkov and co-workers have employed a novel catalyst Mo $(acac)_2(OTf)_2$ for the



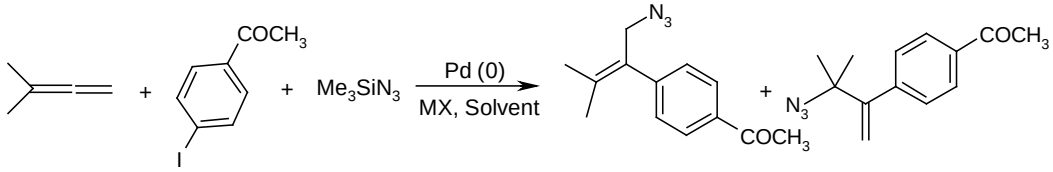
direct conversion of allylic alcohols to azides using Me_3SiN_3 under mild reaction conditions.[19]



7. Allylic azides were also prepared from allyl alcohols by the reaction with NaN_3 and $BF_3.Et_2O$ in dioxane or using NaN_3 and PPh_3 in CCl_4-DMF system.[20]

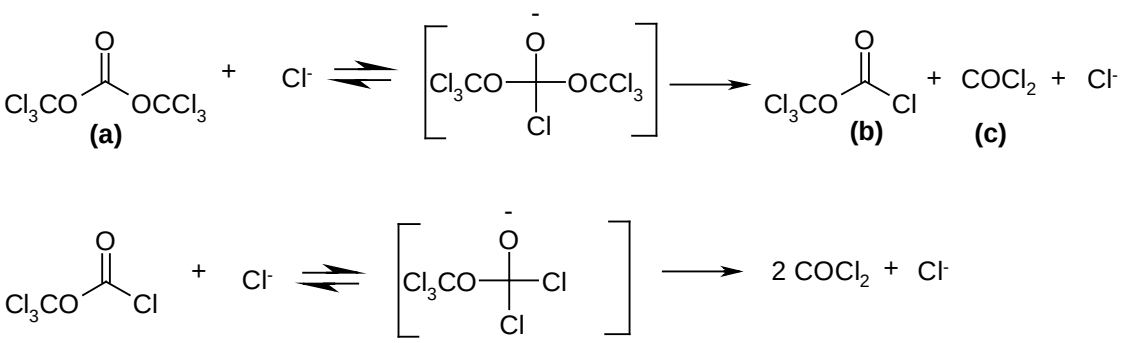


8. An intramolecular Pd-catalyzed carboazidation of allenes using aryl iodides and trimethylsilyl azide was reported by Chang et al. to synthesize allyl azides. The regioselectivity of the products depended on the palladium catalyst, solvent, temperature, time, base and the amount of phosphine ligands used.[21]



Triphosgene- a mild activator for heteroatom nucleophiles:

Triphosgene [bis(trichloromethyl)carbonate] is a reagent well known as a solid phosgene equivalent. Although more than a century old, (first prepared in 1880 by Couneler), only in the last few years has there been a tremendous increase in the use of triphosgene to synthesize various classes of organic compounds and for industrial applications.[22] The extensive application of triphosgene in synthesis is mainly because of its safe use and easy handling compared to its gaseous congener phosgene. The specific reactivity of triphosgene for heteroatom nucleophiles provides unsymmetrical ureas,[23] carbamoyl chlorides and iscyanates,[24-25] (poly)carbonates,[26] alkyl and acyl chlorides,[27] acid anhydrides[28] and biologically important heterocyclic compounds.[22] Reactions with triphosgene are generally carried out under mild reaction conditions affording good to excellent yields and have thus found extensive application in large-scale synthesis.

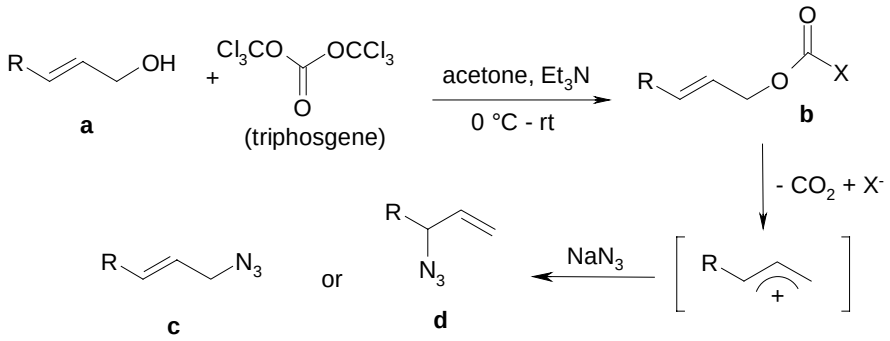


The nucleophilic attack of chloride ion on the carbonyl carbon of triphosgene (**a**) gives diphosgene (**b**) and phosgene (**c**). Diphosgene reacts with another chloride ion to afford two molecules of phosgene. It is well understood from the above mechanism that reactions involving phosgene can be carried out safely by generating it in situ in this fashion from triphosgene. Triphosgene is hence a safe as well as easily handled phosgene equivalent.[29]

Present Work:

Although the previous methods reported in literature for the direct synthesis of allyl azides from the corresponding alcohols work very well, the high cost and difficulty in work-up procedure render them inappropriate for large scale synthesis. We were interested to exploit triphosgene for the activation of alcohol instead of TMSCl/NaI, BF_3/Et_2O or PPh_3 in CCl_4/DMF to conquer this problem and thus provide us a mild and simple methodology for the one-pot synthesis of allyl azides from commercially available allylic alcohols.

Scheme 1

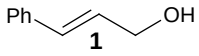
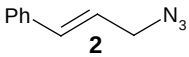
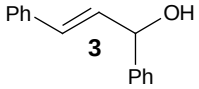
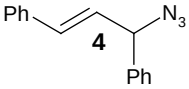
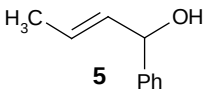
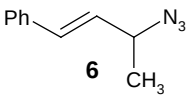
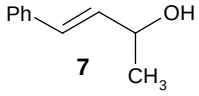
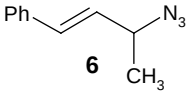
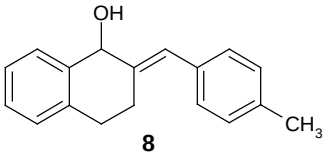
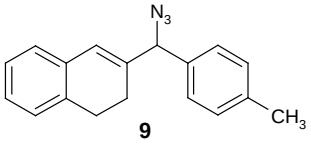
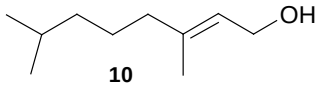
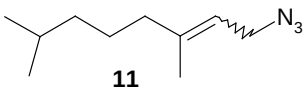


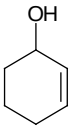
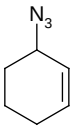
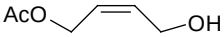
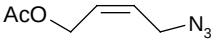
A solution of mixture of alcohol and triethylamine in acetone was added at 0 °C to a solution of triphosgene in acetone and stirred for 3 h at room temperature. Sodium azide

was then added to provide allylic azides (Scheme 1) in moderate to good yields. Several allylic azides were prepared under similar reaction conditions as shown in Table 1. The mechanism of azidation of allyl alcohol involves the formation of π–allylic cation intermediate from the initially formed allyl chloroformate with expulsion of carbon dioxide and the subsequent nucleophilic attack by azide ion from the less hindered side of the resulting π–allylic cation intermediate (Scheme 1).

Allylic alcohols **3**, **5** and **7** were prepared via Grignard reaction of corresponding aldehydes with either PhMgBr or MeMgBr and subjected for the azidation reaction under similar reaction conditions to afford the respective allyl azides **4** and **6** (entry 2, 3 and 4) in 90-60% yields. Both 1-phenyl-but-2-en-1-ol **5** and 4-phenyl-but-3-en-2-ol **7** furnished the same allyl azide **6** indicating that the π-allyl intermediate was trapped by azide ion selectively at the less substituted terminus. Same is the case with tetralone derived allyl alcohol **8**.

Table 1: **Preparation of allyl azides using triphosgene and sodium azide**

S. No.	Substrate	Product	Yield (%)
1	 **1**	 **2**	80
2	 **3**	 **4**	90
3	 **5**	 **6**	66
4	 **7**	 **6**	60
5	 **8**	 **9**	91
6	 **10**	 **11**	66

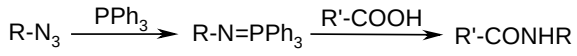
7	 **12**	 **13**	46 (GC yield)
8	 **14**	 **15**	63
9	$PhCH_2OH$ **16**	$PhCH_2N_3$ **17**	64

Geraniol (**10**) gave an *E*/*Z* mixture (55:45 ratio) of geranyl azide (**11**) in 66% yield along with a small amount of rearranged product linanyl azide. Benzyl alcohol (**16**) also gave benzyl azide (**17**) in 64% yield when reacted with triphosgene and sodium azide. The low yield of azides in the case of lower allyl alcohols may be due to low reactivity of alcohols and the volatile nature of the allyl azides formed. All the compounds were characterized thoroughly by IR, ^{1}H and ^{13}C NMR.

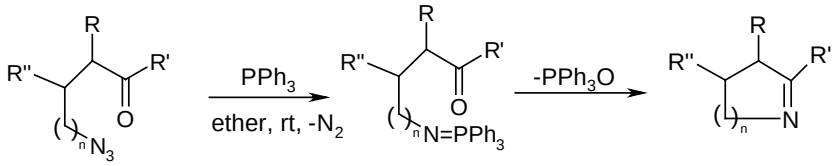
Synthesis of N1-cinnamyl β-lactams:

The combination of a sequence of individual synthetic methods often has a value in synthesis considerably greater than the sum of the individual methods and E. J. Corey names such a kind of method as a tactical combination.[30] A case in point is that of iminophosphorane derived from the reaction of tertiary phosphines with an organic azide after nitrogen extrusion reported by Staudinger,[31] which has received little attention in this point of view. The synthetic importance of iminophosphorane can be judged from its conversion in one-pot starting from azides into various nitrogen containing compounds such as amides, imines, nitro compounds, nitriles, primary allyl amines and secondary amines under mild reaction conditions. A glimpse of the applications of iminophosphoranes derived from azides has been given here.

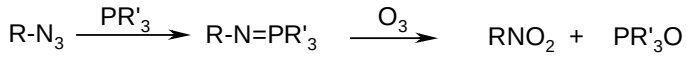
1. Garcia and co-workers have reported an efficient method for the introduction of amide group into a carbon backbone through phosphine mediated amide formation from carboxylic acids and azides under non-acidic condition and without the use of any additional reagents.[10]



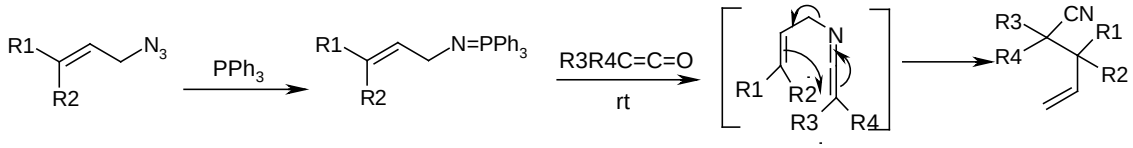
2. Lambert et al. have developed a methodology for the synthesis of cyclic imines via an intramolecular Aza-Wittig reaction.[11]



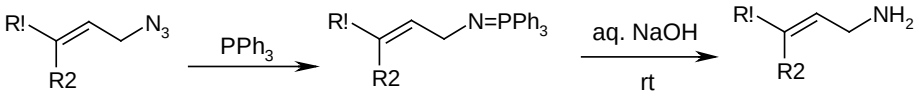
3. Iminophosphoranes generated in situ from azides, on cycloaddition with ozone gave the corresponding nitro compounds in good yields and the reaction was found to be applicable to those substrates that can withstand ozone at -78 °C.[12]



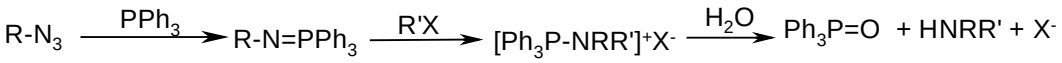
4. Molina and co-workers have reported a convenient one-pot synthesis of allyl nitriles from allyl azides wherein the phosphoniumimines generated from azides, react with ketenes to give highly reactive keteneimine which in turn got converted into the corresponding nitriles via a 3-aza-Claisen rearrangement.[13]



5. Allyl azides on treatment with triphenylphosphine followed by aqueous sodium hydroxide solution gave primary allyl amines found in many biologically important compounds such as gabaculine, oryzoxymycin and cytosinine etc.[4]



6. Zimmer et al. have reported the synthesis of secondary amines from azides by converting them into the corresponding iminophosphoranes followed by addition of alkyl halides. This method was restricted to addition of methyl and ethyl groups and reaction with higher alkyl halides resulted in the formation of alkylaminotriphenylphosphonium halides via HX elimination from alkyl halides.[9]

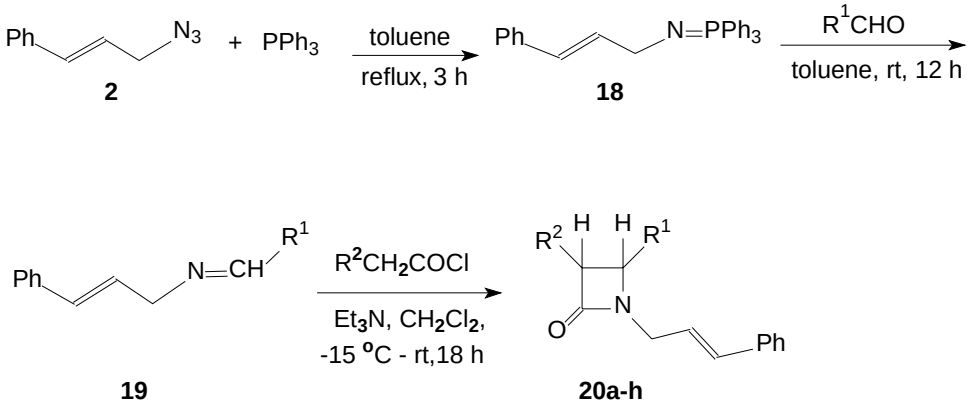


Present Work:

Due to the wide-range significance of β-lactams for their biological activity and their utility as a synthetic intermediate for the synthesis of various natural products and amino acids, there is a constant demand for designing more efficient synthetic methods towards β-lactam synthesis. Though several methods have been reported for the preparation of β-lactams, Staudinger reaction of ketene-imine cycloaddition is considered to be the best method because of its simplicity and predictability of the stereochemical outcome of the reaction.

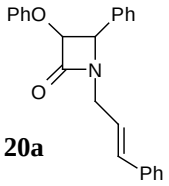
We have been studying Staudinger reaction for the synthesis of various β-lactams, which could be used as an intermediate in the synthesis of taxol side chain,[32] biologically important pyridones[33] and quinolones[34] etc. Hence we have utilized the synthesized allyl azides for the synthesis of *N*1-allyl substituted β-lactams by employing Aza-Wittig reaction of iminophosphorane with aldehydes followed by Staudinger reaction as represented below.

Scheme 2



Cinnamyl azide (**2**) was chosen as an example and treated with triphenylphosphine in refluxing toluene. The obtained iminophosphorane (**18**) was subjected to aza-Wittig reaction with benzaldehyde to get the corresponding imine, *N*-benzylidenecinnamylamine (**19**) (R^1 = Ph), which was then used as such for the cycloaddition reaction with ketene, generated from phenoxyacetyl chloride and triethylamine, to give a white crystalline solid **20a** in 84% yield (Scheme 2).

The IR spectrum of this solid **20a** showed a sharp band at 1757 cm^{-1} corresponding to the β-lactam carbonyl group. The ^1H NM spectrum of the product gave two doublet of doublets at 3.66 and 4.4 ppm (J = 5-7 Hz, 14-15 Hz) indicating the presence of methylene protor attached to the β-lactam nitrogen.



20a

Doublets at 4.99 (J = 4.5 Hz) and 5.48 ppm (J = 4.5 Hz) corresp am protons at C-4 and C-3 positions. The geometry of β-lactam protons was found to be *cis* to each other from the coupling constant value (J = 4-6 Hz for *cis* & J = 1-2 Hz for *trans* β-lactams). The two olefinic protons were seen at 6.03 ppm and 6.43 ppm as a multiplet and doublet (J = 15.5 Hz) respectively. The aromatic ring protons appeared as multiplets in the region of 6.73-7.33 ppm. The ^{13}C NMR of the product showed a signal at 165.5 ppm supporting the formation of *N1*-cinnamyl β-lactam **20a**. Elemental analysis also gave satisfactory result.

Various substituted and unsubstituted benzaldehyde derived imines **19** (R^1 = Ph, 2-BrPh, 4-MeOPh) were used with acid chlorides in the presence of excess triethylamine to afford *N*1-cinnamyl substituted β-lactams **20a-h** in good yields (Scheme 2). All the compounds were characterized by IR, ^1H and ^{13}C NMR. The geometry of β-lactam protons was confirmed to be *cis* based on the coupling constant value of C-3 and C-4 protons in all the cases.

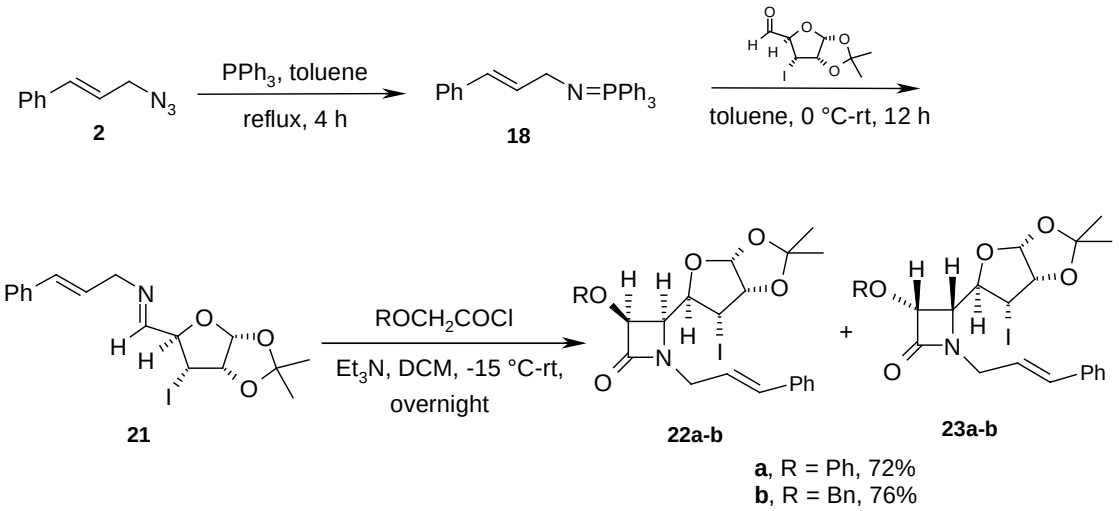
Table 2. Synthesis of N1-cinnamyl substituted β-lactams 20a-h

S. No.	Compound	R^1	R^2	Yield (%)
1	**20a**	Ph	-OPh	84
2	**20b**	Ph	$-OCH_2Ph$	74
3	**20c**	Ph	-OMe	84
4	**20d**	2-BrPh	$-OCH_2Ph$	72

5	**20e**	2-BrPh	-OMe	82
6	**20f**	4-MeOPh	-OMe	61
7	**20g**	4-MeOPh	-OCH_2Ph	78
8	**20h**	4-MeOPh	-OPh	69

The D-glucose derived iodoaldehyde as seen before in **Part A** was used as a chiral source in the asymmetric Staudinger reaction for the synthesis of optically pure *N*1-cinnamyl substituted β-lactams (Scheme 3).

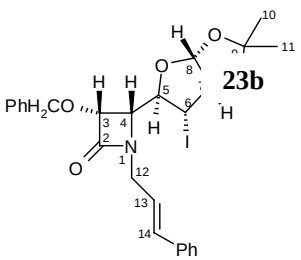
Scheme 3



Iminophosphorane **18** obtained from cinnamyl azide (**2**) was treated with iodoaldehyde and the resulting imine **21** on Staudinger reaction with ketenes generated from phenoxy and benzyloxyacetyl chlorides and triethylamine under standard reaction conditions gave a 1:1 diastereomeric mixture of β-lactams **22a** & **23a** and **22b** & **23b** in 72% and 76% yields respectively. Both the diastereomers were separated by flash column chromatography and characterized by NMR spectral studies.

The structure and stereochemistry of one of the isomers **23b** was studied by 1D and 2D NMR techniques. The IR spectrum of this isomer showed a sharp band at 1754 cm^{-1} indicating the presence of carbonyl group of β-lactam. The ^1H NMR of this β-lactam **23b** showed two singlets at 1.36 and 1.53 ppm for methyl groups of acetonide moiety.

The anomeric proton H-8 appeared as a doublet at 5.80 ppm (*J* = 3.5 Hz) a the proton H-7 adjacent to the anome proton gave a doublet of doublet at 4.



ppm (*J* = 3.2, 3.5 Hz). A triplet at (triplet got merged with doublet of doublet of H-7 proton but was seen clearly in the COSY spectrum at 500 MHz) 4.53 ppm corresponds to H-5 proton.

The H-5 proton actually couples with both H-4 and H-6 protons to give a doublet of doublet but in this case since the H-4 and H-5 protons are *trans* to each other, the dihedral angle gives rise to two doublets, which merge into a triplet.

Similarly, a triplet was obtained for H-4 proton at 4.05 ppm (*J* = 3.9, 4.3 Hz). The H-6 proton appeared as a multiplet at 3.87-4.00 ppm along with the one of the nitrogen attached methylene protons (H-12). The other nitrogen attached methylene proton (H-12) was seen at 4.26 ppm as a doublet of doublet (*J* = 5.8, 15.8 Hz). A multiplet at 4.73-4.81 ppm was assigned for H-3 and one of the benzylic protons, which was later identified as two doublets while carrying out COSY experiment in 500 MHz. The other benzylic proton showed a doublet at 4.95 ppm (*J* = 11.8 Hz).

An allylic olefinic proton appeared as a multiplet at 6.03-6.18 ppm and the other olefinic proton resonated as a doublet at 6.55 ppm (*J* = 15.8 Hz). The aromatic protons appeared in the region of 7.27-7.40 ppm.

The bond connectivity and stereo alignment of protons present in β-lactam **23b** were further confirmed from its two dimensional NMR analysis. In the COSY spectrum, the anomeric proton H-8 showed a strong coupling with H-7 proton. The proton H-7 was further connected with H-6 proton, which in turn connected with H-5. The proton H-5 showed a connectivity with H-4 proton, whereas the H-4 proton in turn showed connectivity with H-3 (Figure 1).

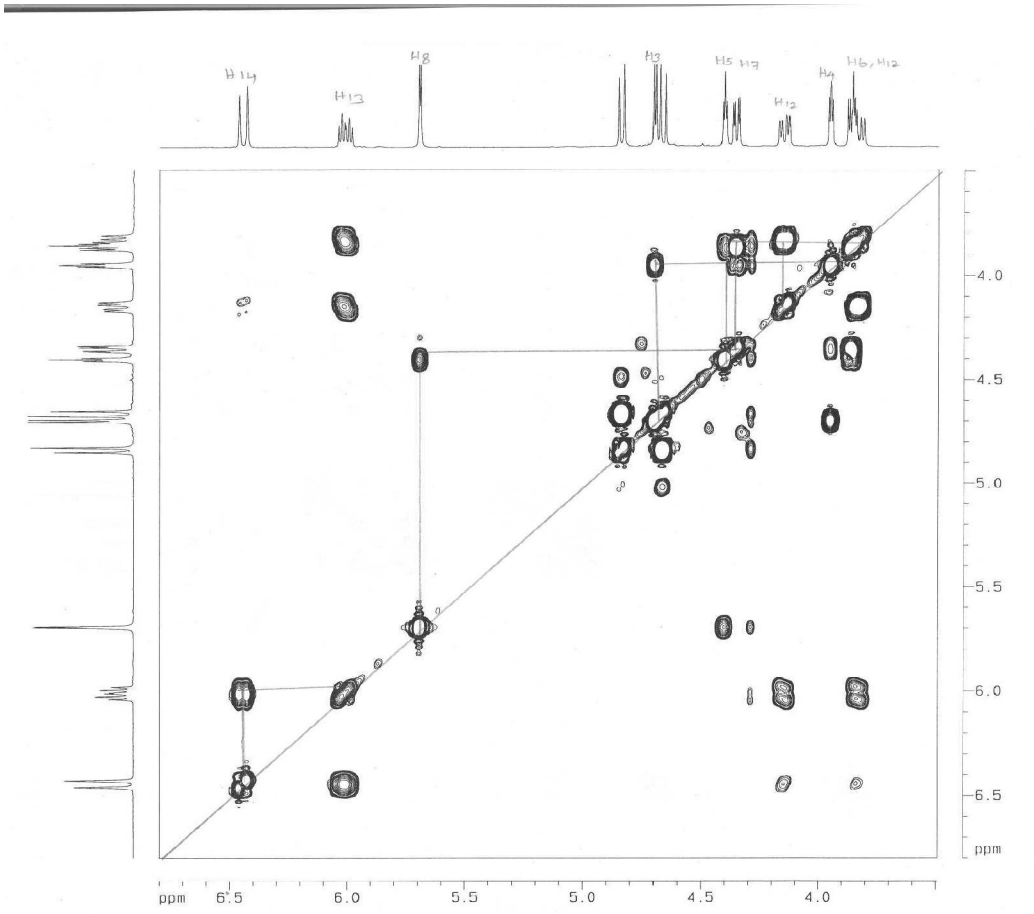


Figure 1. COSY NMR spectrum of **23b** (selected region is shown)

Table 3. Important connectivities in the COSY NMR of 23b

proton	ppm	^{1}H-^{1}H connectivity
H-8	5.80 (d)	H-7
H-7	**4.42 (dd)**	H-8, H-6
H-6		H-5, H-7
H-5	3.87-4.00 (m)	H-4, H-6
H-4	4.53 (t)	H-3, H-5
H-3	4.05 (t)	H-4
	4.81 (d)	

The stereo alignment of H-8 and H-7 was already known to be beta. Based on this, the spatial connectivity of H-3 and H-4 protons at newly generated chiral centers C-3 and C-4 of **23b** was studied through its NOESY spectrum (Figure 2). The proton H-8 showed spatial interaction with H-7 and the proton H-7 further showed interaction with H-4 and H-

3 indicating that H-3, H-4, H-7 and H-8 are on the same side and thus the structure and stereochemistry of β-lactam **23b** was confirmed.

The ^{13}C NMR spectrum of **23b** gave a sharp signal at 167.3 ppm corresponding to the carbonyl group of the β-lactam moiety. The methine carbon bearing iodo substituent and acetonide methyl groups appeared at 21.9, 26.5 and 26.6 ppm respectively. The *N*CH_2 and benzylic methylene carbons appeared respectively at 43.9 and 73.1 ppm. The C-3, C-4, C-5 and C-7 carbons appeared at 56.6, 79.4, 80.7 and 81.5 ppm respectively. The anomeric carbon C-8 and quaternary carbon of acetonide C-9 showed sharp peaks at 103.4 and 111.9 ppm correspondingly. The other olefinic and aromatic carbons appeared in the region between 123.0-137.1 ppm.

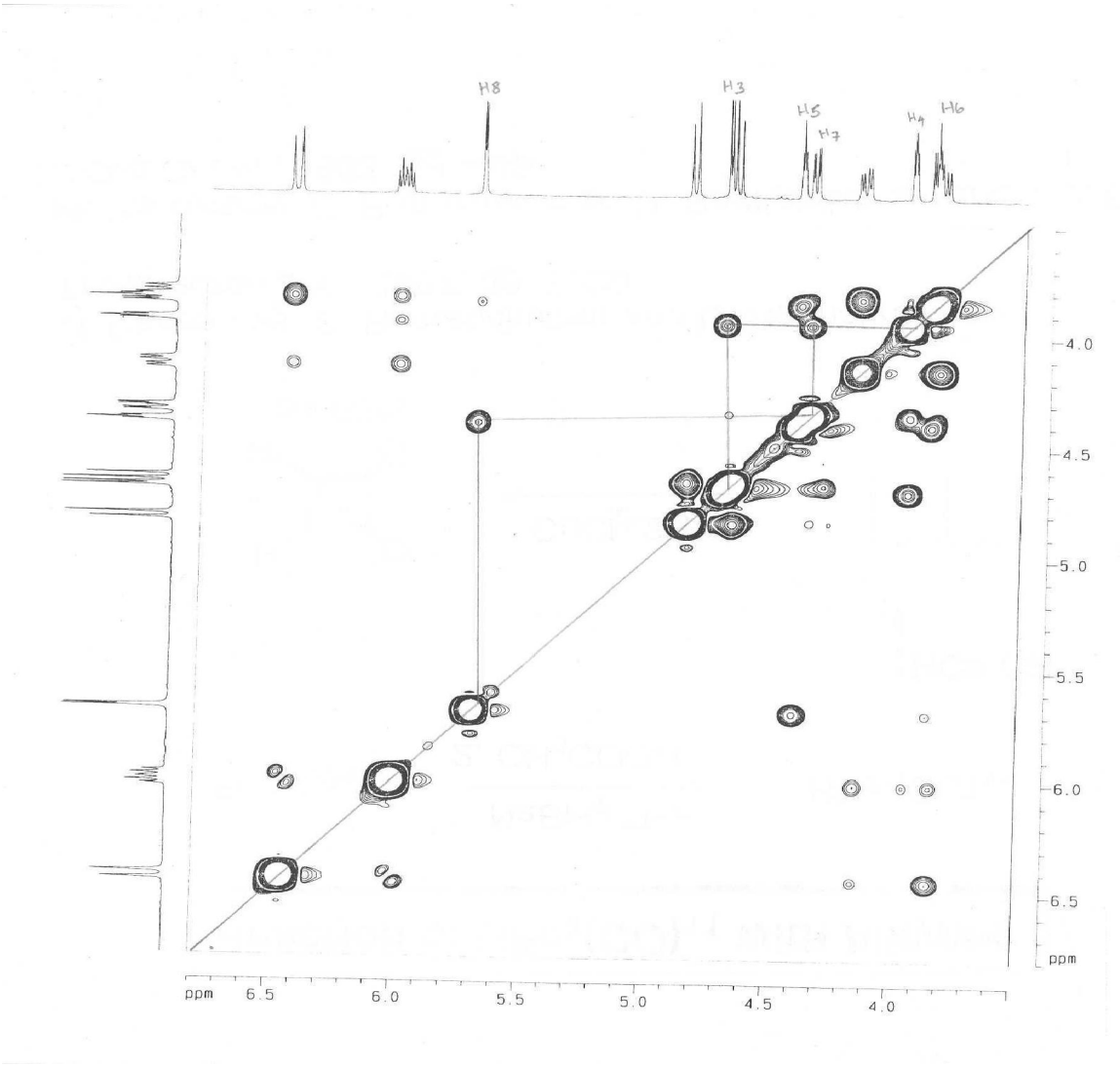


Figure 2. NOESY spectrum of **23b**

Since the NOESY experiment of **23b** confirmed the stereochemistry of C-3 and C-4 protons as *3R*, *4S*, we have assigned the opposite stereochemistry for the other isomer **22b**. The compounds **22a** and **23a** were characterized similarly.

Synthesis of polycyclic β-lactams via intramolecular radical cyclization:

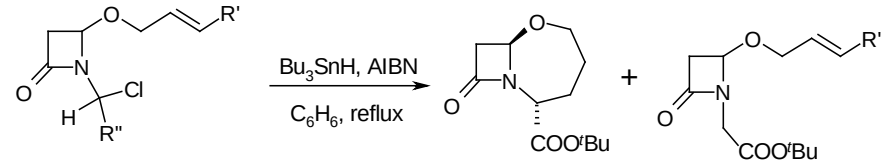
One of the major worldwide problems in medicinal chemistry demanding imperative action was (and still is) the increasing resistance of bacteria towards clinically employed common antibiotics such as penicillin and cephalosporin by mutation and β-lactamase gene transfer. To overcome this difficulty, there was an urge to construct a new variety of nonconventional fused polycyclic β-lactams for use as β-lactamase inhibitors.

Since the monocyclic azetidin-2-ones can be used as a template on which to build the heterocyclic structure fused to the four-membered ring using the chirality and functionalization of the β-lactam nucleus as a stereocontrolling element, several methodologies have been utilized in literature (discussed in **Part A**) on suitably susbstituted azetidin-2-ones to get highly strained and non-classical polycyclic β-lactams. Among them, intramolecular radical cyclization has been considered as an efficient methodology for the formation of polycyclic β-lactams and has also been well studied in natural product synthesis.[35]

Synthesis of oxacepham and oxahomocepham bicyclic β-lactams:

Bachi[36] is the person who introduced radical cyclization in the β-lactam field. Considering the susceptibility of β-lactam ring to the nucleophilic agents, he reasoned that intramolecular radical cyclization would be the better choice for the polycyclic β-lactam

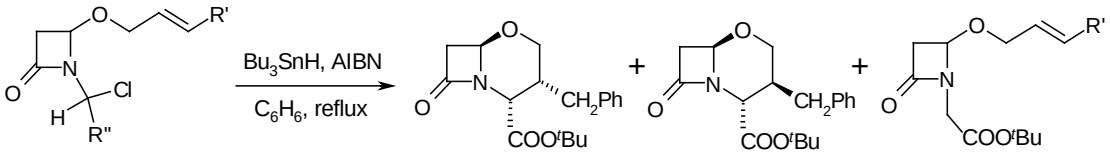
synthesis and applied the same for the synthesis of oxacepham derivatives from the *N*-chloro substituted azetidin-2-ones. The allylic substituents at C4 position acted as radical acceptors. The cyclization at the terminal olefinic bond proceeded in *endo* fashion to afford oxahomocepham whereas substituted olefinic derivatives gave oxacephams via *exo* mode of cyclization in high regio- and stereoselectivity. In both the cases, formation of reduced product was considerable.



R' = H, R'' = COO^{t}Bu

47%

22%



R' = Ph, R'' = COO^{t}Bu

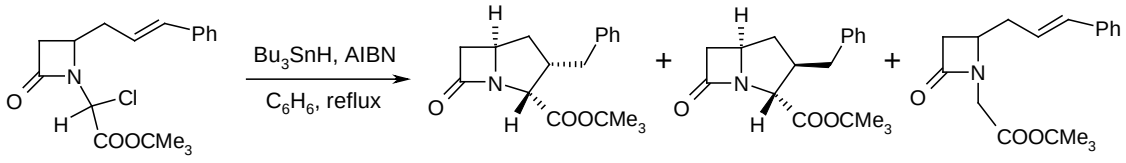
68%, 1:1 ratio

10%

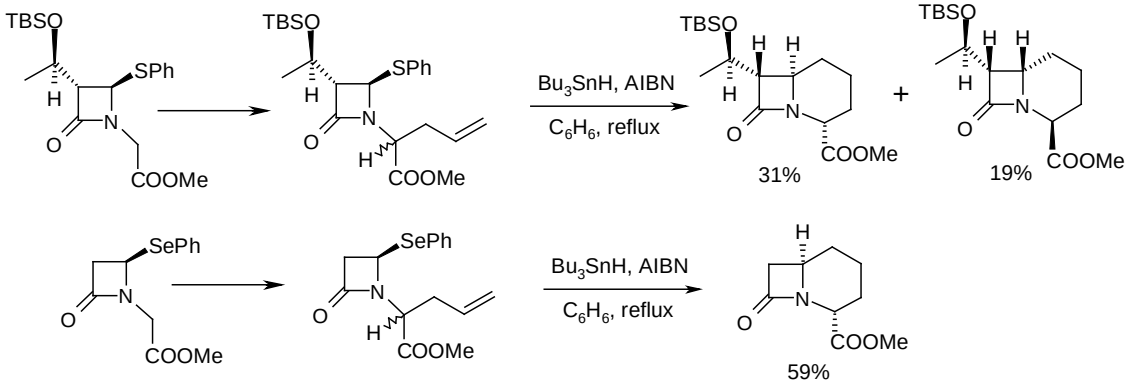
Since the *N*-chloro substituted azetidin-2-ones were unstable, the corresponding *N*-phenylthio- and *N*-phenylseleno- precursors were studied and free radical annulation followed the similar mode of cyclization depending upon the nature of the substituents at the double bond.[37]

Synthesis of carbapenam and carbacepham analogues:

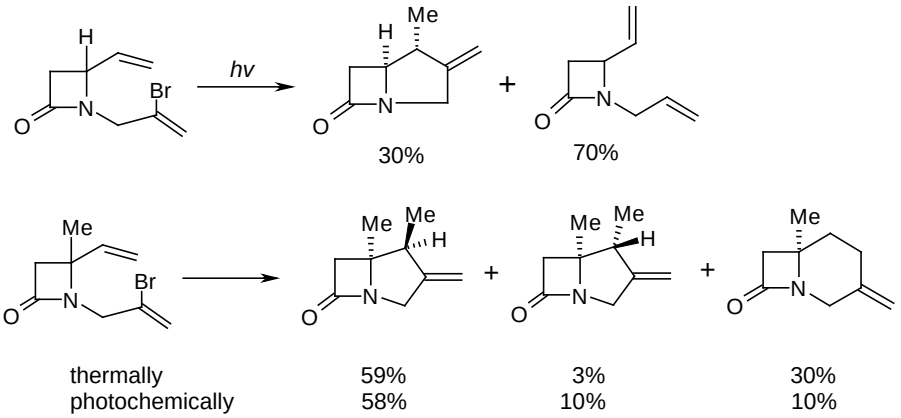
Carbodethia analogues of penems and cephems are called as carbapenem and carbacephem and they are known to be efficient β-lactamase inhibitors. Bachi has synthesized these analogues by following the same methodology he had used in the synthesis of 1-oxacepham and 1-oxahomocephams. The homolytic cyclization of C-4 alkenyl β-lactams afforded carbapenams by *exo* addition, when a vicinally disubstituted double bond was involved and carbacephams were formed exclusively via *endo* addition to the terminal double bond. These synthesized carbacepham and carbapenam bicyclic heterocycles are structurally related to penicillin and β-lactamase inhibitor clavulonic acid respectively.[38]



Later, Kametani and co-workers also reported the same strategy for the intramolecular radical annulation of 4-phenylthio- and 4-phenylseleno- azetidinones to construct carbacepham derivatives. The double bond in the group attached to nitrogen acted as a radical acceptor. The cyclization proceeded by *endo-mode* and led to the formation of 1-azabicyclic[4.2.0]octan-7-one systems in good yields.[39]



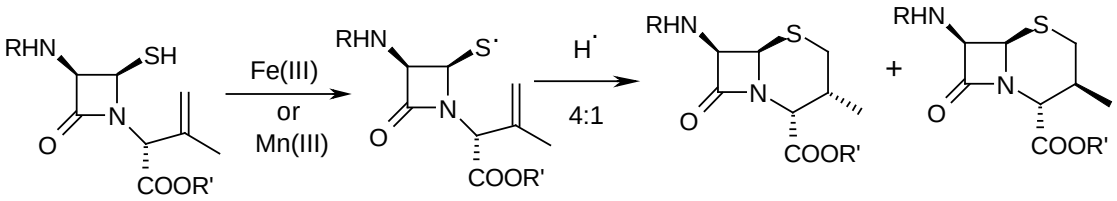
Parsons methodology is based on vinyl radical cyclization. He has studied the cyclization of 4-vinyl azetidinones under photochemical as well as thermal conditions.[40]



The C-4 substituted analogues cyclized efficiently in 5-*exo* mode and provided 1α-methylcarbapenam and 1β-methylcarbapenam derivatives with high diastereoselectivity.

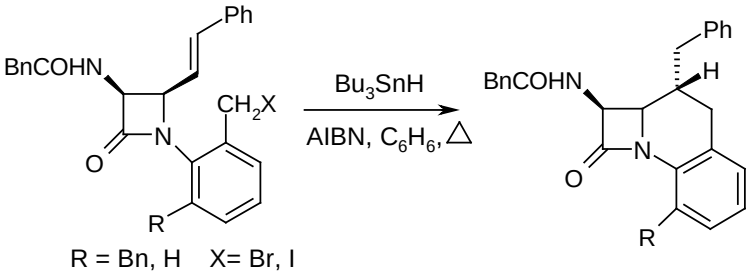
Cabri et al. have reported intramolecular thiyl radical addition to a double bond promoted by Fe(III) and Mn(III) to synthesize β-lactam antibiotics. The

stabilized radical intermediate afforded cephams by subsequent hydrogen abstraction.[41]

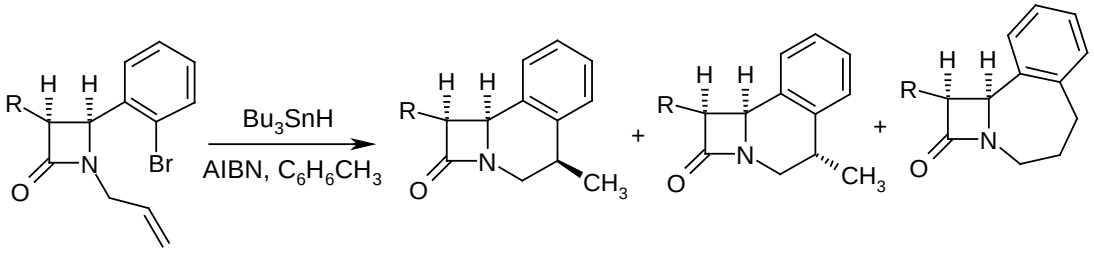


Synthesis of benzocarbapenam and benzocarbacepham derivatives:

Benzocarbapenams are tricyclic β-lactams and clinically used as efficient β-lactamase inhibitors. Just has reported intramolecular aryl radical cyclization to furnish benzocarbapenams. The tricylic β-lactams obtained via 5-*exo* addition were found to be unstable in solution whereas 6-*exo* annulation of aryl radical gave stable cyclized compounds.[42]

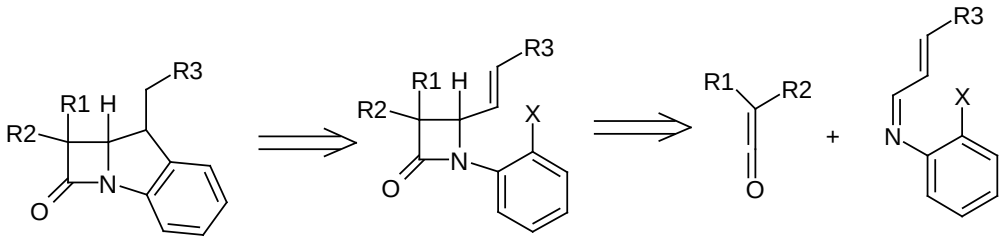


Banik et al. have developed a convenient route involving the same strategy of intramolecular aryl radical cyclization with modified *N*-allyl azetidinones as precursors. The fused 6-membered tricyclic azetidinones were formed as major products by 1,6-bond coupling of *exo* cyclization along with small amount of *endo* cyclized β-lactams.[43]

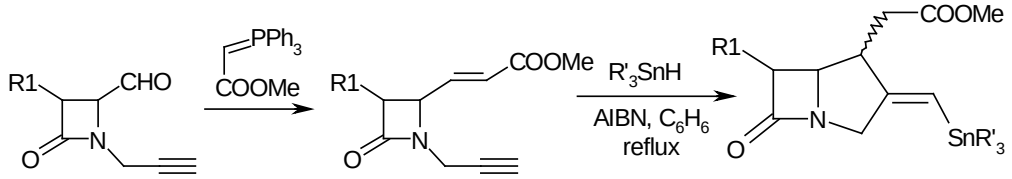


In another aryl radical mediated cyclization, Alcaide et al. have employed imines derived from *o*-haloanilines and α,β-unsaturated aldehydes. The resulting β-lactams

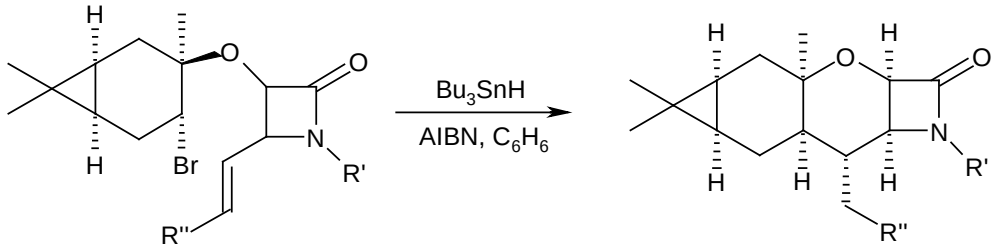
cyclized predominantly in 5-*exo* mode. However, with terminal double bonded derivatives, 6-*endo* was a competing pathway.[44]



Later Alcaide has reported radical mediated cycloisomerization of enyne β-lactams to furnish fused bicyclic β-lactams stereoselectively.[45]



More recently, Joshi et al. reported a highly strained tetracyclic [3.6.6.4] ring system containing a fused tetrahydropyran β-lactam moiety using tributyltin hydride mediated radical cyclization of Δ-3-carene derived 4-allyl azetidinones in a highly stereoselective manner.[46]

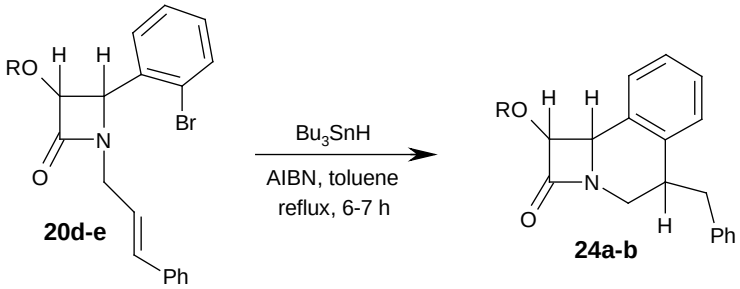


Present Work:

Since radical cyclization reactions have advantages of high functional group tolerance, mild reaction conditions and high levels of regio- and stereoselectivity, we have used *N*1-cinnamyl substituted azetidin-2-ones prepared from cinnamyl azide as precursors, for the construction of polycyclic β-lactams using tributyltin hydride and AIBN mediated intramolecular radical cyclization.

Azetidin-2-ones **20d-e** synthesized from bromobenzaldehyde derived imine are suitable substrates to study the intramolecular radical annulation wherein bromo substituent of aryl ring can be used as radical progenitor and phenyl substituted double bond can act as a radical acceptor (Scheme 4).

Scheme 4



20d-e

20d, R = Bn
20e, R = Me

24a-b

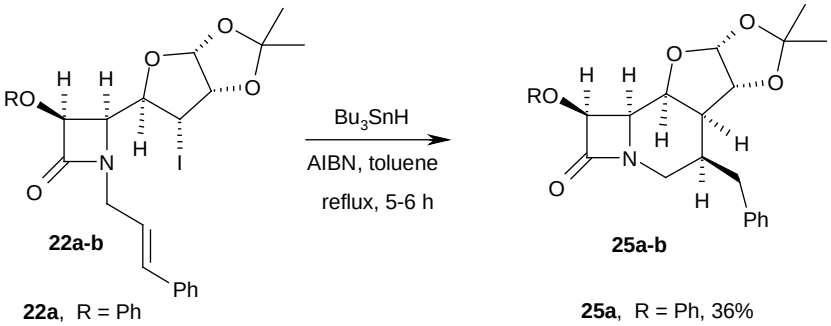
24a, R = Bn, 26%
24b, R = Me, 28%

The treatment of β-lactams **20d-e** with 1.5 equivalent of Bu_3SnH in the presence of catalytic amount of AIBN in refluxing toluene gave a complex reaction mixture and we were able to isolate the 6-*exo trig* annulated tricyclic β-lactams **24a-b** in 26 and 28 % yield respectively. The benzocarbacepham derivatives have been characterized by IR and NMR analysis.

Radical cyclization of 22a-b:

Similarly, we have utilized glucose derived *N*1-cinnamyl azetidin-2-ones **22-23** to prepare optically pure polycyclic β-lactams. The α-diastereomers **22a-b** were heated in toluene followed by a slow addition of a solution of 1.5 equivalent of tributyltin hydride and catalytic amount of AIBN in toluene over a period of 2-3 h. The reaction mixture was then heated for additional 3-4 h. The crude NMR of the reaction mixture of **22a** showed a formation of a single diastereomer of cyclized product along with some impurities. The cyclized product which was obtained as a solid was not pure even after flash column chromatography. It was then purified by crystallization with ethanol to give a pure pale yellow solid **25a** in 36% yield.

Scheme 5



22a-b

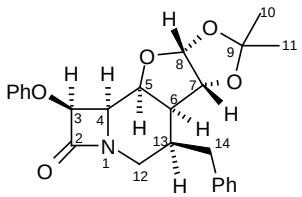
22a, R = Ph
22b, R = Bn

25a-b

25a, R = Ph, 36%
25b, R = Bn, 28%

The IR spectrum of the cyclized product **25a** gave a strong band at 1763 cm^{-1} indicating the presence of carbonyl group of β-lactam. In the ^1H NMR spectrum, two singlets at 1.37 and 1.43 ppm were assigned for methyl protons of acetonide moiety. The H-13 proton appeared as a multiplet at 2.31-2.43 ppm and a multiplet at 2.54-2.87 ppm integrated for four protons correspond to H-6, one of the nitrogen attached methylene proton H-12 and H-14 protons.

The other nitrogen methylene proton was seen as a doublet of doublet at 3.51 ppm (J = 5.5, 13.3 Hz). The β-lactam proton H-4 gave a triplet at 3.90 ppm (J = 3.9 Hz). The proton H-5 and H-7 were seen as a multiplet at 4.76-4.84 ppm. The tw



25a

doublets at 5.31 ppm (J = 3.9 Hz) and 5.91 ppm (J = 3.9 Hz) were assigned for the β-lactam protons H-3 and anomeric proton H-8 respectively. The aromatic protons appeared in the region between 7.01-7.35 ppm.

The COSY spectrum of the cyclized product **25a** also supported the above assignments (Figure 3). The anomeric proton H-8 showed a strong interaction with H-7 proton, which in turn was related to the H-6 proton. Further, the H-6 proton correlated with H-5 and H-13 protons. H-13 proton showed connectivity with both benzylic protons and *N*CH_2 protons. The H-4 proton showed a strong interaction with H-3 proton.

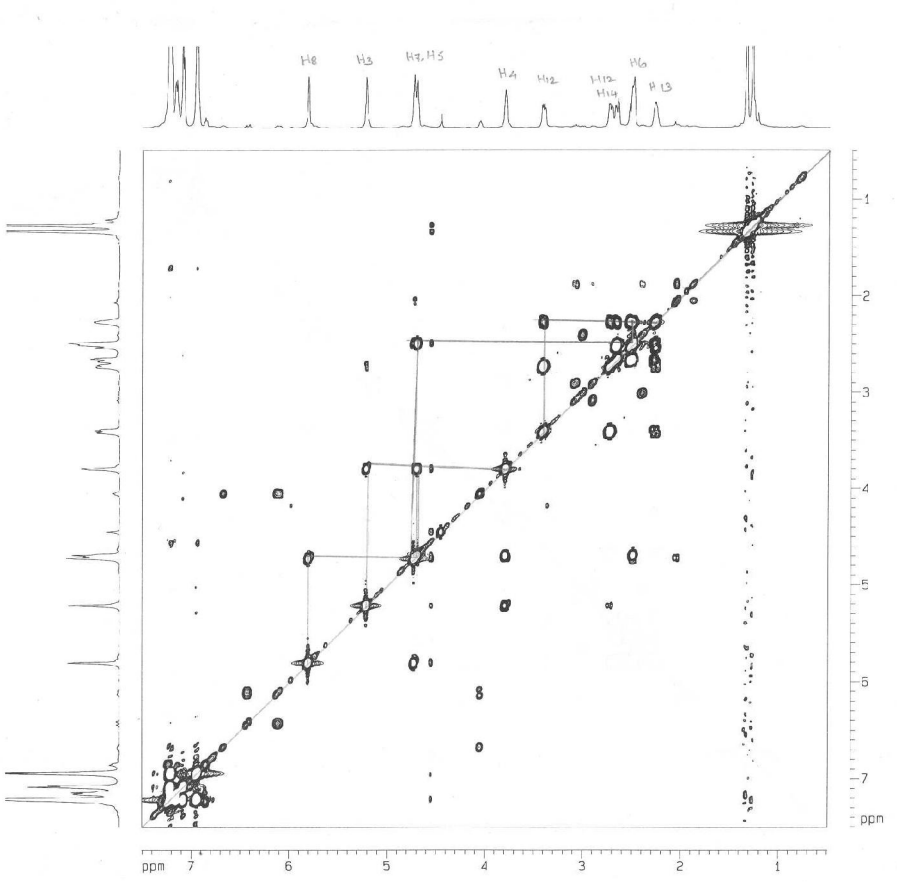


Figure 3. COSY NMR spectrum of **25a**

Table 4: Important connectivities in the COSY spectrum of 25a

proton	ppm	^{1}H-^{1}H connectivity
	5.91	H-7
H-8	4.76-4.84	H-6, H-8
H-7	2.54-2.87	H-7, H-13, H-5
H-6	4.76-4.84	H-6
H-5	3.90	H-3
H-4	2.31-2.43	H-6, H-12, H-14
H-13		

The probable stereochemistry of cyclized product **25a** was assigned from the NOESY spectrum (Figure 4). The H-5 proton showed spatial connectivity with H-6. The H-6 proton further showed spatial connectivity with H-13. This confirmed the same spatial alignment of α-oriented H-5 proton with H-6 and H-13 protons.

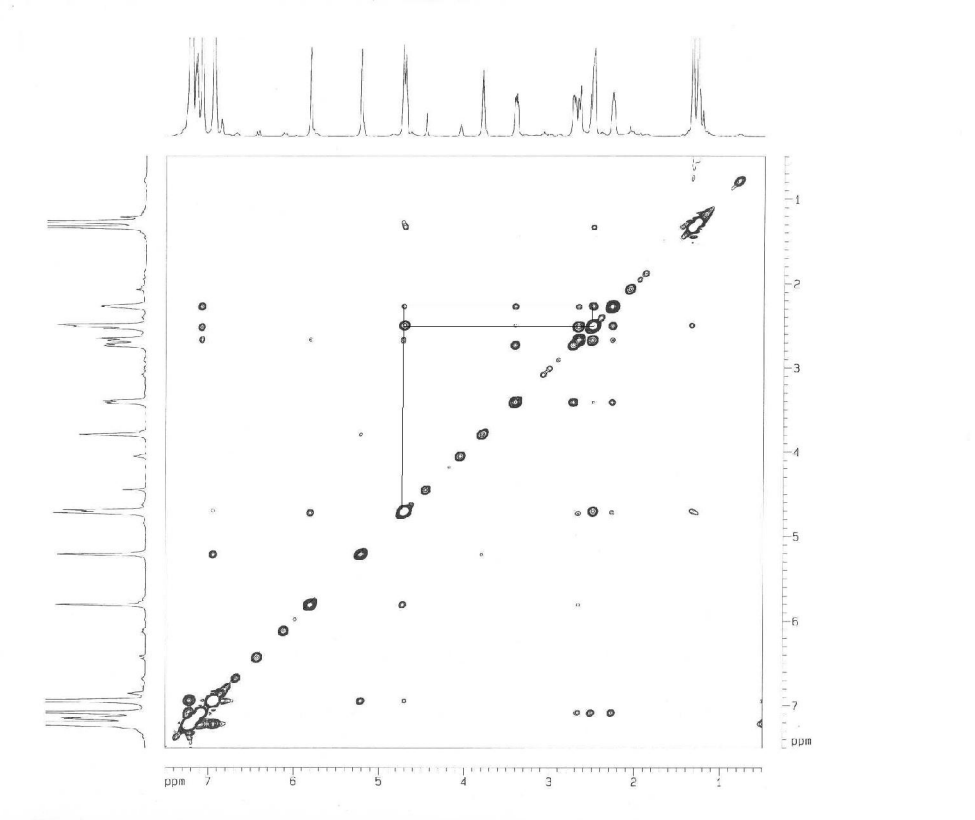


Figure 4. NOESY NMR spectrum of **25a**

In the ^{13}C NMR, the carbonyl carbon appeared at 165.7 ppm. The acetonide methyl carbons, C-6, *N*CH_2 and benzylic CH_2 carbons appeared at 35.5, 37.3 and 39.1 ppm correspondingly. The β-lactam carbon C-4 and C-3 appeared at 55.0 and 72.5 ppm. The chiral backbone C-7, C-5 and C-8 appeared at 81.3, 82.0 and 106.5 ppm respectively. The C-13 carbon was seen at 47.5 ppm whereas the aromatic carbons were observed in the

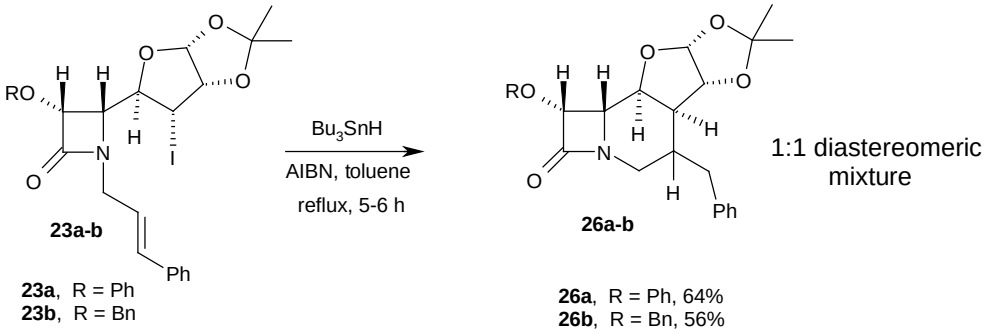
region of 122.5-157.0 ppm. In the ^{13}C-DEPT experiment, *N*CH_2 and benzylic methylene peaks appeared below at 37.3 and 39.1 ppm confirming the *exo-trig* mode of cyclization with the alpha diastereomer **22a**.

Similarly, benzyloxy substituted *N*1-cinnamyl β-lactam **22b** also gave *6-exo-trig* annulation product **25b** under similar reaction conditions in 28% yield and was characterized by NMR spectral analysis.

Radical cyclization of beta-diastereomers 23a-b:

The other diastereomers **23a-b** were treated with tributyltin hydride in the presence of catalytic amount of AIBN in refluxing toluene for 4-6 h. The crude reaction mixture showed the formation of a diastereomeric mixture of cyclized products in nearly 1:1 ratio. Column purification of the crude reaction mixture gave an inseparable diastereomeric mixture of *6-exo-trig* addition products **26a-b** in 64% and 56% yield correspondingly (Scheme 6).

Scheme 6

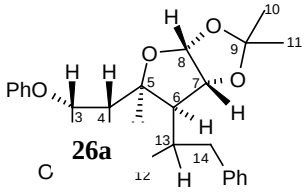


23a, R = Ph
23b, R = Bn

26a, R = Ph, 64%
26b, R = Bn, 56%

Attempts to separate the diastereomers **26a-b** by recrystallization with methanol, DCM-petroleum ether and petroleum ether-acetone were unsuccessful. The diasteromeric mixture of β-lactams **26a** showed a strong band at 1763 cm^{-1} for the β-lactam carbonyl group.

The ^{1}H NMR spectrum of the mixture **26a** showed singlets for acetonide methyl protons in the region of 1.28-1.3 ppm. The H-13 proton appeared as a doublet of doublet ar multiplet at 2.04 and 2.28-2.30 ppm. The H-14 protons were see as multiplets at 2.32-2.64 ppm along with H-6 proton and also 2.75-2.95 ppm.



26a

The doublet at 3.06 ppm (J = 8.0 Hz) and a multi assigned for H-12 protons along with β-lactam proton H-4. The triplet at 4.23 (J = 3.9 Hz) was attributed to the presence of the β-lactam proton H-4 of the other isomer. The H-5 protons were seen as doublets at 4.53 (J = 3.9 Hz) and 4.60 ppm (J = 5.8 Hz). The β-lactam protons H-3 of the two isomers appeared as two doublets at 4.76 ppm (J = 3.9 Hz) and 5.30 (J = 3.9 Hz). The H-7 and anomeric H-8 protons were seen as doublets in the region of 5.39-5.93 ppm. Aromatic protons appeared in the region of 6.99-7.32 ppm.

The ^{13}C NMR spectrum of the diastereomeric mixture **26a** showed peaks at 163.9 and 168.2 indicating the presence of carbonyl carbons of two isomers. The acetonide methyl carbons, *N*CH_2, benzylic CH_2 carbons appeared in the region of 26.1-38.3 ppm. The C-6, C-4, C-3, benzyloxy CH_2 carbon and C-13 carbons were seen in the region of 40.2-79.5 ppm.

The chiral backbone C-5, C-7, C-8, C-9 carbons appeared in the region of 80.8-115.6 ppm. The aromatic carbons were seen in the region of 122.0-157.6 ppm.

The appearance of four methylene carbons below in the ^{13}C-DEPT experiment of this mixture gave evidence for the 6-*exo-trig* mode of radical cyclization with beta-diastereomers **23a**.

The *exo-trig* selectivity with *N*1-cinnamyl β-lactams in all the above mentioned cyclization may be attributed to the formation of stable benzyl radical due to *capto dative* effect. The reason for the observed diastereoselectivity is not clear. The possible explanation could be that in the alpha diastereomers **22a-b**, the proximity of the acetonide moiety to the reaction site makes the radical attack the double bond from only one side, leading to the formation of a single diasteromer of carbacepham kind of derivatives **25a-b**. This also explains the low yield of cyclized products. On the contrary, the acetonide moiety in the beta isomer **23a-b** is far away from the reaction site thus giving a 1:1 mixture of diasteromers **26a-b** in moderate yield.

Conclusion:

A simple one-pot methodology for the synthesis of various substituted allyl azides was developed from the commercially available allyl alcohols using triphosgene and sodium azide. The prepared allylic azides were used for the synthesis of various *N*1-cinnamyl substituted β-lactams in good to excellent yields. Bromobenzaldehyde imine derived *N*1-cinnamyl β-lactams gave benzocarbacephams by *6-exo-trig* mode of cyclization. The alpha diastereomers of glucose derived *N*1-cinnamyl β-lactams underwent cyclization through *exo-trig* addition and gave a single diastereomer, while beta-diasteromers furnished a diasteromeric mixture of *exo* cyclized products.

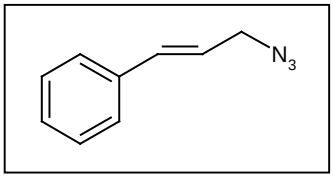
EXPERIMENTAL SECTION

General procedure for the preparation of allyl azides:

A solution of a mixture of allyl alcohol (10.00 mmol) and triethylamine (12.00 mmol) was prepared in dry acetone (25 mL) and added slowly to a solution of triphosgene (5.00 mmol) in acetone (15 mL) at 0 °C and stirred for 1 h at 0 °C and 3 h at room temperature. Sodium azide (15.00 mmol) was then added to the

reaction mixture at 0 °C and stirred at room temperature overnight. The solvent was distilled off under reduced pressure and the residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$, H_2O and brine. The organic layer was dried over sodium sulphate, concentrated *in vacuo* and the crude material was column chromatographed to give allyl azides in good to excellent yields.

[(1E)-3-Azidoprop-1-enyl]benzene (2):



Following the general procedure given above, cinnamyl alcohol (1) (2.68 g, 20.00 mmol) was reacted with triethylamine (3.3 mL, 24.00 mmol) and triphosgene

(2.96 g, 10.00 mmol) followed by addition of sodium azide (1.95 g, 30.00 mmol) to obtain cinnamyl azide (2) in 80% yield (2.56 g) as a yellow oil after silica gel column chromatography using petroleum ether as an eluent (100-200 mesh).

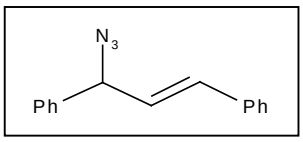
yellow oil

IR ($CHCl_3$): ν_{max} **2100 cm^{-1}**

^{1}H NMR (500 MHz, $CDCl_3$): δ **3.86 (d, *J* 6.4 Hz, 2H, C*H*$_2$N$_3$), 6.13-6.19 (m, 1H, PhCH=C*H*), 6.57 (d, *J* 16.0 Hz, 1H, PhC*H*=CH), 7.17-7.33 (m, 5H, *aromatic*)**

^{13}C NMR (125 MHz, $CDCl_3$): δ **52.7, 122.2, 126.4, 128.0, 128.4, 134.2**

[(1E)-3-Azido-3-phenylprop-1-enyl]benzene (4):



Phenyl substituted cinnamyl alcohol 3 **was prepared *via* Grignard addition of PhMgBr to cinnamaldehyde. Following the general procedure, alcohol** 3 **(0.63 g, 3.00 mmol) on treatment with Et_3N (0.5 mL, 3.60 mmol) and triphosgene (0.445 g, 1.50 mmol) followed by addition of NaN_3 (0.292 g, 4.50 mmol) and purification by column chromatography using 2-3% acetone-petroleum ether (100-200 mesh) furnished the corresponding allyl azide** 4 **in 90% yield (0.634 g) as a yellow liquid.**

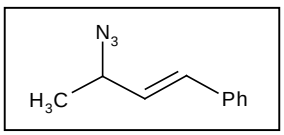
yellow liquid

IR (Neat): ν_{max} 2098 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.17 (d, *J* 7.4 Hz, 1H, C*H*N_3), 6.27 (dd, *J* 7.0, 15.6 Hz, 1H, CH=C*H*CHN_3), 6.69 (d, *J* 15.7 Hz, 1H, Ph-C*H*=CH), 7.25-7.40 (m, 10H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 68.0, 127.6, 127.9, 129.0, 129.5, 129.7, 133.7

[(1E)-3-Azidobut-1-enyl]benzene (6):



Phenyl substituted crotyl alcohol **5** was prepared via Grignard addition of PhMgBr to crotonaldehyde. Following the general procedure, alcohol **5** (0.444 g, 3.00 mmol) was treated with Et_3N (0.5 mL, 3.60 mmol) and triphosgene (0.445 g, 1.50 mmol) and then with

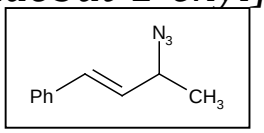
sodium azide (0.292 g, 4.50 mmol) to obtain the corresponding azide **6** in 66% yield (0.340 g) as a colourless oil after purification by column chromatography (100-200 mesh, 2-3% acetone-petroleum ether).

IR ($CHCl_3$): ν_{max} 2104 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 4.12-4.25 (m, 1H, C*H*N_3), 6.16 (dd, *J* 7.4, 15.6 Hz, 1H, CH=C*H*CHN_3), 6.62 (d, *J* 16.0 Hz, 1H, C*H*=CHCHN_3), 7.26-7.44 (m, 5H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.0, 59.5, 126.5, 127.9, 128.2, 128.5, 132.0, 135.9

[(1E)-3-Azidobut-1-enyl]benzene (6):



Methyl substituted cinnamyl alcohol 7 **was prepared *via* Grignard addition of CH_3MgBr to cinnamaldehyde. Following the general procedure, alcohol** 7 **(0.444 g, 3.00 mmol) on treatment with Et_3N (0.5 mL, 3.60 mmol) and triphosgene (0.445 g, 1.50 mmol) followed by addition of NaN_3 (0.292 g, 4.50 mmol) furnished the corresponding allyl azide** 6 **in 60% yield (0.310 g) upon column chromatographic purification using 2-3% acetone-petroleum ether (100-200 mesh).**

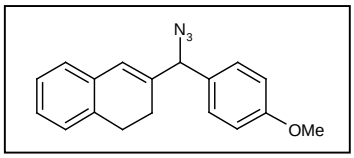
colourless liquid

IR ($CHCl_3$): ν_{max} 2104 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 4.12-4.25 (m, 1H, C*H*N_3), 6.16 (dd, *J* 7.4, 15.6 Hz, 1H, CH=C*H*CHN_3), 6.62 (d, *J* 16.0 Hz, 1H, C*H*=$CHCHN_3$), 7.26-7.44 (m, 5H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.0, 59.5, 126.5, 127.9, 128.2, 128.5, 132.0, 135.9

3-Azido(4-anisyl]-1,2-dihydronaphthalene (9):



Tetralone alcohol 8 **was prepared according to Luche's method for the reduction of α, β-unsaturated carbonyl compounds from the corresponding ketone.**[47] **Following the general procedure, tetralone alcohol** 8 **(0.251 g, 1.00 mmol) on reaction with Et_3N (0.17 mL, 1.20 mmol) and triphosgene (0.148 g, 0.50 mmol) followed by addition of NaN_3 (0.097 g, 1.50 mmol) afforded allyl azide** 9 **in 91% yield (0.252 g) after column chromatographic**

purification of the crude material (100-200 mesh, 2-3% acetone-petroleum ether).

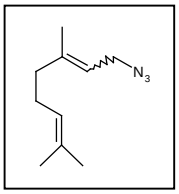
colourless liquid

IR ($CHCl_3$): ν_{max} 2098 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03-2.26 (m, 2H, C*H*$_2$), 2.37 (s, 3H, C*H*$_3$), 2.79 (t, *J* 8.0 Hz, 2H, C*H*$_2$CH$_2$), 5.21 (s, 1H, C*H*N$_3$), 6.67 (s, 1H, C=C*H*), 7.13-7.29 (m, 8H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 24.1, 27.8, 69.9, 125.3, 126.6, 127.2, 127.4, 129.3, 133.5, 134.4, 135.0, 137.9

1-Azido-3,7-dimethylocta-2,6-diene (11):



Applying the general procedure for azide preparation, geraniol (10**) (1.0 g, 6.50 mmol) was treated with triethylamine (1.08 mL, 7.80 mmol) and triphosgene (0.96 g, 3.20 mmol) at 0 °C. Sodium azide (0.632 g, 9.72**

mmol) was then added at 0 °C and the reaction mixture was stirred at room temperature overnight. Usual work up and column purification of the crude material provided a *E-Z* geometrical mixture (1:1) of geraniol azide (11**) in 66% yield (0.77 g).**

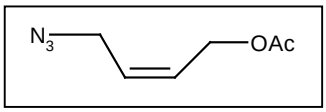
colourless liquid

IR ($CHCl_3$): ν_{max} **2100 cm^{-1}**

^{1}H NMR (200 MHz, $CDCl_3$): δ **1.58 (s, 3H, C*H*$_3$), 1.62 (s, 6H, *gem methyl*), 1.71 (s, 6H, *gem methyl*), 1.81 (s, 3H, C*H*$_3$), 2.11 (s, 4H, C*H*$_2$C*H*$_2$), 3.74-3.80 (m, 2H, C*H*$_2$N$_3$), 5.04 (bs, 1H, C*H*CH$_2$CH$_2$), 5.28-5.38 (m, 1H, C*H*CH$_2$N$_3$)**

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0, 17.5, 17.6, 23.2, 23.6, 25.5, 25.6, 26.3, 32.0, 39.4, 40.0, 47.9, 114.5, 117.0, 117.9, 123.4, 123.5, 132.3, 140.0, 142.9, 143.0, 149.3

(2Z)-4-Azidobut-2-enyl acetate (15):



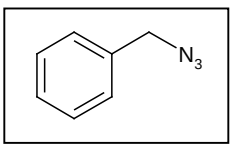
Monoacetate of 1,4-butenediol 14 **was prepared according to the reported procedure using one equivalent of acetic anhydride.**[48] **Following the general procedure, monoacetate** 14 **(0.39 g, 3.00 mmol) on treatment with** Et_3N **(0.5 mL, 3.60 mmol) and triphosgene (0.445 g, 1.50 mmol) followed by addition of** NaN_3 **(0.292 g, 4.50 mmol) furnished the corresponding allyl azide** 15 **in 63% yield (0.294 g) as a yellow liquid after column chromatography using 2-3% acetone-petroleum ether (100-200 mesh).**

IR **(**$CHCl_3$**):** ν_{max} **2172, 1738 cm^{-1}**

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.06 (s, 3H, C*H*$_3$), 4.67 (d, *J* 6.0 Hz, 2H, C*H*$_2$), 4.80 (d, *J* 6.0 Hz, 2H, C*H*$_2$OAc), 5.69-5.88 (m, 2H, C*H*=C*H*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 59.4, 63.3, 126.1, 129.1, 170.2

(Azidomethyl)benzene (17):



Following the general procedure, 16 **(2.16 g, 20.00 mmol) was converted to** 17 **by treating it with triethylamine (3.3 mL, 24.00 mmol) and triphosgene (2.97 g, 10.00 mmol) and then with sodium azide (1.95 g, 30.00 mmol) in 64% yield (1.69 g) after column chromatography with petroleum ether as an eluent (100-200 mesh).**

colourless liquid

IR ($CHCl_3$): ν_{max} 2096 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.33 (s, 2H, CH_2N_3), 7.24-7.44 (m, 5H, *aromatic*).

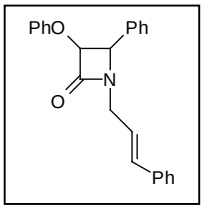
^{13}C NMR (50 MHz, $CDCl_3$)**: δ 55.05, 128.6, 129.1, 135.6.**

General procedure for the synthesis of N1-cinnamyl β-lactams:

To a solution of cinnamyl azide (**2**) (2.00 mmol) in toluene (20 mL), an equivalent quantity of triphenylphosphine was added and the reaction mixture was heated under reflux for 5-6 h. The reaction mixture was then cooled to 0 °C and a solution of aldehyde (2.00 mmol) was added and stirred at room temperature overnight. The solvent was distilled off under reduced pressure and the residue was dissolved in dichloromethane (20 mL). Triethylamine (4.5 equiv. with respect to cinnamyl azide assuming 100% conversion of azide to amine) was added to the mixture and cooled to –15 °C. A solution of

phenoxyacetyl chloride (1.5 equiv. with respect to cinnamyl azide) in dichloromethane (10 mL) was added slowly to the reaction mixture. It was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then washed with aqueous $NaHCO_3$, H_2O and brine, dried over sodium sulphate and concentrated *in vacuo*. In most of the cases, addition of methanol to the crude product gave β-lactam as a solid, which was then filtered, dried and characterized by analytical methods.

3-Phenoxy-4-phenyl-1-(3-phenyl-allyl)-azetidin-2-one (20a):



Following the optimized general procedure, a solution of mixture of imine and Ph_3PO in DCM (20 mL), obtained from the reaction of iminophosphorane **18** (from 0.321 g, 2.00 mmol of cinnamyl azide **2**) with benzaldehyde (0.2 mL, 2.00 mmol), was treated with triethylamine (1.25 mL, 9.00 mmol) and phenoxyacetyl chloride (0.42 mL, 3.04 mmol) at -15 °C. A white crystalline solid of **20a** was obtained after the addition of methanol to the crude material in 84% yield (0.604 g).

white solid; mp 160-162 °C

IR ($CHCl_3$): ν_{max} 1757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.66 (dd, *J* 7.7, 15.0 Hz, 1H, NCH_aH_b), 4.41 (dd, *J* 5.5 Hz, 15.0 Hz, 1H, NCH_aH_b), 4.99 (d, *J* 4.5 Hz, 1H, PhOCHC*H*), 5.48 (d, *J* 4.5 Hz, 1H, PhOC*H*), 6.03-6.13 (m, 1H, CH_2C*H*=CH), 6.43 (d, *J* 15.5 Hz, 1H, CH=C*H*Ph), 6.73-7.33 (m, 15H, *aromatic*)

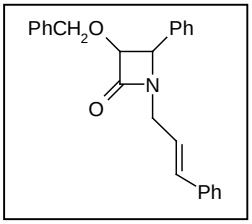
^{13}C NMR (125 MHz, $CDCl_3$): δ 42.3, 61.7, 81.9, 115.5, 121.8, 126.4, 127.9, 128.2, 129.1, 132.9, 134.9, 136.0, 156.8, 165.5

MS: *m/z* = 356 (M+1)

Anal. **Calcd**. for **$C_{24}H_{21}NO_2$**: C, 81.1 %; H, 5.96 %; N, 3.94 %

Found: C, 80.9 %; H, 6.01 %: N, 3.96 %

3-Benzyloxy-4-phenyl-1-(3-phenyl-allyl)-azetidin-2-one (20b):



Following the optimized general procedure, iminophosphorane **18** obtained from cinnamyl azide (0.333 g, 2.10 mmol) and PPh_3 (0.548 g, 2.10 mmol) was reacted with a solution of benzaldehyde (0.2 mL, 2.10 mmol) and then with Et_3N (1.3 mL, 9.40 mmol) and benzyloxyacetyl chloride (0.5 mL, 3.20 mmol). Column purification of the crude material (100-200 mesh, 14-15% acetone-petroleum ether) yielded **20b** as a white solid in 74% yield (0.570 g)

white solid; mp 140-141 °C

IR ($CHCl_3$): ν_{max} 1751 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (dd, *J* 7.8, 15.1 Hz, 1H, NC*H*$_a$H$_b$), 4.15-4.21 (m, 3H, OC*H*$_a$*H*$_b$ & NCH$_a$*H*$_b$), 4.79 (d, *J* 4.4 Hz, 1H, BnOCHC*H*), 4.92 (d, *J* 4.4 Hz, 1H, BnOC*H*), 5.96-6.11 (m, 1H, CH_2C*H*=CH), 6.39 (d, *J* 15.6 Hz, 1H, CH_2CH=C*H*), 6.94-7.40 (m, 15H, *aromatic*)

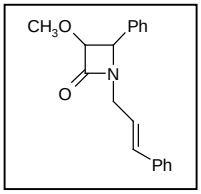
^{13}C NMR (125 MHz, $CDCl_3$): δ 42.1, 61.6, 72.1, 83.6, 122.1, 126.3, 127.7, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 134.2, 136.1, 136.3, 166.7

MS: *m/z* = 370 (M+1)

Anal. **Calcd**. for **$C_{25}H_{23}NO_2$**: C, 81.26 %; H, 6.28 %; N, 3.79 %

Found: C, 81.12 %; H, 6.35 %; N, 3.91 %

3-Methoxy-4-phenyl-1-(3-phenyl-allyl)-azetidin-2-one (20c):



According to the general procedure, a solution of mixture of imine and Ph_3PO, obtained upon reaction of cinnamyl azide (0.310 g, 1.95 mmol) with triphenylphosphine and benzaldehyde (0.2 mL, 2.00 mmol), was treated with Et_3N (1.2 mL, 8.63 mmol) and methoxyacetyl chloride (0.27 mL, 2.97 mmol) to provide **20c** as a pale yellow solid (0.480 g, 84%) after silica gel column chromatography (100-200 mesh, 14-15% acetone-petroleum ether).

yellow solid; mp 90-92 °C

IR ($CHCl_3$): ν_{max} 1755 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.04 (s, 3H, O*CH*$_3$), 3.51 (dd, *J* 7.8, 15.1 Hz, 1H, NC*H*$_a$H$_b$), 4.24 (dd, *J* 4.6, 15.1 Hz, 1H, NCH$_a$*H*$_b$), 4.64 (d, *J* 4.6 Hz, 1H, CH_3OCHCH), 4.70 (d, *J* 4.6 Hz, 1H, CH_3OCH), 5.92-5.97 (m, 1H, CH_2CH=CH), 6.28 (d, *J* 16.1 Hz, 1H, CH=C*H*Ph), 7.15-7.32 (m, 10H, *aromatic*)

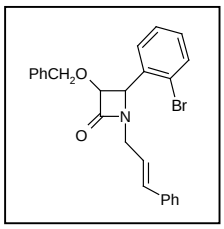
^{13}C NMR (125 MHz, $CDCl_3$): δ 41.9, 57.8, 61.2, 85.5, 121.9, 126.2, 127.7, 128.2, 128.3, 133.6, 134.0, 135.9, 166.6

MS: *m/z* = 294 (M+1)

Anal. **Cad**. for **$C_{19}H_{19}NO_2$** : C, 77.78 %; H, 6.53 %; N, 4.78 %

Found: C, 77.59 %; H, 6.43 %; N, 4.67 %

3-Benzyloxy-4-(2-bromo-phenyl)-1-(3-phenyl-allyl)-azetidin-2-one (20d):



Following the general procedure, iminophosphorane **18** obtained from cinnamyl azide (0.317 g, 1.99 mmol) was subjected to the aza-Wittig reaction with 2-bromobenzaldehyde (0.23 mL, 1.97 mmol) followed by treatment with Et_3N (1.24 mL, 8.92 mmol) and benzyloxyacetyl chloride (0.47 mL, 2.99 mmol) at –15 °C to precipitate a white crystalline solid of **20d** in 72% yield (0.640 g) after the addition of methanol to the crude material.

white solid; mp 120-122 °C

IR ($CHCl_3$): ν_{max} 1758 cm^{-1}

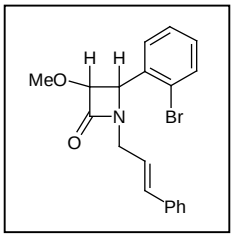
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (dd, *J* 7.4, 15.1 Hz, 1H, NC*H*$_a$H$_b$), 4.22-4.31 (m, 3H, OC*H*$_2$, NCH$_a$*H*$_b$), 4.90 (d, *J* 4.6 Hz, 1H, BnOCHC*H*), 5.20 (d, *J* 4.6 Hz, 1H, BnOC*H*), 5.96-6.02 (m, 1H, CH_2C*H*=CH), 6.36 (d, *J* 15.6 Hz, 1H, CH_2CH=C*H*), 6.90-7.52 (m, 14H, *aromatic*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 42.5, 60.9, 72.4, 83.5, 121.7, 123.7, 126.3, 127.3, 127.7, 127.9, 128.1, 128.4, 129.4, 129.6, 132.8, 134.5, 136.0, 166.6

Anal. Calcd. for **$C_{25}H_{22}NO_2Br$**: C, 67.10 %; H, 4.96 %; N, 3.13 %

Found: C, 67.12 %; H, 4.83 %; N, 3.03 %

4-(2-bromo-phenyl)-3-methoxy-1-(3-phenyl-allyl)-azetidin-2-one (20e):



Adopting the general procedure, a solution of mixture of cinnamyl imine of 2-bromobenzaldehyde (0.304 g, 1.90 mmol of cinnamyl azide) and Ph_3PO in DCM (20 mL), was reacted with Et_3N (1.2 mL, 8.63 mmol) and methoxyacetyl chloride (0.26 mL, 2.86 mmol) to give **20e** as a thick oil in 82% yield (0.580 g) after column purification using 4-6% acetone - petroleum ether mixture (100-200 mesh).

thick oil

IR ($CHCl_3$): ν_{max} 1755 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.21 (s, 3H, OC*H*$_3$), 3.66 (dd, *J* 7.4, 16.1 Hz, 1H, NC*H*$_a$H$_b$), 4.39 (dd, *J* 5.9, 16.1 Hz, 1H, NCH$_a$*H*$_b$), 4.81 (d, *J* 4.7 Hz, 1H, CH_3OCHC*H*),

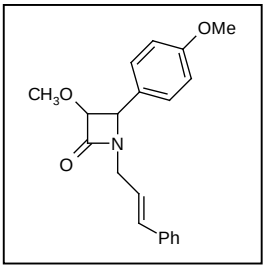
5.27 (d, *J* 4.7 Hz, 1H, CH_3OCH), 6.01-6.16 (m, 1H, NCH_2CH=CHPh), 6.46 (d, *J* 15.6 Hz, 1H, NCH_2CH=C*H*Ph), 7.21-7.61 (m, 9H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 42.5, 58.7, 60.8, 85.8, 121.7, 126.4, 127.3, 128.0, 128.5, 129.1, 129.6, 132.8, 133.3, 134.6, 135.9, 166.8

Anal. **Calcd**. for **$C_{19}H_{18}NO_2Br$**: C, 61.45 %; H, 4.89 %; N, 3.77 %

Found: C, 61.32 %; H, 5.00 %; N, 3.82 %

3-Methoxy-4-(4-anisyl)-1-(3-phenyl-allyl)-azetidin-2-one (20f):



Applying the general procedure, iminophosphorane **18**, obtained from cinnamyl azide (0.341 g, 2.14 mmol) and PPh_3, was treated with *p*-anisaldehyde (0.26 mL, 2.16 mmol) followed by addition of Et_3N (1.33 mL, 9.57 mmol) and methoxyacetyl chloride (0.29 mL, 3.19 mmol). The compound **20f** (0.423 g, 61%) was crystallized out from the crude material by the addition of methanol under ice-cold condition.

white solid; mp 122-123 °C

IR ($CHCl_3$): ν_{max} 1753 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.05 (s, 3H, OCH_3), 3.48 (dd, *J* 7.8, 15.1 Hz, 1H, NCH_aH_b), 3.73 (s, 3H, Ar-OCH_3), 4.19 (dd, *J* 6.0, 15.1 Hz, 1H, NCH_aH_b), 4.59 (d, *J* 4.2 Hz, 1H, MeOCHCH), 4.64 (d, *J* 4.2 Hz, 1H, MeOCH), 5.90-5.96 (m, 1H, NCH_2CH=CHPh), 6.28 (d, *J* 16.1 Hz, 1H, CH=C*H*Ph), 6.82-7.21 (m, 9H, *aromatic*)

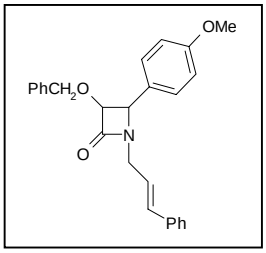
^{13}C NMR (125 MHz, $CDCl_3$): δ 41.8, 55.1, 57.9, 60.8, 85.5, 113.7, 122.2, 126.3, 127.8, 128.4, 129.6, 134.0, 136.1, 159.8, 166.7

MS: *m/z* = 324 (M+1)

Anal. **Calcd**. for **$C_{20}H_{21}NO_3$:** C, 74.27 %; H, 6.55 %; N, 4.33 %.

Found: C, 74.38 %; H, 6.71 %; N, 4.50 %.

3-Benzyloxy-4-(4-anisyl)-1-(3-phenyl-allyl)-azetidin-2-one (20g):



In accordance with the general procedure, iminophosphorane **18**, derived from cinnamyl azide (0.309 g, 1.94 mmol) and PPh_3 (0.508 g, 1.94 mmol), was reacted with *p*-anisaldehyde (0.24 mL, 1.97 mmol) and then with Et_3N (1.21 mL, 8.70 mmol) and benzyloxyacetyl chloride (0.46 mL, 2.91 mmol) to afford **20g** as a white solid in 78% yield (0.604 g) after crystallization of the crude material from methanol.

white solid; mp 119-120 °C

IR ($CHCl_3$): ν_{max} 1735 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.49 (dd, *J* 7.6, 15.2 Hz, 1H, NC*H*$_a$H$_b$), 3.74 (s, 3H, OC*H*$_3$), 4.12-4.24 (m, 3H, NCH$_a$*H*$_b$ & OC*H*$_2$), 4.64 (d, *J* 4.1 Hz, 1H, BnOCHC*H*), 4.78 (d, *J* 4.1 Hz, 1H, BnOC*H*), 5.90-5.94 (m, 1H, CH_2C*H*=CHPh), 6.28 (d, *J* 16.0 Hz, 1H, CH=C*H*Ph), 6.83-7.22 (m, 14 H, *aromatic*)

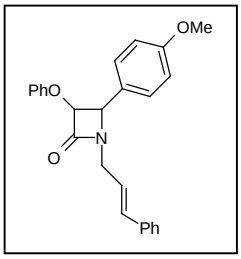
^{13}C NMR (125 MHz, $CDCl_3$): δ 41.9, 55.2, 61.1, 72.1, 83.4, 113.8, 122.2, 126.3, 127.7, 127.8, 128.1, 128.5, 129.8, 134.1, 136.1, 136.4, 159.9, 166.7

MS: *m/z* = 400 (M+1)

Anal. Calcd. for **$C_{26}H_{25}NO_3$**: C, 78.16 %; H, 6.31 %; N, 3.51 %

Found: C, 78.32 %; H, 6.21 %; N, 3.62 %

3-Phenoxy-4-(4-anisyl)-1-(3-phenyl-allyl)-azetidin-2-one (20h):



By adopting the general procedure, iminophosphorane **18** (from 0.307 g of cinnamyl azide, 1.93 mmol) on reaction with *p*-anisaldehyde (0.24 mL, 1.98 mmol) gave a mixture of the corresponding imine and Ph_3PO. This imine mixture was then reacted with Et_3N (1.2

ml, 8.63 mmol) and phenoxyacetyl chloride (0.4 mL, 2.90 mmol) to precipitate **20h** as a white solid in 69% yield (0.510 g) after the addition of methanol to the crude material.

white solid; mp 136-137 °C

IR ($CHCl_3$): ν_{max} 1757 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.56 (dd, *J* 7.9, 15.1 Hz, 1H, NC*H*$_a$H$_b$), 3.69 (s, 3H, OC*H*$_3$), 4.30 (dd, *J* 4.9, 15.2 Hz, 1H, NCH$_a$*H*$_b$), 4.87 (d, *J* 4.4 Hz, 1H, PhOCHC*H*), 5.36 (d, *J* 4.4 Hz, 1H, PhOC*H*), 5.96-6.02 (m, 1H, C*H*=CHPh), 6.34 (d, *J* 15.7 Hz, 1H, CH=C*H*Ph), 6.67-7.24 (m, 14H, *aromatic*)

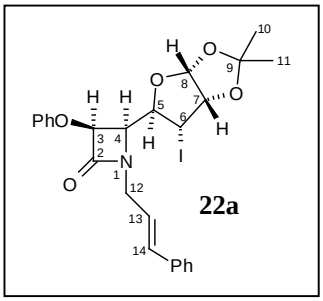
^{13}C NMR (125 MHz, $CDCl_3$): δ 42.1, 55.1, 61.3, 82.0, 113.7, 115.5, 121.8, 126.3, 127.9, 128.5, 129.9, 134.3, 136.0, 156.9, 159.8, 165.5

MS: *m/z* = 386 (M+1)

Anal Calcd. for **$C_{25}H_{23}NO_3$**: C, 77.89 %; H, 6.02 %; N, 3.64 %

Found: C, 77.78 %; H, 5.82 %; N, 3.72 %

To a solution of cinnamyl azide (**2**) (0.3 g, 1.88 mmol) in toluene (20 mL), PPh_3 (0.493 g, 1.88 mmol) was added and the mixture was heated under reflux for 4 h. The reaction mixture was then cooled to 0 °C and a solution of iodoaldehyde (0.560 g, 1.88 mmol) derived from D-glucose in toluene and benzene mixture (4:1, 25 mL) was added and stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (20 mL). Triethylamine (0.87 g. 8.63 mmol) was added to the mixture and cooled to -15 °C. A solution of phenoxyacetyl chloride (0.48 g, 2.82 mmol) in methylene chloride (10 mL) was added slowly to the reaction mixture. It was then allowed to stir overnight at room temperature. Usual work-up gave a 1:1 diastereomeric mixture of β-lactams **22a** and **23a** (0.740 g, 72%), which were then separated by flash chromatography using 10% acetone-petroleum ether.



22a

white solid; mp 112-113 °C

$[\alpha]_D^{25}$ = +118.17 (*c* 0.69, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1763 cm^{-1}

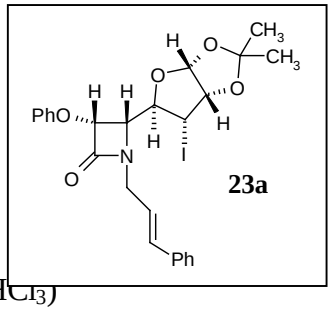
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 6H, 2xCH_3), 4.11-4.13 (3H, m, *H-12* & *H-6*), 4.24 (dd, *J* 2.7, 4.1 Hz, 1H, *H-4*), 4.60 (t, *J* 3.7 Hz, 1H, *H-7*), 4.66 (dd, *J* 2.7, 2.8 Hz, 1H, *H-5*), 5.35 (d, *J* 4.1 Hz, 1H, *H-3*), 5.89 (d, *J* 3.7 Hz, 1H, *H-8*), 6.19-6.25 (m, 1H, *H-13*), 6.63 (d, *J* 15.6 Hz, 1H, *H-14*), 7.05-7.41 (m, 10H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 26.6, 43.2, 56.1, 80.0, 80.5, 81.3, 103.3, 112.1, 115.6, 122.5, 122.6, 126.5, 127.9, 128.5, 129.6, 134.0, 135.9, 157.4, 166.0

MS: *m/z* = 548 (M+1)

Anal Calcd. for **$C_{25}H_{26}NO_5I$**: C, 54.84 %; H, 4.79 %; N, 2.56 %

Found: C, 54.67 %; H, 4.60 %; N, 2.64 %



23a

carbon numbering is same as in **22a**

thick oil

$[\alpha]_D^{25}$ = -1.5 (*c* 0.43, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1762 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.90 (t, *J* 4.0 Hz, 1H, *H-6*), 4.00 (dd, *J* 8.2, 15.7 Hz, 1H, *H-12*), 4.24-4.29 (m, 2H, *H-4* & *H-12*), 4.42-4.54 (m, 2H, *H-5* & *H-7*), 5.37 (d, *J* 5.1 Hz, 1H, *H-3*), 5.73 (d, *J* 3.5 Hz, 1H, *H-8*), 6.08-6.12 (m, 1H, *H-13*), 6.59 (d, *J* 16.0 Hz, 1H, *H-14*), 6.97-7.40 (m, 10H, *aromatic*)

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 21.9, 26.3, 26.6, 44.0, 56.0, 56.7, 78.9, 80.0, 80.6, 103.2, 112.0, 115.6, 122.2, 122.7, 126.4, 128.1, 128.6, 129.4, 134.3, 136.0, 157.2, 165.5

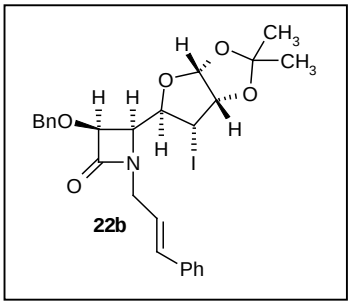
MS: *m/z* = 548 (M+1).

Anal. Calcd for **$C_{25}H_{26}NO_5I$**: C, 54.84 %; H, 4.79 %; N, 2.56 %

Found: C, 54.72 %; H, 4.86 %; N, 2.67 %

Following the general procedure, glucose derived chiral iodoaldehyde (0.529 g, 1.78 mmol) was subjected to aza-Wittig reaction with iminophosphorane derived from cinnamyl

azide (0.270 g, 1.69 mmol) followed by treatment with triethylamine (1.05 mL, 7.55 mmol) and benzyloxyacetyl chloride (0.4 mL, 2.53 mmol) at -15 °C to form a 1:1 diastereomeric mixture of β-lactams **22b** and **23b** in 76% yield (0.720 g). Diastereomers were separated by flash column chromatography using 8-10% acetone-petroleum ether mixture.



carbon numbering is same as in **22a**

thick oil

$[\alpha]_D^{25}$ = +98.5 (*c* 0.54, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1753 cm^{-1}

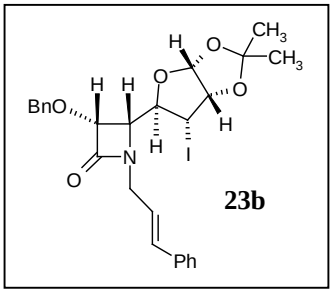
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 3.88 (t, *J* 3.6 Hz, 1H, *H-6*), 3.98 (dd, *J* 5.5, 10.1 Hz, 1H, *H-12*), 4.03 (dd, *J* 4.6, 10.1 Hz, 1H, *H-4*), 4.10 (dd, *J* 5.5, 10.1 Hz, 1H, *H-12*), 4.38 (t, *J* 3.2 Hz, 1H, *H-7*), 4.49 (dd, *J* 3.6, 10.1 Hz, 1H, *H-5*), 4.61 (d, *J* 11.5 Hz, 1H, PhC$H_a$$H_b$O), 4.72 (d, *J* 4.6 Hz, 1H, *H-3*), 4.83 (d, *J* 11.5 Hz, 1H, PhC$H_a$$H_b$O), 5.62 (d, *J* 3.2 Hz, 1H, *H-8*), 6.04-6.10 (m, 1H, *H-13*), 6.51 (d, *J* 15.6 Hz, 1H, *H-14*), 7.16-7.29 (m, 10H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 26.7, 43.3, 56.5, 73.3, 80.5, 81.6, 81.7, 103.5, 112.2, 122.9, 126.6, 127.8, 128.0, 128.5, 128.6, 134.1, 136.2, 137.2, 167.5

MS: *m/z* = 562 **(**M+1)

Anal. Calcd for **$C_{26}H_{28}NO_5I$**: C, 55.61 %; H, 5.03 %; N, 2.50 %

Found: C, 55.43 %; H, 5.15 %; N, 2.56 %



carbon numbering is same as in **22a**

white solid; mp 142-143 °C

$[\alpha]_D^{25}$ = +20.8 (*c* 0.62, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1754 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 3H, C*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 3.87-4.00 (m, 2H, *H-6* & *H-12*), 4.05 (t, *J* 4.3 Hz, 1H, *H-4*), 4.26 (dd, *J* 5.8, 15.8 Hz, 1H, *H-12*), 4.42-4.53 (m, 2H, *H-5* & *H-7*), 4.73-4.81 (m, 2H, PhC$H_a$$H_b$O & *H-3*), 4.95 (d, *J* 11.8 Hz, 1H, PhC$H_a$$H_b$O), 5.80 (d, *J* 3.5 Hz, 1H, *H-8*), 6.03-6.18 (m, 1H, *H-13*), 6.55 (d, *J* 15.8 Hz, 1H, *H-14*), 7.27-7.40 (m, 10H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$,): δ 21.9, 26.5, 26.6, 43.9, 56.6, 73.1, 79.4, 80.7, 81.5, 103.4, 111.9, 123.0, 126.4, 127.8, 128.1, 128.3, 128.7, 134.3, 136.1, 137.1, 167.3

MS: *m/z* = 562 (M+1)

Anal. Calcd. for **$C_{26}H_{28}NO_5I$**: C. 55.61 %; H, 5.03 %; N, 2.49 %

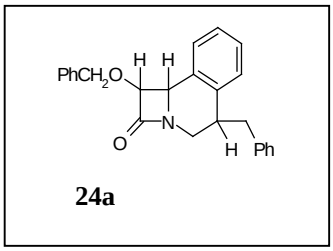
Found: C, 55.48 %; H, 5.22 %; N, 2.68 %

General procedure for radical cyclization of* β*-lactams 20d-e & 22-23:

A solution of Bu_3SnH (0.2 mL, 0.75 mmol) and AIBN (16 mg, 0.10 mmol) in toluene (24 mL) was added to a refluxing solution of β-lactam (0.50 mmol) in toluene (48 mL) over a period of 3 h. The reaction mixture was refluxed for a further 2-3 h. After completion of the reaction (TLC), the solvent was distilled off under reduced pressure. The crude reaction mixture was purified by flash column chromatography to get pure cyclized products.

Intramolecular radical cyclization of 20d:

Bromo β-lactam **20d** (0.220 g, 0.49 mmol) was dissolved in toluene (47 mL) and refluxed for 1 h. A solution of Bu_3SnH (0.2 mL, 0.74 mmol) and AIBN (16 mg, 0.10 mmol) in toluene (20 mL) was added over a period of 3 h and refluxed for an additional 3 h. The solvent was distilled off under reduced pressure and a white solid of *exo* cyclized tricyclic β-lactam **24a** was obtained in 26% yield (47 mg) after flash column chromatography using 4-6% acetone-petroleum ether mixture.



24a

white solid; mp 139-140 °C

IR ($CHCl_3$): ν_{max} 1751 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.70 (dd, *J* 9.0, 13.3 Hz, 1H, $NCH_2CHCH_aH_b$), 2.92 (dd, *J* 7.1, 13.0 Hz, 1H, $NCH_aH_bCHCH_2$), 3.30-3.51 (m, 2H, $NCH_aH_bCHCH_aH_bPh$), 3.84 (dd, *J* 6.2, 13.3 Hz, 1H, $NCH_aH_bCHCH_2$), 4.64 (d, *J* 4.3 Hz, 1H, BnOCHCH), 4.73 (s, 2H, $PhCH_2O$), 4.99 (d, *J* 4.3 Hz, 1H, BnOCH), 7.12-7.38 (m, 14H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 37.9, 40.4, 41.8, 53.4, 72.3, 82.8, 126.2, 126.5, 127.4, 127.7, 128.3, 128.6, 129.0, 131.3, 137.1, 138.1, 138.6, 170.0

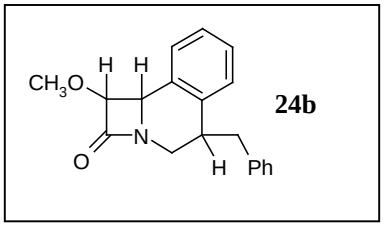
MS: *m/z* = 370 (M+1)

Anal. Calcd. for **$C_{25}H_{23}NO_2$**: C, 81.27 %; H, 6.28 %; N, 3.79 %

Found: C, 81.31 %; H, 6.17 %; N, 3.84 %

Radical cyclization of 20e:

Following the general procedure, methoxy derivative of β-lactam **20e** (0.48 mmol) was cyclized on treatment with Bu_3SnH and AIBN to give *exo* cyclized product **24b** in 28% (40 mg).



24b

white solid; mp 74-75 °C

IR ($CHCl_3$): ν_{max} 1749 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.63-2.74 (m, 1H, $NCH_2CHCH_aH_b$), 2.90 (dd, *J* 7.8, 12.9 Hz, 1H, $NCH_aH_bCHCH_2$), 3.31-3.40 (m, 2H, $NCH_2CHCH_aH_b$), 3.50 (s, 3H, OCH_3), 3.82 (dd, *J* 6.6, 12.9 Hz, 1H, $NCH_aH_bCHCH_2$), 4.65 (d, *J* 4.3 Hz, 1H, CH_3OCHCH), 4.82 (d, *J* 4.3 Hz, 1H, CH_3OCH), 7.13-7.41 (m, 9H, *aromatic*)

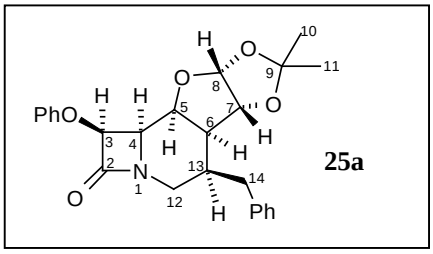
^{13}C NMR (50 MHz, $CDCl_3$): δ 37.1, 40.2, 41.6, 53.4, 58.8, 85.3, 126.2, 126.5, 127.2, 127.5, 128.5, 128.9, 131.1, 137.9, 169.9

Anal. Calcd. for **$C_{19}H_{19}NO_2$**: C, 77.78 %; H, 6.53 %; N, 4.78 %

Found: C, 77.67 %; H, 6.47 %; N, 4.01 %

Intramolecular radical cyclization of 22a:

Following the general procedure, iodo β-lactam **22a** (0.231 g, 0.42 mmol) dissolved in toluene (40 mL), was treated with a solution of Bu_3SnH (0.17 mL, 0.63 mmol) and AIBN (13 mg, 0.08 mmol) in toluene (20 mL) under reflux condition for 6 h. The solvent was then removed under reduced pressure and the crude material was purified by flash chromatography using 10-15% acetone-petroleum ether mixture. A pale yellow solid was obtained, which was further purified by washing with anhydrous ethanol to get pure *exo* cyclized tetracyclic β-lactam **25a** in 36% yield (64 mg).



25a

white solid; mp 160-161 °C

$[\alpha]_D$ = + 25.87 (*c* 1.55, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.31-2.43 (m, 1H, *H-13*), 2.54- 2.87 (m, 4H, *H-6*, *H-12* & *H-14*), 3.51 (dd, *J* 5.5, 13.3 Hz, 1H, *H-12*), 3.90 (t, *J*

3.9 Hz, 1H, *H-4*), 4.76-4.84 (m, 2H, *H-5* & *H-7*), 5.31 (d, *J* 3.9 Hz, 1H, *H-3*), 5.91 (d, *J* 3.9 Hz, 1H, *H-8*), 7.01-7.35 (m, 10H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$)**: δ 27.1, 27.3, 35.5, 37.3, 39.1, 47.5, 55.0, 72.5, 81.3, 82.0, 106.5, 115.7, 122.5, 126.7, 128.7, 129.0, 129.6, 138.4, 157.0, 165.7**

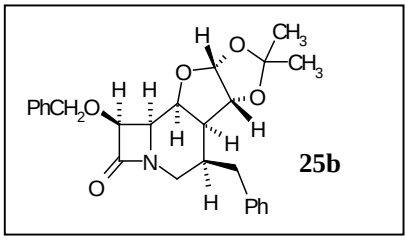
MS: *m/z* = 422 (M+1)

Anal. **Calcd**. for $\mathbf{C_{25}H_{27}NO_5}$: C, 71.23 %; H, 6.46 %; N, 3.33 %

Found: C, 71.38 %; H, 6.60 %; N, 3.18 %

Intramolecular radical cyclization of 22b:

Following the general procedure, iodo β-lactam **22b** (0.233 g, 0.42 mmol) was taken in toluene (40 mL) and heated under reflux condition for 1 h. A solution of Bu_3SnH (0.17 mL, 0.63 mmol) and AIBN (13.6 mg, 0.08 mmol) in toluene (20 mL) was then added over a period of 2.5 h and refluxed for a further 3 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography using 10-15% acetone-petroleum ether mixture. Treatment of the resulting solid with anhydrous ethanol gave pure *exo* cyclized tricyclic β-lactam **25b** in 28% yield (50.6 mg).



25b

carbon numbering is same as in **25a**

pale yellow solid; mp 135-136 °C

$[\alpha]_D$ = + 34.14 (*c* 1.6, $CHCl_3$)

IR ($CHCl_3$): ν_{max} 1760 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H, C*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 2.27-2.40 (m, 1H, *H-13*), 2.52-2.81 (m, 4H, *H-6, H-12* & *H-14*), 3.45 (dd, *J* 5.4, 13.3 Hz, 1H, *H-12*), 3.65 (t, *J* 4.3 Hz, 1H, *H-4*), 4.71 (s, 2H, PhC*H*$_2$O), 4.67-4.80 (m, 3H, *H-3*, *H-5*, & *H-7*), 5.92 (d, *J* 4.3 Hz, 1H, *H-8*), 7.14-7.38 (m, 10H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.1, 27.5, 35.7, 37.3, 38.8, 47.5, 54.4, 72.6, 72.7, 81.8, 82.1, 105.5, 112.9, 126.6, 128.1, 128.4, 128.6, 129.0, 136.4, 138.5, 166.9

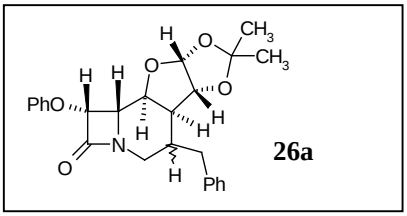
MS: *m/z* = 437 (M+1)

Anal. **Calcd**. for **$C_{26}H_{29}NO_5$**: C, 71.69 %; H, 6.72 %; N, 3.22 %

Found: C, 71.89 %; H, 6.85 %; N, 3.40 %

Radical cyclization of 23a:

Following the general procedure, a solution of Bu_3SnH (0.13 mL, 0.49 mmol) and AIBN (11 mg, 0.07 mmol) in toluene (16 mL) was added into the refluxing solution of iodo β-lactam **23a** (0.175 g, 0.32 mmol) in toluene (31 mL) for 2.5 h and refluxed for another 2.5 h. An inseparable 1:1 diastereomeric mixture of *exo-trig* cyclized product **26a** (86 mg, 64%) was isolated after flash column chromatography using 15-20% acetone-petroleum ether.



26a

carbon numbering is same as in **25a**

white solid; mp 165-166 °C

IR ($CHCl_3$): ν_{max} 1763 cm^{-1}

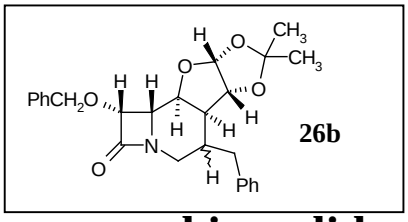
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H, C*H*$_3$), 1.29 (s, 3H, C*H*$_3$), 1.32 (s, 3H, C*H*$_3$), 1.39 (s, 3H, C*H*$_3$), 2.04 (dd, *J* 2.8, 11.0 Hz, 1H, *H-13*), 2.28-2.30 (m, 1H, *H-13*), 2.32-2.64 (m, 4H, *H-6* & *H-14*), 2.75-2.95 (m, 2H, *H-14*), 3.06 (d, *J* 8.0 Hz, 2H, *H-12*), 3.66-3.86 (m, 3H, *H-12* & *H-4*), 4.23 (t, *J* 3.9 Hz, 1H, *H-4*), 4.53 (d, *J* 3.5 Hz, 1H, *H-5*), 4.60 (d, *J* 5.8 Hz, 1H, *H-5*), 4.76 (d, *J* 3.9 Hz, 1H, *H-3*), 5.30 (d, *J* 3.9 Hz, 1H, *H-3*), 5.39 (d, *J* 3.9 Hz, 1H, *H-7*), 5.86 (d, *J* 3.5 Hz, 1H, *H-7*), 5.93 (d, *J* 3.5 Hz, 1H, *H-8*), 5.93 (d, *J* 3.5 Hz, 1H, *H-8*), 6.99-7.32 (m, 10H, *aromatic*)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.4, 26.9, 32.9, 34.8, 36.5, 38.3, 40.2, 40.5, 47.0, 48.0, 52.9, 70.9, 73.9, 79.5, 80.8, 81.5, 82.1, 104.9, 105.5, 111.2, 115.5, 115.6, 122.0, 126.7, 128.6, 128.7 128.9, 129.3, 137.5, 138.6, 157.5, 157.6, 163.9, 168.2

MS: *m/z* = 422 (M+1)

Radical cyclization of 23b:

Adopting the general procedure, benzyloxy derivative of iodo β-lactam **23b** (0.12 g, 0.21 mmol) also gave an inseparable diastereomeric mixture (55:45) of cyclized product **26b** (52 mg, 56%) after flash column chromatography using 15-20% acetone-petroleum ether.



26b

carbon numbering is same as in **25a**

white solid; mp 191-192 ºC

IR ($CHCl_3$): ν_{max} 1757 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 1.88 (dd, *J* 2.8, 11.0 Hz, 1H, *H-13*), 1.95-2.03 (m, 3H, *H-13*, *H-6*), 2.26 (dd, *J* 10.1, 13.8 Hz, 2H, *H-14*), 2.40 (t, *J* 6.0 Hz, 1H, *H-14*), 2.47 (dd, *J* 10.6, 13.8 Hz, 1H, *H-14*), 2.64 (dd, *J* 5.0 Hz, 13.7 Hz, 1H, *H-12*), 2.83 (dd, *J* 4.2, 12.4 Hz, 1H, *H-12*), 2.89-2.95 (m, 2H, *H-12*), 3.32 (t, *J* 3.2 Hz, 1H, *H-4*), 3.54 (dd, *J* 5.0, 13.7 Hz, 1H, *H-12*), 4.08 (br s, 2H, PhC*H*$_2$O), 4.24 (d, *J* 5.5 Hz, 1H, *H-4*), 4.46 (d, *J* 3.7 Hz, 1H, *H-5*), 4.50 (d, *J* 5.0 Hz, 1H, *H-3*), 4.52 (d, *J* 5.0 Hz, 1H, *H-3*), 4.66 (d, *J* 3.2 Hz, 2H, *H-5* & *H-7*), 4.68 (d, *J* 11.5 Hz, 1H, PhC*H*$_2$O), 4.72 (t, 1H, *J* 3.9 Hz, *H-7*), 4.77 (d, *J* 11.5 Hz, 1H, PhC*H*$_2$O), 5.86 (d, *J* 3.6 Hz, 2H, *H-8*), 6.99-7.44 (m, 10H, *aromatic*)

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9, 26.3, 26.5, 27.0, 32.9, 34.9, 36.3, 38.3, 39.9, 40.3, 47.1, 48.3, 53.0, 53.2, 71.4, 73.8, 73.9, 81.0, 81.6, 82.0, 83.6, 105.2, 105.5, 126.5, 126.7, 128.0, 128.4, 128.6, 128.7, 128.8, 128.9, 128.9, 136.8, 137.1, 137.6, 138.7, 165.3, 169.5.

MS: *m/z* = 436 (M+1)

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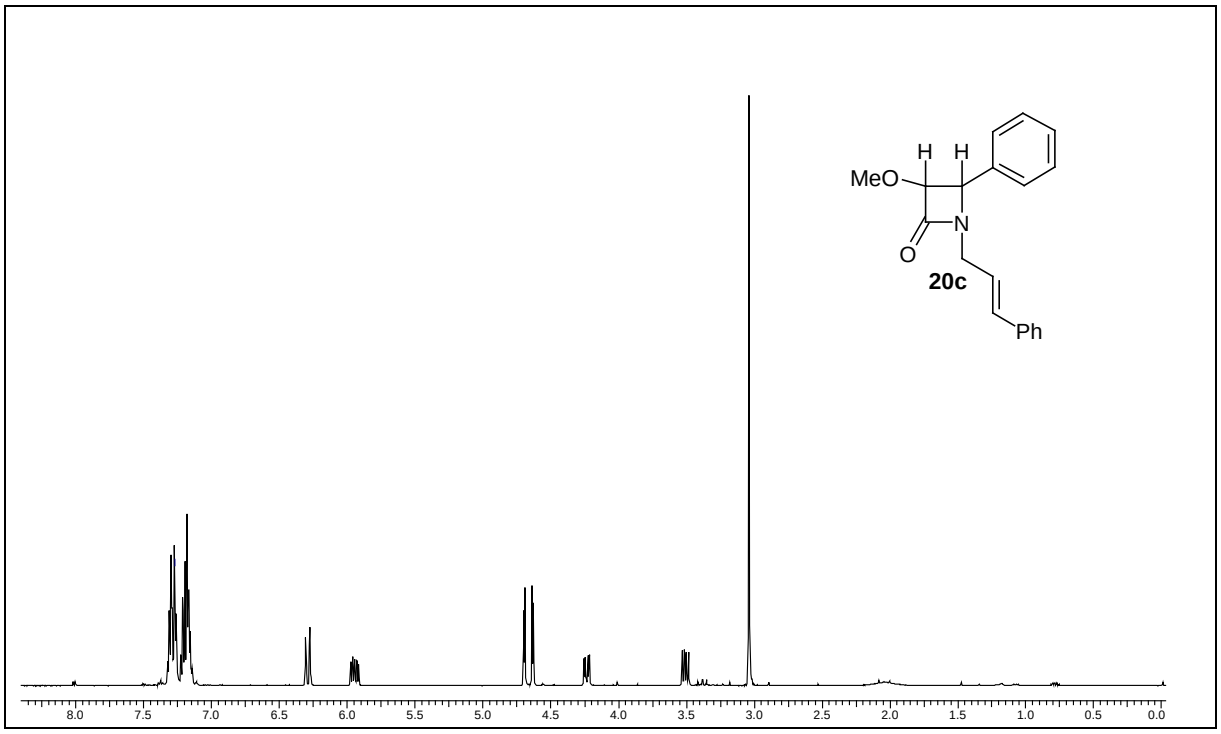
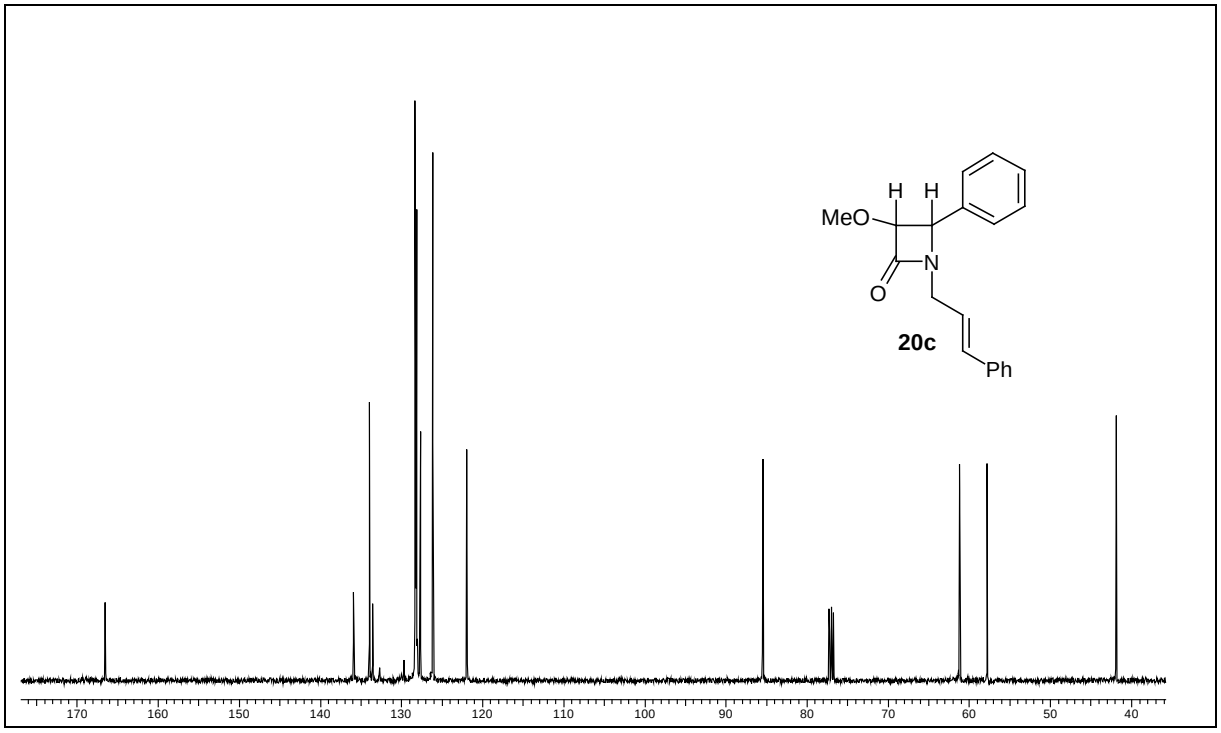
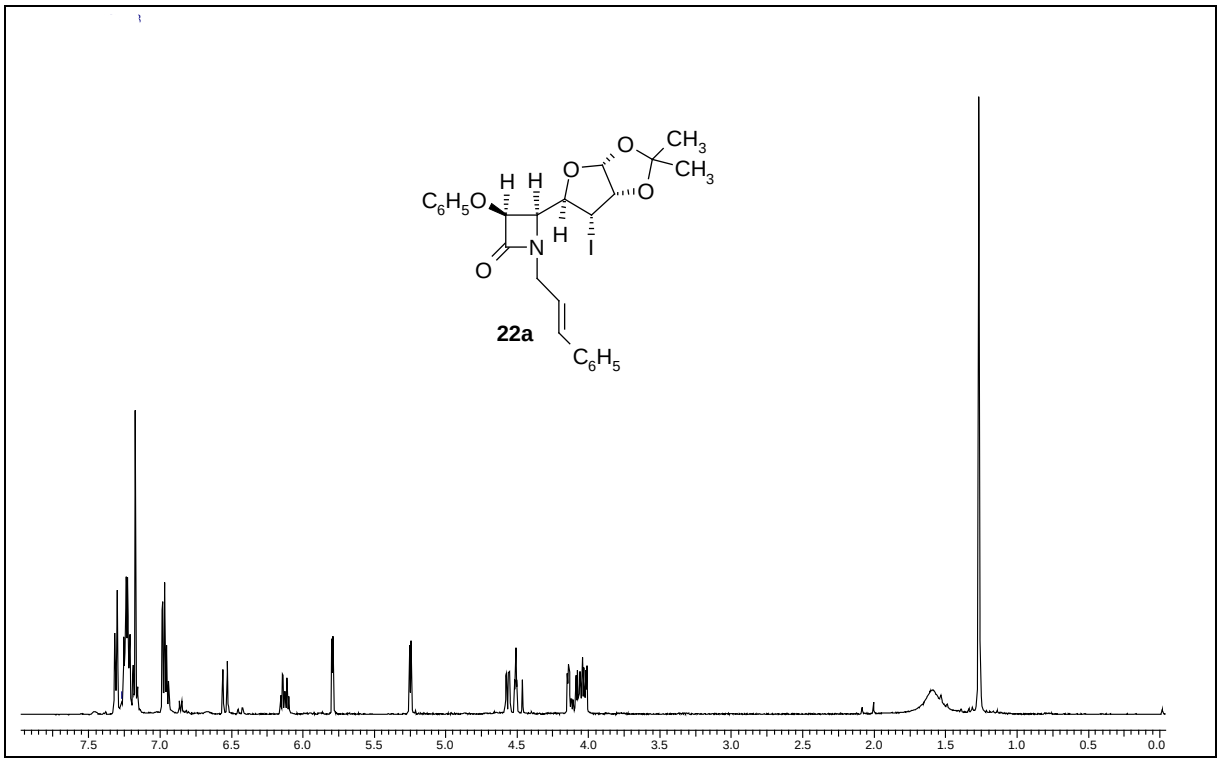
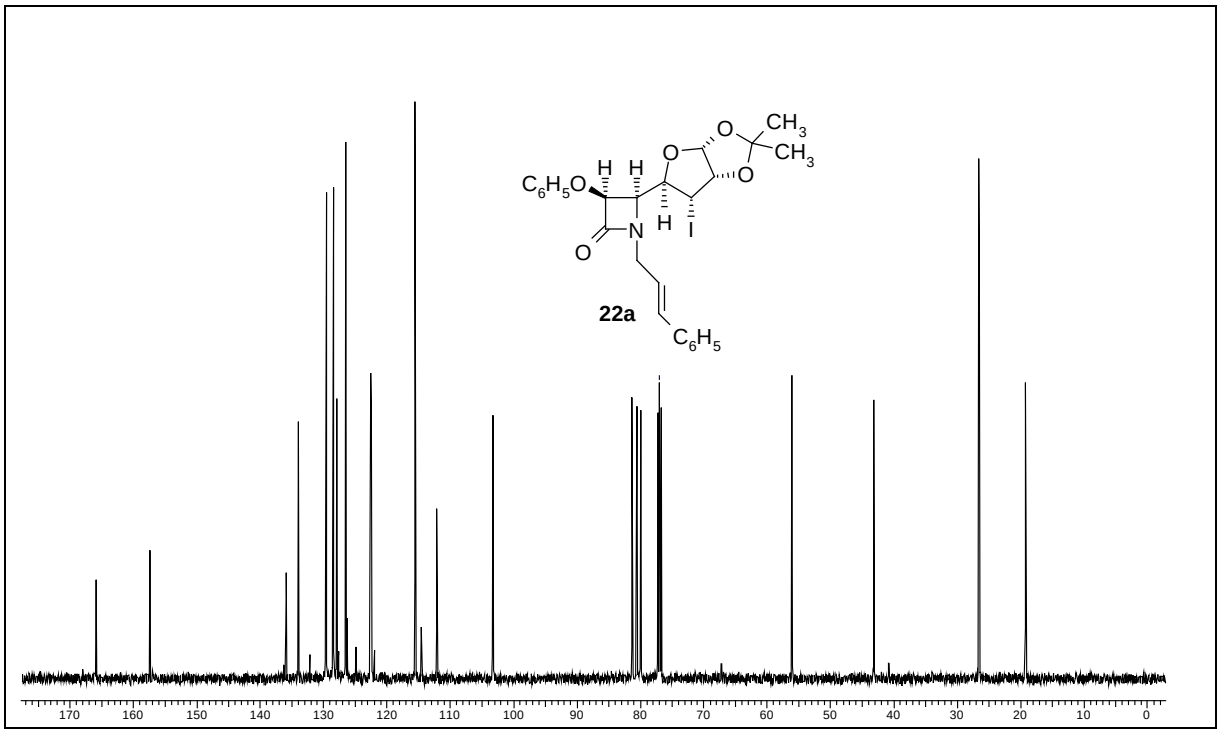
Part B

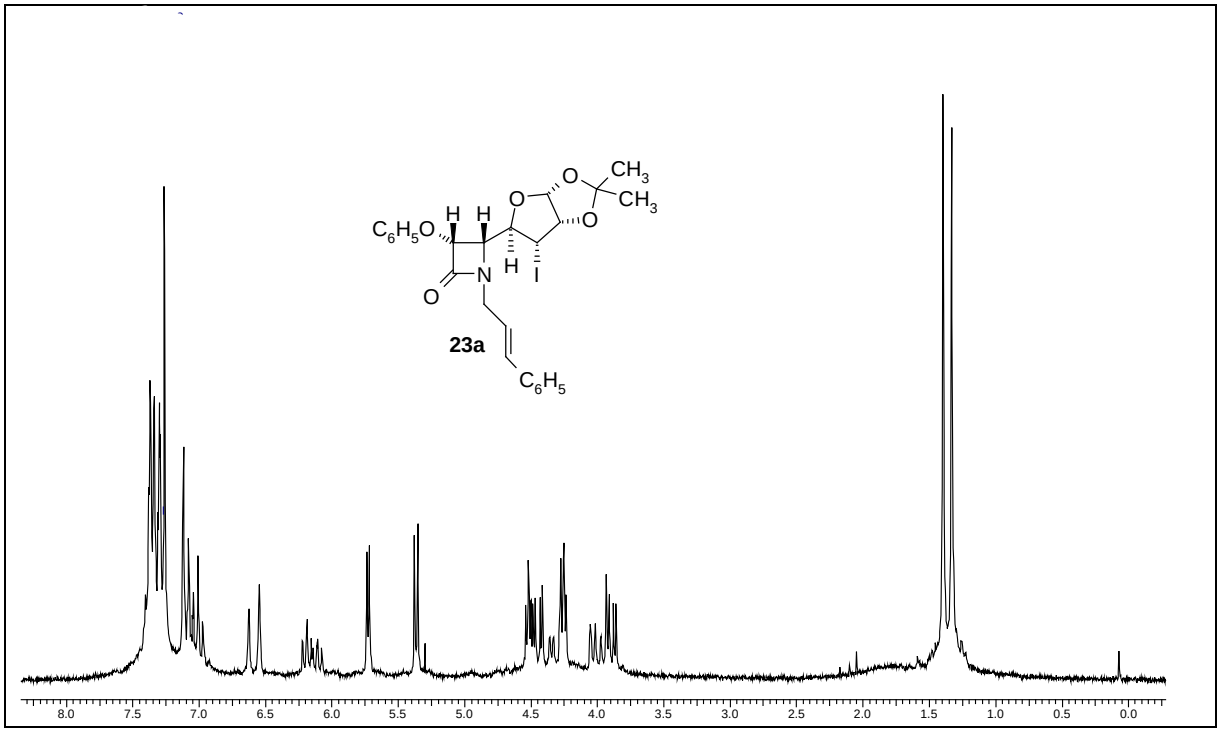
Spectra

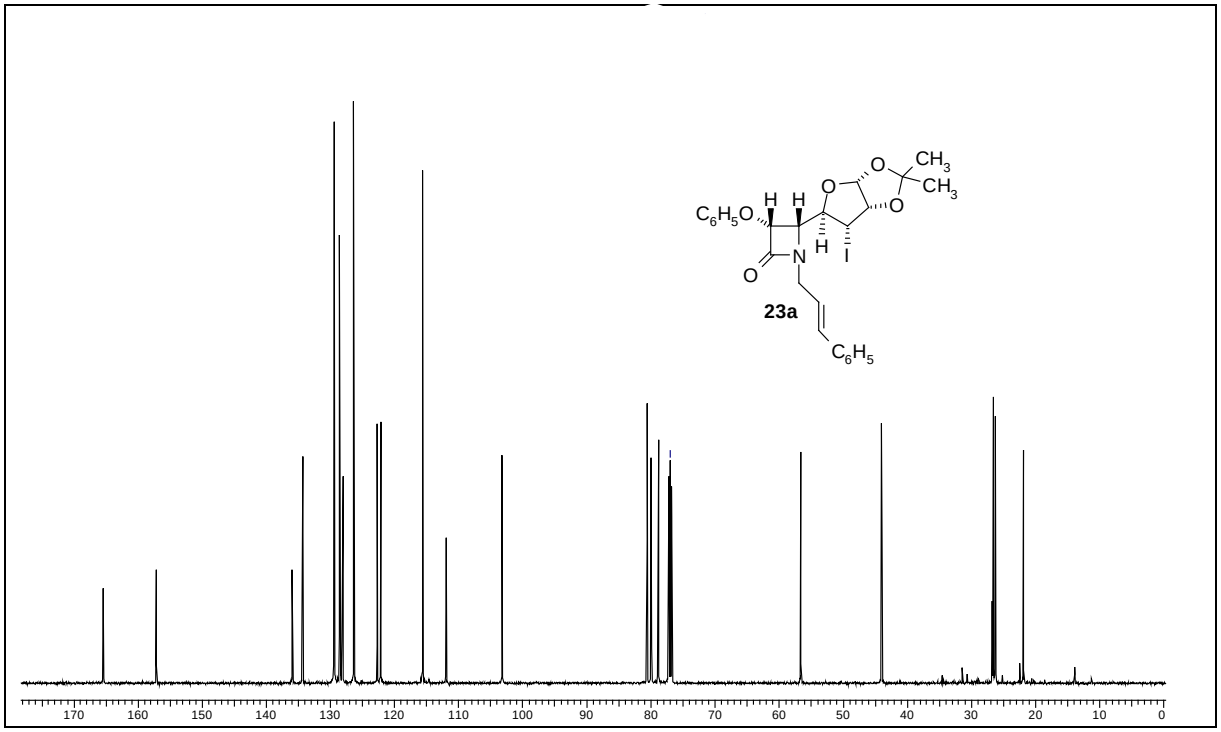


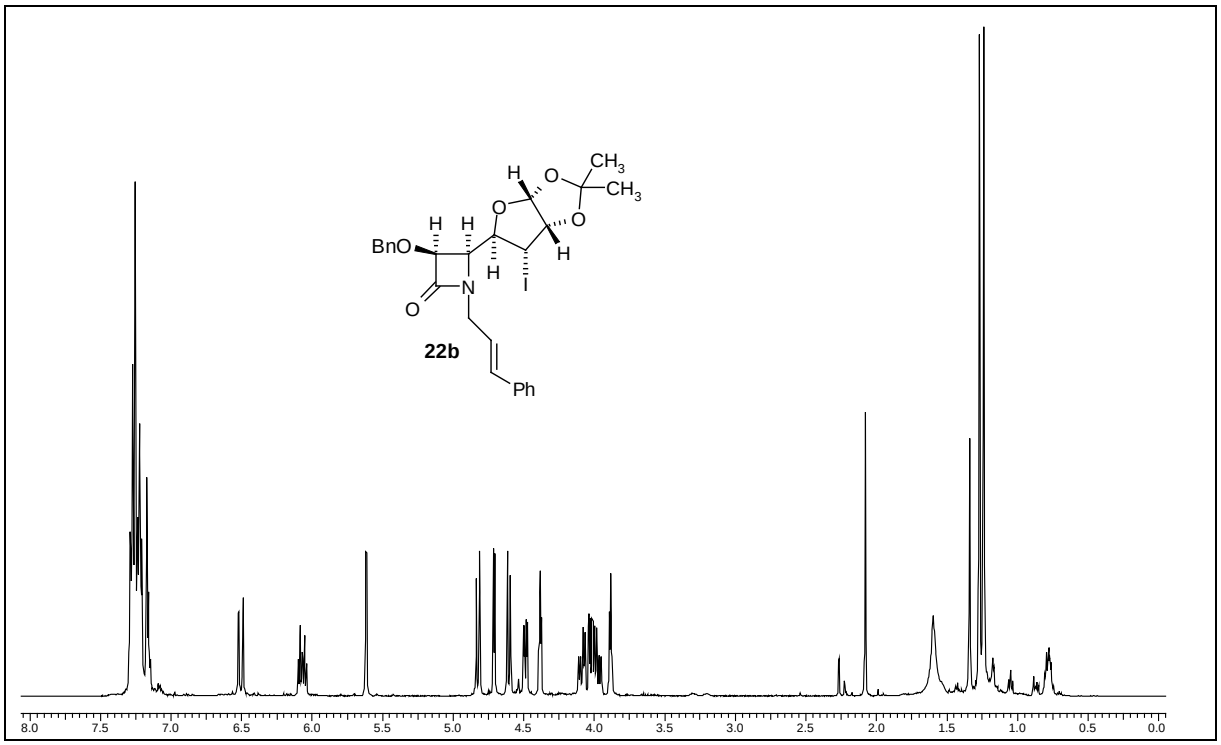


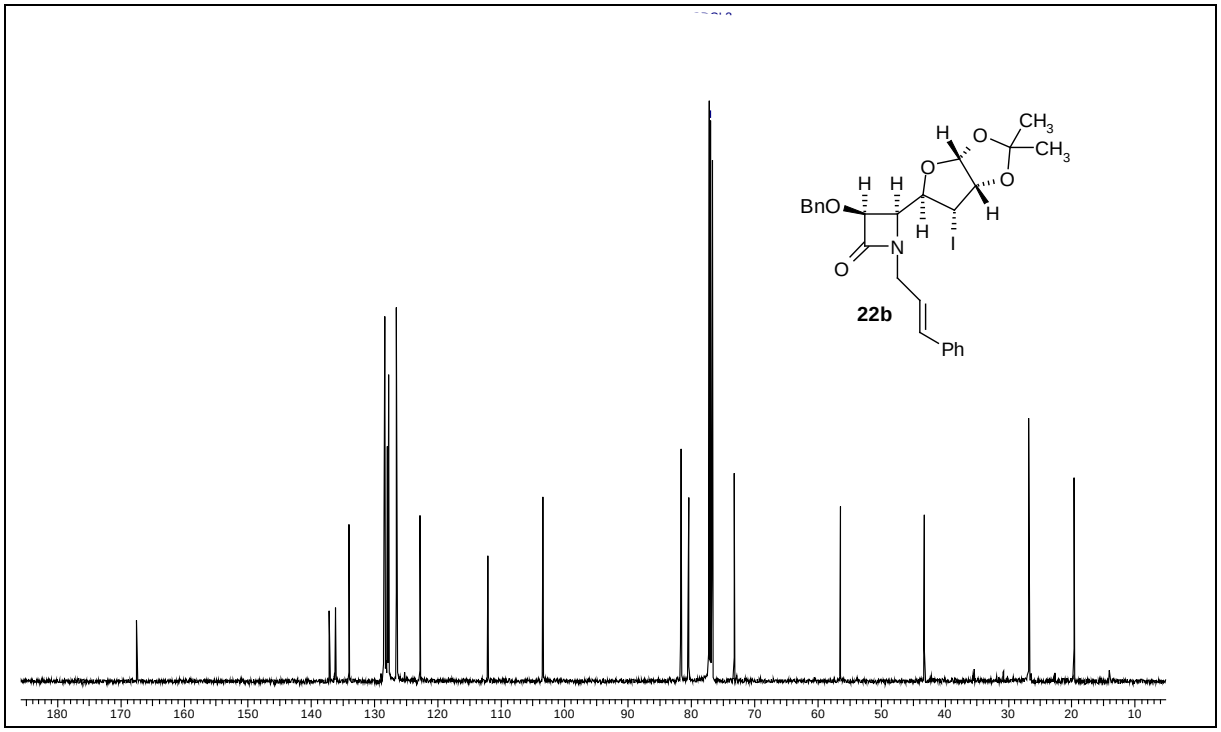


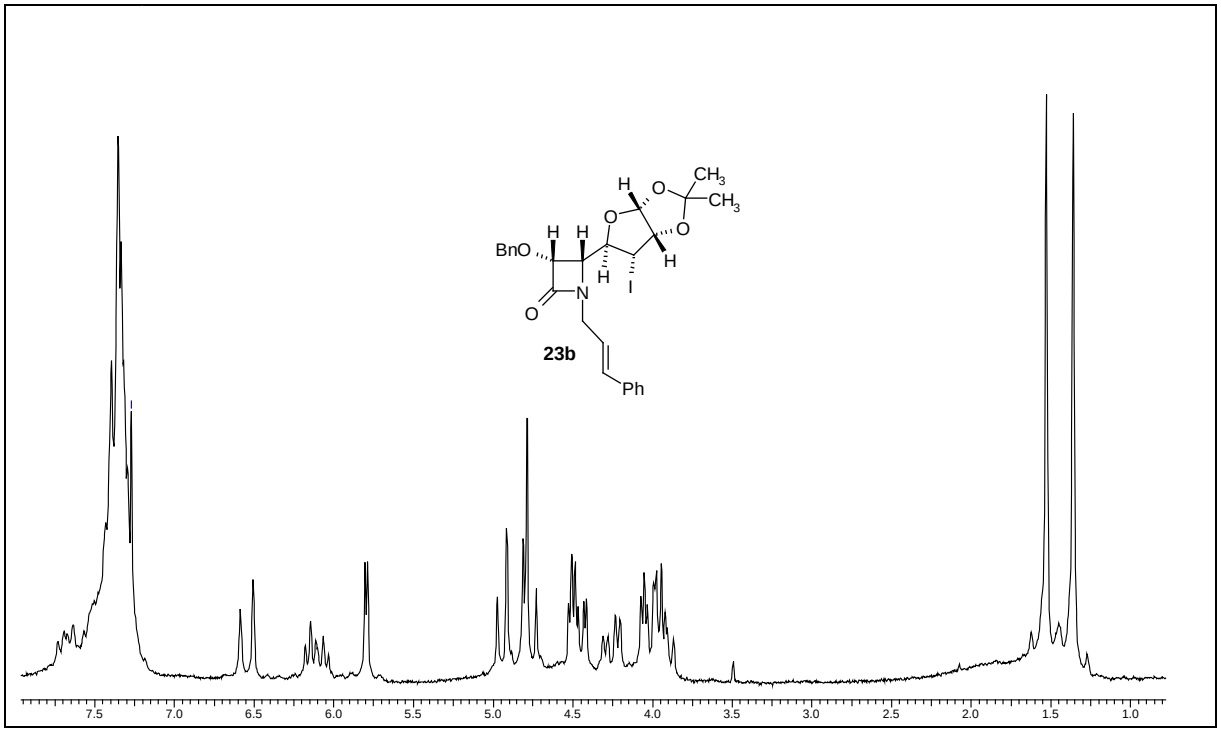


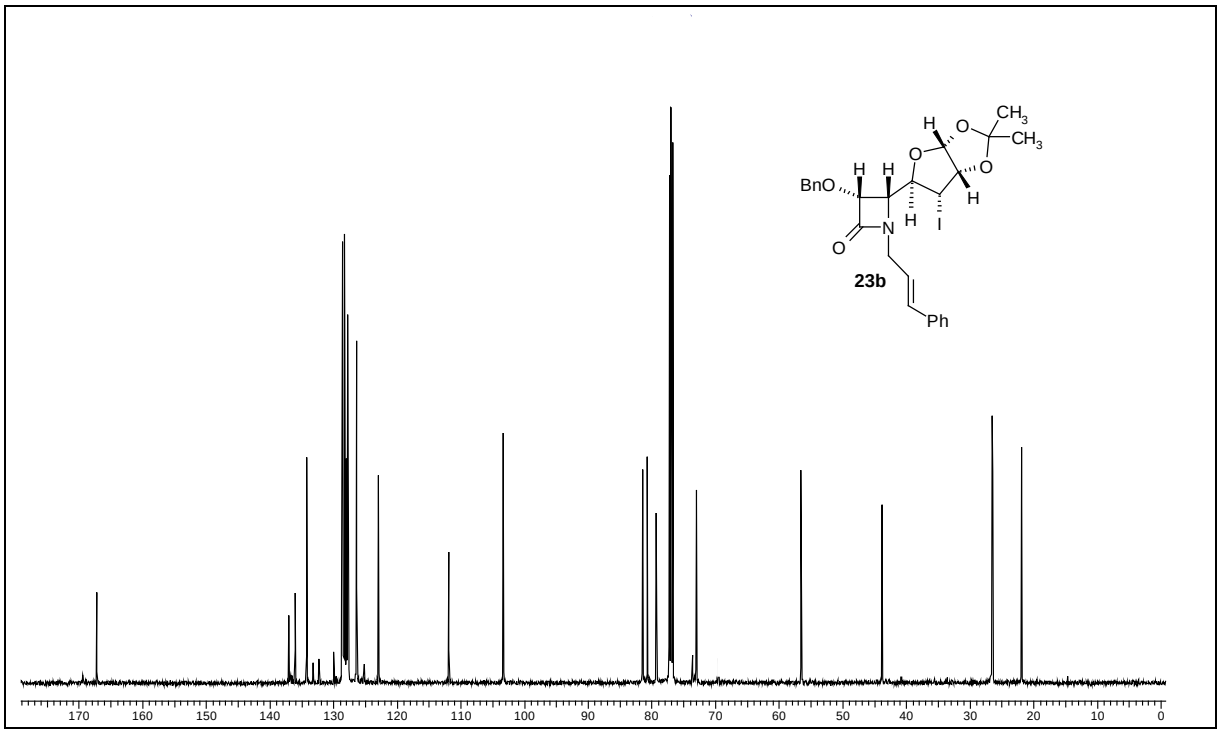


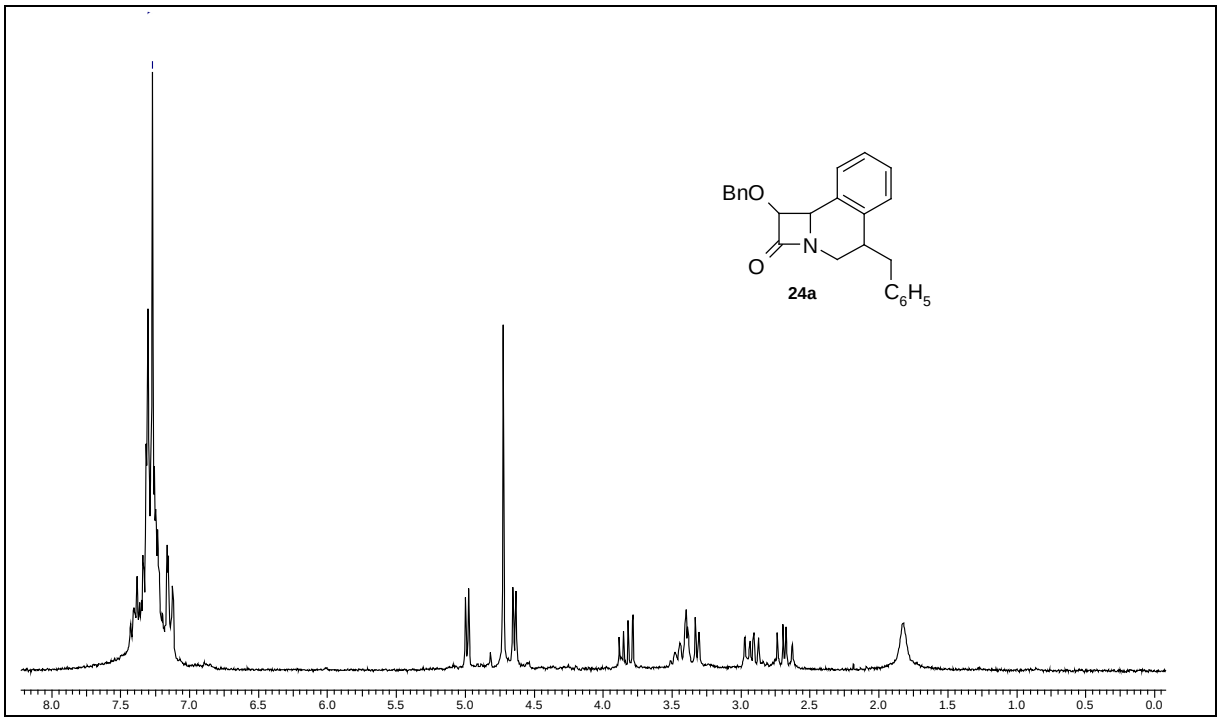


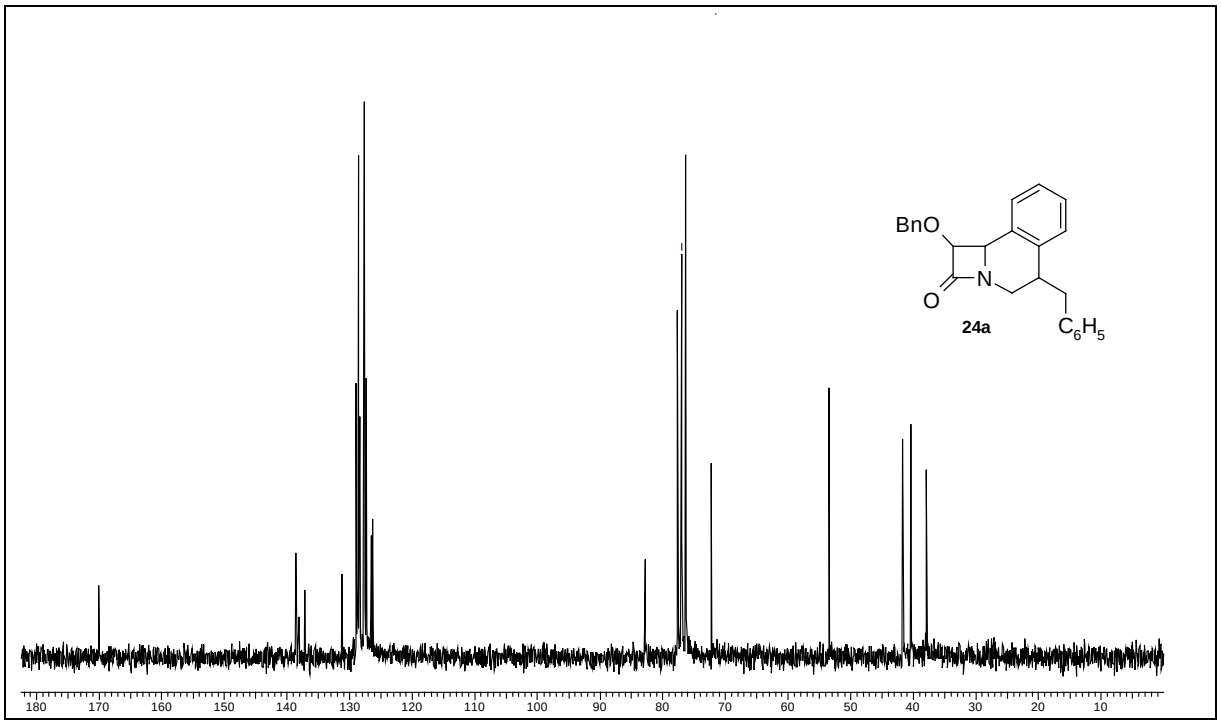


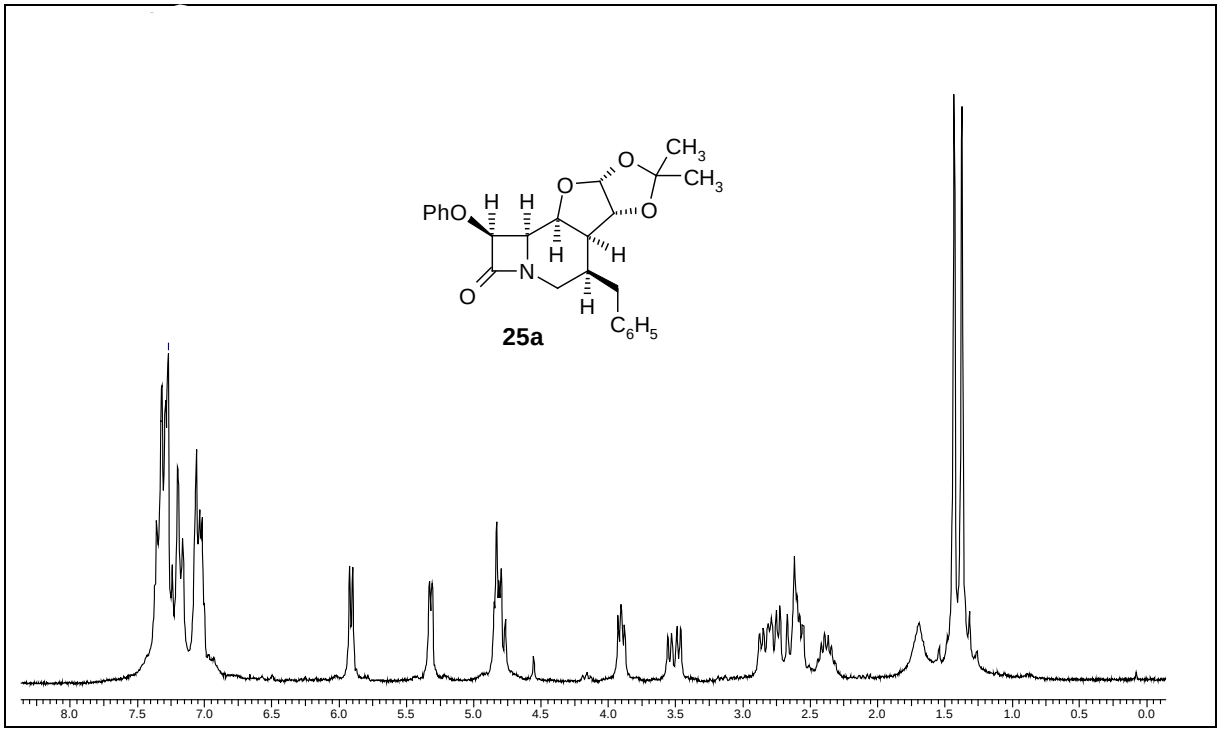


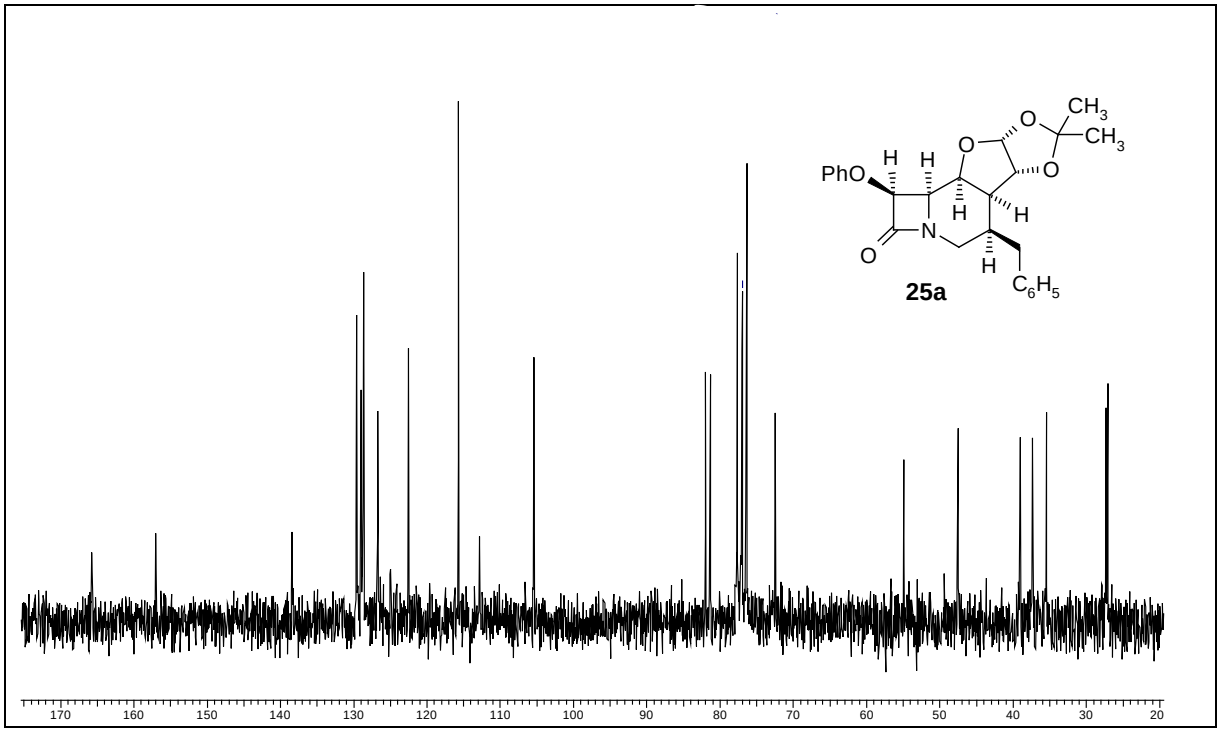




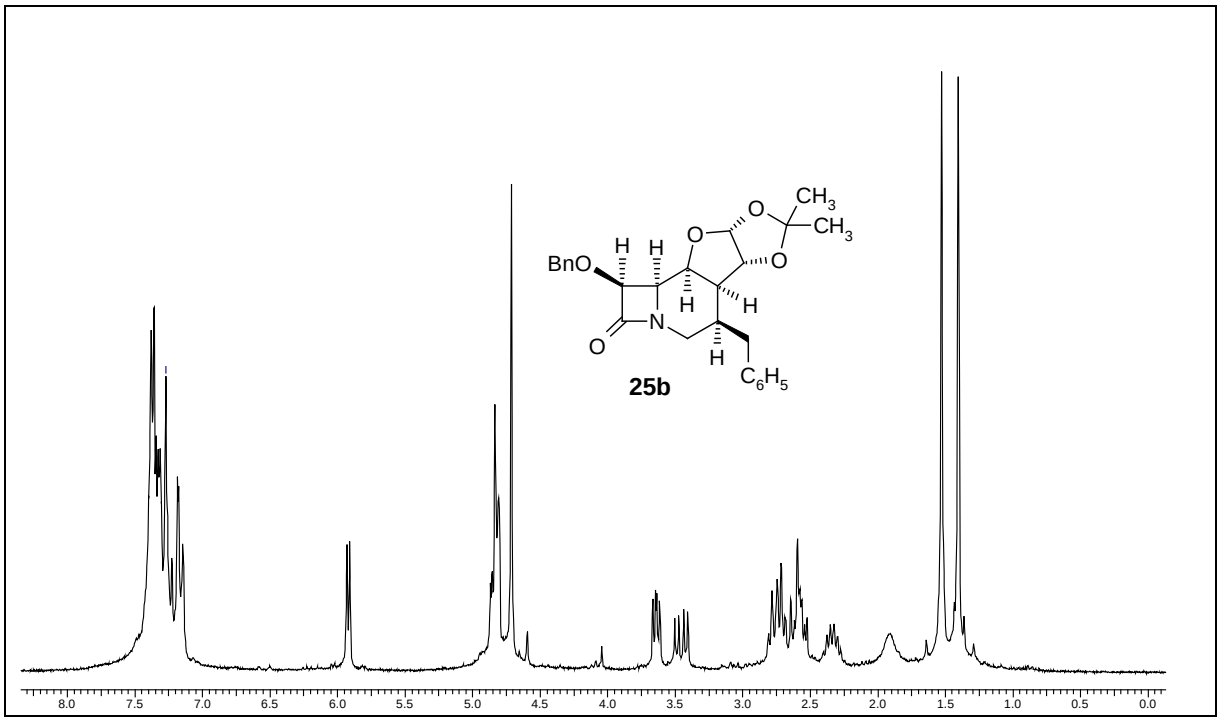


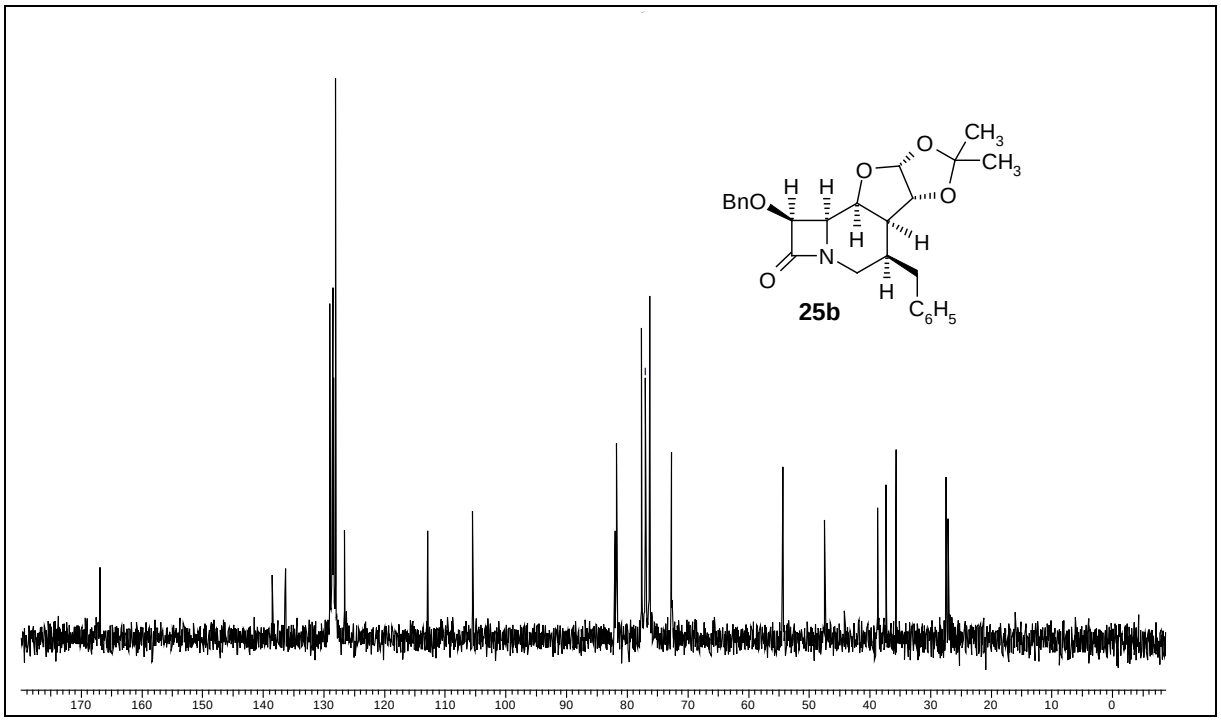


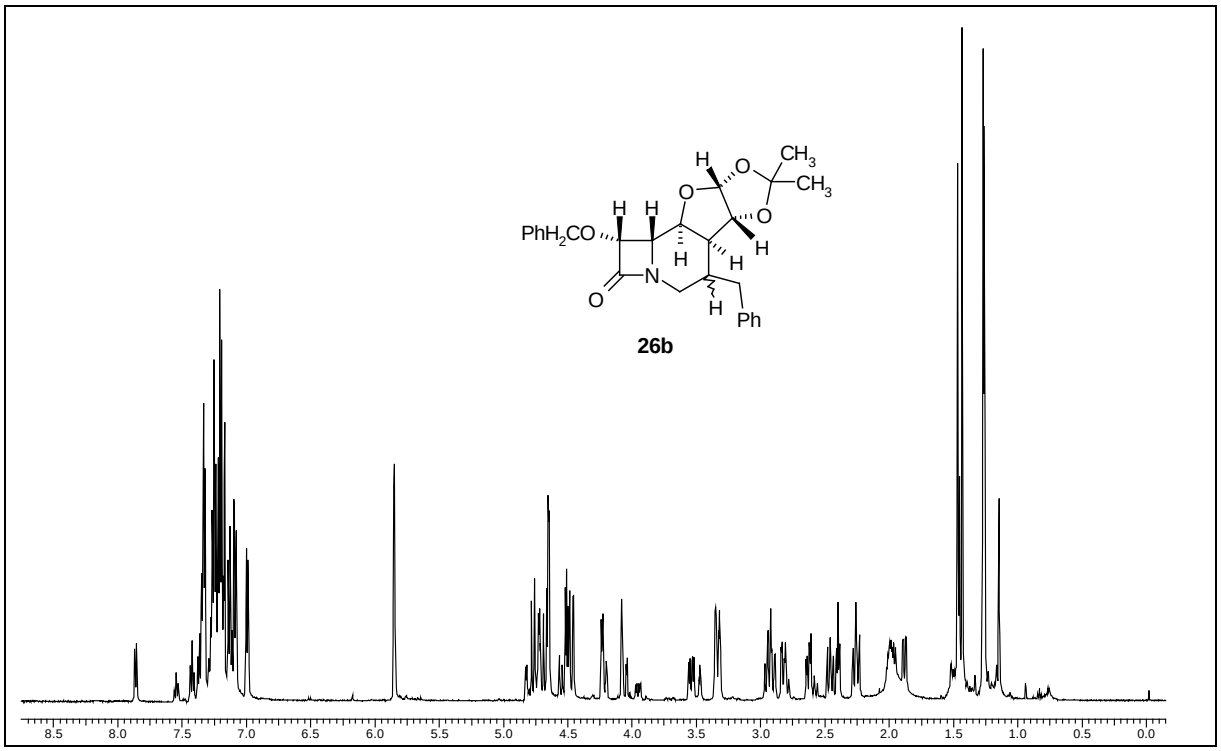




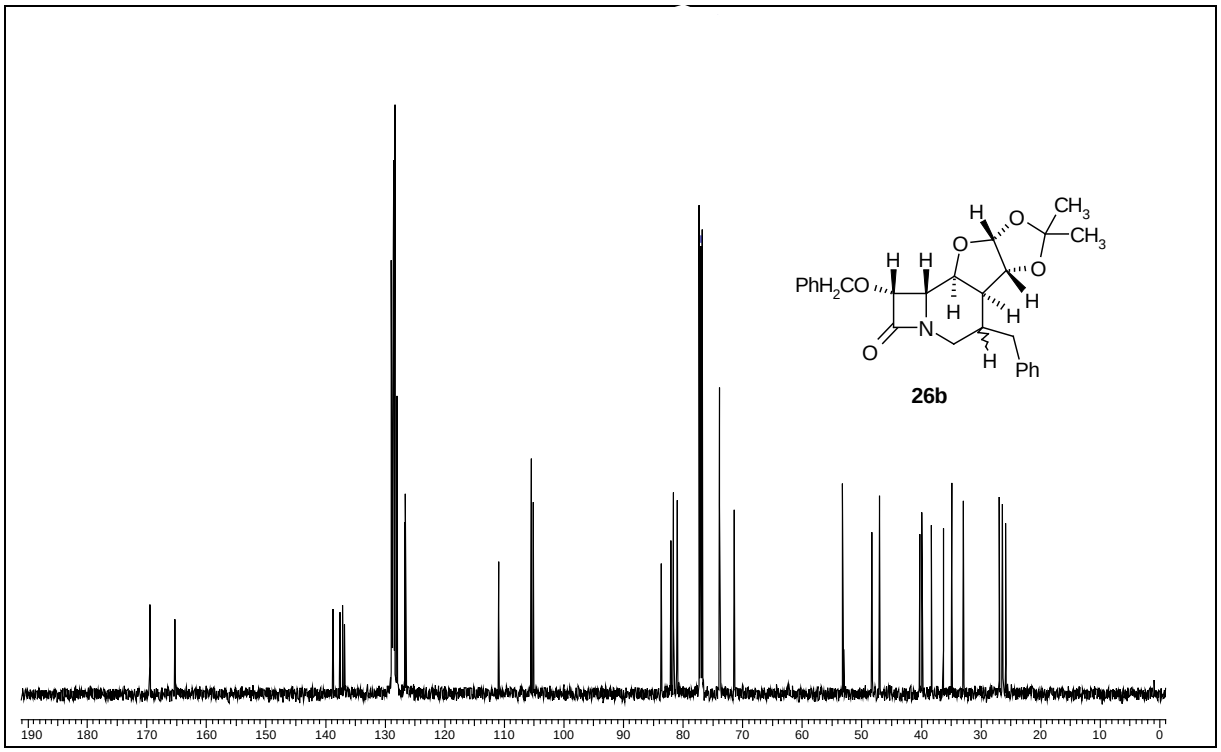
25a







26b



26b

Abbreviations

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

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

LIST OF PUBLICATIONS

1. Acetylferrocenyloxime palladacycle-catalyzed Heck reactions.
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2. Saturated N-heterocyclic carbene oxime and amine palladacycle catalysis of the Mizoroki-Heck and the Suzuki reactions.
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3. A simple one-pot method for the preparation of allyl azides from allyl alcohols using triphosgene: Synthesis of *N*1-cinnamyl azetidin-2-ones.
   A. Jayanthi, V. K. Gumaste and A. R. A. S. Deshmukh, *Synlett* **2004**, 979.

4. Synthesis of novel polycyclic β-lactams from D-glucose via unusual substrate-controlled radical cyclization.
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5. Synthesis of polycyclic β-lactams from D-Glucose derived chiral template via substrate-controlled radical cyclization.
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6. Azetidin-2-ones, synthon for biologically important compounds
   A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, Vidyesh V. Govande, Bidhan A. Shinkre and **A. Jayanthi**, *Curr. Med. Chem*. **2004**, 1889.

Erratum