Diastereoselective Synthesis of *b*-Lactams

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

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IN CHEMISTRY

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PUNE - 411 008

.....To my Parents

CERTIFICATE

*This is to certify that the work incorporated in the thesis entitled "**Diastereoselective Synthesis of b-Lactams**" submitted by Sudhir Narahari Joshi was carried out by him under my supervision at the National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

Date :

National Chemical Laboratory (Dr. B. M. Bhawal)

Pune 411 008 Research Guide

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Spectra

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or chloroform, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FT-IR and ATI Mattson, UK, Model-RS-1 FT-IR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, Bruker MSL-300, Bruker DRX-500 and Bruker AMX-500. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz*., s = singlet, d = doublet, t = triplet, dd = doublet of doublet, brs = broad singlet, br = broad peak, dt=doublet of triplet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker MSL-300 and Bruker AC-200 instrument operating at 75.2 MHz and 50.3 MHz respectively.
5. Elemental analyses (C, H, N) were obtained on a Carlo-Erba 1100 automatic analyzer by Dr. S. Y. Kulkarni and his group at NCL.
6. Optical rotation was measured on a JASCO-181 digital polarimeter using sodium line (5893 Å). Concentration is expressed in gm/100mL.
7. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck). Purification of the products was carried out by flash column chromatography using silica gel obtained from Merck (230-400 mesh, 9385 grade).
8. ^{1}H NMR & ^{13}C NMR spectra of the compounds are attached at the end of corresponding chapter.
9. Pet. ether refers to the petroleum fraction boiling between 60-80 °C.
10. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.

ABBREVIATIONS

AIBN	2,2′-Azobisisobutyronitrile [$Me_2C(CN)N=NC(CN)Me_2$]
NBS	*N*-Bromosuccinmide
NCS	*N*-Chlorosuccinimide
COSY	2D-Correlation spectroscopy
Cy	Cyclohexyl
p	Para
de	Diastereomeric excess
DMF	Dimethylformamide
HETCOSY	Heteronuclear 2D-correlation spectroscopy
h	Hour
M.P.	Melting point
M. F.	Molecular formula
m	Meta
o	Ortho
PMP	*p*-methoxy phenyl
Ph	Phenyl
Pr	Propyl
r.t	Room temperature
ROESY	Rotating frame overhauser enhancement spectroscopy
t-Bu	Tertiary butyl
TBAF	Tetrabutylammonium fluoride
n-Bu_3SnH	Tributyl tin hydride
NOESY	Two dimensional nuclear overhauser spectroscopy

Synopsis of the thesis

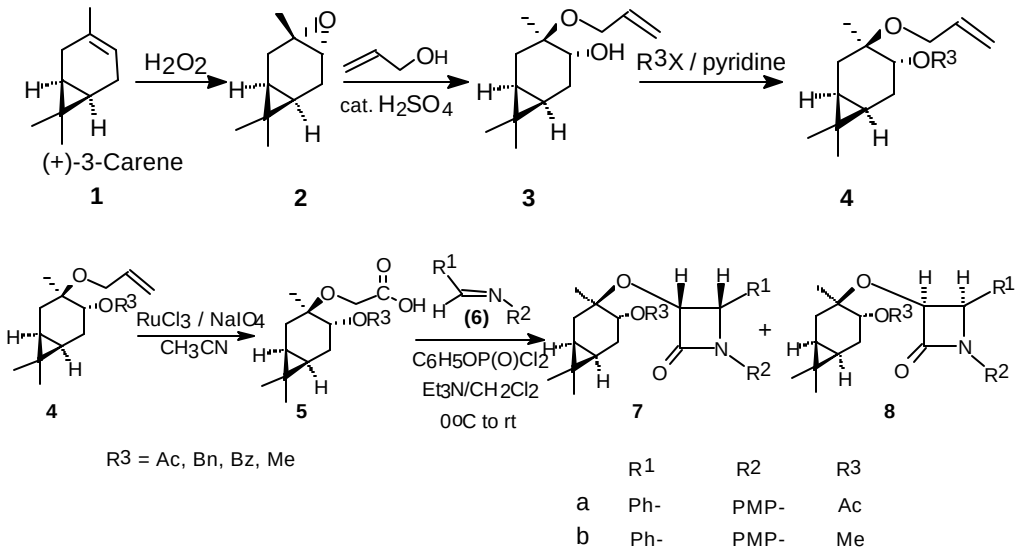
Chapter I Diastereoselective synthesis of b-lactams using chiral acids derived from (+)-3-carene

Section A Synthesis of 3-hydroxy protected b-lactams : effect of steric bulk on diastereoselectivity

In order to study the effect of the steric disposition on the stereoselectivity in the β-lactam ring construction *via* Staudinger reaction, sterically demanding acids as ketene precursors were selected. These acids were prepared from optically pure (+)-3-carene.

The acids (**5**) were obtained by opening of carane epoxide with allyl alcohol, protection of secondary hydroxyl group with different protecting groups followed by oxidation of allyl group. The cycloaddition of various imines (**6**) with acid (**5**) in presence triethyl amine and phenyldichlorophosphate, an acid activator gave a diastereomeric mixture (60:40) of *cis*-β-lactams (**7** & **8**) in good yields (Scheme 1). These diastereomers were separated either by column chromatography or crystallisation. The absolute stereochemistry of these β-lactams was established from single crystal X-ray analysis.

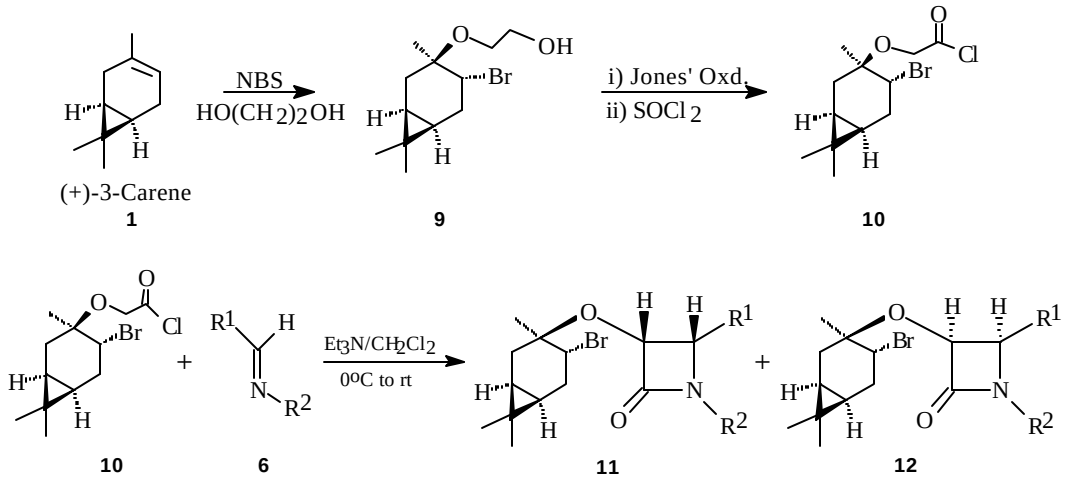
Scheme – 1



Section B Synthesis and systematic study in b-lactam ring construction using ketenes derived from halo carane derivative

The halo substituted acid chloride **10** was synthesised from (+)-3-carene (**1**) as depicted in Scheme-2. The reaction of acid chloride **10** with imines **6** under Stuadinger reaction condition gave substituted β-lactams in good to excellent yields with modest diastereoselectivity. In most of the cases diastereomers (**11**& **12**) were separated either by column or crystallisation. The absolute stereochemistry was established from single crystal X-ray analysis of one of the diastereomer.

Scheme – 2

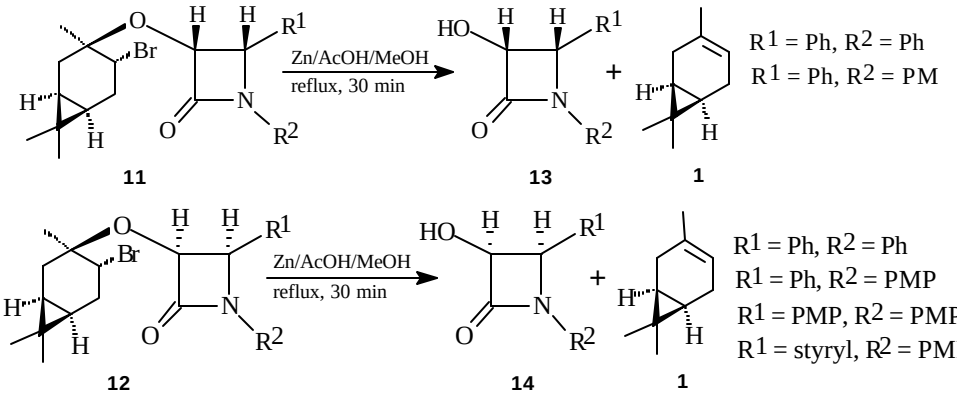


	R^1	R^2		R^1	R^2		R^1	R^2
a.	Ph	PMP	**e.**	Styryl	Ph	**i.**	Styryl	α-methylbenzyl
b.	Ph	Ph	**f.**	Styryl	PMP	**j.**	Styryl	t-butyl
c.	PMP	PMP	**g.**	Styryl	n-Propyl	**k.**	Styryl	Bz
d.	Ph	Bz	**h.**	Styryl	cyclohehyl	**l.**	Styryl	furfuryl

Chapter II Practical synthesis of optically pure 3-hydroxy b-lactams by zinc induced removal of chiral auxiliary.

The removal of the chiral auxiliary of β-lactams **11** & **12** was effected under mild conditions using zinc/acetic acid to get optically pure 3-hydroxy-β-lactams (**13** or **14**) in almost quantitative yields (scheme 3). In this process the (+)-3-carene, used as chiral auxiliary was recovered in almost quantitative yield. One of compounds, 3-hydroxy-4-phenyl-β-lactam can serve as a key intermediate for the taxol side chain.

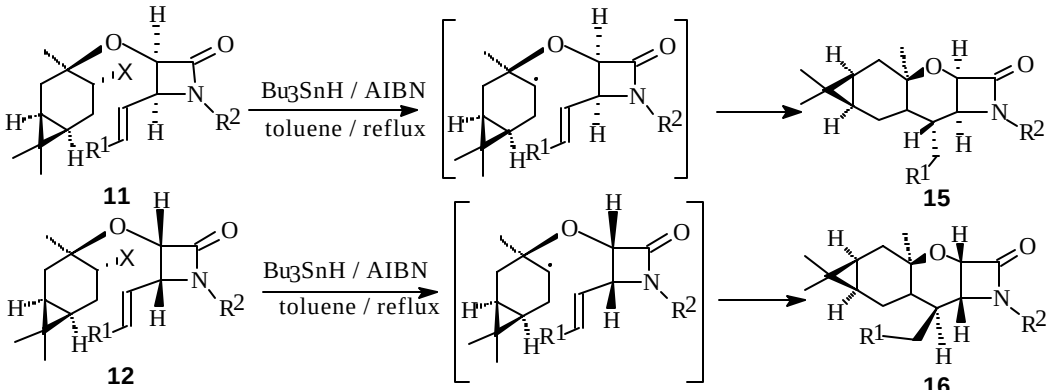
Scheme - 3



Chapter III Diastereoselective synthesis of tetracyclic b-lactams using radical cyclisation

The halo series of β-lactams (**11** & **12**) with 4-styryl or 4-methacrolyl substitutents were prepared in good yields with moderate diastereoselectivity. The diastereomers were separated by column chromatography. These β-lactams (**11** & **12**) on treatment with Bu_3SnH underwent 6-exo trig radical cyclisation with complete diastereoselctivity to furnish novel tetracyclic azetidinones (**16** or **17**) in high yields (scheme 4). The absolute stereochemistry was established from the single crystal X-ray analysis of one of the compounds.

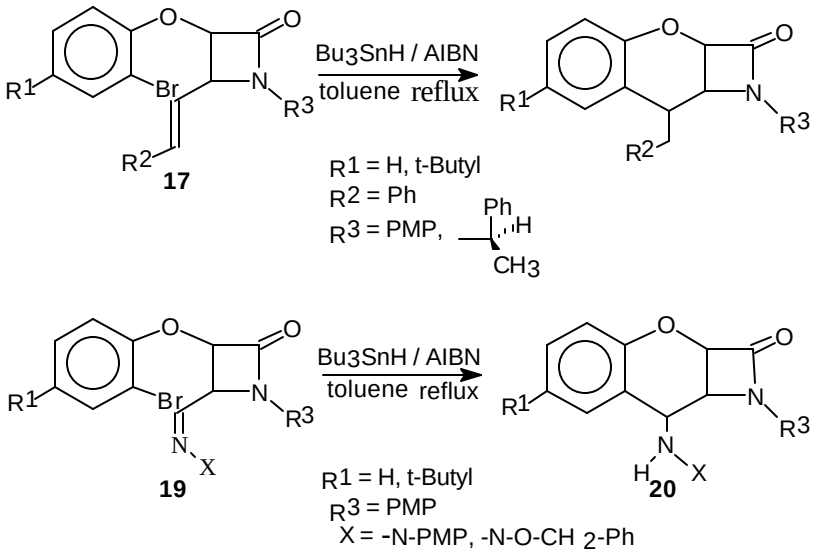
Scheme – 4



Chapter IV **Heterocyclic ring formation using radicals derived from aromatic system**

The reactivity and selectivity of the radicals derived from the aromatic substrates has also been studied in radical cyclization of appropriately substituted β-lactams. The reactivity of styryl double bond as radical acceptor in C-C bond formation was appreciably high (scheme 5). Similarly, C-3 imino and oxime ether variants of azetidinones were prepared and used as radical traps with effective C-N bond formation.

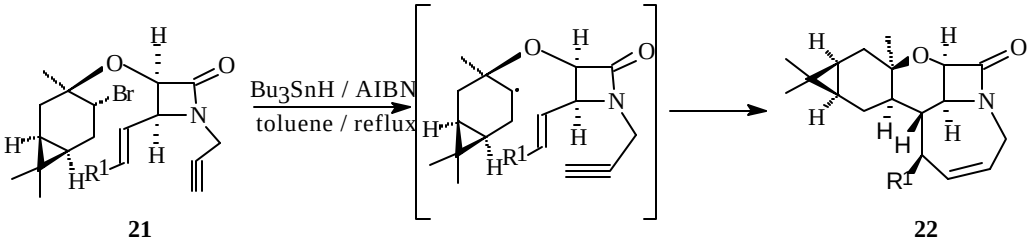
Scheme – 5



Chapter V **Tandem radical cyclisation : diastereoselctive synthesis of 3:6:6:6:4 ring system**

Viability of tandem radical cyclisation was studied by preparing corresponding radical cascade (scheme 6). The cyclisation resulted in the formation of 3:6:6:4:6 type of fused ring system with appreciably high diastereoselectivity.

Scheme – 6



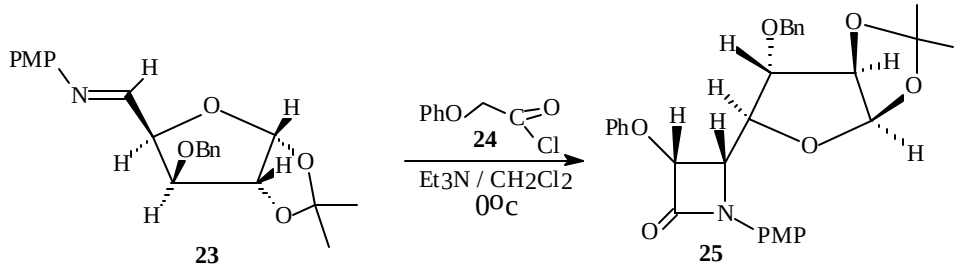
21 **22**

R^1 = Ph

Chapter VI Stereoselective synthesis of *cis*-β-lactams using glucose derived chiral aldehyde *via* asymmetric staudinger reaction.

Diastereospecific synthesis of β-lactam (scheme 7) was achieved in asymmetric Staudinger reaction by using chiral imine derived from protected glucose derivative. The absolute stereochemistry of the β-lactam was determined from single crystal X-ray analysis.

Scheme – 7



23 **25**

Note : *Compound numbers in the synopsis are not related to the numbers in the Chapters*

Chapter I

Diastereoselective Synthesis of *b*-Lactams Using Chiral Acids Derived From (+)-3-Carene

---

The most exciting phrase to hear in science, the one that heralds the most discoveries, is not 'Eureka!' (I found it!) but 'That's funny...'

Isaac Asimov

1.1 : Introduction

History

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

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

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

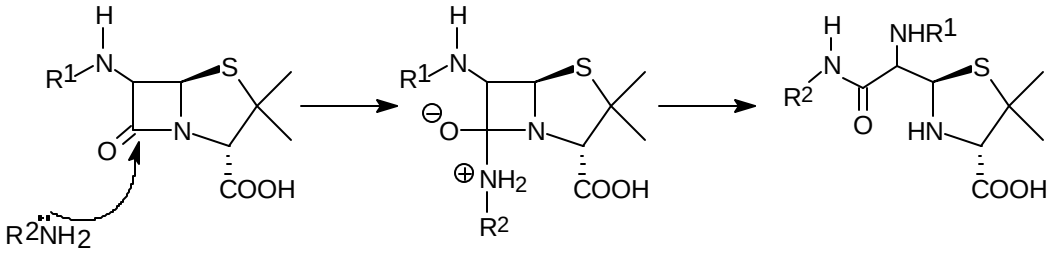
Mode of Action

The biological activity of these antibiotics is mainly due to the presence of *b*-lactam ring. The SAR studies[5] have shown that the essential requirement for an antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in an active form to the target site. Penicillin binds to the so-called 'penicillin-binding proteins' (PCBs) which are specific molecules on the inner membrane of the cell

wall. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[6] The schematic representation of this phenomenon in the case of penicillin *(Scheme 1)* and cephalosporin *(Scheme 2)* is shown below.

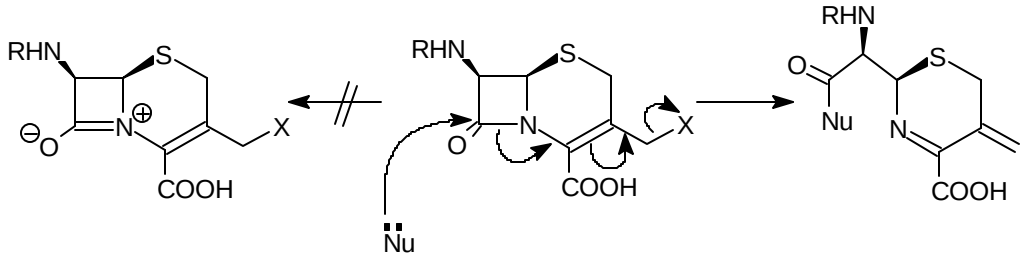
Biological Activity of Penicillin[7]

Scheme 1



Biological Activity of Cephalosporin[8]

Scheme 2



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

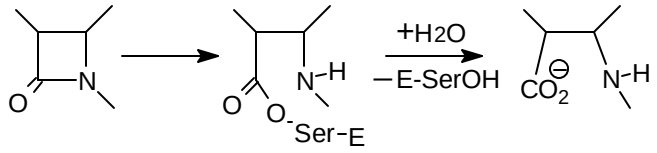
b-Lactamases[9] are the enzymes that bacteria produce to defend themselves against ***b***-lactam antibiotics. There are mainly two classes of ***b***-lactamases:

1) Serine enzyme lactamases

2) Zinc enzyme lactamases.

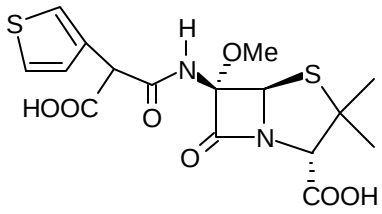
The serine type enzyme lactamases act by covalent acyl enzyme mechanism *(scheme 3)*.[9] These are further classified into class A, class C and class D. The zinc enzyme lactamases are class B type lactamases and they act by non-covalent intermediate method.

Scheme 3

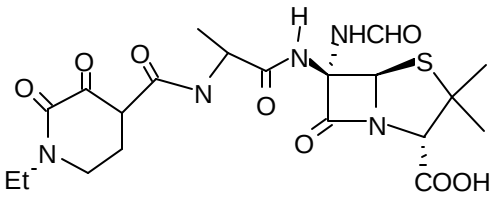


The *b*-lactamases affect the action of *b*-lactam antibiotics making it inactive against the bacteria. This drastically limits the therauptic use of *b*-lactam antibiotics and the bacteria are said to have developed resistance against the drug derivative. The phenomenon of bacterial resistance led to a serious research in this field and paved the way for development of novel *b*-lactam antibiotics called as the *b*-lactamase inhibitors.[10,11] Inhibitor, as the name suggests, inhibits the action of lactamases. Basically *b*-lactamase inhibitors are compounds which are structural variants of the classical *b*-lactams with modified skeleton. They may not have antibiotic activity of their own but they are used in the combination with biologically active antibiotics. Specifically, they associate themselves with the lactamases, thereby preventing prior interaction of *b*-lactamase with the *b*-lactam antibiotics. The antibiotic activity of the *b*-lactams is thereby safeguarded and it can penetrate through the bacterial cell wall.

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



Temocillin



Formidacillin

With the extensive SAR studies and the discovery of novel, biologically active molecules the earlier conceptions regarding the comparison of chemical and biological activity have started becoming somewhat irrelevant. Earlier it was suggested that the antibacterial activity was mainly due to inherent strain in the 4-membered ring or due to the reduced amide resonance. But both, kinetic and ground state effects do not indicate a significant degree of inhibition of amide resonance in penicillin and cephalosporin. The

bicyclic *b*-lactams also does not show exceptional reactivity. Monocyclic *b*-lactams with suitable electron withdrawing substituents may be as reactive as bicyclic *b*-lactams. Strained *b*-lactams are not necessarily better antibiotics and so the biological reactivity is not directly correlated with the chemical reactivity.

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

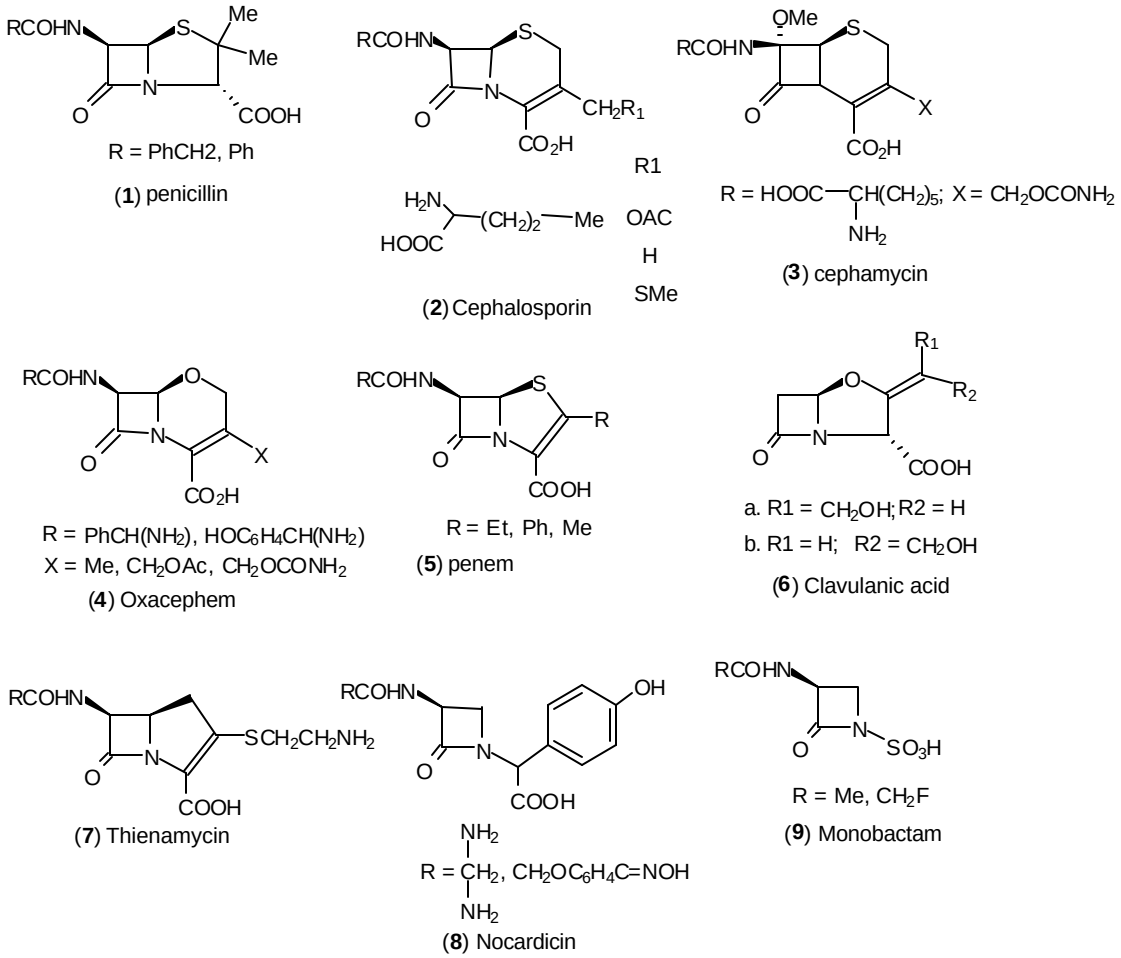
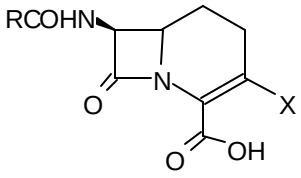


Fig. 1. Different classes of *b*-lactam antibiotics.

Recent Developments in the Field of b-Lactam Antibiotics

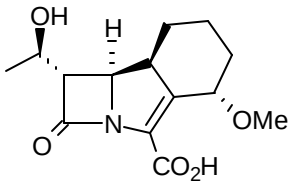
Carbacephems,[13] which are the carbon analogues of cephalosporins, are sensational new antibiotics. Superior stability of this antibiotic over cephalosporin and the ease with which it can be derivatised at 3-position, is synthetically attractive. With the approval of first carbacephem, loracarbef (lorabid)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



Lorarbid

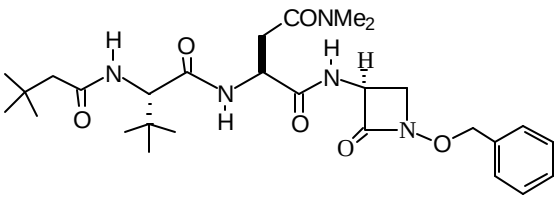
(X = Cl, R = $PhCH_2NH_2$)

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

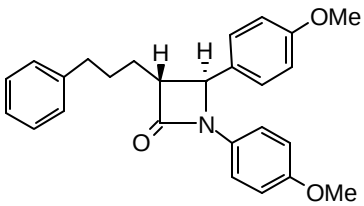


GV 104326 (tribactam)

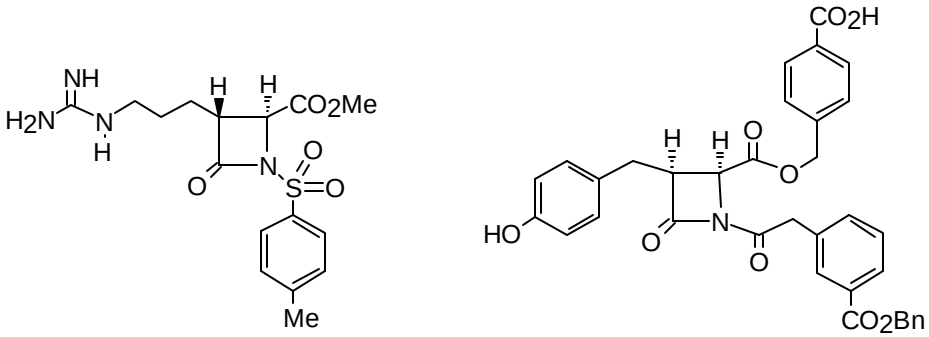
Discovery of new active *b*-lactam compounds such as thrombin inhibitor,[15] prostate specific antigen,[16] human cytomegalovirus protease[17] or the new cholesterol absorption inhibitor[18] has renewed interest in the field.



Human Cytomegalovirus Protease Inhibitor



Cholesterol absorption Inhibitor



General Methods of β-Lactam Synthesis

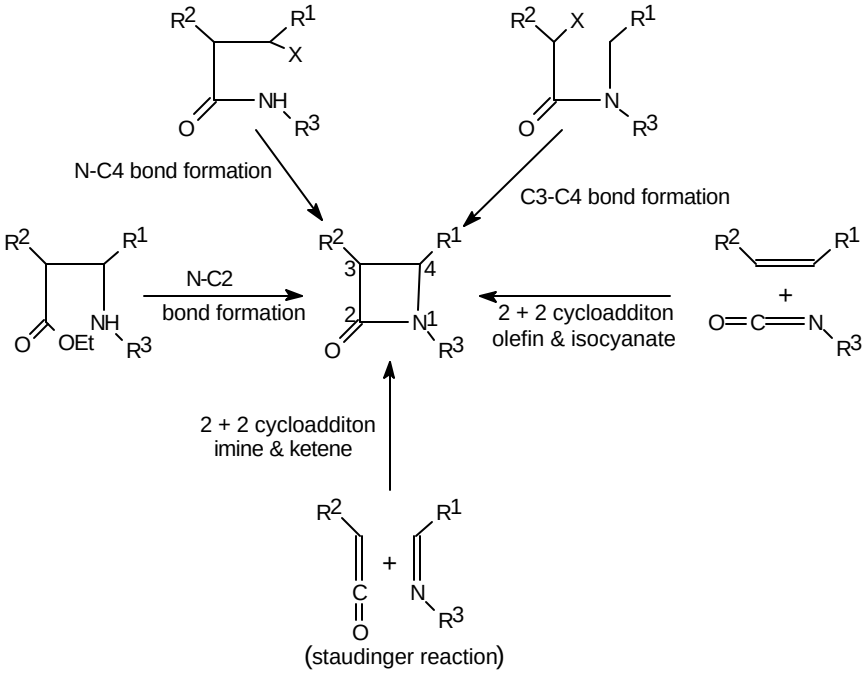
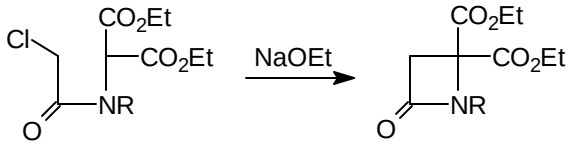


Fig. 2. Schematic representation of conventional methods of *β*-lactam synthesis.

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

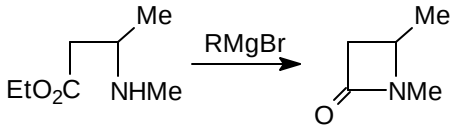
$C_3 - C_4$ Bond Formation[19]

Scheme 4



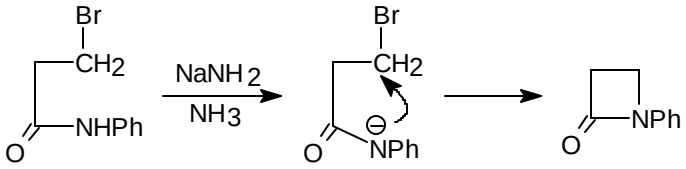
N – C_2 Ring Closure[20]

Scheme 5



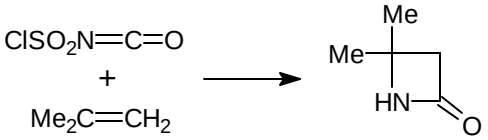
N – C_4 Bond Formation[21]

Scheme 6



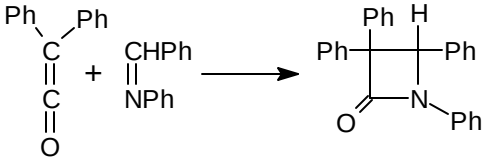
Cycloaddition Reactions[22]

Scheme 7



Staudinger Reaction[23]

Scheme 8

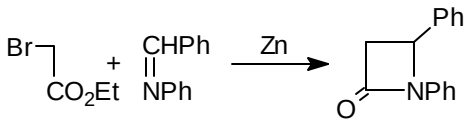


Reformatsky Type Reaction Approach

Gilman-Speeter Approach

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

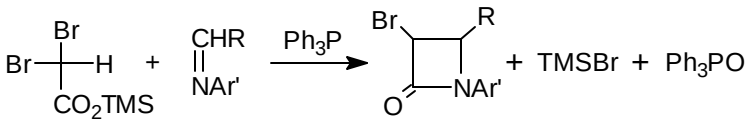
Scheme 9



Manhas α-Bromo-β-Lactam Approach

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

Scheme 10



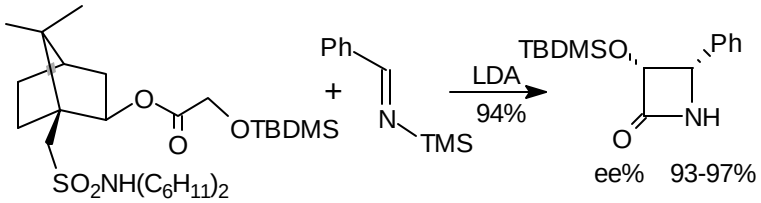
Asymmetric Synthesis of β-Lactams

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

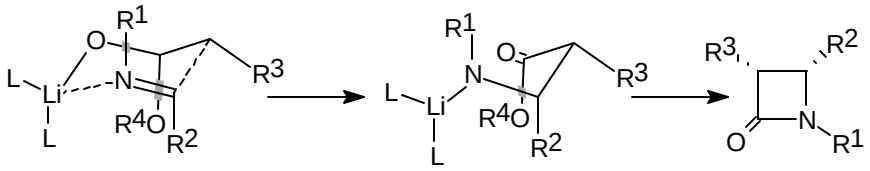
Ester Enolate-Imine Condensation[27]

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

Scheme 11



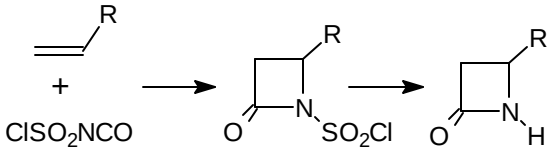
The proposed Transition State for the ester enolate-imine cycloaddition reaction involved a six membered transition state[29,30] similar to aldol condensation.



Isocyanate-Olefin Cycloaddition[31]

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

Scheme 12



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

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

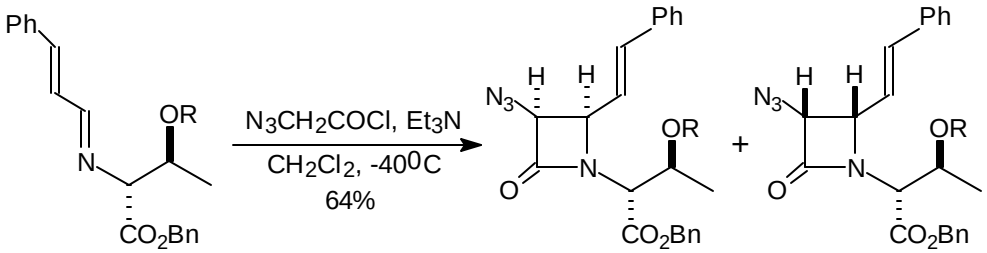
1) Chiral imine and achiral acid chloride
1) Achiral imine and chiral acid chloride
2) Double stereodifferentiation in which both components i. e. acid chloride and imine are chiral.

Asymmetric Induction Using Chiral Imines

Among the chiral imines the possible combination can be chiral aldehyde and achiral amine or chiral amine and achiral aldehyde. The use of chiral aldehydes derived from sugar derivatives is well known. The diastereoselectivity with the use of these aldehydes is also exceptionally high (This will be discussed in details, in the Chapter 6).

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

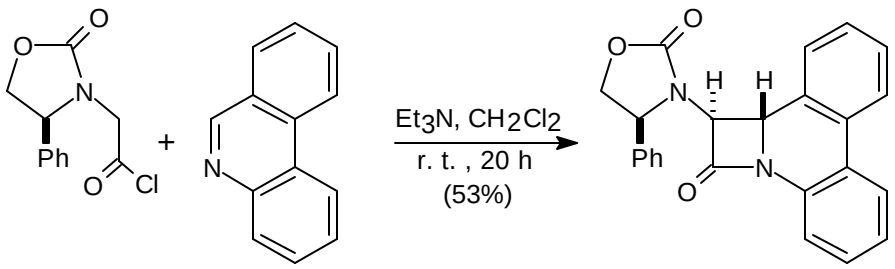
Scheme 13



R: TPS ($SiPh_3$) 95:5
R: TBS ($SIMe_2{}^tBu$) 90:10

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

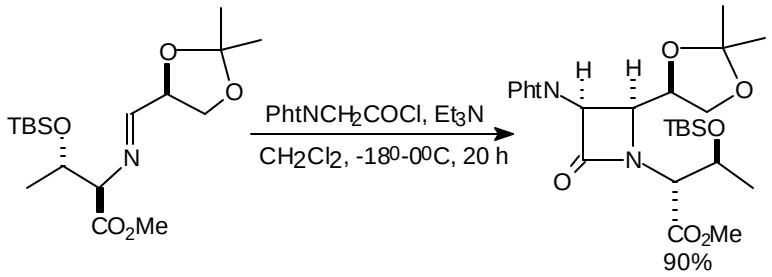
Scheme 14



The concept of double stereodifferentiation is applied with variable success to the [2 + 2] cycloaddition reaction. High levels of double asymmetric induction is observed

when Evans-Sjogren ketenes and imines derived from (*R*) & (*S*)-α-amino acid esters were used *(scheme 15)*.[35]

Scheme 15



Mechanism (Acid Chloride-Imine Cycloaddtion)

According to the accepted model, the reaction between acyl chlorides and imines is assumed to proceed thorough in situ formation of ketene,[36] followed by interaction with the imine to form a zwitterionic intermediate, which undergoes an electrocyclic conrotatory ring closure to give the *b*-lactam ring (Fig. 3).

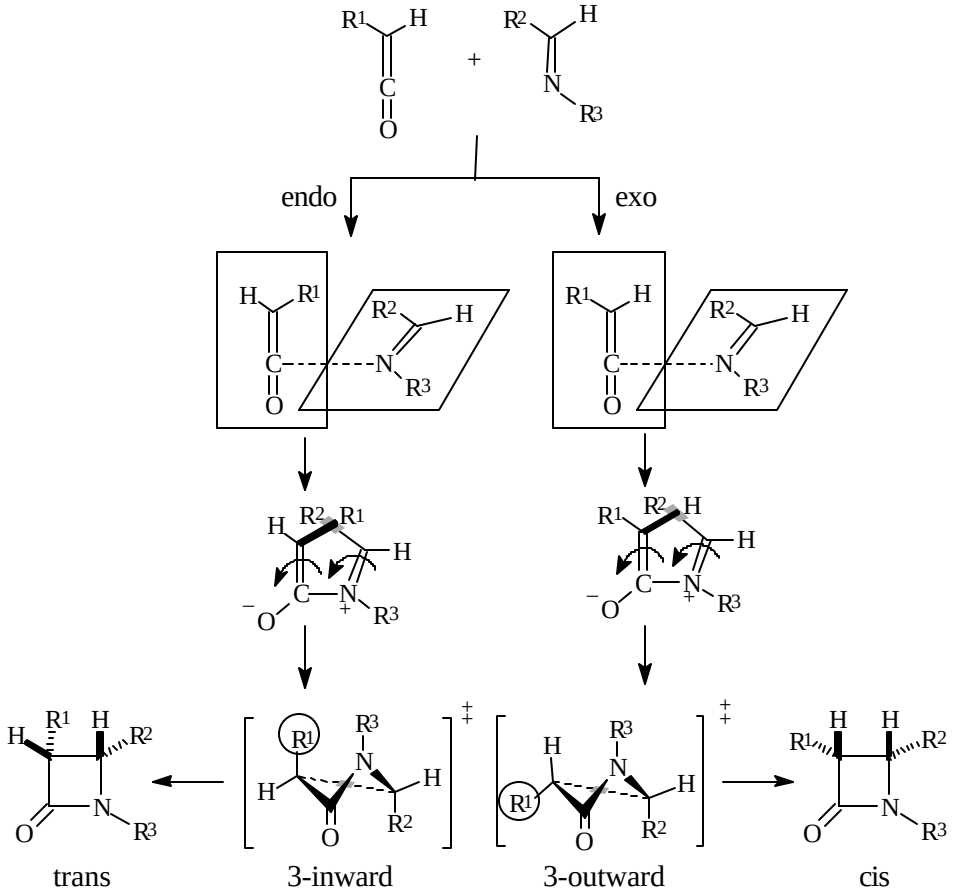


Fig. 3. Mechanism of Ketene – Imine cycloaddition.

In general, (E) imines lead preferentially to the more hindered *cis*-**b**-lactams, while (Z) imines give predominantly the corresponding trans isomers.[32c,37]

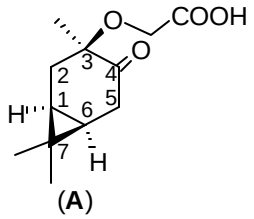
Theoretical studies undertaken to establish the origin of the cis/trans stereoselection revealed that the relative energies of the rate-determining transition states, leading from zwitterions to **b**-lactams, are dictated not necessarily by steric effects, but by electronic torquoselectivity.[38] For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

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

Section A : Synthesis of 3-Hydroxy Protected *b*-Lactams: Effect of Steric Bulk on Diastereoselectivity

1.2 : Present Work

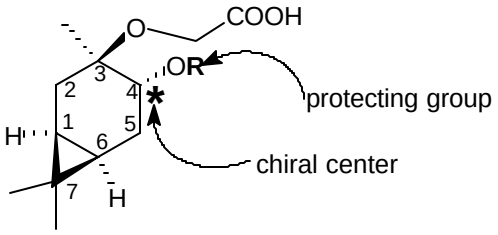
The use of chiral acids in the asymmetric synthesis of *b*-lactams has been reported to give moderate chiral induction. Our group has reported previously,[39] asymmetric synthesis of 3-hydroxy-*b*-lactam, a precursor for taxol side chain, using sterically demanding chiral acid (**A**), derived from (+)-3-carene. It was used as a ketene precursor in the Staudinger reaction and was removed by oxidative cleavage using MCPBA. However, the overall efficiency of the chiral acid (**A**) was moderate as the resulting *b*-lactams were obtained as a diastereomeric mixture in about 60:40 ratio. The other important weakness being, that it was difficult to separate the diastereomers formed.



(**A**)

The carane system being a sterically demanding moiety, was expected to differentiate the chiral faces by the virtue of its rigid bicyclic skeleton with *gem*-dimethyl group on cyclopropane ring. The moderate diastereoselectivity in Staudinger reaction with this acid (**A**) can be attributed to the presence of planar group in the form of C-4 keto functionality, which not only removed the chirality at C-4 center but also flattened the ring to a considerable extent.

Then, does the chiral center at C-4 influences the diastereoselectivity in the ketene-imine cycloaddition? To answer this question, we thought that it was worthwhile to study the modification at the C-4 center of the carane system and the subsequent effect on the diastereoselectivity in cycloaddition reaction.



Acid (**B**)

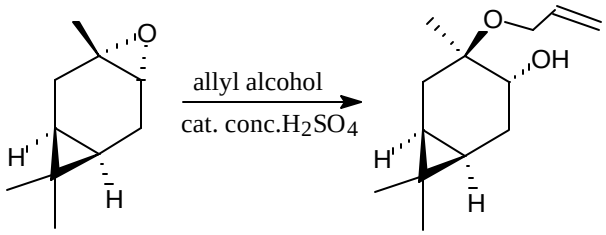
This section deals with the synthesis of functionally substituted, C-4 derivatised carane acids (**B**) and their use as chiral ketene precursor in the Asymmetric Staudinger reaction.

1.3 : Results & Discussion

***Preparation of Chiral alcohol* 1.02**

Carane epoxide was used as a starting material. The treatment of carane epoxide **1.01** with allyl alcohol in acidic conditions underwent epoxide opening in a highly regioselective manner to give substituted 3-allyloxy-4-caranol **1.02** as a major product *(Scheme 16)*.

Scheme 16



1.01 **1.02**

A small amount of other isomeric product, 4-allyloxy-3-caranol was also obtained during the reaction, which was separated by fractional distillation.

The IR spectrum of the alcohol **1.02** showed a broad peak at 3450 cm^{-1} typical of alcohol. The mass spectrum showed M^+ peak at 210 (2%). The ^1H NMR showed the two-cyclopropyl methine protons in the region 0.50-0.80. Two gem dimethyl groups were seen as singlets at 0.98 & 1.0, while the tertiary methyl group resonated as a singlet at 1.20. The methylene protons of the carane skeleton were seen in the region between 0.80

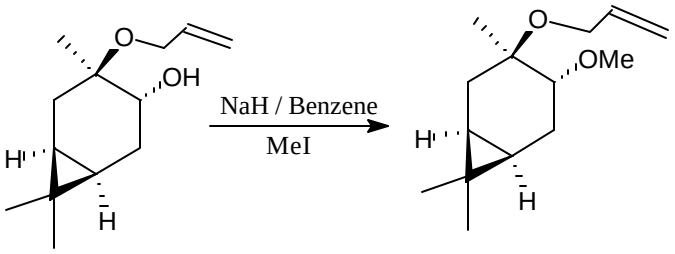
to 2.40. The methylene protons from the allyloxy group appeared as a doublet at 3.95 with coupling constant J = 5.50 Hz. The terminal olefin protons of the allyloxy group were seen as multiplets in the region 5.05-5.50. The remaining olefinic proton of the allyl group appeared in the region 5.80-6.10 as a multiplet.

The secondary alcoholic group of **1.02** was protected using different protecting groups.

***Preparation of* 1.03a**

The alcohol **1.02** was treated with NaH in benzene so as to form a sodium salt, which on quenching with methyl iodide gave methyl ether **1.03a** in 75% yield *(Scheme 17)*.

Scheme 17



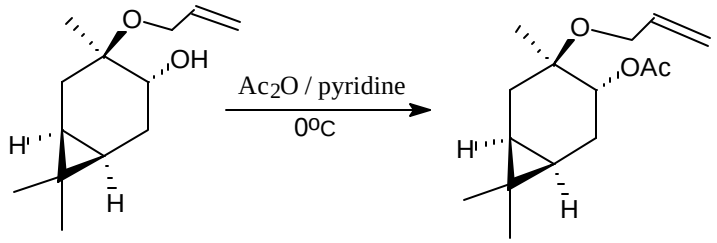
1.02 **1.03a**

The mass spectrum of ether **1.03a** showed a molecular ion peak at 222 (2%). The ^{1}H NMR was similar to the alcohol **1.02** and it showed two gem dimethyl groups in the form of two singlets at 0.94 & 0.97. The tertiary methyl group at C-3′ appeared as a singlet at 1.20 while the methylene protons from the carane part appeared as multiplets in the region 1.5 to 2.40. The proton at C-4′ appeared at 3.05 as a dd with J = 8 & 10 Hz. The methoxy group appeared as a singlet at 3.37 while the methylene protons of the allyloxy part appeared as a multiplet in the region between 3.80 to 4.2. The terminal olefin protons of the allyl group appeared as a multiplet between 5.0 to 5.40 and the other olefinic proton resonated as a multiplet, slightly downfield, in the region of 5.75 to 6.10.

***Preparation of* 1.03b**

The alcohol **1.02** on treatment with acetic anhydride in presence of pyridine at 0°C gave 4-acetoxy derivative **1.03b** in 70% yield *(Scheme 18)*.

Scheme 18



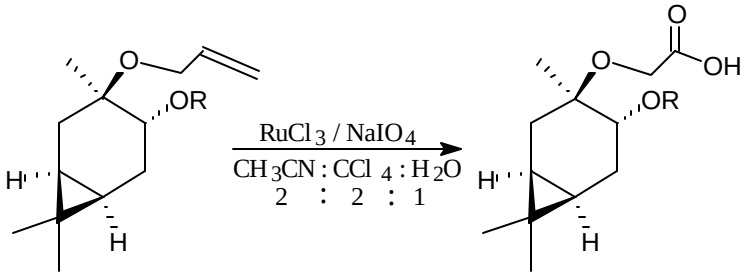
1.02 **1.03b**

The IR of the acetate **1.03b** showed a sharp peak at 1750 cm^{-1} for the carbonyl of the acetoxy group. The ^1H NMR spectrum showed two singlets at 0.97 & 1.0 for gem dimethyl groups. The other methyl group appeared as a singlet at 1.27. The methyl from –OAc group appeared as a singlet at 2.02. The proton at C-4 was appreciably deshielded and appeared as a dd with J = 8.5 & 10 Hz at 4.78. The olefinic protons from the allyl group appeared in the region of 5.0 to 6.0.

***Preparation of Acid* 1.04a & 1.04b**

The oxidiation of **1.03a** & **1.03b** under *Lemieux-Von Rudloff* conditions (catalytic $RuCl_3$ & $NaIO_4$) in a mixed solvent system of acetonitrile, carbontetrachloride and water in the ratio of 2:2:1, gave the acids **1.04a** (45%) & **1.04b** (40%) *(Scheme 19)*.

Scheme 19



1.03a,b **1.04a,b**

a, R = Me
b, R = Ac

The acid **1.04a** showed M^+ peak in mass spectrum at 242 (0.5%). The IR spectrum showed a broad peak in the region 3000-3500 cm^{-1} typical of an acid. The ^1H NMR spectrum showed two singlets at 0.90 & 0.93 for two gem dimethyl protons. The methyl at C-3′ appeared as a singlet at 1.18 while the methylene protons appeared in the region

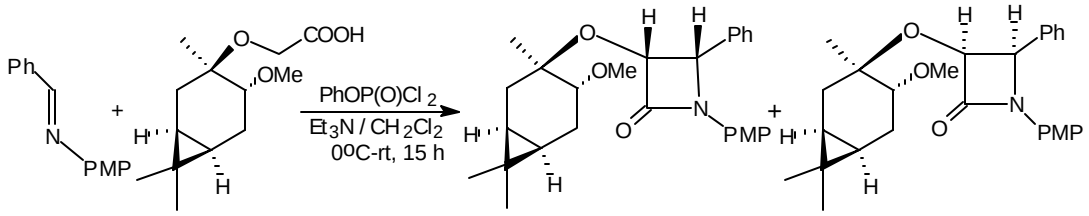
between 1.0 to 2.40. The methoxy protons appeared as a singlet at 3.25. The methylene protons on the carbon adjacent to the acid group were diastereotopic and appeared as two doublets at 4.05 & 4.20 with J = 21 Hz. The acidic -COOH proton appeared as a broad peak in the region of 7.3 to 8.4.

The acetoxy acid **1.04b** could not be obtained in the analytically pure form. The IR of a sample (>95% purity) showed a broad peak in the region 3000-3600 cm^{-1} typical for an acid. The ^1H NMR spectrum showed two singlets at 0.98 & 1.0 for the two gem dimethyl protons. The C-3′ methyl group appeared as a singlet at 1.14 while the methyl group of the acetoxy group appeared as a singlet at 2.20. The methylene protons adjacent to the acid group appeared as a multiplet in the region 3.90-4.10. The H-4 proton appeared as a dd at 4.66, with J = 8 & 9.50 Hz. The acidic proton resonated as a broad singlet in the region of 6.90-8.10.

***Preparation of β-Lactam* 1.05a & 1.06a**

The acid **1.04a** on reaction with imine in presence of Et_3N and phenyl dichlorophosphate gave diastereomeric mixture of β-lactam **1.05a** & **1.06a** in 60% yield. The diastereomers **1.05a** & **1.06a** were obtained in 61:39 ratio, as could be confirmed from the ^1H NMR of the diastereomeric mixture.

Scheme 20



1.04a **1.05a** **1.06a**

The mass spectrum showed a significant molecular ion peak at 435 (50%). The IR specturm of the diastereomeric mixture showed β-lactam carbonyl amide peak at 1740 cm^{-1}.

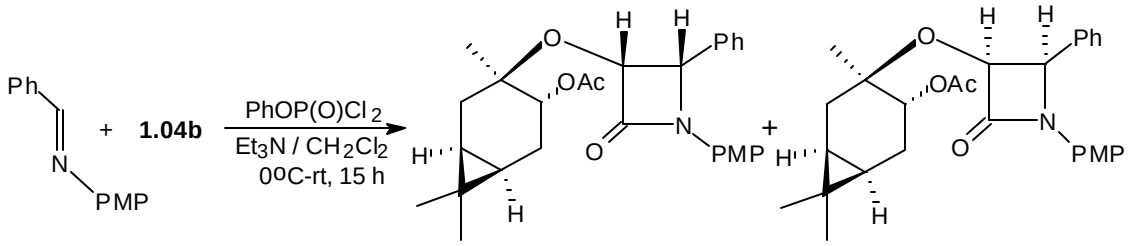
^1H NMR spectrum showed gem dimethyl peaks as singlets at 0.74, 0.79, 0.86 & 0.90. The C-3′ methyl appeared as two singlets at 1.03 & 1.10 from the two diastereomers. The ring protons of the carane system appeared as multiplets in between

0.35-2.80. The methoxy protons of the PMP as well as the C4′-OMe appeared as singlets at 2.86, 3.36 & 3.70. The *b*-lactam protons H-4 appeared as a doublet at 5.01 with J = 4.8 Hz & 5.10 with J = 5.1 Hz respectively. The other *b*-lactam proton H-3, appeared as a doublet at 5.26 (J = 5.1 Hz) & 5.47 (J = 4.8 Hz). The aromatic protons appeared as multiplets between 6.7-7.60.

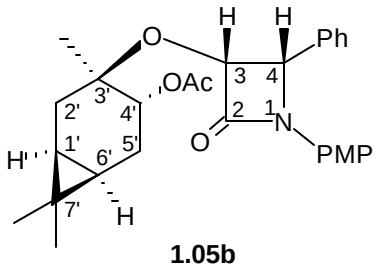
***Preparation of b-Lactam* 1.05b & 1.06b**

The carane acid **1.04b** was treated with imine using phenyldichlorophosphate as an acid activator, in the presence of Et_3N as a base. The *b*-lactam was isolated as a diastereomeric mixture of **1.05b** & **1.06b**. The ^1H NMR of the diastereomeric mixture showed peaks in the ratio 60:40 indicating a diastereomeric excess of 20%. From the diastereomeric mixture, the major diastereomer was separated by fractional crystallization using pet ether/ethyl acetate system to get **1.05b** as a white crystalline solid with mp 167-168°C *(scheme 21)*.

Scheme 21



***NMR of Acetate* 1.05b**



1.05b

The IR spectrum of **1.05b** showed a peak at 1735 cm^{-1} for *b*-lactam carbonyl. The ^1H NMR showed two singlets at 0.96 and 0.97 for gem dimethyl groups attached to the C-7′, while the methyl at C-3′ could be seen at 1.15. The singlet at 1.82 accounted for the

methyl of the acetate group at C-4′. The *b*-lactam proton H-4, was seen as a doublet at 5.08 while the other proton, H-3, resonated as a doublet at 5.16. The coupling constant (J = 5.0 Hz) was typical for a *cis* *b*-lactam. Triplet at 4.60 could be assigned to the proton H-4′, to which the acetoxy group is attached. A sharp singlet at 3.72 was due to the methoxy group of *p*-anisyl moiety. The aromatic protons were seen as multiplets in the region 6.70-7.50.

The ^{13}C NMR spectrum of the diastereomeric mixture (**1.05b & 1.06b**) confirmed the backbone of the molecule. The peaks in the region 19 to 32 belonged to the carane skeleton, which included the three-methyl groups and the methine carbons. The signals from the methoxy group of PMP moiety as well as the *b*-lactam carbons resonated as 4 peaks at 55.41, 63.13, 73.61 and 77.98. The aromatic carbons were seen in the region between 114 to 134. The *b*-lactam carbonyl peak from C-2 appeared at 165.42 while the carbonyl peak of the acetate resonated at 170.33.

***X-ray Crystal Structure Determination of* 1.05b**

To decide the relative stereochemistry of **1.05b**, its crystal structure analysis was undertaken. The *b*-lactam **1.05b** was crystallized from pet ether/dichloromethane system to obtain suitable crystals for single crystal X-ray analysis.

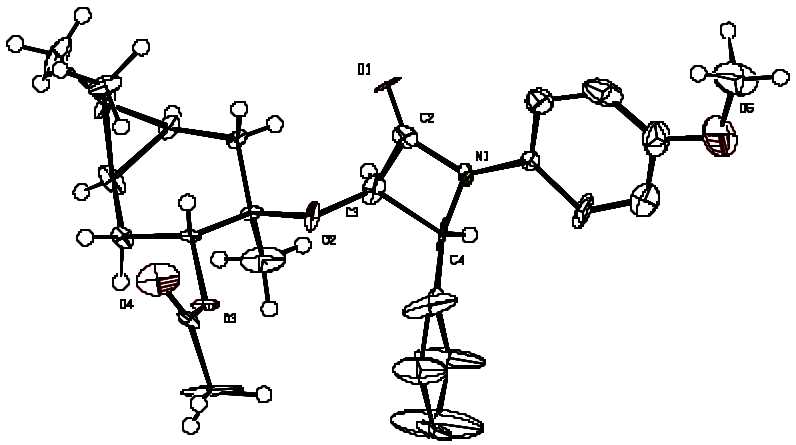


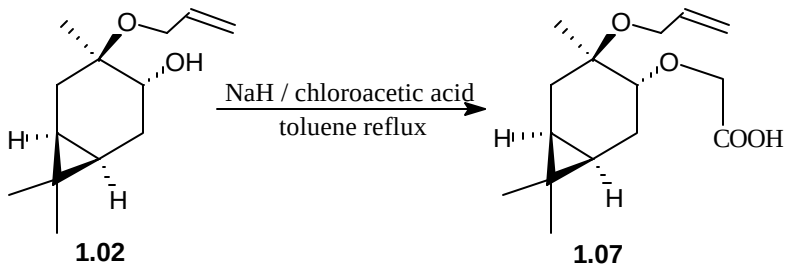
Fig. 4. *ORTEP* diagram of **1.05b**.

The X-ray structure of **1.05b** (Fig. 4) clearly indicated the absolute stereochemistry for newly formed stereocenters as 3*R*, 4*S* on the basis of known absolute stereochemistry of carane ring system which is 1′*R*, 3′*R*, 4′*R*, 6′*S*.

***Preparation of Acid* 1.07**

The sodium salt of alcohol **1.02** on refluxing with chloroacetic acid in toluene provided carane acid **1.07** *(Scheme 22)*.

Scheme 22



1.02 **1.07**

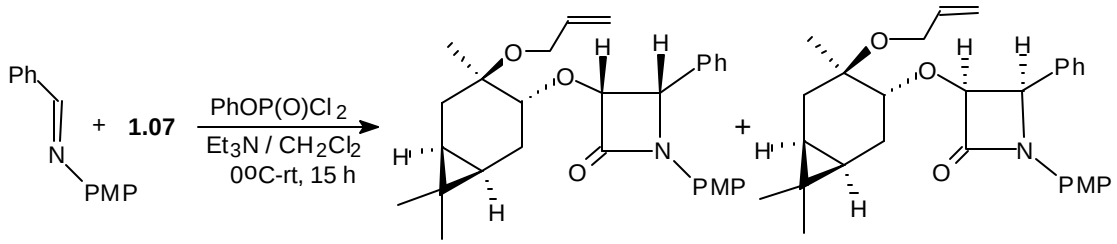
The mass spectrum of allyloxy acid **1.07** showed a molecular ion peak at 268 (6%). In the IR spectrum of **1.07** was seen, a broad peak in the region of 3050-3650 cm^{-1}, typical of COOH group. The ^{1}H NMR showed two singlets at 0.95 and 1.0 for two gem dimethyl group while the other methyl group was seen as a singlet at 1.30. The H-4′ proton was seen as a multiplet in the region 4.0 to 4.1. The diastereotopic protons from –CH2-COOH were seen as two doublets at 3.90 & 4.30 with J = 18 Hz. The terminal olefinic protons from $-CH=CH_2$ of the allyl group were seen as a multiplet between 5.18-5.40. The other olefinic proton was appreciably downfield and resonated as a multiplet in the region 5.75-6.05.

The ^{13}C NMR spectrum of acid **1.07** showed peaks at 25.60 & 30.00 for the two methylene of the carane ring. Other two methylenes groups from $O-CH_2-COOH$ and $O-CH_2$ (allyl) were seen at 62.54 and 67.56. The terminal olefinic carbon appeared at 117.38.

***Preparation of* 1.08 & 1.09**

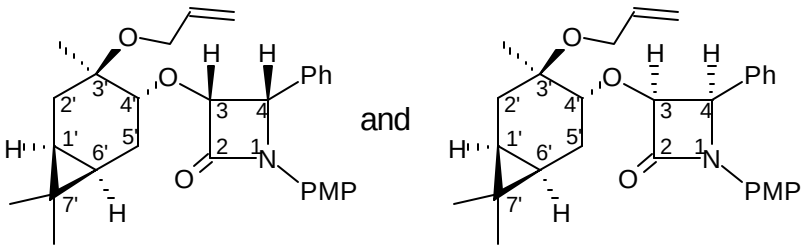
The carane acid **1.07** was treated with imine using phenyldichlorophosphate as an acid activator, in the presence of Et_3N as a base. The *b*-lactam **1.08** & **1.09** was isolated as an inseparable diastereomeric mixture. The diastereomeric ratio was 65:35, which was deduced, from the ^{1}H NMR of **1.08** & **1.09** *(Scheme 23)*.

Scheme 23



The IR of the diastereomeric mixture showed a typical amide peak of the *b*-lactam ring carbonyl, at 1740 cm^{-1}. Molecular ion peak at 461 (17%) in the mass spectrum confirmed the molecular weight of the compound.

***^{1}H NMR of* 1.08 & 1.09**



The ^{1}H NMR spectrum of diastereomeric mixture of **1.08** & **1.09** showed singlets at 0.50, 0.70, 0.85, 0.95 and 1.20 for gem dimethyls attached to the C7′ and the methyl group at C3′. The methoxy group from the *p*-anisyl could be seen as two singlets at 3.73 and 3.74 for the diastereomeric mixture. The methylene protons of the allyloxy group were seen as close dd at 2.90 and 3.30 with coupling of 8 and 10 Hz. The H-4′ proton was seen as a multiplet in the region 3.80 to 4.10. The terminal olefinic protons from the allyloxy group resonated as a multiplet in the region 5.05 to 5.40. The other olefinic proton of the allyl group was seen downfield and appeared as a multiplet in the region

5.70 to 6.10. The *b*-lactam proton H-3 appeared as a doublet at 5.65 with coupling constant J = 4.7 Hz. H-4, the other *b*-lactam proton, was seen around 5.20. A high coupling constant indicated a cis *b*-lactam being present. The aromatic peaks resonated in the region 6.70 to 7.50.

The ^{13}C NMR of the diastereomeric mixture showed methylene carbons from the carane skeleton at 25.44, 26.51, 28.36 and 28.53. The methylene carbons of the allyloxy part resonated at 62.19 & 62.61 while the methoxy carbon of the PMP group appeared at 55.41. The *b*-lactam carbon G3 resonated at 62.48 & 63.20 and the G4 at 84.84 & 86.00 respectively. The C4′ ethereal carbon resonated at 79. The terminal olefinic carbon of the allyloxy group resonated as two peaks at 114.95 and 115.12. The aromatic protons were seen in the region 128 to 156. The β-lactam amide carbonyl at C2 was seen as two peaks at 164 and 166 for the diastereomeric mixture.

1.4 : Summary

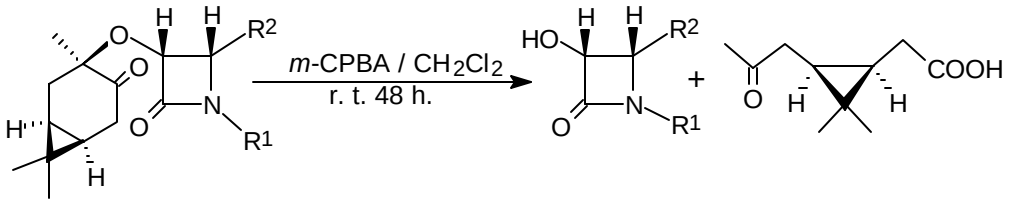
(+)-3-Carene could be functionalised in a practical manner to synthesize a series of 4-hydroxy protected of *b*-lactams in good yields. The diastereomers could be separated by fractional crystallization in case of 4-acteoxy-β-lactam. The absolute stereochemistry of these derivatives was established from the single crystal X-ray analysis of the 4-acetoxy-β-lactam derivative. The overall low diastereoselectivity (de~20-25%) suggested that the chiral center at C-4 of acid doesn't have appreciable effect on the stereochemical outcome of the cycloaddition reaction. Moreover there is no appreciable influence of different protecting groups for hydroxy fuction at C-4, on the stereochemical outcome of the cycloaddition reaction.

Section B : Synthesis and Systematic Study in *b*-Lactam Ring Construction Using Ketenes Derived from Halo Carane Derivatives.

1.5 : Present Work

Earlier, we have reported the synthesis of 3-hydroxy-*b*-lactams by oxidative cleavage of carane based chiral auxiliary with keto functionality at C-3, using MCPBA. However, the chiral auxiliary could not be isolated and destruction of chiral auxiliary occurred during oxidative cleavage *(Scheme 24)*.[39]

Scheme 24



The possible solution to this problem involved functionalisation of the carane skeleton with an easily removable group. This prompted us to design and synthesize a chiral acid with a functional group that can be easily removed. Halides like Br and Cl were promising functional groups in this context. They could provide a handle, useful in the removal of carane part from the *b*-lactam derivatives. Also, functionalisation of the 4-halo systems can lead to the synthesis of novel multicyclic *b*-lactam derivatives.

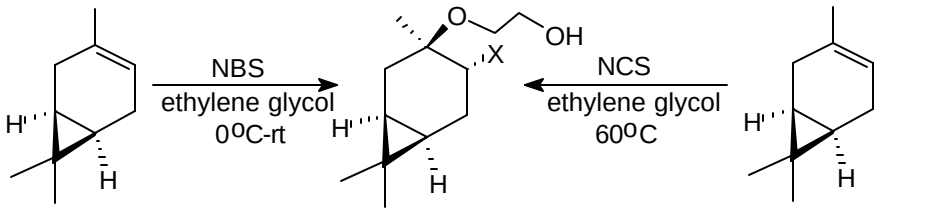
This section presents the synthesis of novel *b*-lactam derivatives using carane derived chiral halo acids. It mainly deals with the study regarding synthesis, characterization and structure determination of these *b*-lactam derivatives.

1.6 : Results & Discussion

Preparation of Haloalcohols 1.10a-b

(+)-3-Carene on reaction with NBS in presence of ethylene glycol at 0°C to room temperature yielded bromo alcohol **1.10a** in modest yield. Similarly, NCS reaction at 60°C gave chloro alcohol **1.10b** in 20% yield. (*Scheme 25)*.

Scheme 25



(+)-3-Carene **1.10a,b** (+)-3-Carene

a, X = Br
b, X = Cl

The IR of the bromo alcohol **1.10a** showed a peak at 3400 cm^{-1} typical of hydroxy group. The ^{1}H NMR showed 3 singlets at 0.97, 1.0 and 1.35 belonging to the gem dimethyl and the other methyl at C-3 respectively. The proton attached to the C-4 bromo center resonated as a triplet at 4.07 typical of secondary bromide.

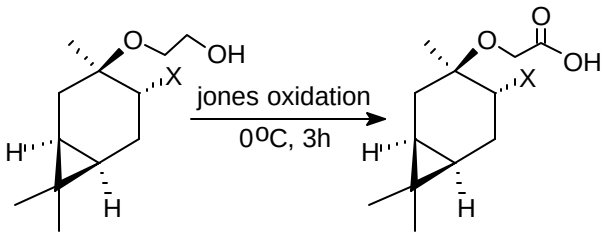
The ^{13}C NMR of **1.10a** showed peaks at 29.96 and 31.80 for the methylene carbons of the carane skeleton. The C-4 carbon attached to bromine appeared at 59.92 while the two methylene carbons from the glycol moiety resonated at 61.83 and 62.04. The C-3 carbon was located at 75.25.

The chloroalcohol **1.10b** could not be obtained in pure form and was used as such for the further reaction.

***Preparation of Acids* 1.11a,b**

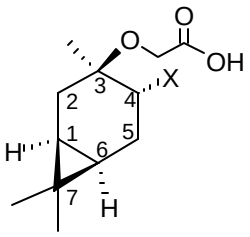
The halo alcohols **1.10a** & **1.10b** were oxidized with Jones reagent. The bromo acid **1.11a** was obtained in 80% yield, while the chloro acid **1.11b** was obtained in 60% yield *(Scheme 26)*.

Scheme 26



1.10a,b **1.11a,b** **a**, X = Br
b, X = Cl

The IR of the bromo acid **1.11a** showed a broad peak between 2600-3700 cm^{-1} typical of the acid group. The ^{1}H NMR spectrum showed three methyl groups as three singlets at 0.98, 1.0 and 1.40. The proton attached to the C-4 and the methylene protons at C-2 & C-5 were seen in the region 1.30 to 4.20. The methine protons H-1 and H-6 were seen upfield in the region 0.65-0.90, while the acidic proton was seen as a broad singlet in the region 7.30 to 9.0.



1.11a,b **a**, X = Br
b, X = Cl

The ^{13}C NMR spectrum of **1.11a** showed peaks at 30.89 and 31.99 corresponding to the two methylene carbons of the carane skeleton. The C-4 carbon and the methylene carbon from the acid function were seen at 59.75 and 59.90 respectively. The tertiary carbon C-3 appeared at 78.12.

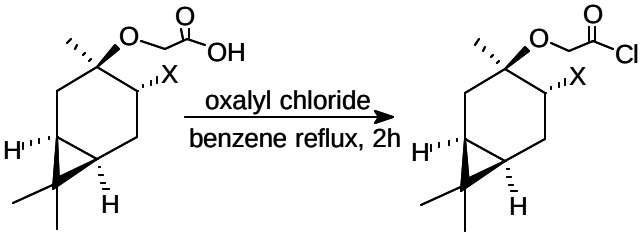
The chloro acid **1.11b** was obtained as an oil which showed IR peaks at 1750 & a broad peak in the region 2500-3600 cm^{-1}. In ^{1}H NMR spectrum methyl at C-3 appeared as a singlet at 1.40. Singlet due to the gem dimethyl groups at C-7 was seen at 1.05. The cyclopropyl methine protons H-1 & H-6 appeared between 0.65-0.90. The methylene protons at C-2 & C-5 appeared as multiplets between 1.2-2.6. A multiplet in the region 3.80-3.95 was assigned to the H-4, while the methylene protons, O-C**H_2**-COOH appeared as a multiplet in the region 44.20. The proton –COOH appeared as a broad peak between 7.5-8.2.

The ^{13}C NMR spectrum of **1.11b** was consistent with the assigned structure. The gem dimethyl at C-7, methyl at C-3 and the cyclopropyl carbons C-1 & C-6 appeared as 5 peaks at 15.82, 16.30, 19.51, 21.15 & 28.60. C-7 carbon appeared at 18.35 while the two-methylene carbons C-2 & C-5 were seen at 31.07 & 31.26. The methylene carbon of O-CH2-COOH was seen at 60.23 while G4 resonated at 65.42. The G3 carbon appeared at 79 and the –COOH was found at 175.

***Preparation of Acid Chlorides* 1.12a,b**

The acids **1.11a**,**b** were refluxed with oxalyl chloride in benzene to get corresponding acid chlorides **1.12a**,**b** (*Scheme 27*). The acid chlorides were used without further purification, in the next step.

Scheme 27

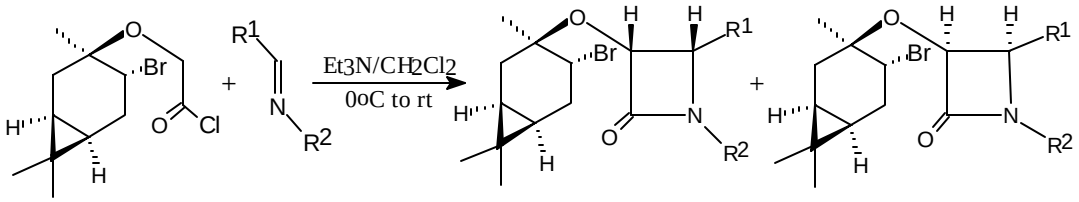


1.11a,b **1.12a**, X = Br
1.12b, X = Cl

***Preparation of b-Lactams* 1.14a-l**

The acid chloride **1.12a** reacted smoothly with imines in the presence of triethylamine in a ketene imine cycloaddition reaction (*Staudinger reaction*) to furnish a diastereomeric mixture of *cis-b*-lactams **1.14a-l** & **1.15a-l** (*scheme 28*).

Scheme 28



1.12a **1.13a-l** **1.14a-l** **1.15a-l**

a, R^1 = Ph, R^2 = Ph
b, R^1 = Ph, R^2 = PMP
c, R^1 = PMP, R^2 = PMP
d, R^1 = styryl, R^2 = PMP
e, R^1 = styryl, R^2 = Ph
f, R^1 = styryl, R^2 = Propyl
g, R^1 = styryl, R^2 = Cyclohexyl
h, R^1 = styryl, R^2 = tert. butyl
i, R^1 = styryl, R^2 = (R)-Ph(CH)Me
j, R^1 = styryl, R^2 = Benzyl
k, R^1 = styryl, R^2 = furfuryl
l, R^1 = crotyl, R^2 = Ph

The diastereomeric mixture of *b*-lactams (**1.14a-l** & **1.15a-l**) was isolated in good to excellent yield (Table 1). The diastereomeric ratio was determined from the ^{1}H NMR spectral data of the crude reaction mixture. In all the cases, a low to moderate diastereoselectivity was observed. The diastereomers were separated either by flash column chromatography or by fractional crystallization.

Table 1. Synthesis of *b*-lactams **1.14a-l** & **1.15a-l***

Entry	R^1	R^2	Yield
1.14a & **1.15a**	Ph	Ph	65
1.14b & **1.15b**	Ph	PMP	70
1.14c & **1.15c**	PMP	PMP	70
1.14d & **1.15d**	Styryl	PMP	60
1.14e & **1.15e**	Styryl	Ph	62
1.14f & **1.15f**	Styryl	Propyl	32
1.14g & **1.15g**	Styryl	Cyclohexyl	45
1.14h & **1.15h**	Styryl	Tert. butyl	65
1.14i & **1.15i**	Styryl	(R)-Ph(CH)Me	48
1.14j & **1.15j**	Styryl	Benzyl	47
1.14k & **1.15k**	Styryl	Frufuryl	37
1.14l & **1.15l**	Crotyl	Ph	29

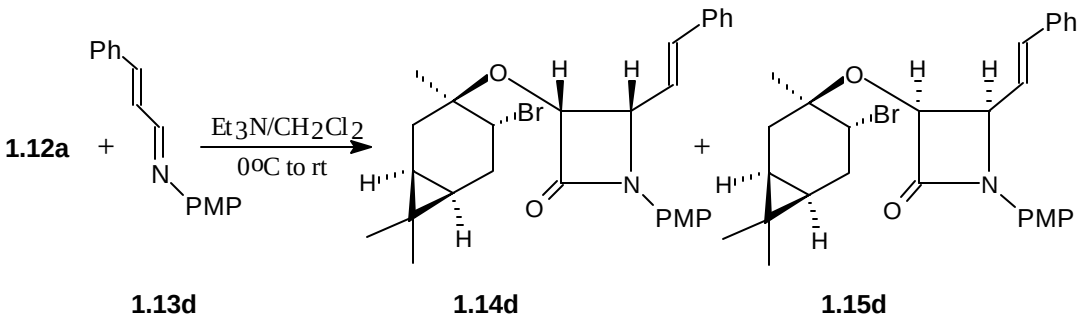
* diastereoselectivity was around 60:40 in most of the cases.

The *b*-lactams **1.14d** & **1.15d** are chosen as representative examples for the discussion.

***Preparation of* 1.14d &1.15d**

The Imine **1.13d** on reaction with acid chloride **1.12a**, in the presence of triethylamine, underwent cycloaddition reaction to give a diastereomeric mixture of *b*-lactams **1.14d** & **1.15d** in 60% yield *(Scheme 29)*.

Scheme 29



The de was 20% as could be deduced from the ^{1}H NMR of the mixture. It was possible to separate the diastereomers by fractional crystallization.

The polar diastereomer **1.14d** was a crystalline solid (mp 166°C) with a typical IR peak at 1750 cm^{-1} for *b*-lactam amide. A molecular ion peak was obtained at 509 (2%) in the mass spectrum.

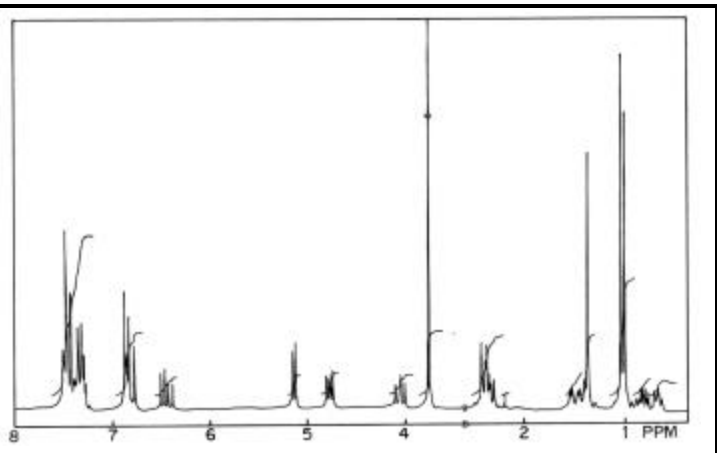
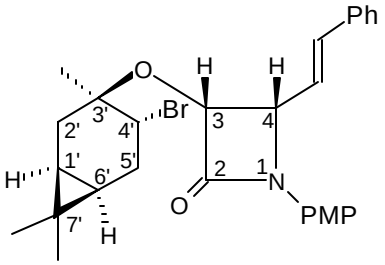


Fig. 5. ^{1}H NMR of **1.14d**.



1.14d

The ^{1}H NMR (Fig. 5) showed multiplets in the region 0.50-0.80 for cyclopropyl methine protons H-1′ & H-6′. The gem dimethyl groups at C-7′ appeared as two singlets at 0.97 & 1.02. The methyl group at C-3′ appeared as singlet at 1.37. The carane ring protons appeared as multiplets in the region 1.5 to 2.50. The methoxy group of the PMP moiety appeared as a singlet at 3.77. The H-4′ proton resonated downfield and appeared as a dd at 4.05 with J = 8 & 12 Hz. The *b*-lactam proton H-4 resonated as a dd at 4.77, with J = 5 & 10 Hz. The other *b*-lactam proton H-3, appeared as a doublet with J = 5 Hz at 5.12. A high coupling constant indicated the presence of *cis* *b*-lactam. One of the styryl protons resonated as a dd at 6.40 with J = 10 & 15 Hz. The other styryl proton and the aromatic protons appeared as multiplets in the region 6.7 to 7.5 ppm.

In the ^{13}C NMR spectrum the C-1′, C-6′, C3′-CH3 and the two gem dimethyl carbons appeared at 15.43, 17.70, 17.79, 19.33 & 21.60. The methyl group at C-3′ appeared at 17.70. The OMe from PMP group, C-4′ carbon & the *b*-lactam C-4 carbon appeared at 55.27, 60.05 & 62.25. The C-3′ carbon appeared at 77.39 while the *b*-lactam

C-3 carbon was seen downfield at 77.72. The styryl as well as the aromatic carbons appeared in the region 110 to 160. The *b*-lactam amide carbonyl appeared at 164.72.

The absolute stereochemistry of **1.14d** was established from the single crystal X-ray analysis of **1.14d**.

***X-ray Crystallographic Data of* 1.14d**

The *b*-lactam **1.14d** was crystallized from pet ether/dichloromethane system to obtain crystals, suitable for single crystal X-ray analysis.

$C_{28}H_{32}BrNO_3$, M_r = 510.46, a = 5.851(3), b = 18.672 (4) , c = 23.497 Å , $\alpha = 90^0$, $\beta = 90^0$, $\gamma = 90^0$, V = 2567 (2) Å 3, Z = 4, r_{calcd} = 1.321 Mg m^{-3}, Rw = 0.1320, T = 293 (2) K, GOF – 0.894.

Data were collected on Enariuf Nonius CAD-4 single crystal X-ray diffractometer using Cu-Kα radiation (λ = o.71070 Å) and ω-2θ scan mode to a θ range of 2.05 to 24.95^0. The structure was solved by direct positional and anisotropic thermal parameters for non hydrogen atom converged to R*w* = 0.1125 R1 = 0.0556 for 2597 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference Fourier, which was held fixed during the refinement. The refinements were carried out using SHELEX-97.

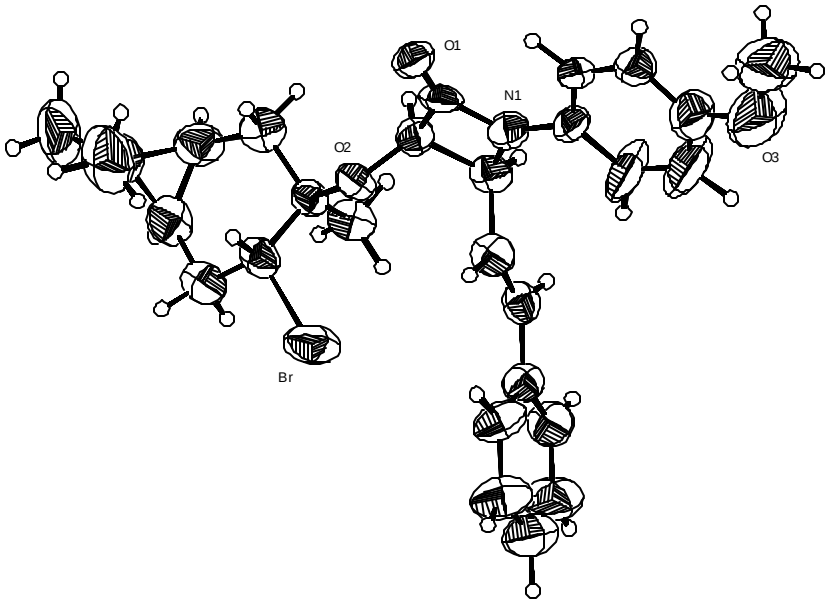
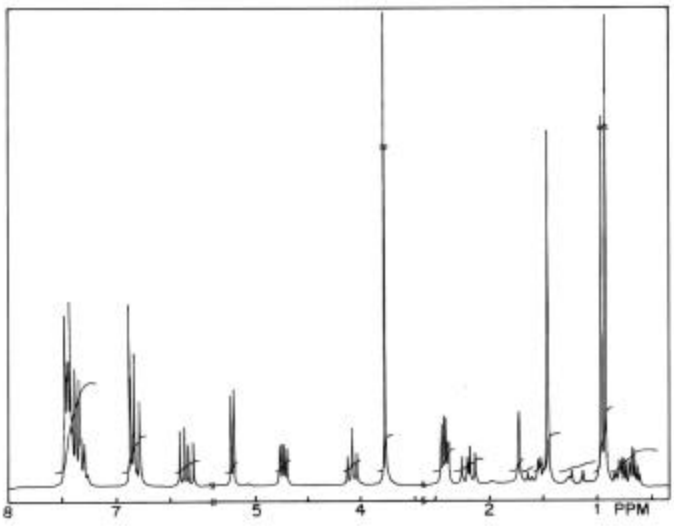
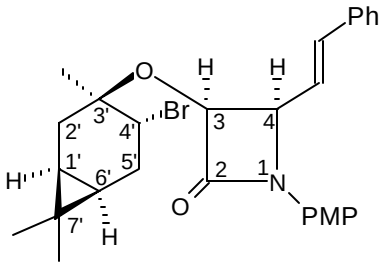


Fig. 6. *ORTEP* diagram of **1.14d**.

From the X-ray crystal structure analysis the absolute stereochemistry at the C-3 and C-4 of *b*-lactam was established as 3*R*, 4*S*.

The nonpolar diastereomer **1.15d** was also a crystalline solid with mp 158-160°C. The IR of 1.15d showed a *b*-lactam amide peak at 1750 cm^{-1}.





1.15d

Fig. 7. ^{1}H NMR of **1.15d**.

The ^{1}H NMR of **1.15d** showed the two cyclopropyl methine protons H-1′ & H-6′, as a multiplet in the region 0.20-0.70. The gem dimethyl protons at C-7′ resonated as two singlets at 0.93 & 0.95. The methyl at C-3′ appeared as a singlet at 1.45. The methylene protons H-2′ & H-5′ resonated as multiplets in the region 1.40-2.40. The methoxy group appeared as a singlet at 3.75. The H-4′ was seen at 4.07, as a triplet with *J* = 10 Hz. The *b*-lactam proton H-4 resonated at 4.72 as a dd, with J = 5 & 10 Hz. The other *b*-lactam proton H-3 appeared at 5.22 as a doublet with coupling constant 5 Hz. A high coupling constant indicating presence of *cis* *b*-lactam ring. One of the olefinic protons from the styryl part appeared at 6.34 (dd with *J* = 10 & 15 Hz). The other styryl proton and the aromatic protons gave multiplets in the region 6.70-7.50.

The positions of different protons was further confirmed from their COSY NMR spectra.

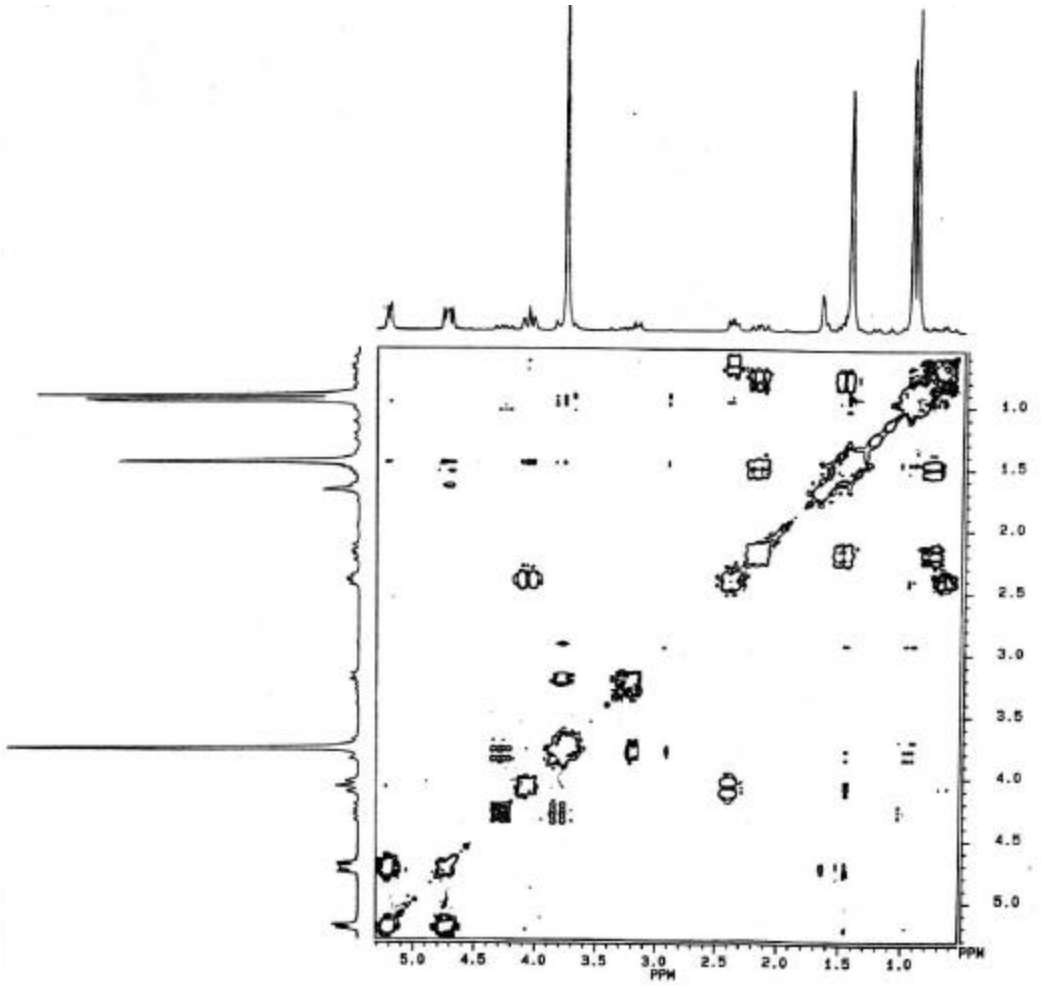
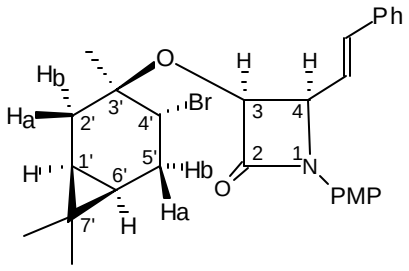


Fig. 8. COSY NMR spectra of **1.15d**.

Table 2. Connectivity among adjacent protons in the COSY NMR of **1.15d**

Proton no.	Chemical shift (multiplicity)	COSY connectivity
Ha-2′	1.45-1.57 (m)	Hb-2′, H-1′
Hb-2′	2.20 (dd)	Ha-2′, H-1′
Ha-5′, Hb-5′	2.4 (dd)	H-4′, H-6′
H-4′	4.07 (t)	Ha-5′, Hb-5′
H-4	4.72 (dd)	H-3, styryl
H-3	5.22 (d)	H-4



1.15d

The COSY NMR (Table 2) affirmed the positions of methylene protons at C-2′ & C-5′. The two protons at C-5′ were not appreciably diastereotopic. Both of them

resonated around the same position. But, the protons at C-2′ (Ha-2′ & Hb-2′) were appreciably diastereotopic and they appeared at different positions.

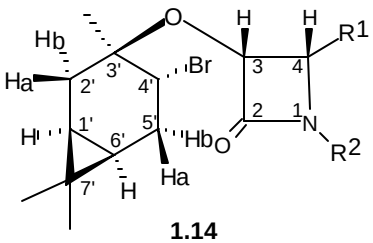
Both the diastereomers showed a peculiar trend in the optical rotation (Table 3).

Table 3: Optical rotation of individual diastereomers

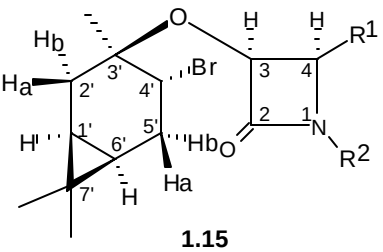
Sr. No.	R^1 & R^2	Compd. No.	$[\alpha]_D$(Conc. in g/100 ml of CH_2Cl_2)	Config.
1.	R^1 = Ph; R^2 = Ph	**1.14a**	+21° (c 0.2)	3*R*, 4*S*
		1.15a	-100.90° (c 0.22)	3*S*, 4*R*
2.	R^1 = Ph; R^2 = PMP	**1.14b**	+18.70° (c 0.31)	*3R*, 4*S*
		1.15b	-114.17° (c 0.48)	3*S*, 4*R*
3.	R^1 = PMP; R^2 = PMP	**1.14c**	+20° (c 0.23)	3*R*, 4*S*
		1.15c	-123.56° (c 0.23)	3*S*, 4*R*
4.	R^1 = styryl; R^2 = PMP	**1.14d**	+33° (c 1.85)	3*R*, 4*S*
		1.15d	-122.9° (c 1.85)	3*S*, 4*R*
5.	R^1 = styryl; R^2 = Ph	**1.14e**	+20° (c 0.28)	3*R*, 4*S*
		1.15e	-103.90° (c 0.41)	3*S*, 4*R*
6.	R^1= styryl; R^2 = *t*-butyl	**1.15h**	-33.70° (c 0.54)	3*S*, 4*R*
7.	R^1 = -CH=CH-Me; R^2 = Ph	**1.14l**	+30° (c 0.52)	3*R*, 4*S*

In case of **1.14d**, the absolute configuration was assigned by X-ray analysis to be 3*R*, 4*S* at the azetidinone ring centers. The optical rotation for **1.14d** was +33°. All the diastereomers (**1.14**) with positive optical rotation showed similar NMR spectral patterns, therefore 3*R*, 4*S* configuration was assigned to these diastereomers. The absolute configuration of 3*S*, 4*R* was assigned to all the diastereomers (**1.15**) with negative optical rotation. This was strongly supported by ^{1}H NMR spectral data, which showed similar pattern for all the diastereomers.

Table 4 shows the characteristic ^{1}H NMR data for the important protons in case of diastereomers **1.14** & **1.15**.



1.14



1.15

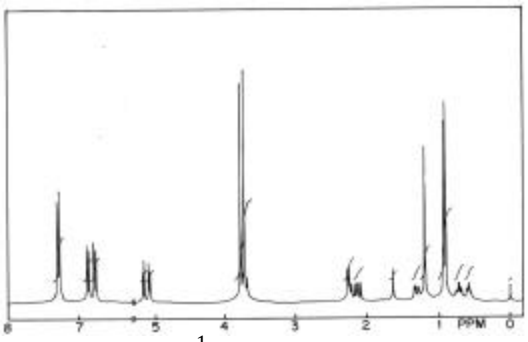


Fig. 9. ^{1}H NMR of **1.14c**.

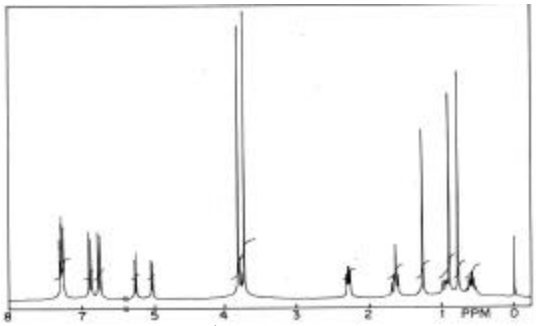


Fig. 10. ^{1}H NMR of **1.15c**.

Table 4. Characteristic ^{1}H NMR data for **1.14** & **1.15**

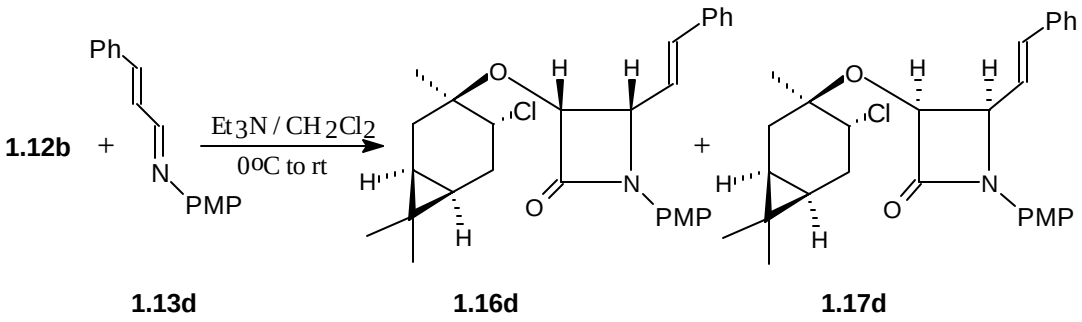
R^1 & R^2	Diast.	H-3	H-4	Gem Dimethyl C-7′	C-3′ methyl	Ha-2′	Hb-2′
R^1 = Ph	**1.14a**	5.23	5.18	0.89 & 0.93	1.21	1.23-1.27	2.04-2.20
R^2 = Ph	**1.15a**	5.31	5.12	0.74 & 0.89	1.27	0.89-1.04	1.59-1.62
R^1 = Ph	**1.14b**	5.19	5.12	0.87 & 0.91	1.19	1.32	2.18
R^2 = PMP	**1.15b**	5.27	5.05	0.74 & 0.87	1.24	0.94	1.57
R^1 = PMP	**1.14c**	5.15	5.07	0.89 & 0.92	1.18	1.33	2.12
R^2 = PMP	**1.15c**	5.24	5.0	0.76 & 0.88	1.24	0.94	1.54-1.70
R^1 = styryl	**1.14d**	5.12	4.77	0.97 & 1.02	1.37	1.50	2.25-2.40
R^2 = PMP	**1.15d**	5.22	4.72	0.93 & 0.95	1.45	1.45-1.57	2.20
R^1 = styryl	**1.14e**	5.15	4.82	0.99 & 1.02	1.37	1.40	2.30-2.40
R^2 = Ph	**1.15e**	5.23	4.78	0.92 & 0.95	1.45	1.40-1.60	2.18
R^1= styryl R^2= t-butyl	**1.15h**	4.93	4.33	0.87 & 0.90	1.36	1.30-1.50	2.08
R^1 = crotyl R^2 = Ph	**1.14l**	4.98	4.58	0.97 & 1.02	1.33	1.45	2.25-2.40

Table 1 indicated that the overall selectivity is poor to moderate in the series **1.14** & **1.15**. Still a notable observation among the synthesis of **1.14** & **1.15** series of *b*-lactams is a marginal reversal in the diastereoselectivity. In case of *b*-lactams **1.14a-c** & **1.15a-c**, a diastereoselectivity of 60:40 was observed. However, in case of 4-styryl-*b*-lactams **1.14d-l** & **1.15d-l** a diastereomeric ratio of about 45:55 in favor of **1.15** was observed, with a reversal of diastereoselectivity. Though this is a marginal change and doesn't involve any substantial enhancement in the diastereoselectivity. However, it is not possible to give a concrete and rational analysis for this observation at this stage.

***Preparation of* 1.16d & 1.17d**

The Imine **1.13d** on cycloaddition with acid chloride **1.12b** in the presence of triethylamine underwent cycloaddition reaction to give a diastereomeric mixture of *b*-lactams **1.16d** & **1.17d** in 60% yield (*Scheme 30*).

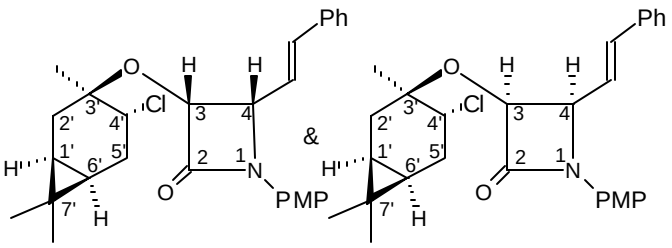
Scheme 30



The diastereomeric mixture was isolated as a white solid (mp 128-131°C) with very low diastereoselectivity (de 20%). The individual diastereomers couldn't be separated from the diastereomeric mixture. The IR of the mixture showed a peak at 1750 cm^{-1} typical of *b*-lactam amide. A small molecular ion peak at 465 (0.1%) was seen in the mass spectrum.

The ^{1}H NMR spectrum of the diastereomeric mixture showed cyclopropyl methine protons in the region 0.55- 0.85. The singlets for to the gem dimethyl groups were seen at 0.90, 0.96 & 0.98. The methyl group at G3 resonated as singlets at 1.33 & 1.40. The methylene protons H′-2 & H′-5 appeared as multiplets in the region 1.30 2.50. The OMe protons from the PMP moiety appeared as a singlet at 3.76. The H′-4 proton

resonated as a multiplet in the region 3.78-4.20. The *b*-lactam proton H-4 appeared at 4.60 (dd, J =4.7 & 8.9 Hz) & 4.84 (dd, J = 4.8 & 8.9 Hz). The other β-lactam proton H-3



1.16d **1.17d**

appeared as a doublet at 5.18 (d, J = 4.7 Hz) & 5.26 (d, J = 4.8 Hz) for the diastereomeric mixture. One of the olefinic protons belonging to the styryl part appeared as a dd at 6.32 & 6.40 while the other one was seen in the region 6.60-7.50, where the aromatic protons also resonated.

The ^{13}C NMR of the diastereomeric mixture showed the carbons C-1, C-6, gem dimethyl and C-3 methyl in the region 15 to 30. The methylene carbons at C-2 & C-5 appeared at 30.67, 31.04, 32.21 & 32.41. The C′-4 appeared at 55.42 while the carbons C-4 & the OMe appeared at 61.95, 62.55 & 65.08, 66.08 respectively for the diastereomeric mixture. The *b*-lactam carbon C-3 appeared at 76.62 & 77.48 while C-3 carbon resonated at 77.90 & 78.38. The styryl and the aromatic carbons resonated in the region 114-131. The amide carbonyl peak belonging to the *b*-lactam was seen at 155.28.

The reaction of **1.12b** as a ketene precursor with other imines was also tried. But the products obtained were non-polar liquids and were difficult to purify by column chromatography. The yields and diastereoselectivity was also disappointing.

1.7 : Summary

A novel chiral auxiliary in the form of 4-bromo and 4-chloro carane acid was synthesized from (+)-3-Carene as a chiral source. The subsequent acid chlorides smoothly reacted with imines under typical ketene-imine cycloaddition reaction conditions to furnish novel *b*-lactams. The overall yields were good and diastereoselectivity was low to moderate. In most of the cases the diastereomers could be separated either by flash column chromatography or by fractional crystallization. A low level of diastereoselectivity demonstrated that a bulkier group like bromine, directly attached to the C-4 center of the carane skeleton, doesn't have appreciable effect on the stereochemical outcome of the cycloaddition reaction.

1.8 : Experimental

SECTION A

***Synthesis of (1R, 3R, 4R, 6S) 4-Allyloxy-4,7,7-trimethyl-bicyclo[4.1.0]heptan-3-ol* 1.02**

To a stirred mixture of carane oxide **1.01** (0.760 g, 5 mmol) and allyl alcohol (5 mL), catalytic amount of cons. H_2SO_4 was added at 0°C. The reaction mixture was allowed to stir for 1 h. After the completion of the reaction (TLC), the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extract was washed with sat. $NaHCO_3$ (20 mL), water (2 x 20 mL), brine (15 mL) and dried over Na_2SO_4. Concentration under reduced pressure afforded crude oil, which was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to get 0.63 g (60%) of alcohol **1.02** as a pale yellow oil.

$[\alpha]^{D}_{25}$: -3.92° (c 3.75, $CHCl_3$).

IR (cm^{-1}) : 3450.

^1H NMR : δ 0.50-0.80 (m, 2H), 0.98, 1.0 (2s, 6H), 1.20 (s, 3H), 0.80-2.40 (m, 4H), 3.45 (dd, *J* = 9.50, 11 Hz, 1H), 3.95 (d, *J* = 5.50 Hz, 2H), 5.05-5.50 (m, 2H), 5.80-6.10 (m, 1H).

MS [m/e (%)] : 211 (M^++1, 2), 210 (M^+, 2), 151 (50), 137 (100), 123 (42), 109 (85), 97 (55), 74 (75), 67 (55).

***Synthesis of (1S, 3R, 4R, 6R) 3-Allyloxy-4-methoxy-3,7,7-trimethylbicyclo[4.1.0]-heptane* 1.03a.**

To a stirred solution of alcohol **1.02** (1.05 g, 5 mmol), in dry benzene (30 mL), NaH (50% dispersion in oil, 298 mg, 6 mmol) was added over 20 minutes at 0°C. The reaction mixture was allowed to come to room temperature and further stirred for 1 h. After 1 h, the reaction mixture was again cooled to 0°C and MeI (0.49 mL, 8 mmol) was added slowly over 15 minutes to it. The reaction mixture was allowed to attain room temperature and stirred further for 8 h. The reaction mixture was then diluted with ice cold water (40 mL) and glacial acetic acid (0.5 mL) was added to it. It was

extracted with ethyl acetate (3 x 25 mL) and the combined organic extract was washed with sat. $NaHCO_3$ (20 mL), water (3 x 20 mL), brine (20 mL). Drying over Na_2SO_4 followed by concentration under reduced pressure afforded crude oil, which was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to get 0.89 g (80%) of **1.03a** as a colourless oil.

$[\alpha]^{D}_{25}$: -4.91° (c 0.57, CH_2Cl_2).

IR (cm^{-1}) : 1050, 1360, 2950.

^{1}H NMR : δ 0.5-0.95 (m, 2H), 0.94 & 0.97 (2s, 6H), 1.20 (s, 3H), 1.5-2.40 (m, 4H), 3.05 (dd, *J* = 8, 10 Hz, 1H), 3.37 (s, 3H), 3.80-4.20 (m, 2H).

MS [m/e (%)] : 223 (M^++1, 1), 222 (M^+, 2), 151 (50), 123 (88), 109 (100), 99 (92), 93 (87).

Synthesis of (1R, 3R, 4R, 6S) 4-Allyloxy-4,7,7-trimethylbicyclo[4.1.0]hept-3-yl acetate. **1.03b.**

To a stirred solution of alcohol **1.02** (1.05 g, 5 mmol) and pyridine (0.42 mL, 5 mmol) in dichloromethane (30 mL) was added acetyl chloride (0.42 mL, 6 mmol) slowly over 10 min at 0°C. The reaction mixture was allowed to stir at room temperature for 6 h. After completion of the reaction (TLC), it was diluted with ice cold water (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic extract was washed with sat. $NaHCO_3$ (20 mL), water (3 x 20 mL), brine (20 mL). Drying over Na_2SO_4 followed by concentration under reduced pressure afforded crude oil, which was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to get 1.0 g (80%) of **1.03b** as a colourless oil.

$[\alpha]^{D}_{25}$: -5.75° (c 5.65, $CHCl_3$).

IR (cm^{-1}) : 1750.

^{1}H NMR : δ 0.60-0.75 (m, 2H), 0.97 & 1.0 (2s, 6H), 1.27 (s, 3H), 2.02 (s, 3H), 0.85-2.50 (m, 4H), 3.80-4.00 (m, 2H), 4.78 (dd, *J* = 8.5, 10 Hz, 1H), 5.0-5.35 (m, 2H), 5.25-6.0 (m, 1H).

MS [m/e (%)] : 253 (M^++1, 0.5), 135 (59), 119 (55), 109 (87), 94 (82), 93 (100), 90 (55).

Synthesis of (1¢S, 3¢R, 4¢R, 6¢R) 2-[4¢-Methoxy-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3-yloxy]acetic acid **1.04a.**

To a stirred solution of ether **1.03a** (0.224 g, 1 mmol), in the solvent system of CH_3CN: CCl_4: H_2O (2: 2: 3; 25 mL), powered $NaIO_4$ (0.64 g, 3 mmol) was added followed by cat. $RuCl_3$ (2 mg) at 0°C. The reaction mixture was stirred at this temperature for 4 h. After completion of the reaction (TLC), isopropanol (0.5 mL) was added to destroy any unreacted oxidant. The reaction mixture was basified with sat. $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (2 x 20 mL). The aqueous layer was acidified with dil. HCl (15 ml) at 0°C and extracted with ethyl acetate (3 x 20 mL). The combined organic extract was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration under reduced pressure afforded **1.04a** (0.109 g, 80%) as an oil.

$[\alpha]^{D}_{25}$: -19.16° (c 0.72, CH_2Cl_2).

IR (cm^{-1}) : 1740, 3000-3500 (broad).

^{1}H NMR : δ 0.40-0.75 (m, 2H), 0.90, 0.93 (2s, 6H), 1.18 (s, 3H), 1.00-2.40 (m, 4H), 3.05 (dd, *J* = 8, 9.50 Hz, 1H), 3.25 (s, 3H), 4.02 (d, *J* = 21 Hz, 1H), 4.18 (d, *J* = 21 Hz, 1H), 7.3-8.4 (bs, 1H).

MS [m/e (%)] : 242 (M^+, 0.5), 166 (33), 151 (46), 123 (60), 109 (75), 93 (100), 85 (64), 81 (50).

Synthesis of (1¢S, 3¢R, 4¢R, 6¢R) 2-[3¢,7¢,7¢-trimethyl-4¢-Methylcarbonyloxybicyclo-[4.1.0]hept-3¢-yloxy]acetic acid **1.04b.**

1.03b (0.252 g, 1 mmol) was oxidised by jones oxidation using a Procedure similar to the preparation of **1.04a** to get an acid **1.04b** (0.108 g, 40%) as an oil.

$[\alpha]^{D}_{25}$: +11.0° (c 1, $CHCl_3$).

IR (cm^{-1}) : 1740, 1750, 3000-3600.

^{1}H NMR : δ 0.60-0.80 (m, 2H), 0.98, 1.0 (2s, 6H), 1.14 (s, 3H), 2.20 (s, 3H), 1.1-2.3 (m, 4H), 3.90-4.10 (m, 2H), 4.66 (dd, *J* = 8, 9.50 Hz, 1H), 6.90-8 (bs, 1H).

$^{!3}$C NMR δ 15.53, 16.24, 17.62, 18.91, 19.99, 20.87, 25.15, 28.03, 30.08,

59.80, 74.37, 77.45, 170.79, 173.35.

MS [m/e (%)] : 137 (47), 119 (65), 109 (65), 93 (100).

***Synthesis of (1′S, 3′R, 4′R, 6′R)1-(4′-Methoxyphenyl)-3-[4′-methoxy-3,7,7-trimethylbicyclo[4.1.0]hept-3′-yloxy]-4-phenyl-(3S, 4R)-azetan-2-one*.1.05a & 1.06a**

To a stirred solution of imine (0.211 g, 1 mmol) and Et_3N (0.303 mL, 3 mmol) in dry dichloromethane (15 mL), a solution of acid **1.04a** (0.540 g, 2 mmol), phenyl dichlorophosphate (0.420 g, 2 mmol) in dry dichloromethane (5 mL) was added drop-wise at 0°C over a period of 1 h. The reaction mixture was allowed to warm up to room temperature and stirred overnight. It was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue on column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) gave 0.301 g (65%) of diastereomeric mixture of *cis*-*b*-lactams **1.05a** & **1.06a** in the ratio of 60:40, which was determined from the ^1H NMR spectral data.

M.P. : 125°C.

$[\alpha]^{D}_{25}$: -23.33° (c 0.06, CH_2Cl_2).

IR (cm^{-1}) : 1510, 1740.

^1H NMR : δ 0.35-0.65 (m, 2H), 0.74, 0.79, 0.86, 0.90 (4s, total 6H), 1.03 & 1.10 (2s, total 3H), 1.0-1.38 (m, 1H), 1.40-1.65 (m, 1H), 1.80-2.10 (m, 1H), 2.57 & 2.80 (dd, *J* = 9, 9.50 Hz, total 1H), 2.86 & 3.36 (2s, total 1H), 3.70 (s, 1H), 5.01 & 5.10 (d, *J* = 4.8 Hz & d, *J* = 5.1 Hz respect., total 1H), 5.26 & 5.45 (d, *J* = 5.1 & d, *J* = 4.8 Hz respect., total 1H), 6.70-6.80 (m, 2H), 7.18-7.60 (m, 7H).

MS [m/e (%)] : 437 (M^++2, 10), 435 (M^+, 50), 269 (47), 212 (100), 167 (79), 135 (66).

Microanalysis : M. F. $C_{27}H_{33}NO_4$.

Calculated	C : 74.46	H : 7.64	N : 3.22
Obtained	C : 74.20	H : 7.90	N : 3.01

Synthesis of 1-(4¢-Methoxyphenyl)-3-[4¢¢-methoxy-3¢¢,7¢¢,7¢¢-trimethyl-(1¢¢S, 3¢¢R, 4¢¢R, 6¢¢R)-bicyclo[4.1.0]hept-3¢¢-yloxy]-4-phenyl-(3S, 4R)-azetan-2-one **1.05b & 1.06b.**

The treatment of acid **1.04b** (0.484 g, 2 mmol) and phenyl dichlorophosphate (0.420 g, 2 mmol) with a mixture of imine (0.211 g, 1 mmol) and Et_3N (0.303 mL, 3 mmol) at 0ºC provided a mixture of *cis-b*-lactams **1.05b** & **1.06b**, 0.261 g (60%) in the ratio, 58:42, which was confirmed by ^{1}H NMR spectral data. The diastereomers were separated by fractional crystallization when the major diastereomer **1.05b** could be isolated in the pure form after single crystallization (30%) from pet ether/ethyl acetate system.

M.P. : 167-168°C.

$[\alpha]^{D}_{25}$: +48.94° (c 1.4, CH_2Cl_2).

IR (cm^{-1}) : 1735.

^{1}H NMR : δ 0.50-0.75 (m, 2H), 0.96, 0.97 (2s, 6H), 1.15 (s, 3H), 0.85-2.10 (m, 4H), 1.82 (s, 3H), 3.72 (s, 3H), 4.60 (dd, *J* = 7.8, 8.4 Hz, 1H), 5.08 (d, *J* = 5.0 Hz, 1H), 5.16 (d, *J* = 5.0 Hz, 1H), 6.78 (d, *J* = 8 Hz, 2H), 7.1-7.5 (m, 7H).

$^{!3}$C NMR (Mix.) δ 19.15, 19.36, 20.19, 20.35, 21.13, 21,27, 25.42, 28.38, 29.69, 31.42, 31.56, 55.41, 63.14, 73.61, 74.00, 76.82, 114.28, 118.72, 128.26, 128.75, 130.91, 134.30, 156.14, 165.42, 170.33.

MS [m/e (%)] : 464 (M^++1, 10), 463 (M^+, 49), 269 (53), 268 (66), 212 (83), 211 (100), 135 (50), 93 (53).

Microanalysis : M. F. $C_{28}H_{35}NO_5$.

Calculated	C : 72.55	H : 7.18	N : 3.02
Obtained	C : 72.26	H : 6.90	N : 2.80

***Synthesis of 2-[4′-Allyloxy-4′,7′,7′-trimethyl-(1′R, 3′R, 4′R, 6′S)-bicyclo[4.1.0]hept-3-yloxy]acetic acid* 1.07.**

To a solution of **1.02** (6.3 g, 30 mmol) in dry toluene (30 mL), clean pieces of sodium (1 g) were added and the reaction mixture was refluxed for 15 h. The reaction mixture was stirred at such a rate that the sodium was broken into fine globules. The reaction mixture was cooled to room temperature and the unreacted sodium was removed by filtration through glass wool. The filtrate was heated to 85-90°C and a solution of chloroacetic acid (1.2 g, 12.5 mmol) in dry toluene (30 mL) was added with stirring in such a way that the refluxing is not vigorous. A heavy precipitate of sodium chloroacetate forms immediately. The reaction mixture was refluxed for 48 h. It was cooled and diluted with toluene (120 mL) and extracted with water (3 x 100 mL). The aqueous layer was acidified with 20% HCl. The crude acid, which separated, was extracted with benzene (2 x 15 mL). The removal of benzene by distillation under reduced pressure afforded crude product, which was purified by column chromatography so as to give **1.07** as an oil (4.82 g, 60%).

$[\alpha]^{D}_{25}$	:	+11.0° (c 0.5, $CHCl_3$).
IR (cm^{-1})	:	1380, 1751, 2939, 3050-3650.
^{1}H NMR	:	δ 0.55-0.85 (m, 2H), 0.95 & 1.0 (2s, 6H), 1.30 (s, 3H), 1.65-1.90 (m, 1H), 2.05-2.40 (m, 2H), 3.05 (dd, *J* = 8, 10.50 Hz, 1H), 3.90 (d, *J* = 18 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 2H), 4.30 (d, *J* = 18 Hz, 1H), 5.10-5.40 (m, 2H), 5.75-6.05 (m, 1H).
^{13}C NMR		δ 14.63, 15.86, 17.76, 18.92, 20.48, 25.60, 28.38, 30.00, 62.54, 67.56, 78.45, 84.51, 117.38, 134.46, 173.11.
MS [m/e (%)]	:	270 (M^++2, 0.5), 269 (M+1, 1), 268 (M^+, 6), 151 (24), 121 (35), 109 (58), 93 (100), 90 (57), 79 (26).

***Synthesis of (3R, 4S, 1′R, 3′R, 4′S, 6′S) & (3S, 4R, 1′R, 3′R, 4′S, 6′S) 3-[4′-Allyloxy-4′,7′,7′-trimethylbicyclo[4.1.0]hept-3′-yloxy]-1-(4′′-methoxyphenyl)-4-phenyl-azetan-2-one* 1.08a** & **1.09a**.

To a stirred solution of imine (0.211 g, 1 mmol) and Et_3N (0.303 mL, 3 mmol) in dry dichloromethane (15 mL), a solution of acid **1.07** (0.536 g, 2 mmol), phenyl dichlorophosphate (0.420 g, 2 mmol) in dry dichloromethane (5 mL) was added drop-

wise at 0°C over a period of 1 h. The reaction mixture was allowed to warm-up to room temperature and stirred overnight. It was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue on column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) gave a diastereomeric mixture of **1.08a** & **1.09a** (0.313 g, 68%) in the ratio 62:38 which was determined from the ^{1}H NMR spectral data.

The diastereomeric mixture of **1.08a** & **1.09a** was isolated as a white solid.

M.P. : 117-118°C.

$[\alpha]^D_{25}$: -13.85° (c 1.95, CH_2Cl_2).

IR (cm^{-1}) : 1220, 1240, 1510, 1740.

^{1}H NMR : δ 0.25-0.80 (m, 2H), 0.5, 0.70 (2s, total 3H), 0.85, 0.95 (2s, total 3H), 1.20 (s, 3H), 0.80-2.30 (m, 4H), 2.90 (dd, *J* = 8, 10 Hz, 1H), 3.30 (dd, *J* = 8, 10 Hz, 1H), 3.73 & 3.74 (2s, total 3H), 3.50-4.15 (m, 2H), 5.05-5.40 (m, 3H), 5.65 (d, *J* = 4.7 Hz, 1H), 5.75-6.10 (m, 1H), 6.70-6.85 (m, 2H), 7.15-7.50 (m, 7H).

^{13}C NMR : δ 14.39, 15.08, 15.82, 15.97, 17.60, 17.81, 18.99, 19.28, 20.56, 20.78, 25.44, 26.52, 28.37, 28.53, 30.37, 30.59, 35.41, 62.19, 62.48, 62.61, 63.20, 79.01, 81.62, 84.55, 85.84, 86.00, 114.34, 114.95, 115.52, 118.75, 118.83, 128.17, 128.41, 128.54, 128.77, 130.99, 134.54, 134.98, 136.37, 136.63, 156.20, 164.14, 166.16.

MS [m/e (%)] : 462 (M^++1, 7%), 461 (M^+, 17), 251 (58%), 211 (100%), 210 (75%), 193 (45%), 91 (37%).

Microanalysis : M. F. $C_{29}H_{35}NO_4$.

Calculated	C : 75.46	H : 7.64	N : 3.03
Obtained	C : 75.20	H : 7.48	N : 2.89

Section B :

Preparation of (1¢S,3¢R,4¢R,6¢R)-2-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yl-oxy]ethan-1-ol **1.10a**

To a stirred solution of (+)-3-carene (1.36 g, 10 mmol) and ethylene glycol (3.1 mL, 50 mmol) in dichloromethane (3 mL), powdered NBS (2.23 g, 12.5 mmol) was added in small portions over a period of 30 min at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred further for 4 h. After the completion of the reaction (TLC), cold water (15 mL) was added to the reaction mixture and extracted with dichloromethane (3x20 mL). The combined extracts were washed with sat. $NaHSO_3$ (10 mL), water (10 mL), brine (10 mL) and dried over anhyd. Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to give 1.24 g (45%) of pure bromo alcohol **1.10a** as a pale yellow liquid.

$[\alpha]^{D}_{25}$: -33.45° (c 1.65, $CHCl_3$).

IR (cm^{-1}) : 3400.

^{1}H NMR : δ 0.65-0.90 (m, 2H), 0.97 (s, 3H), 1.0 (s, 3H), 1.30-1.50 (m, 1H), 1.35 (s, 3H), 2.07 – 2.25 (m, 1H), 2.40-2.50 (m, 2H), 3.40-3.60 (m, 2H), 3.65-3.75 (m, 2H), 4.07 (merged dd, *J* = 7.5, 8 Hz, 1H).

^{13}C NMR : δ 15.48, 17.70, 18.32, 19.50, 21.63, 28.39, 29.97, 31.80, 59.92, 61.83, 62.04, 75.25.

MS [m/e (%)] : 276 (M^+, 3.5), 92 (100).

Preparation of (1¢S,3¢R,4¢R,6¢R)-2-[4¢-Chloro-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yl-oxy]ethan-1-ol **1.10a**

Procedure A: To a stirred solution of (+)-3-carene (1.36 g, 10 mmol) and ethylene glycol (3.1 mL, 50 mmol) in dichloromethane (3 mL), powdered NCS (1.67 g, 12.5 mmol) was added in small portions over a period of 30 min at 60°C. After the addition is over the reaction mixture was allowed to stir further for 2 h. After the completion of the reaction (TLC), cold water (15 mL) was added to the reaction mixture and extracted with dichloromethane (3x20 mL). The combined extracts were

washed with sat. $NaHSO_3$ (10 mL), water (10 mL), brine (10 mL) and dried over anhyd. Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to give 0.50 g (~20%) of chloro alcohol **1.10b** as a pale yellow liquid. The crude alcohol could not be purified and was used as such for the further reaction.

Procedure B: In another procedure AIBN was used as an initiator. To the reaction mixture of (+)-3-carene (1.36 g, 10 mmol) and ethylene glycol (3.1 mL, 50 mmol) in dichloromethane (3 mL) was added cat. amount of AIBN. Powdered NCS (1.67 g, 12.5 mmol) was added in small portions over a period of 30 min & a sudden increase in the temperature observed. The reaction was continued further for 2 hrs and the reaction was worked up as described in Procedure A to give chloroalcohol **1.10b** in about 20-25% yield.

***Preparation of (1¢S,3¢R,4¢R,6¢R)-2-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]acetic acid* 1.11a**

To a stirred solution of bromo alcohol **1.10a** (276 mg, 1 mmol) in acetone (10 mL), Jones reagent was added drop by drop at 0°C until decolourisation of the reagent was observed. The reaction mixture was further stirred for 3 h at room temperature, the green precipitate of the chromium salt was filtered off and the excess reagent destroyed by adding isopropyl alcohol at 0°C. The solution was concentrated under vacuum and residue was extracted with ether (3x20 mL). The ether extract was washed with brine and dried over Na_2SO_4. It was then filtered and filtrate on concentration under reduced pressure offered crude bromo acid (232 mg, 80%). The crude bromo acid was purified by crystallization from pet ether/ethyl acetate to give

1.11a as a white crystalline solid.

M.P. : 85°C.

$[\alpha]^{D}_{25}$: -72° (c 0.45, CHC_3).

IR (cm^{-1}) : 1760, 2600, 3700.

^{1}H NMR : δ 0.65-0.90 (m, 2H), 0.98 & 1.00 (2s, 6H), 1.4 (s, 3H), 1.3-1.4 (m, 1H), 2.20 (dd, *J* = 5.5, 10 Hz, 1H), 2.35-2.55 (m, 2H), 4.00 (m, 1H), 4.05 (d, *J* = 18 Hz, 1H), 4.10 (d, *J* = 18 Hz, 1H), 7.30-9.0 (bs, 1H).

^{13}C NMR : δ 15.71, 17.34, 18.18, 19.55, 21.85, 28.57, 30.88, 31.99, 59.74, 59.89, 78.12.

MS [m/e (%)] : 210 (M^+-HBr, 2), 135 (82), 107 (37), 93 (100), 77 (40), 71 (52), 67 (38).

***Preparation of (1¢S,3¢R,4¢R,6¢R)-2-[4¢-Chloro-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]acetic acid* 1.11b**

Crude chloro alcohol **1.10b** was oxidized by Jones oxidation using a procedure similar to **1.10a**. The chloro acid **1.11b** was obtained as a pale liquid (60%).

$[\alpha]^{D}_{25}$: -72° (c 0.45, CHC_3).

IR (cm^{-1}) : 1760, 2600, 3700.

^{1}H NMR : δ 0.65-0.90 (m, 2H), 0.98 & 1.00 (2s, 6H), 1.4 (s, 3H), 1.3-1.4 (m, 1H), 2.20 (dd, *J* = 5.5, 10 Hz, 1H), 2.35-2.55 (m, 2H), 4.00 (m, 1H), 4.05 (d, *J* = 18 Hz, 1H), 4.10 (d, *J* = 18 Hz, 1H), 7.30-9.0 (bs, 1H).

^{13}C NMR : δ 15.82, 16.30, 18.15, 19.51, 21.15, 28.60, 31.07, 31.07, 31.26, 60.23, 65.42, 79, 175.

***Preparation of (1′S,3′R,4′R,6′R)-2-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]acetyl chloride* 1.12a**

A mixture of acid **1.11a** (5.8 g, 20 mmol), $SOCl_2$ (2.18 mL, 1.5 mmol) in dry benzene (40 mL) was refluxed for 1 hour. The benzene was removed by distillation to give acid chloride **1.12a**, which was used as such in the next step without further purification.

***Preparation of (1¢S,3¢R,4¢R,6¢R)-2-[4¢-Chloro-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]acetyl chloride* 1.12b**

A mixture of acid **1.11b** (4.92 g, 20 mmol), $SOCl_2$ (2.18 mL, 1.5 mmol) in dry benzene (40 mL) was refluxed for 1 hour. The benzene was removed by distillation to give acid chloride **1.12b**, which was used as such in the next step without prior purification.

***General proecedure for the Preparation of b-lactams* 1.14a-l** & **1.15a-l**

To a stirred solution of imine (**1.13a-l**, 1 mmol) and Et_3N (0.303 mL, 3 mmol) in dry dichloromethane (15 mL), a solution of acid chloride (**1.12a**, 617 mg, 2 mmol) in dry dichloromethane (5 mL) was added drop-wise at 0°C over a period of 1 h. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhyd. Na_2SO_4. The solvent was removed under vacuum and residue was purified by column chromatography (silica gel, 60-120, pet. ether/ethyl acetate) to yield a diastereomeric mixture of *b*-lactams **1.14a-l** & **1.15a-l**. the diastereomeric ratio was determined from the analysis of crude ^{1}H NMR. In most of the cases the diastereomers were separated by flash column chromatography or by fractional crystallization.

***Preparation of* 1.14a & 1.15a**

The imine **1.13a** (0.181 g, 1 mmol) on reaction with acid chloride **1.12a** (617 mg, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) furnished a diastereomeric mixture of β-lactams **1.14a** & **1.15a** (294 mg, 65%), in the ratio of 58:42, which was determined from the ^{1}H NMR spectral data. The diastereomers were separated by flash column chromatography to get nonpolar diastereomer **1.14a** & polar diastereomer **1.15a**. The data for the individual diastereomer and for the diastereomeric mixture is as follows.

(3R,4S,1¢S,3¢R,4¢R,6¢R)-3-[4'-Bromo-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]-1,4-diphenyl-azetidin-2-one 1.14a

Isolated as a white solid

M.P. : 181°C.

$[\alpha]^{D}_{25}$: +21° (c 0.2, CH_2Cl_2).

IR (cm^{-1}) : 1753.

^{1}H NMR : δ 0.50-0.65 (m, 1H), 0.65-0.80 (m, 1H), 0.90 (s, 3H), 0.95 (s, 3H), 1.20 (s, 3H), 1.20-1.40 (m, 1H), 2.00-2.40 (m, 3H), 3.70 (t, *J* = 9 Hz, 1H), 5.18 (d, *J* = 5 Hz, 1H), 5.25 (d, *J* = 5 Hz, 1H), 6.95-7.50 (m, 10H).

***(3S,4R,1¢S,3¢R,4¢R,6¢R)-3-[4'-Bromo-3¢,7¢,7¢-trimethylbicyclo(4.1.0)hept-3¢-yloxy]-1,4-diphenyl-azetidin-2-one* 1.15a**

Isolated as a white solid

M.P. : 159°C.

$[\alpha]^{D}_{25}$: –100.90 (c 0.22, CH_2Cl_2).

IR (cm^{-1}) : 1755.

^{1}H NMR : δ 0.45-0.70 (m, 2H), 0.74 (s, 3H), 0.89 (s, 3H), 0.90-1.10 (m, 1H), 1.27 (s, 3H), 1.55-1.75 (m, 1H), 2.25 (dd, *J* = 4.4, 8 Hz, 2H), 3.75 (t, *J* = 8 Hz, 1H), 5.12 (d, *J* = 5 Hz, 1H), 5.31 (d, *J* = 5 Hz, 1H), 7.15-7.50 (m, 10H).

Data for the mixture of **1.14a & 1.15a**

^{13}C NMR : δ 15.25, 15.39, 17.77, 18.21, 18.83, 19.33, 19.46, 21.21, 21.47, 28.41, 31.40, 31.84, 31.93, 32.05, 59.16, 59.37, 62.91, 63.01, 76, 77.61, 117.42, 124.07, 128.18, 128.42, 128.61, 128.97, 133.87, 134.13, 137.34, 165.54, 166.

MS [m/e (%)] : 455 (M+2, 3), 453 (M^+, 3), 238 (68), 182 (90), 135 (66), 120 (79), 93 (100), 91 (99), 77 (72), 55 (45).

Microanalysis : M. F. $C_{27}H_{32}BrNO_4$.

Calculated	C : 66.08	H : 6.21	N : 3.08
Obtained	C : 66.32	H : 6.49	N : 3.17

Preparation of **1.14b & 1.15b**

The imine 1.13b (0.211 g, 1 mmol) on reaction with acid chloride **1.12a** (617 mg, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) furnished a diastereomeric mixture of β-lactams **1.14b & 1.15b** (360 mg, 70%) in the ratio of 60:40, which was determined from the ^{1}H NMR spectral data. The diastereomers were separated by flash column chromatography to get nonpolar diastereomer **1.14b** & polar diastereomer **1.15b**. The data for **1.14b**, **1.15b** & mixture of **1.14b** & **1.15b** is given below.

(3R,4S,1′S,3′R,4′R,6′R)-1-(4-Methoxyphenyl)-3-[4′-bromo-3′,7′,7′-trimethylbicyclo-(4.1.0)hept-3′-yloxy]-4-phenylazetidin-2-one **1.14b**

Isolated as a white solid.

M.P. : 148°C.

$[\alpha]^{D}_{25}$: +18.70° (c 0.31, CH_2Cl_2).

IR (cm^{-1}) : 1752.

^{1}H NMR : δ 0.5-0.6 (m, 1H), 0.65-0.80 (m, 1H), 0.87 (s, 3H), 0.91 (s, 3H), 1.19 (s, 3H), 1.32 (dd, *J* = 5, 15 Hz, 1H), 2.18 (dd, *J* = 10, 15 Hz, 1H), 2.20-2.30 (m, 2H), 3.70 (t, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 5.12 (d, *J* = 5 Hz, 1H), 5.19 (d, *J* = 5 Hz, 1H), 6.74 (d, *J* = 9 Hz, 2H), 7.20-7.40 (m, 7H).

(3S,4R,1¢S,3¢R,4¢R,6¢R)-1-(4-Methoxyphenyl)-3-[4¢-bromo-3¢,7¢,7¢-trimethylbicyclo-(4.1.0)hept-3¢-yloxy]-4-phenylazetidin-2-one **1.15b**

Isolated as a white solid.

M.P. : 176°C.

$[\alpha]^{D}_{25}$: –114.17° (c 0.48, CH_2Cl_2).

IR (cm^{-1}) : 1755.

^{1}H NMR : δ 0.50-0.70 (m, 2H), 0.74 (s, 3H), 0.87 (s, 3H), 0.94 (dd, *J* = 4.5, 14.5 Hz, 1H), 1.24 (s, 3H), 1.57 (9.5, 14.5 Hz, 1H), 2.25 (dd, *J* = 4.5, 8.7 Hz, 2H), 3.70 (s, 3H), 3.73 (t, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 4.8 Hz, 1H), 5.27 (d, *J* = 4.8 Hz, 1H), 6.73 (d, *J* = 9 Hz, 2H), 7.24 (d, *J* = 9 Hz), 7.29-7.39 (m, 3H).

Data for Mixture of **1.14b** & **1.15b**

^{13}C NMR : δ 15.27, 15.40, 17.81, 18.20, 18.86, 19.36, 19.49, 21.24, 21.50, 28.42, 31.42, 31.87, 31.96, 32.08, 35.39, 59.44, 59.60, 63.07, 63.18, 77.48, 77.68, 114.31, 118.73, 128.18, 128.40, 128.48, 128.66, 130.93, 134.04, 134.31, 156.19, 164.91, 165.31.

MS [m/e (%)] : 485 (M^++2, 5), 483 (M^+, 4), 268 (49), 211 (62), 135 (58), 134 (51), 120 (80), 93 (100), 91 (89), 77 (52).

Microanalysis : M. F. $C_{26}H_{30}BrNO_3$.

Calculated	C : 64.46	H : 6.24	N : 2.89
Obtained	C : 64.91	H : 6.48	N : 3.02

Preparation of **1.14c** & **1.15c**

The imine **1.13c** (0.211 g, 1 mmol) on reaction with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) furnished a diastereomeric mixture of β-lactams **1.14c** & **1.15c** (0.338 g, 70%) in the ratio of 64:36, which was determined from the ^1H NMR spectral data.. The diastereomers were separated by flash column chromatography to get nonpolar diastereomer **1.14c** & polar diastereomer **1.15c**. The data for **1.14c**, **1.15c** & mixture of **1.14c** & **1.15c** is given below.

(3R,4S,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1,4-di(4-methoxyphenyl)- azetan-2-one **1.14c**

Isolated as a white solid.

M.P. : 157°c.

$[\alpha]^{D}_{25}$: +20 (c 0.23, CH_2Cl_2).

IR (cm^{-1}) : 1750.

^1H NMR : δ 0.50-0.60 (m, 1H), 0.65-0.80 (m, 1H), 0.90 (s, 3H), 0.92 (s, 3H), 1.18 (s, 3H), 1.30 (dd, *J* = 6, 12 Hz, 1H), 2.15 (dd, *J* = 12, 15 Hz, 1H), 2.20-2.35 (m, 2H), 3.70 (s, 3H), 3.60-3.75 (m, 1H), 3.78 (s, 3H), 5.05 (d, *J* = 4.9 Hz, 1H), 5.15 (d, *J* = 4.9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.85 (d, *J* = 9 Hz, 2H), 7.25 (d, *J* = 8 Hz, 4H)..

(3S,4R,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1,4-di(4-methoxyphenyl)- azetan-2-one **1.15c**

Isolated as a white solid.

M.P. : 167°C.

$[\alpha]^{D}_{25}$: -123.56 (c 0.23, CH_2Cl_2).

IR (cm^{-1}) : 1751.

^{1}H NMR : δ 0.50-0.70 (m, 2H), 0.76 (s, 3H), 0.88 (s, 3H), 0.94 (dd, *J* = 6, 15 Hz, 1H), 1.24 (s, 3H), 1.54-1.70 (m, 1H), 2.27 (dd, *J* = 3, 12 Hz, 2H0, 3.7 (s, 3H), 3.76 (m, 1H), 3.79 (s, 3H), 5.0 (d, *J* = 6 Hz, 1H), 5.24 (d, *J* = 6 Hz, 1H), 6.72 (d, *J* = 9 Hz, 2H), 6.86 (d, *J* = 9 Hz, 2H), 7.24 (d, *J* = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 2H).

***Data for mixture of* 1.14c & 1.15c**

^{13}C NMR : δ 15.51, 15.69, 18.01, 18.63, 18.98, 19.60, 21.46, 21.71, 28.65, 31.64, 32.06, 55.46, 59.65, 62.98, 76, 77.70, 113.19, 114.48, 118.97, 126.19, 126.41, 130.07, 130.22, 131.19, 156.34, 159.96, 165.23, 165.58.

MS [m/e (%)] : 515 (M^++2, 0.18), 513 (M^+, 0.2), 241 (39), 134 (60), 121 (57), 93 (57), 77 (38).

Microanalysis : M. F. $C_{27}H_{32}BrNO_4$.

Calculated	C : 63.04	H : 6.27	N : 2.72
Obtained	C : 62.79	H : 6.31	N : 3.01

***Preparation of* 1.14d & 1.15d**

The imine **1.13d** (0.237 g, 1 mmol) on reaction with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of β-lactams **1.14d** & **1.15d** (0.305 g, 60%) in the ratio of 40:60, which was determined from the ^{1}H NMR spectral data. The diastereomers were separated by flash column chromatography. The data for them is given below.

***(3R,4S,1′S,3′R,4′R,6′R)-3-[4-Bromo-3′,7′,7′-trimethylbicyclo[4.1.0]hept-3′-yloxy]-1-(4′′-methoxyphenyl)-4-[2′′′-phenyl-(E)-1-ethenyl]-azetan-2-one* 1.14d**

Isolated as a white solid.

M.P. : 166°C.

$[\alpha]^{D}_{25}$: +33° (c 1.85, CH_2Cl_2).

IR (cm^{-1}) : 1520, 1750.

^{1}H NMR : δ 0.55-0.75 (m, 1H), 0.75-0.95 (m, 1H), 1.00 (s, 3H), 1.05 (s,

3H), 1.35 (s, 3H), 1.50 (dd, *J* = 5, 15 Hz, 1H), 2.20-2.50 (m, 3H), 3.75 (s, 3H), 4.05 (dd, *J* = 8, 10 Hz, 1H), 4.75 (dd, *J* = 5, 10 Hz, 1H), 5.15 (d, *J* = 5 Hz, 1H), 6.45 (dd, *J* = 10, 15 Hz, 1H), 6.70-6.95 (m, 3H), 7.20-7.60 (m, 7H).

(3S,4R,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1-(4¢¢-methoxyphenyl)-4-[2¢¢¢-phenyl-(E)-1-ethenyl]-azetan-2-one **1.15d**.

Isolated as a white solid.

M.P. : 158-160°C.

$[\alpha]^{D}_{25}$: –122.9° (c 1.85, CH_2Cl_2).

IR (cm^{-1}) : 1750.

^{1}H NMR : δ 0.55-0.85 (m, 2H), 0.93 (s, 3H), 0.95 (s, 3H), 1.45 (s, 3H), 1.45-1.60 (m, 1H), 2.20 (dd, *J* = 12.5, 15 Hz, 1 H), 2.40 (dd, *J* = 6, 10 Hz, 1H), 3.75 (s, 3H), 4.05 (t, *J* = 10 Hz, 1H), 4.75 (dd, *J* = 5, 10 Hz, 1H), 5.20 (d, *J* = 5 Hz, 1H), 6.35 (dd, *J* = 10, 15 Hz, 1H), 6.70-6.90 (m, 3H), 7.20-7.55 (m, 7H).

Data for the mixture of **1.14d** & **1.15d**

^{13}C NMR : δ 15.36, 15.52, 17.82, 17.88, 19.35, 19.44, 19.60, 21.36, 21.70, 28.39, 31.62, 31.87, 32.01, 55.37, 58.85, 60.14, 61.71, 62.33, 77.43, 77.70, 77.87, 114.26, 118.56, 118.63, 125.11, 126.62, 126.78, 128.03, 128.14, 128.48, 128.60, 131.41, 135.76, 135.89, 136.73, 156.20, 164.70, 164.79.

MS [m/e (%)] : 511 (M^++2, 1.8), 509 (M^+, 2), 294 (28), 236 (35), 146 (69), 115 (100), 93 (83), 91 (69), 77 (38).

Microanalysis : M. F. $C_{28}H_{32}BrNO_3$.

Calculated	C : 65.99	H : 6.33	N : 2.75
Obtained	C : 65.85	H : 6.52	N : 2.70

***Preparation of* 1.14e** & **1.15e**

The imine **1.13e** (0.207 g, 1 mmol) on treatment with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of β-lactams **1.14e** & **1.15e** (0.297 g, 62%) in the ratio of 45:55, which was determined from the ^1H NMR spectral data. The diastereomers were separated by flash column chromatography. The data for them is given below.

(3R,4S,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1-phenyl-4-[2¢¢-phenyl-(E)-1¢¢-ethenyl]-azetan-2-one **1.14e**

Isolated as a white solid.

M.P. : 184°C.

$[\alpha]^{D}_{25}$: +20 (c 0.28, CH_2Cl_2).

IR (cm^{-1}) : 1750.

^1H NMR : δ 0.60-0.75 (m, 1H), 0.75-0.92 (m, 1H), 0.99 (s, 3H), 1.02 (s, 3H), 1.37 (s, 3H), 1.48 (dd, *J* = 4.84, 14.44 Hz, 1H), 2.25-2.50 (m, 3H), 4.05 (dd, *J* = 8, 10.44 Hz, 1H), 4.82 (dd, *J* = 4.98, 8.83 Hz, 1H), 5.15 (d, *J* = 5.04 Hz, 1H), 6.43 (dd, *J* = 8.83, 16 Hz, 1H), 6.82 (d, *J* = 15.98 Hz, 1H), 7.09 (t, *J* = 7.40 Hz,1H), 7.20-7.60 (m, 9H).

(3S,4R,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1-phenyl-4-[2¢¢-phenyl-(E)-1¢¢-ethenyl]-azetan-2-one **1.15e**

Isolated as a white solid.

M.P. : 174°C.

$[\alpha]^{D}_{25}$: -103.90° (c 0.41, CH_2Cl_2).

IR (cm^{-1}) : 1758.

^1H NMR : δ 0.58-0.90 (m, 2H), 0.92 (s, 3H), 0.95 (s, 3H), 1.45 (s, 3H), 1.40-1.60 (m, 1H), 2.18 (dd, *J* = 10.18, 13.7 Hz, 1H), 2.40 (dd, *J* = 4.80, 8.80 Hz, 2H), 4.07 (t, *J* = 8.90 Hz, 1H), 4.78 (dd, *J* = 5.10, 8.77 Hz, 1H), 5.23 (d, *J* = 5.10 Hz, 1H), 6.34 (dd, *J* = 8.78, 15.55 Hz, 1H), 6.83 (d, *J* = 15.98 Hz, 1H), 7.08 (t, J = 7.29 Hz, 1H), 7.20-7.55 (m, 9H).

^{13}C NMR : δ 15.66, 17.96, 19.54, 21.79, 28.53, 31.93, 32.14, 60.23, 62.25, 77.91, 78.05, 117.37, 124.24, 125.02, 126.92, 128.20, 128.64, 129.13, 135.96, 136.25, 137.99, 165.55.

Data for the mixture of **1.14e** & **1.15e**

MS [m/e (%)] : 481 (M+2, 0.5%), 479 (M+, 0.5%), 264 (35%), 135 (35%), 115 (100%), 93 (56%), 91 (43%), 77 (34%).

Microanalysis : M. F. $C_{27}H_{30}BrNO_2$.

Calculated	C : 67.62	H : 6.31	N : 2.92
Obtained	C : 67.30	H : 6.58	N : 2.96

Preparation of (3R, 4S, 1′S, 3′R, 4′R, 6′R) & (3S, 4R, 1′S, 3′R, 4′R, 6′R) 3-[4′-Bromo-3′,7′,7′-trimethylbicyclo[4.1.0]hept-3′-yloxy]-4-[2′′-phenyl-(E)-1′′-ethenyl]-1-propyl-azetan-2-one **1.14f** & **1.15f**

The imine **1.13f** (0.173 g, 1 mmol) on reaction with acid chloride **1.13a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of *b*-lactams **1.14f & 1.15f** (0.143 g, 32%) in the ratio of 46:54, which was determined from the ^{1}H NMR spectral data.

The diastereomeric mixture was isolated as an oil.

$[\alpha]^D_{25}$: -43.27° (c 2.63, CH_2Cl_2).

IR (cm^{-1}) : 1648, 1754.

^{1}H NMR : δ 0.5-0.85 (m, 2H), 0.90, 0.93, 0.95, 1.0 (4s, total 6H), 0.85-2.5 (m, 9H), 1.28, 1.39 (2s, total 3H), 3.15-3.4 (m, 1H), 3.95-4.20 (m, 1H), 4.28 (dd, *J* = 4.4, 9.3 Hz, 1H), 4.98 & 5.08 (d, *J* = 4 Hz, total 1H), 6.23 & 6.38 (dd, *J* = 9.3, 16.1 Hz & dd, *J* = 8.8, 16.1 Hz respect. Total 1H), 6.64 (d, *J* = 16.1 Hz, 1H), 7.2-7.6 (m, 5H).

^{13}C NMR : δ 11.13, 14.99, 15.17, 17.41, 18.92, 19.07, 20.72, 21.35, 28.04, 31.20, 31.64, 41.64, 59.94, 61.41, 62.08, 76.12, 77.00, 125.01, 126.22, 126.37, 127.67, 128.20, 135.04, 135.23, 135.96, 167.46.

MS [m/e (%)] : 446 (M+1, 0.5%), 233 (46%), 232 (30%), 230 (100%), 202

(66%), 146 (46%), 135 (57%), 115 (89%), 93 (76%).

Microanalysis : M. F. $C_{24}H_{32}BrNO_2$.

Calculated	C : 64.57	H : 7.23	N : 3.14
Obtained	C : 64.15	H : 7.50	N : 3.39

Preparation of (3R, 4S, 1′S, 3′R, 4′R, 6′R) & (3S, 4R, 1′S, 3′R, 4′R, 6′R) 4-Styryl-3-[4′-bromo-3′,7′,7′-trimethylbicyclo[4.1.0]hept-3′-yloxy]-1-cyclohexyl-azetan-2-one

1.14g & **1.15g**

The imine **1.13g** (0.213 g, 1 mmol) on reaction with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided inseparable diastereomeric mixture of **1.14g** & **1.15g** (0.218 g, 45 %) in the ratio of 44:56, which was determined from the ^{1}H NMR spectral data.

The diastereomeric mixture was isolated as an oil.

$[\alpha]^D_{25}$: -31.50°C (c 2.54, $CHCl_3$).

IR (cm^{-1}) : 1743.

^{1}H NMR : δ 0.55-0.83 (m, 2H), 0.85, 0.90, 0.93, 0.97 (s, total 6H), 1.24, 1.36 (s, total 3H), 1.1-1.95 (m, 11H), 2.05-2.45 (m, 4H), 3.38-3.56 (m, 1H), 3.94-4.06 (m, 1H), 4.87 & 4.98 (d, *J* = 4.5 Hz & d, *J* = 4.7 Hz respect. Total 1H), 6.22 & 6.35 (dd, *J* = 9.45 & dd, *J* = 9.35, 15.88 Hz respect. Total 1H), 6.55 & 6.60 (d, *J* = 15.88 Hz, total 1H), 7.25-7.55 (m, 7H).

^{13}C NMR : δ 15.24, 15.46, 17.81, 19.17, 19.50, 21.23, 21.63, 25.01, 28.32, 30.42, 31.45, 31.70, 31.92, 51.85, 53.46, 59.13, 60.19, 60.60, 61.26, 77.47, 77.87, 126.47, 126.65, 127.05, 127.79, 128.45, 134.33, 134.52, 136.39, 166.90.

MS [m/e (%)] : 487 (M+1, 0.5%), 486 (M+, 0.5%), 272 (40%), 271 (30%), 270 (66%), 242 (66%), 146 (77%), 115 (47%), 93 (90%).

Microanalysis : M. F. $C_{27}H_{36}BrNO_2$.

Calculated	C : 66.66	H : 7.46	N : 2.88
Obtained	C : 66.20	H : 7.80	N : 2.60

***Preparation of* 1.14h *&* 1.15h**

The imine 1.13h (0.187 g, 1 mmol) on treatment with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of *b*-lactams **1.14h & 1.15h** (0.299 mg, 65%) in the ratio of 45:55, which was determined from the ^1H NMR spectral data. One of the diastereomers **1.15h** could be separated by crystallization from pet ether/ dichloromethane system in 25% yield.

(3S,4R,1¢S,3¢R,4¢R,6¢R)-3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1-(tert-butyl)-4-[2¢¢-phenyl-(E)-1¢¢-ethenyl]-azetan-2-one **1.15h**

Isolated as a white solid.

M.P. : 132-133°C.

$[\alpha]^{D}_{25}$: -33.70° (c 0.54, CH_2Cl_2).

IR (cm^{-1}) : 1215, 1365, 1743.

^1H NMR : δ 0.50-0.65 (m, 1H), 0.65-0.80 (m, 1H), 0.87, 0.90 (2s, 6H), 1.32 (9H), 1.36 (s, 3H), 1.30-1.50 (m, 1H), 2.08 (dd, *J* = 9.5, 14 Hz, 1H), 2.30-2.45 (m, 2H), 4.0 (t, *J* = 9.5 Hz, 1H), 4.33 (dd, *J* = 5.9, 9.5 Hz, 1H), 4.93 (d, *J* = 5.1 Hz, 1H), 6.25 (dd, *J* = 9.5, 16.1 Hz, 1H), 6.59 (d, *J* = 16.1 Hz, 1H), 7.15-7.55 (m, 5H).

^{13}C NMR : 15.08, 17.49, 18.92, 19.29, 21.00, 28.05, 31.34, 31.77, 53.90, 58.93, 60.73, 76.05, 76.36, 126.20, 127.63, 128.36, 134.07, 136.15, 166.67.

MS [m/e (%)] : 459 (2.5%), 246 (52%), 243 (40%), 188 (100%), 172 (87%), 146 (82%), 135 (50%), 115 (85%), 93 (70%).

Microanalysis : MF $C_{25}H_{34}BrNO_2$.

Calculated	C : 65.21	H : 7.44	N : 3.04
Obtained	C : 64.88	H : 7.28	N : 3.31

Preparation of (3R, 4S, 1¢S, 3¢R, 4¢R, 6¢R) & (3S, 4R, 1¢S, 3¢R, 4¢R, 6¢R) 3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-4-[2-phenyl-(E)-1-ethenyl]-1-[1-phenyl-(1R)-ethyl]-azetan-2-one **1.14i & 1.15i**

The imine **1.13i** (0.235 g, 1 mmol) on treatment with acid chloride **1.13a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of *b*-lactams **1.14i** & **1.15i** (0.243 g, 48%) in the ratio of 44:56, which was determined from the ^1H NMR spectral data. The data for the diastereomeric mixture is as follows.

$[\alpha]^D_{25}$: -53.14° (c 0.7, CH_2Cl_2).

IR (cm^{-1}) : 1450, 1494, 1743, 2939, 3014.

^1H NMR : δ 0.88, 0.92, 0.95, 1.00 (4s, total 6H), 1.26 & 1.38 (2s, total 3H), 1.6 & 1.76 (d, *J* = 7.3 Hz & d, *J* = 6.9 Hz respect. Total 3H), 1.20-2.55 (m, 4H), 3.90-4.30 (m, 2H), 4.4-4.70 (m, 1H), 4.85-5.20 (m, 2H), 6.15-6.60 (m, 2H), 7.10-7.65 (m, 10H).

^{13}C NMR : δ 15.35, 15.53, 17.76, 19.13, 19.38, 19.53, 21.27, 21.64, 28.38, 31.50, 31.95, 51.27, 53.16, 59.05, 60.15, 60.70, 61.56, 76.73, 77.74, 125.34, 126.50, 126.69, 127.33, 127.69, 127.88, 128.52, 134.47, 136.39, 139.60, 141.09, 167.06, 167.37.

MS [m/e (%)] : 509 (M+2, 1), 508 (M+1, 5), 507 (M^+, 2), 294 (38), 188 (98), 146 (89), 135 (51), 105 (100), 93 (35).

Microanalysis : M. F. $C_{29}H_{34}BrNO_2$.

Calculated	C : 68.50	H : 6.74	N : 2.75
Obtained	C : 68.09	H : 6.98	N : 2.50

***preparation of (3R, 4S, 1¢S, 3¢R, 4¢R, 6¢R) & (3S, 4R, 1¢S, 3¢R, 4¢R, 6¢R)1-Benzyl-3-[4¢-bromo-3¢,7¢,7¢-trimethyl-bicyclo[4.1.0]hept-3¢-yloxy]-4-[2¢¢-phenyl-(E)-1¢¢-ethenyl]-azetan-2-one* 1.14j & 1.15j**

The imine **1.13j** (0.221 g, 1 mmol) on treatment with acid chloride **1.12a** (617 mg, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) furnished **1.14j & 1.15j** (232 mg, 47%) in the ratio of 48:52, which was determined from the ^1H NMR spectral data

The diastereomeric mixture was isolated as an oil.

$[\alpha]^D_{25}$: -64.04° (c 1.73, CH_2Cl_2).

IR (cm^{-1}) : 1215, 1747, 2927, 3018.

^{1}H NMR : δ 0.50-0.85 (m, 2H), 0.87, 0.92, 0.96, 1.02 (4s, total 6H), 1.37 (s, 3H), 1.1-1.5 (m, 1H), 1.95-2.50 (m, 3H), 3.96 (d, J = 15 Hz, 1H), 3.95-4.25 (m, 2H), 4.7 (d, J = 15 Hz, 1H), 4.95, 5.08 (d, J = 4.6 Hz, total 1H), 6.18 & 6.33 (dd, J = 9.0, 15 Hz & dd, J = 8.7, 15.5 Hz respect. Total 1H), 6.5 (close d, J = 15.8 Hz, 1H), 7.05-7.55 (m, 10 H).

^{13}C NMR : δ 15.67, 15.81, 18.18, 19.87, 20.02, 21.70, 28.75, 29.12, 31.85, 32.18, 44.48, 59.9, 61.34, 78.0, 78.48, 125.02, 126.91, 127.96, 128.35, 128.82, 129.01, 135.96, 136.28, 136.70, 167.86.

MS [m/e (%)] : 146 (26%), 135 (30%), 115 (40%), 91 (100%).

The preparation of (3R, 4S, 1¢S, 3¢R, 4¢R, 6¢R) & (3S, 4R, 1¢S, 3¢R, 4¢R, 6¢R)3-[4¢-bromo-3¢,7¢,7¢-trimethyl-(1¢S, 3¢R, 4¢R, 6¢R)-bicyclo[4.1.0]hept-3¢-yloxy]-1-(2¢¢-furylmethyl)-4-[2¢¢¢-phenyl-(E)-1¢¢¢-ethenyl]-azetan-2-one **1.14k** & **1.15k**

The imine **1.13k** (0.181 g, 1 mmol) on reaction with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of *b*-lactams **1.14k** & **1.15k** (242 mg, 50%) in the ratio of 45:55, which was determined from the ^{1}H NMR spectral data.

The diastereomeric mixture was isolated as a gum.

$[\alpha]^{D}_{25}$: -30.38° (c 1.54, CH_2Cl_3).

IR (cm^{-1}) : 1736, 1774.

^{1}H NMR : δ 0.45-0.85 (m, 2H), 0.90, 0.94, 0.97, 1.01 (4s, total 6H), 1.27, 1.38 (2s, total 3H), 1.15-1.80 (m, 1H), 2.05-2.55 (m, 3H), 3.90-4.15 (m, 1H), 4.07 (2d, *J* = 15.8 Hz, 1H), 4.24 & 4.26 (dd, *J* = 4.50, 9.50 Hz & dd, *J* = 4.6, 9.44 Hz respect. Total 1H), 4.58 (d, *J* = 15.5 Hz, 1H), 4.96 & 5.04 (d, *J* = 4.50 Hz & d, *J* = 4.60 Hz respect. Total 1H), 6.10-6.45 (m, 3H), 6.54 (2 close d, *J* = 16 Hz, total 1H), 6.90-7.65 (m, 6H).

^{13}C NMR : 15.81, 18.20, 19.89, 21.73, 22.08, 28.77, 32.10, 32.35, 37.07, 59.11, 60.54, 61.81, 62.26, 77.56, 78.14, 108.88, 110.70,

59.11, 60.54, 61.81, 62.36, 77.56, 78.14, 108.88, 110.79, 124.77, 126.97, 128.33, 128.88, 136.21, 136.82, 142.80, 149.44, 167.66.

Microanalysis : M. F. $C_{26}H_{30}BrNO_3$.

Calculated	C : 64.26	H : 6.24	N : 2.89
Obtained	C : 63.80	H : 6.50	N : 2.60

***Preparation of* 1.14l *&* 1.15l**

The imine **1.13l** (0.145 g, 1 mmol) on reaction with acid chloride **1.13l** (0.617 g, 2 mmol) in the presence of Et_3N (0.84 mL, 6 mmol) provided a diastereomeric mixture of *cis b*-lactams **1.14l & 1.15l** (0.121 g, 29%) in the ratio of 45:55, which was determined from the ^1H NMR spectral data. One of the diastereomers **1.14l** was obtained in the pure form by fractional crystallization.

***(3R, 4S, 1¢S, 3¢R, 4¢R, 6¢R) 3-[4¢-Bromo-3¢,7¢,7¢-trimethylbicyclo[4.1.0]hept-3¢-yloxy]-1-phenyl-4-(1¢¢-propenyl))-azetan-2-one* 1.14l**

Isolated as white solid

M.P. : 148-150°C.

$[\alpha]^{D}_{25}$: +30° (c 2.54, $CHCl_3$).

IR (cm^{-1}) : 1382, 1496, 1598, 1749.

^1H NMR : δ 0.6-0.7 (m, 1H), 0.7-0.88 (m, 1H), 0.97 & 1.02 (s, 6H), 1.33 (s, 3H), 1.45 (dd, *J* = 4.6, 14.4 Hz, 1H), 1.77 (dd, *J* = 1.4, 6.5 Hz, 1H), 2.25-2.50 (m, 3H), 4.03 (dd, *J* = 7.9, 10.4 Hz, 1H), 4.38 (dd, *J* = 5.0, 8.7 Hz, 1H), 4.98 (d, *J* = 5.0 Hz, 1H), 5.57-5.73 (m, 1H), 5.65 (dd, *J* = 8.7, 15.4 Hz, 1H), 7.05 (dd, *J* = 7.4 Hz, 1H), 7.20-7.32 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 2H).

^{13}C NMR : δ 15.56, 17.79, 17.92, 18.00, 19.41, 21.64, 28.39, 31.06, 32.05, 60.15, 61.76, 76.53, 77.75, 117.28, 123.95, 126.62, 128.90, 132.55, 137.84, 165.57.

MS [m/e (%)] : 449 (M+2, 6%), 202 (83%), 172 (50%), 146 (100%), 135 (83%), 93 (98%), 77 (55%).

Microanalysis : M. F. $C_{22}H_{28}BrNO_2$.

Calculated	C : 63.16	H : 6.75	N : 3.35
Obtained	C : 62.88	H : 6.90	N : 3.10

Preparation of (1′S, 3′R, 4′R, 6′R, 3S, 4R) & (1′S, 3′R, 4′R, 6′R, 3R, 4S) 3-[4′-Chloro-3′,7′,7′-trimethyl-bicyclo[4.1.0]hept-3′-yloxy]-1-(4′′-methoxyphenyl)-4-[2′′′-phenyl-(E)-1′′′-ethenyl]-azetan-2-one **1.16d** & **1.17d**

The imine **1.13d** (0.237 g, 1 mmol) on reaction with acid chloride **1.12b** (0.528 g, 2 mmol) in the presence of Et_3N (0.84 ml, 6 mmol) provided a diastereomeric mixture of β-lactams **1.16d** & **1.17d** (0.279 g, 60%) in the ratio of 40:60, which was determined from the ^1H NMR spectral data. The data for the diasteromeric mixture is given below.

M.P. : 128-131°c.

$[\alpha]^{D}_{25}$: -44.63° (c 0.69, CH_2Cl_2).

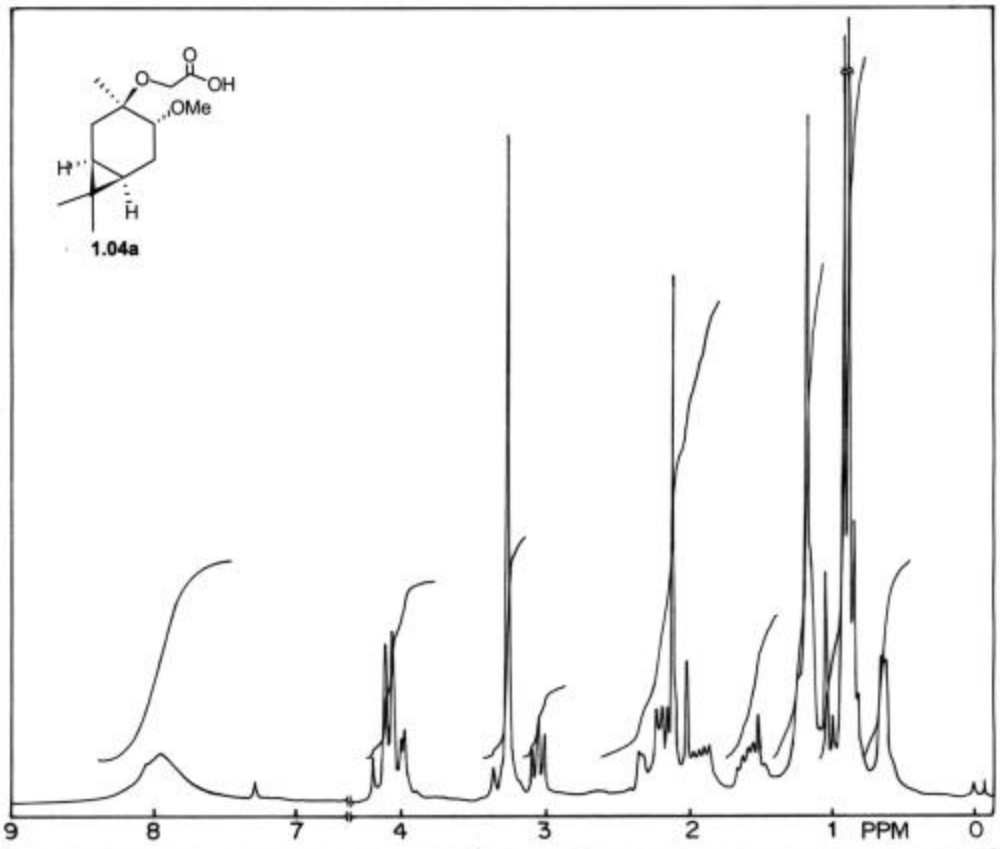
IR (cm^{-1}) : 1750.

^1H NMR : δ 0.55-0.85 (m, 2H), 0.90, 0.96 (2s, total 3H), 0.98 (s, total 3H), 1.33, 1.40 (2s, total 3H), 1.35-1.50 (m, 1H), 1.95-2.04 (m, 3H), 3.76 (s, 3H), 3.78-4.2 (m, 1H), 4.68 & 4.76 (dd, *J* = 4.7, 8.90 Hz & dd, *J* = 4.8, 8.9 Hz, respect. Total 1H), 5.18 & 5.26 (d, *J* = 4.7 Hz & d, *J* = 4.8 Hz respect. Total 1H), 6.32, 6.4 (2dd, *J* = 8.90, 13.2 Hz, total 1H), 6.68-7.58 (total 10H).

^{13}C NMR : δ 15.49, 15.50, 16.70, 17.88, 19.35, 19.49, 20.67, 21, 28.46, 30.67, 31.04, 32.21, 32.41, 35.42, 61.95, 62.55, 65.08, 66.08, 77.90, 77.27, 77.30, 78.38, 114.36, 118.63, 125.23, 126.71, 126.81, 128, 128.27, 128.63, 128.73, 135.90, 136.03, 136.19, 136.30, 155.29.

MS [m/e (%)] : 465 (0.1%), 294 (38%), 266 (55%), 238 (42%), 146 (100%), 135 (36%), 115 (56%), 105 (16%), 91 (16%).

Microanalysis	:	M. F. $C_{28}H_{32}ClNO_3$.			
		Calculated	C : 72.17	H : 6.92	N : 3.01
		Obtained	C : 71.70	H : 7.04	N : 2.87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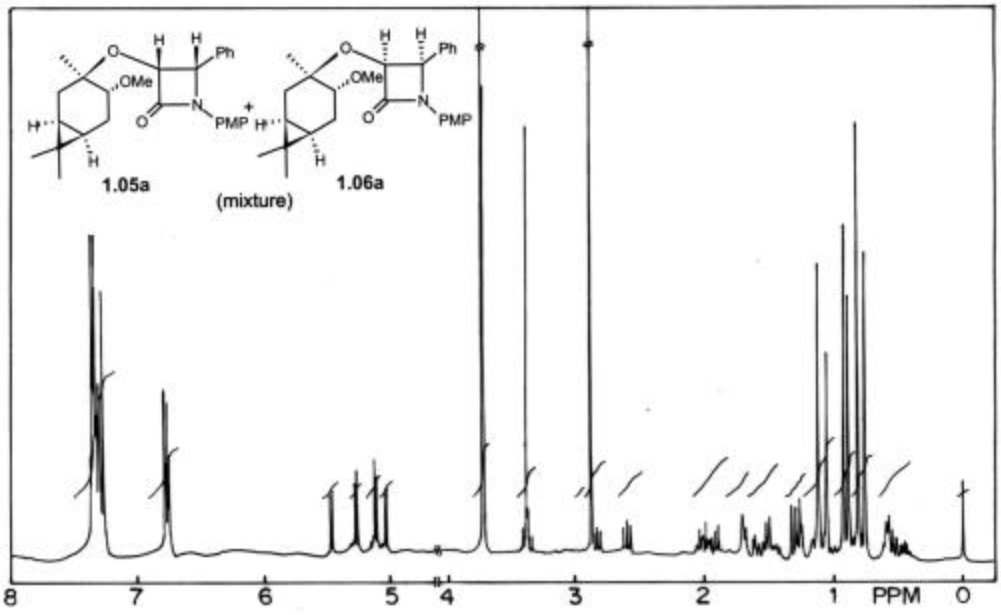
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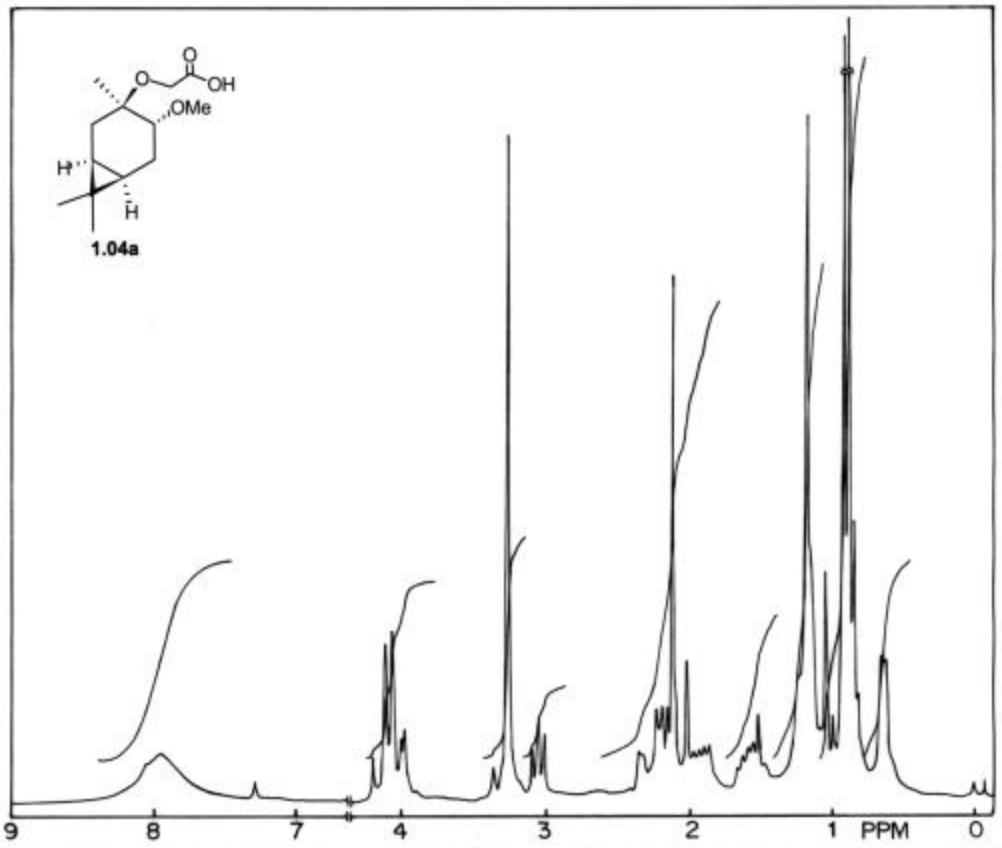
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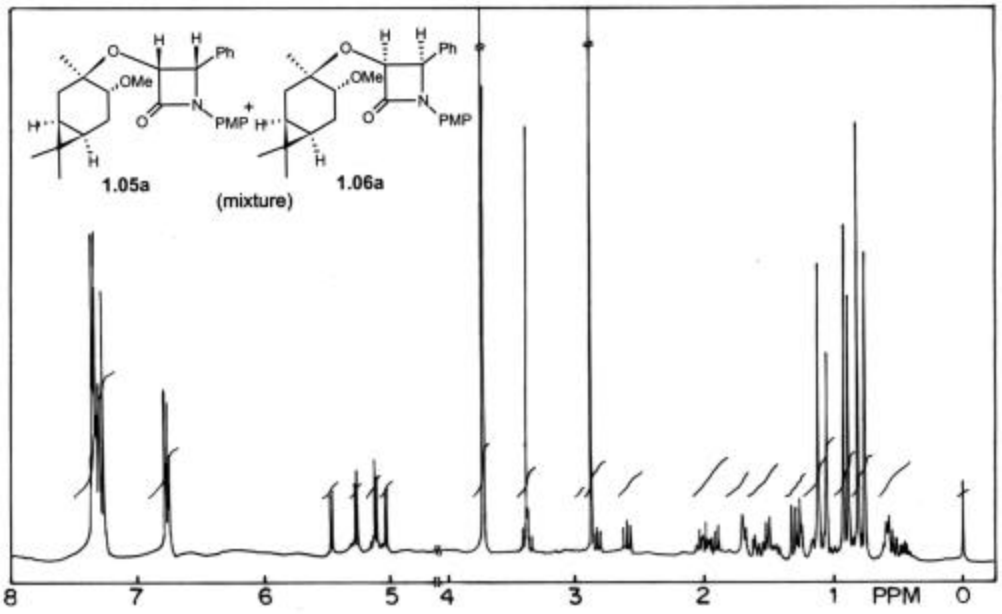
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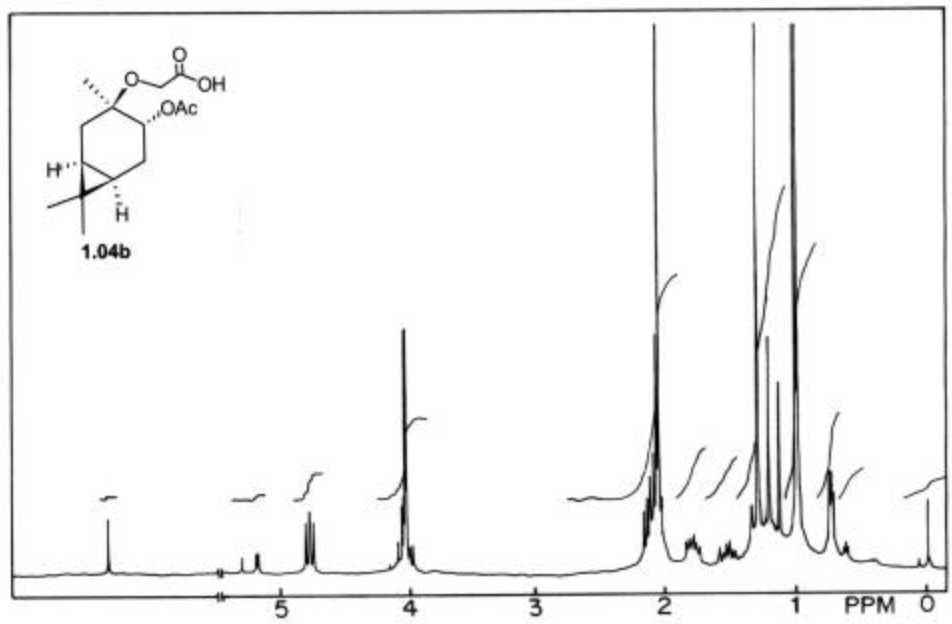
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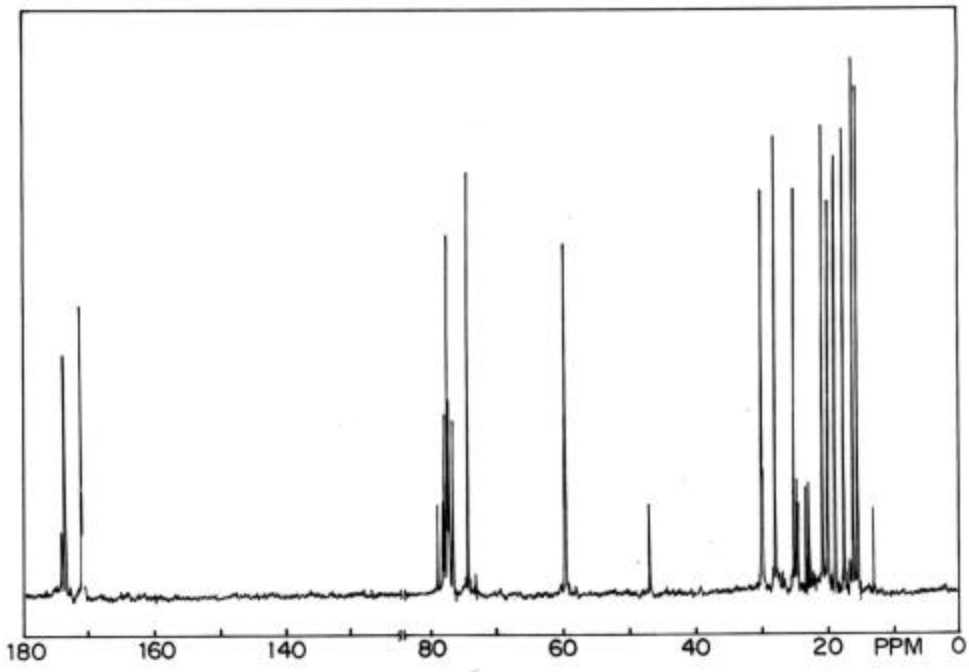
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1.9 References

1. Fleming, A. J. *Exp. Patho.* **1929**, *10*, 226.
2. (a) Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J.; Sanders, A. G. *Lancet 2* **1940**, 226. (b) Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D; Heatley, N. G.; Jennings, M. A.; Florey, H. W. *Lancet 2* **1941**, 177.
3. Abraham, E. P. In the preface of *Chemistry and Biology of b-Lactam Antibiotics;* Morin, R. B., Gorman, M., Ed.; Academic: New York, 1982; Vol. 1.
4. Crowfoot, D.; Bunn, C. W.; Roger-Low, B. W.; Turner-Jones, A. In *The Chemistry of Penicillin*; Varke, H. T., Johnson, J. R., Robinnson, R., Ed.; Princeton University Press: Princeton, p 310.
5. For references on SAR studies on *b*-lactam antibiotics, see: (a) Boyd, D. B.; Eigenbrot, C. H.; Indelicato, J. M.; Miller, M.; Painin, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528. (b) Durkin, K. A.; Sherrod, M. J.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 5839. (c) Cimarusti, C. M. *J. Med. Chem.* **1984**, *27*, 427. (d) Cohen, C. N. *J. Med. Chem.* **1983**, *26*, 259. (e) Boyd, D. B. In *Chemistry and Biology of b-Lactam Antibiotics;* Morin, R. B., Gorman, M., Ed.; Academic: New York, 1982; Vol. 1, p 437. (f) Blainpain, P. C.; Nagy, J. B.; Laurent, G. H.; Durant, F. V. *J. Med. Chem.* **1980**, *146*, 837.
6. For the biochemical modes of action of *b*-lactam antibiotics, see: (a) Waxman, D. J.; Strominger, J. L. In *Chemistry and Biology of b-Lactam Antibiotics;* Morin, R. B., Gorman, M., Ed.; Academic: New York, 1982; Vol. 3. (b) Tipper, D. J. In *Antibiotic Inhibitors of Bacterial Cell Wall Biosynthesis. International Encyclopedia of Pharmacology and Therapeutics*; Tipper, D. J., Ed.; Pergamon: oxford, Section 127, p 133. (c) Tomasz, A. *Rev. Infect. Dis.* **1979**, *1*, 434. (d) Tipper, D. J. *Pharmacol. Ther.* **1985**, *27*, 1.
7. Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144.
8. Page, M. I. In *The Chemistry of b-Lactams;* Page M. I., Ed.; Blackie Academic & Professional: London, 1992; p 129.

9. For the references on A, B, C, D and metalloenzyme type *b*-lactamases, see: (a) Mossakowska, D.; Ali, N. A.; Dale, J. N. *Eur. J. Biochem.* **1989**, *180*, 309. (b) Kelly, J. A. et. al. *Science* **1986**, *231*, 1429. (c) Samraoui, B. et. al. *Nature* (London) **1986**, *320*, 378. (d) Boris, B. et. al. *Biochem. J.* **1988**, *250*, 313. (e) Pratt, R. R., Govardhan, C. P. *Proc. Natt. Acad. Sci. USA* **1984**, *84*, 1302. (f) Tipper, D. J. & Schrominger, J. L. *Proc. Natt. Acad. Sci. USA.* **1965**, *54*, 1133.

10. For general references on *b*-lactamases inhibitors, see: (a) Abraham, E. P.; Chain, E. *Nature* **1940**, *146*, 837. (b) kirby, W. M. M. *Science* **1944**, *99*, 452.

11. Lambert, H. P.; O'Grady, F. W. In *Antibiotics and Chemotherapy;* Lambert, H. P., O'Grady, F. W., Eds.; Churchill: Livingstone, 1992; p 191.

12. Gordon, E. M.; Syker, R. B. In *Chemistry and Biology of b-Lactam Antibiotics;* Morin, R. B., Gorman, M., Ed.; Academic: New York, 1982; Vol. 1, p 199.

13. For detailed discussion, see: Cooper, R. D. J. In *The Chemistry of b-Lactams;* Page M. I., Ed.; Blackie Academic & Professional: London, 1992; p 272.

14. (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D. A.; Gaviraghi, G.; Carlesso, R.; Bismara, C. (Glaxo S. P. A.) Eur. Pat. Appl. **1991**, 0416953 A2, Bulletin 91/11. (b) Chem. Abst. 116, 235337t (1972).

15. Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123.

16. Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689.

17. (a) Ogilvie, W.; Bailey, M.; Poupart, M. –A.; Abraham, A.; Bhavsar, A.; Bonneau, P.; Bordeleau, J.; Bousquet, Y.; Chabot, C.; Duceppe, J. S.; Fazal, G.; Goulet, S.; Grand-Maitre, C.; Guse, I.; Halmos, T.; Lavallee, P.; Leach, M.; Malenfant, E.; O´Meara, J.; Plante, R.; Plouffe, C.; Poirier, M.; Soucy, F.; Yoakim, C.; Deziel, R. *J. Med. Chem.* **1997**, *40*, 4113. (b) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jim, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365.

18. For references, see: (a) Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339. (b) Vaccaro, W. D.; Davis, H. R. Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313 and references sited therein.

19. Sheehan, J. C.; Bose, A. K. *J. Am. Chem. Soc.* **1950**, *72*, 5158.

20. Breckpot, R. *Bull. Soc. Chim. Belg.* **1923**, *32*, 412 (Chem. Abstr. 18: 1113).

21. Knunyants, I. L.; Gambaryan, N. P. *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*. **1955**, 1037.

22. Graf, R. *Liebigs Ann.* **1963**, *666*:111.

23. (a) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*:51. (b) Staudinger, H. in Die Ketene (1912) Enke, stuttgart p 71.

24. (a) Gilman H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255. (b) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (c) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc. Chem. Commun.* **1984**, 86.

25. Manhas, M. S.; Khajavi, M. S.; Bari, S. S.; Bose, A. K. *Tetrahedron Lett.* **1983**, *24*, 2323.

26. For recent reviews on the asymmetric synthesis of *b*-lactams, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (b) Ternasky, R. J.; Morin J. M. Jr. In *The Organic Chemistry of b-Lactams*; Georg, G. I., Ed.; WCH: New York, 1993; p 237. (c) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 85.

27. For the references on Ester enolate-Imine condensation reaction, see: (a) Hart D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (b) Georg, G. I. In *Natural Products Chemistry*; Rahaman A. –ur., Ed.; Elseiver: Amsterdam, 1989; Vol. 4, p 431. (c) Fujisawa, T.; Shimizu, M. *Rev. Heteroatom. Chem.* **1996**, *15*, 203. (d) Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605.

28. Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467.

29. Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

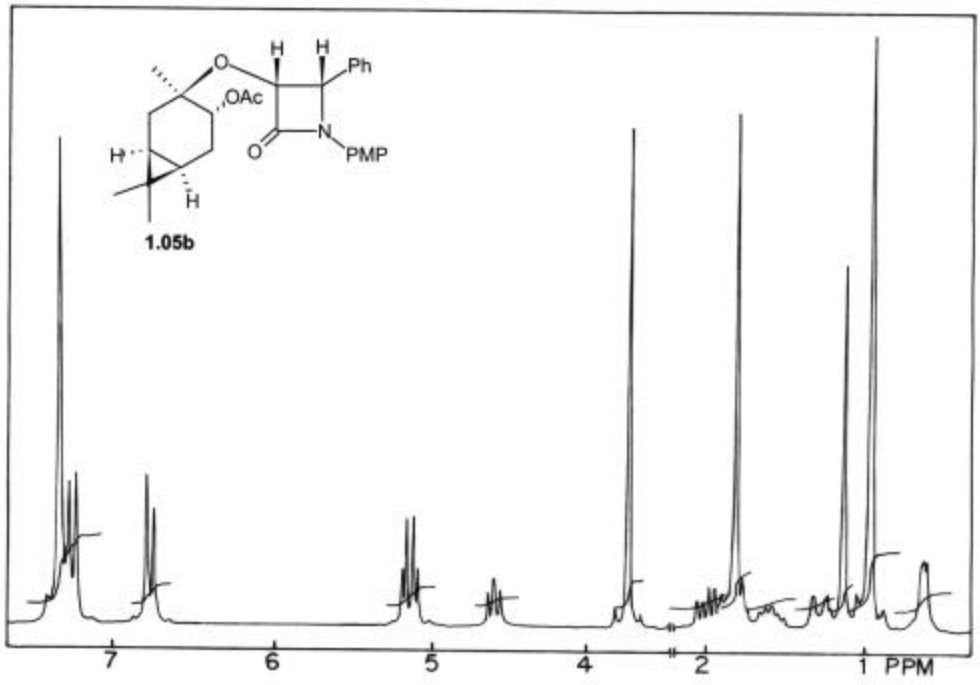
30. Hart, D. J.; Ha, D. –C. *Chem. Rev.* **1989**, 1447.

31. For cycloaddition reaction of Isocyanates with Alkenes, see: (a) Chmielewski, M.; Kaluza, Z.; Furman, B. *Chem. Commun.* **1996**, 2689. (b) Furman, B.; Thurmer, R.; Kaluza, Z.; Voelter, W.; Chmielewski, M. *Tet. Lett.* **1999**, *40*, 5909. (c) Furman, B.; Thurmer, R.; Kaluza, Z.; Lysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem.; Int. Ed.* **1999**, *38 (8)*, 1121.

32. For reviews on the Asymmetric Staudinger Reaction, see: (a) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, *59*, 485. (b) Van Der

Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (c) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of b-Lactams*; Georg, G. I., Ed.; WCH: New York, 1993; p 295.

33. Bose, A. K.; Manhas, M. S.; Van der Veen, J. M.; Bari, S. S.; Wagle, D. R. *Tetrahedron* **1992**, *48*, 4831.
34. Alcaide, B.; Rodriguez-Vicente, A. *Tetrahedron Lett*. **1999**, *40*, 2005.
35. Palomo, C.; Aizpurua, J. M.; Mielgo, A.; Linden, A. *J. Org. Chem.* **1996**, *61*, 9186.
36. Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792.
37. (a) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc*. **1991**, *113*, 5784. (b) Dumas, S.; Hegedus, L. S. *J. Org. chem.* **1994**, *59*, 4967.
38. (a) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc*. **1993**, *115*, 995. (b) Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036. (c) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085.
39. Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5585.



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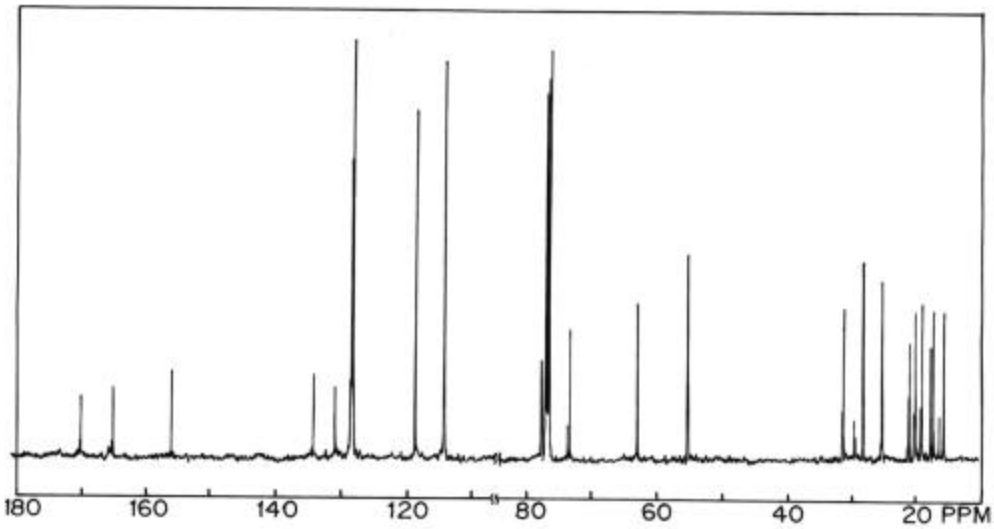

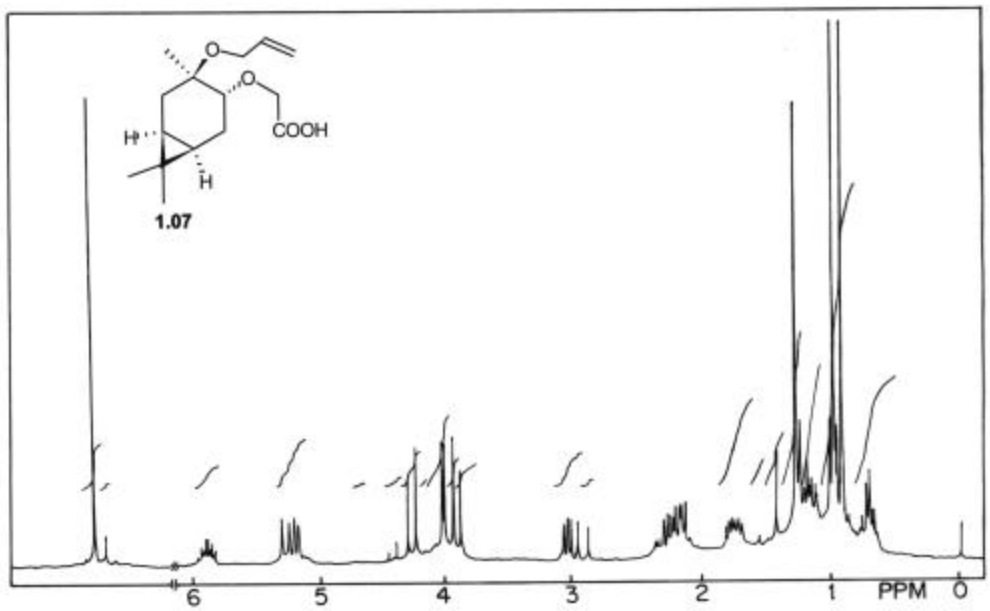
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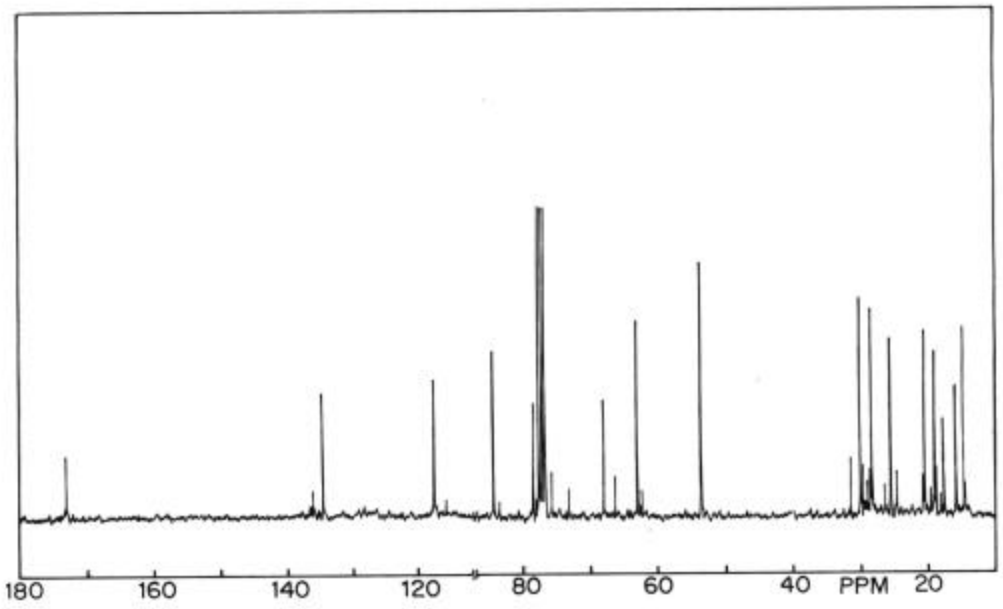
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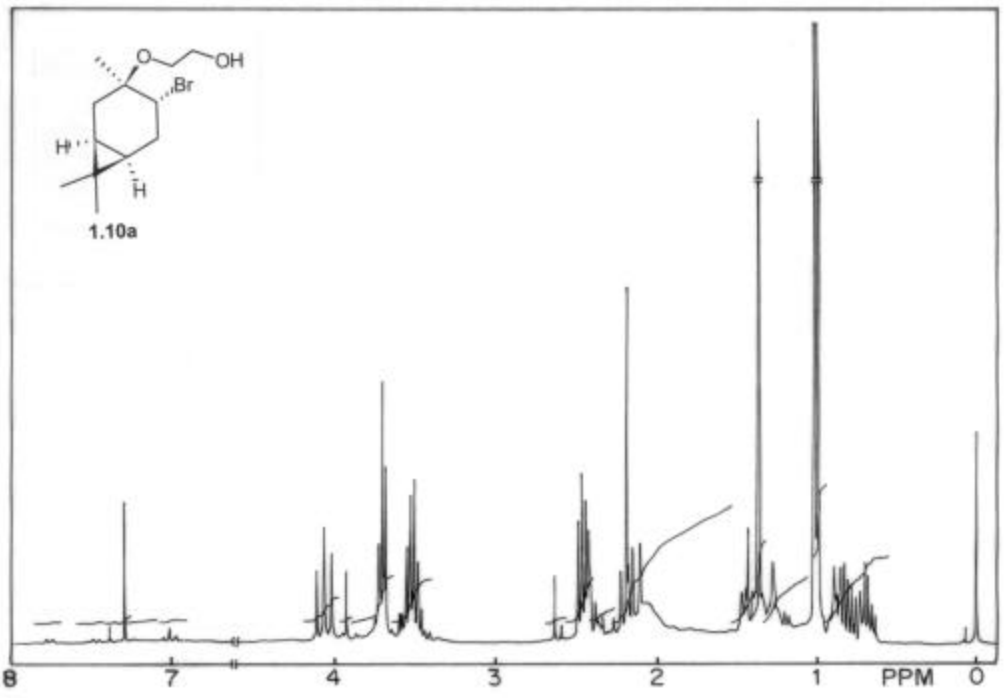

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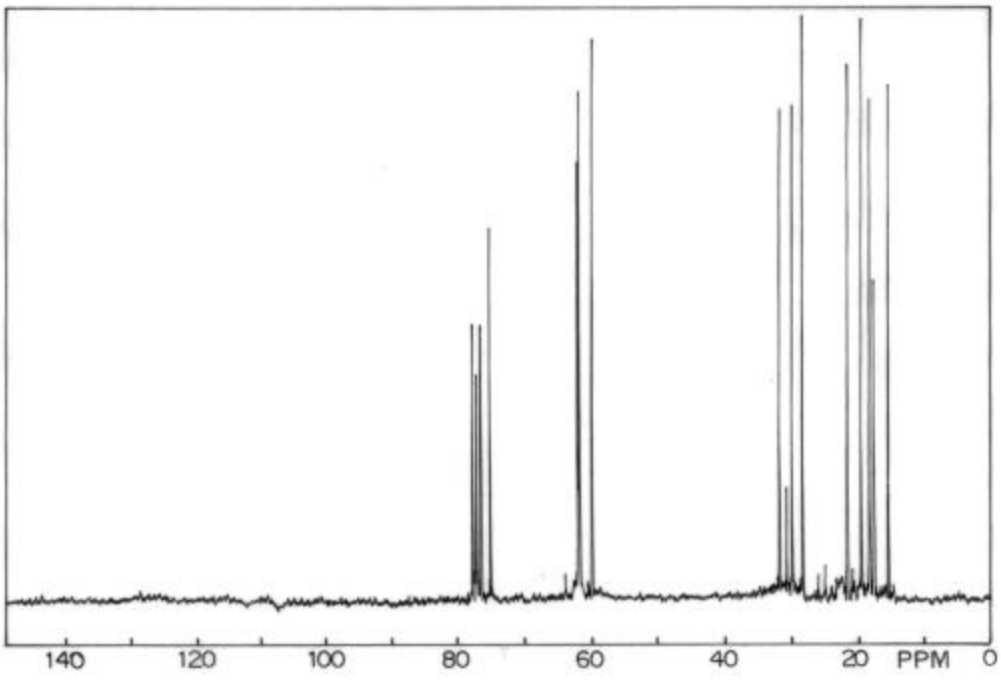

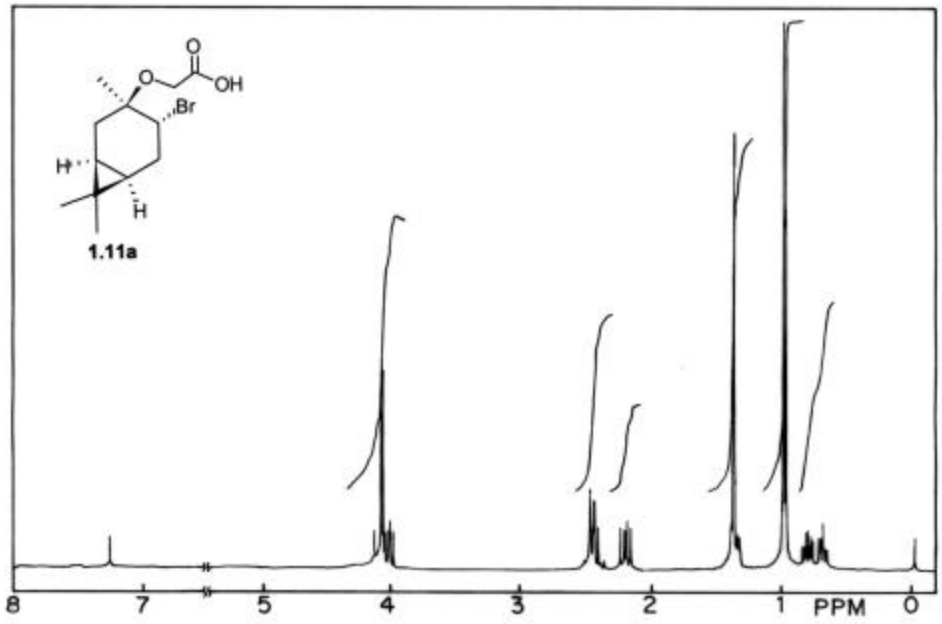

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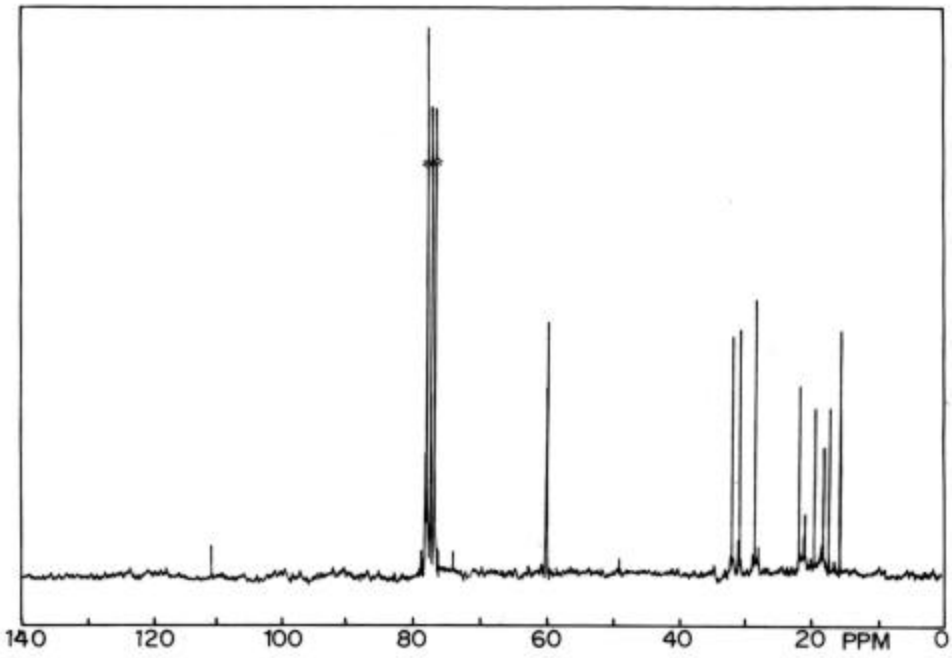

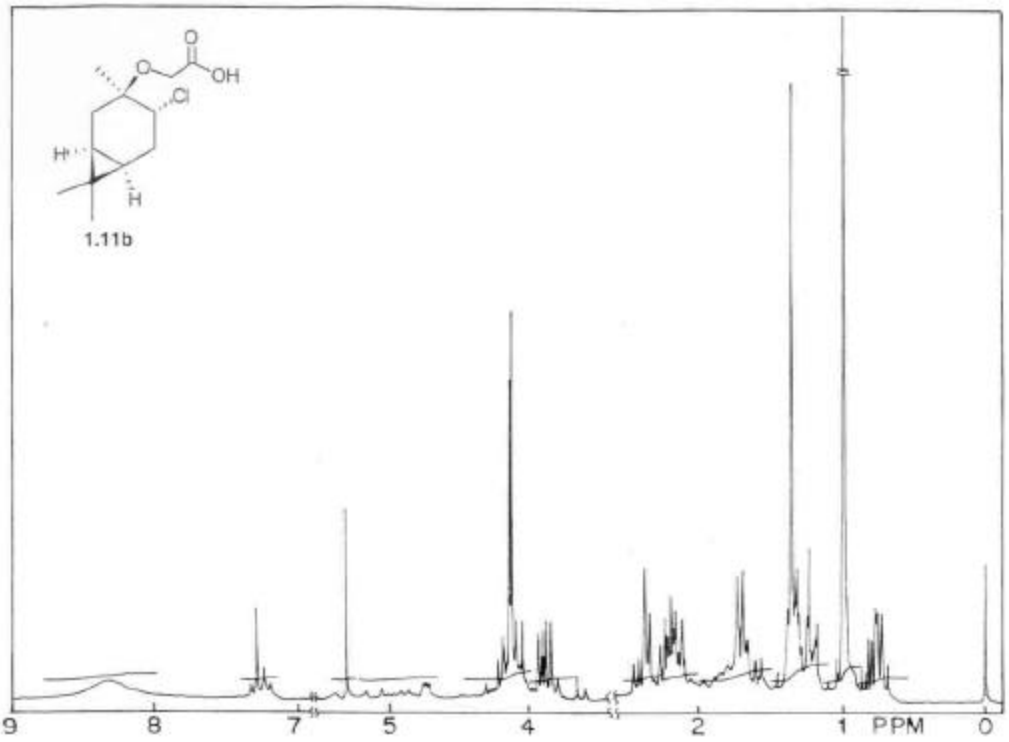

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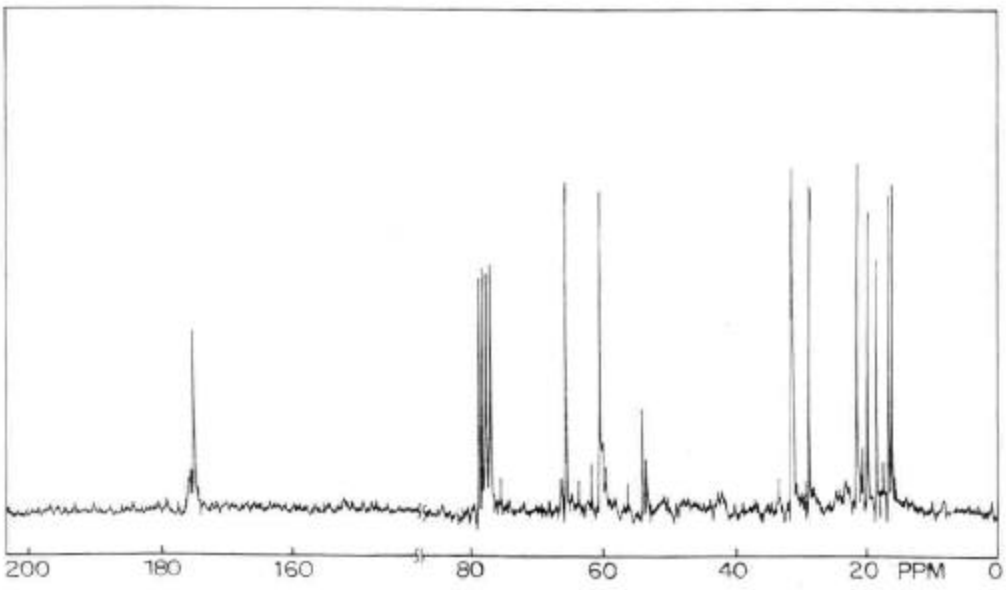

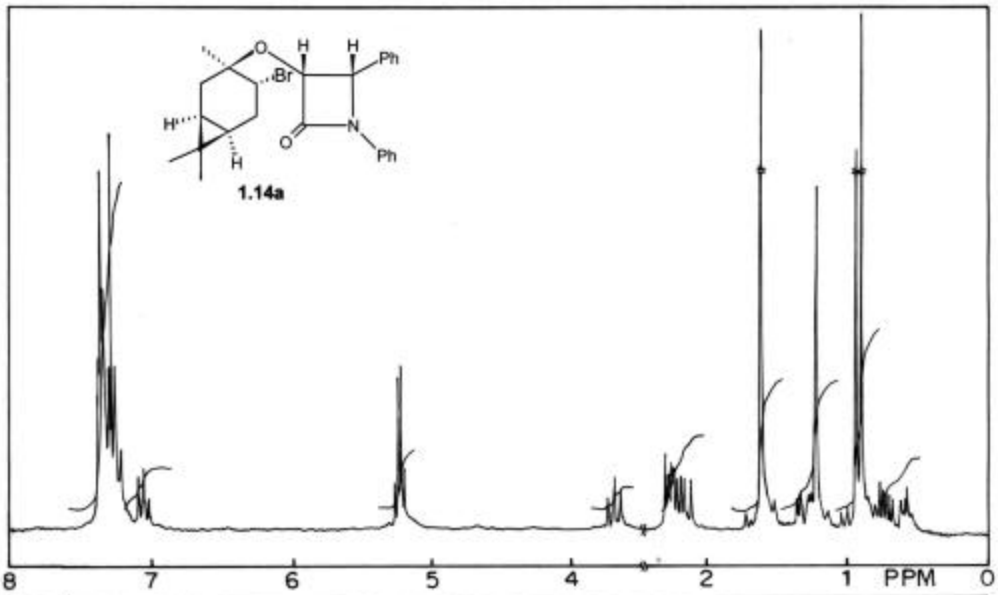
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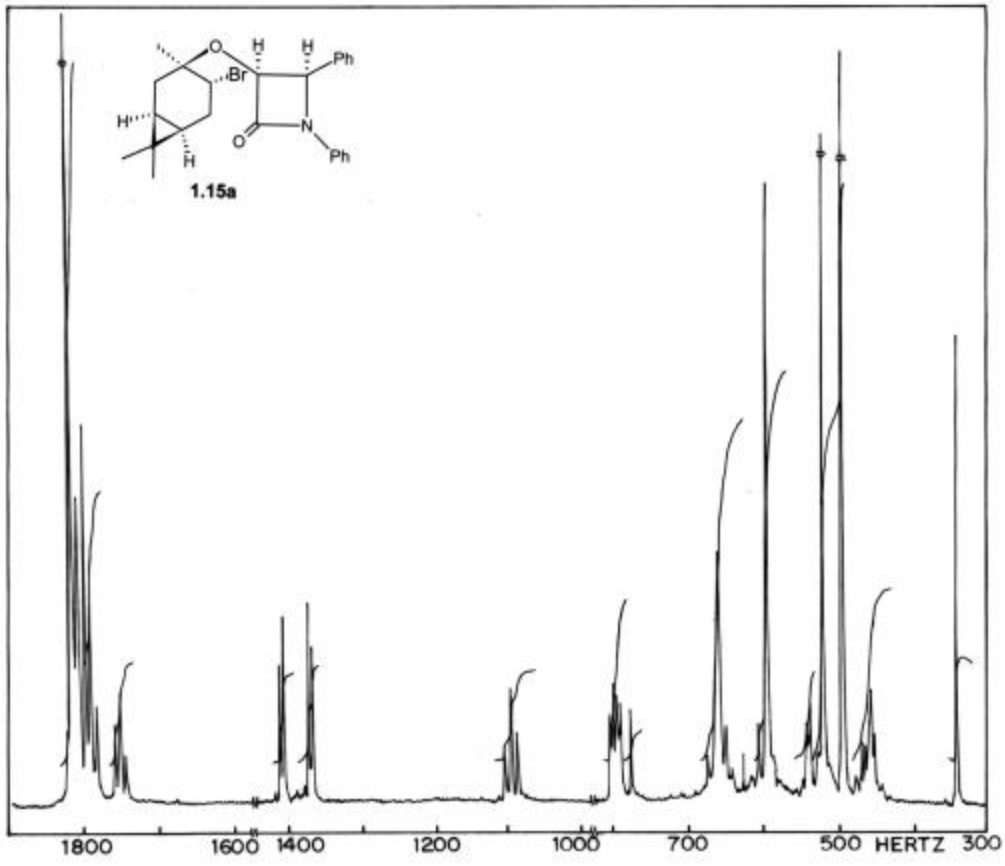
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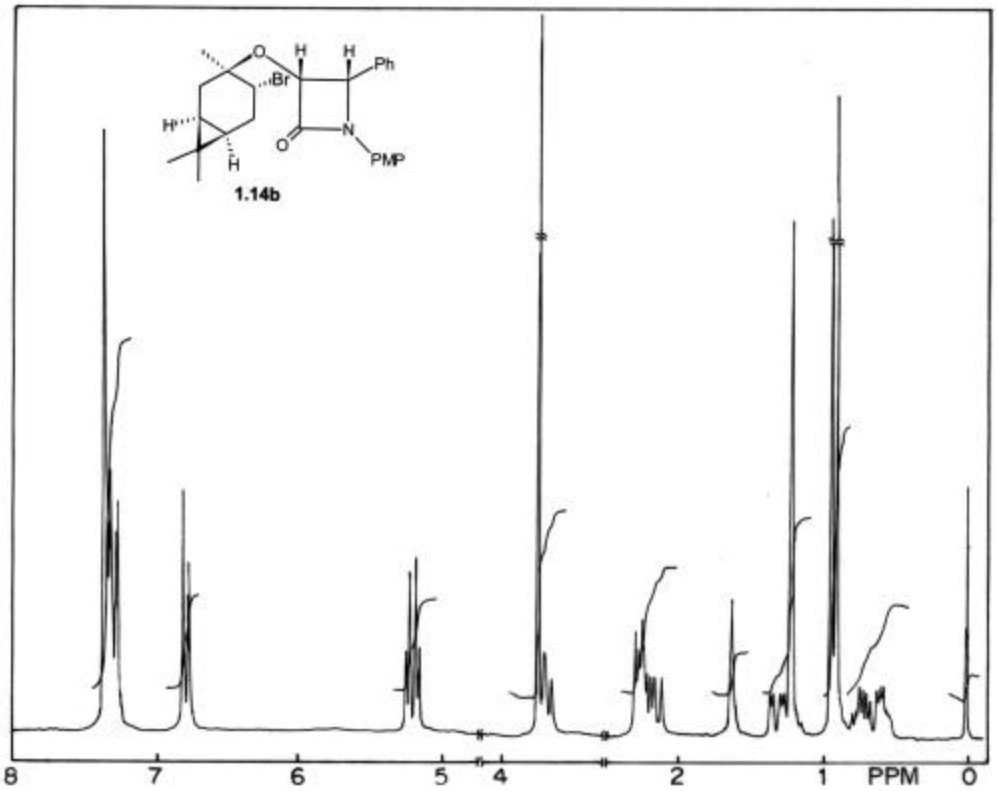
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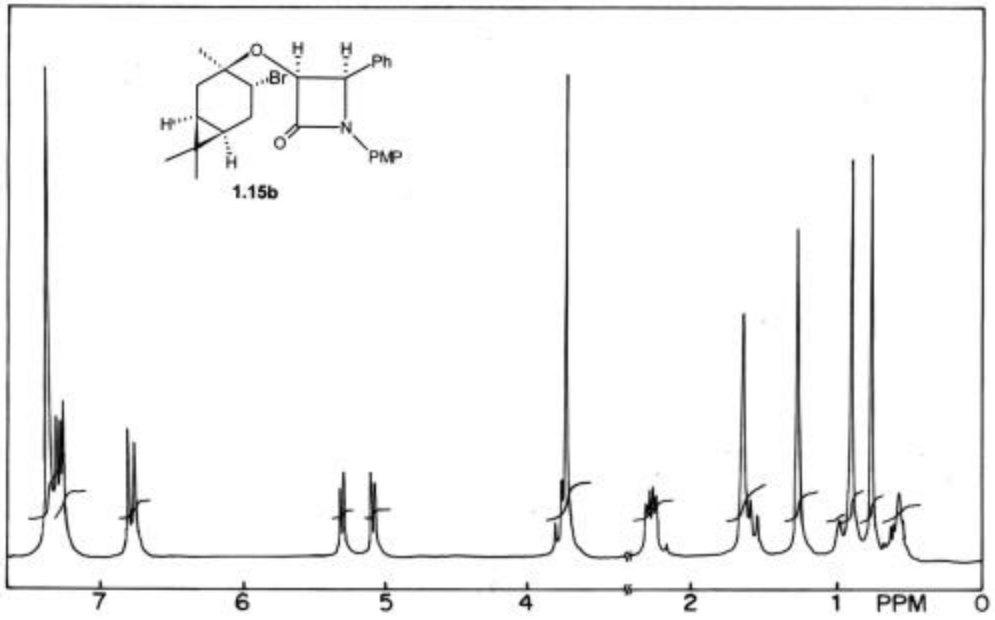
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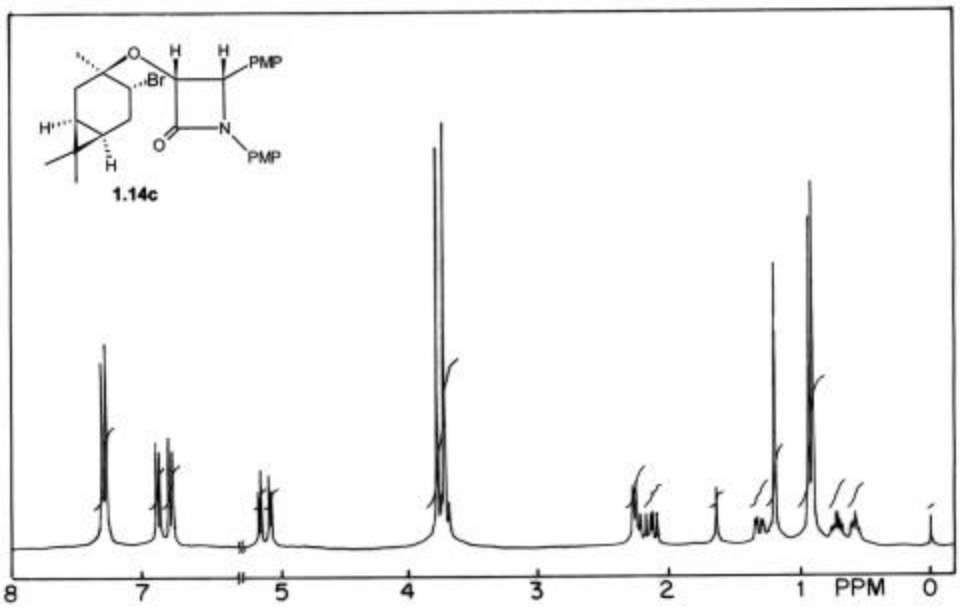
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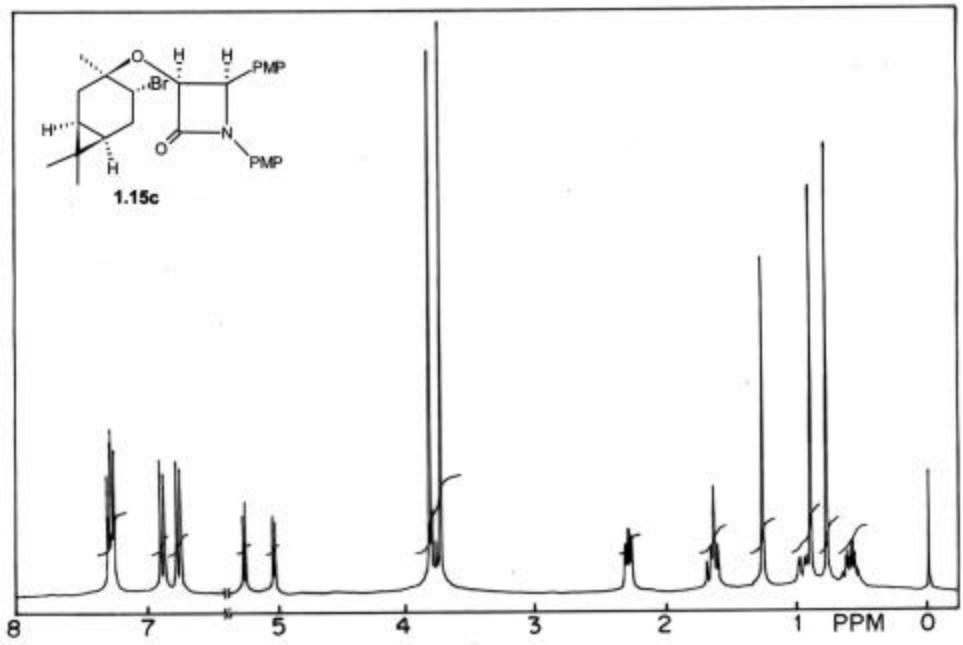
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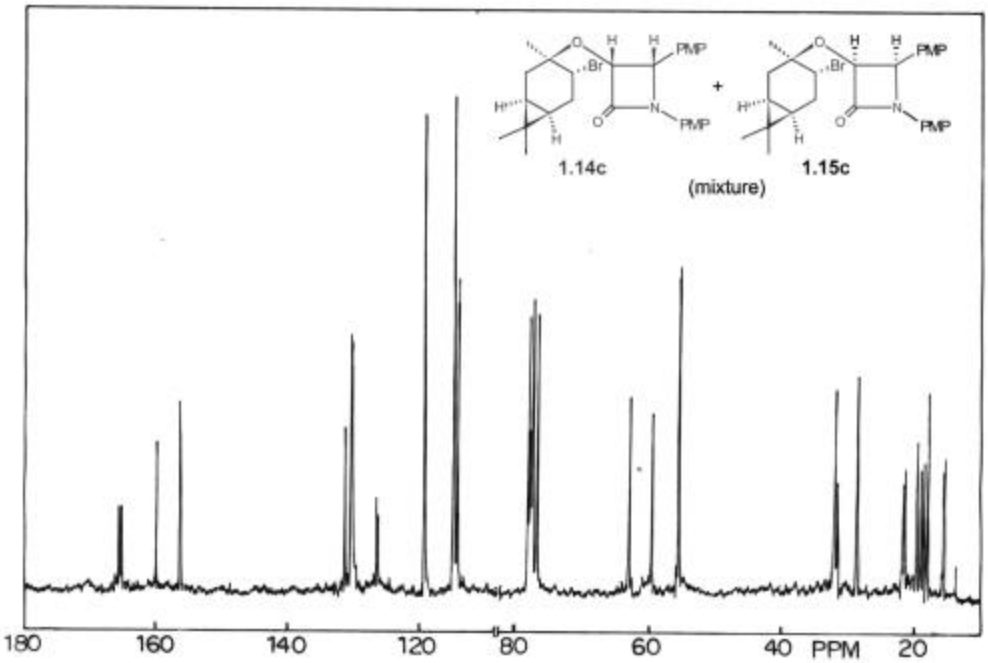
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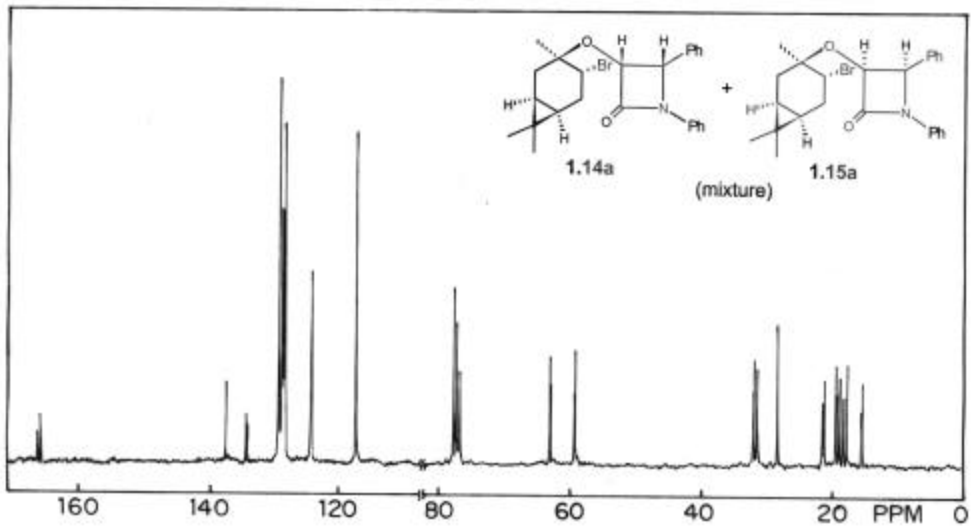
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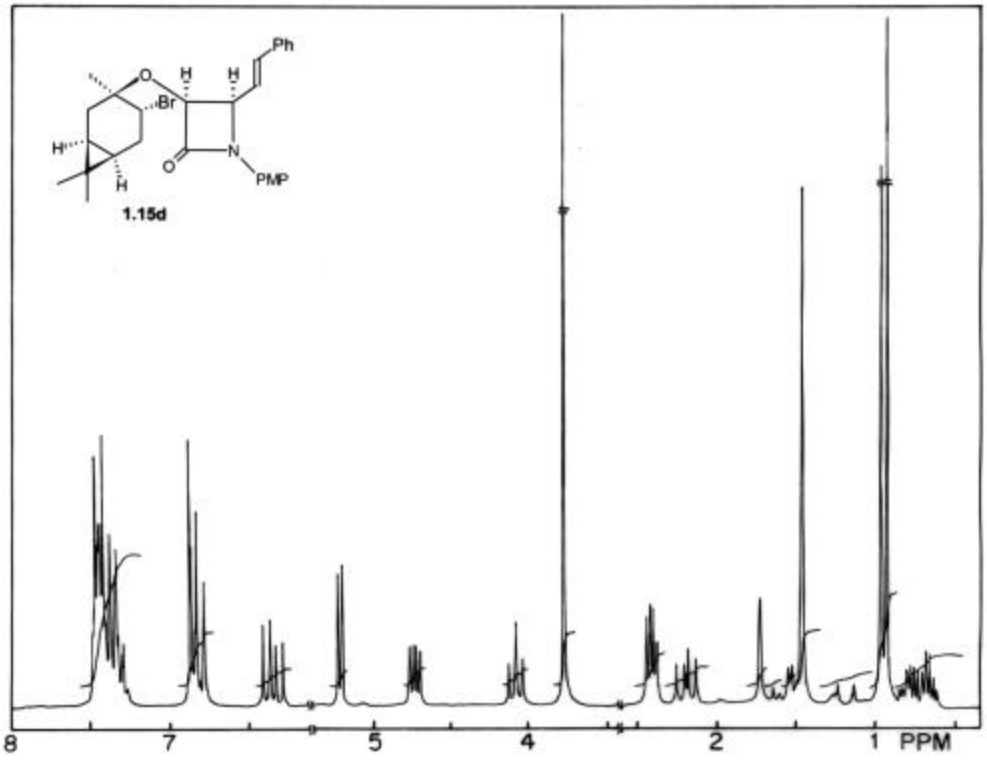
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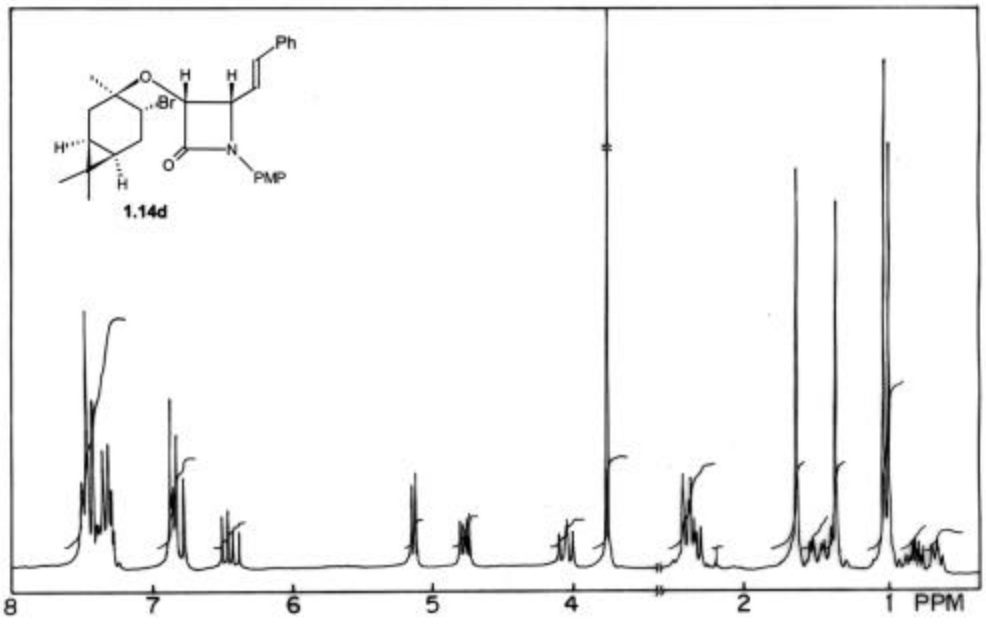
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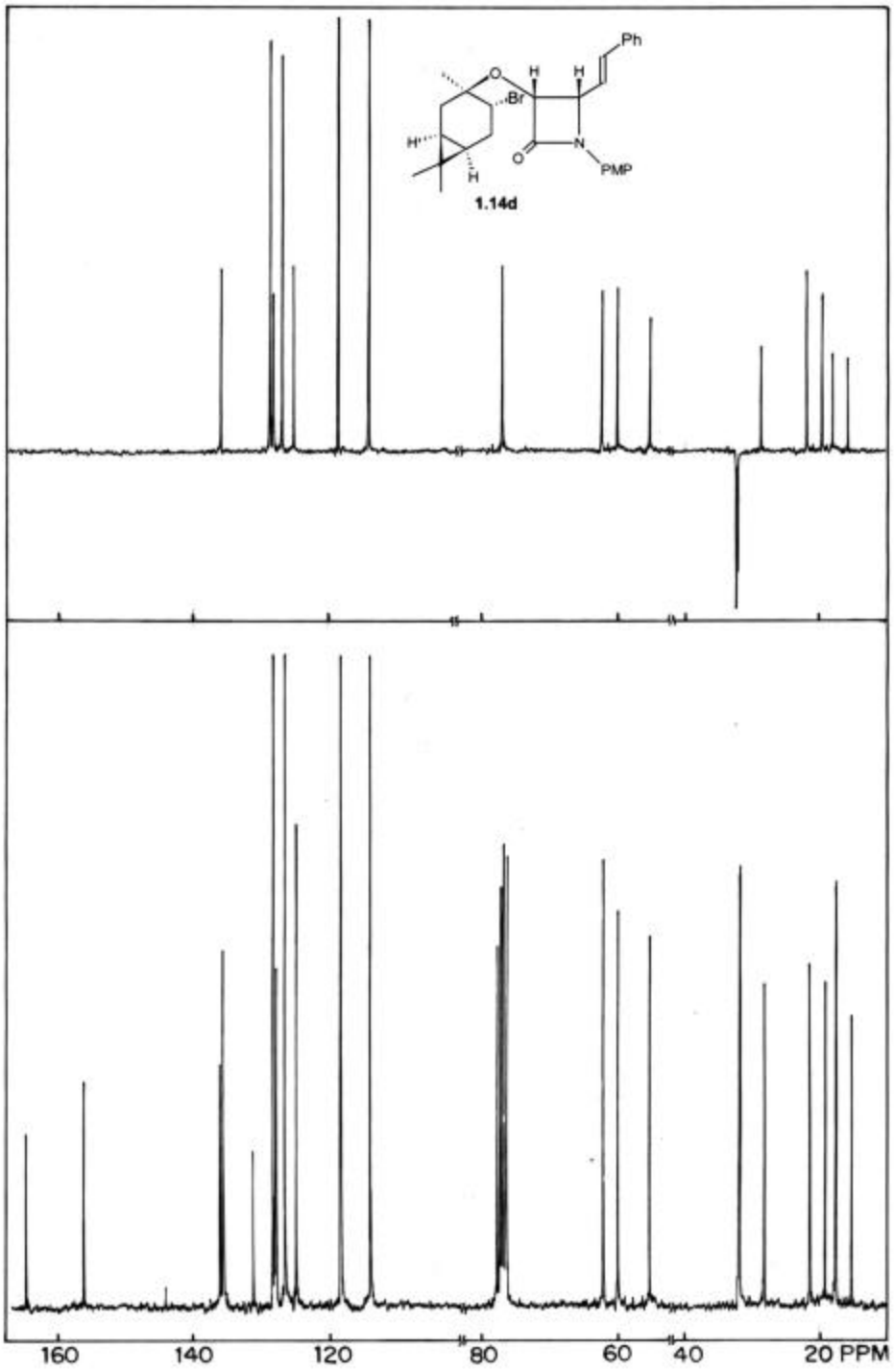

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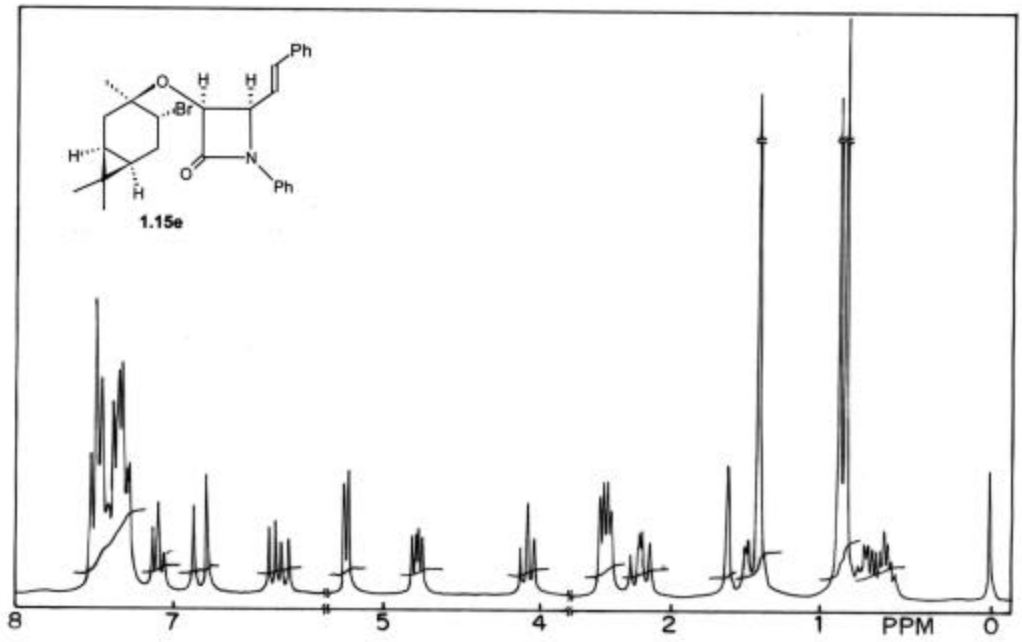

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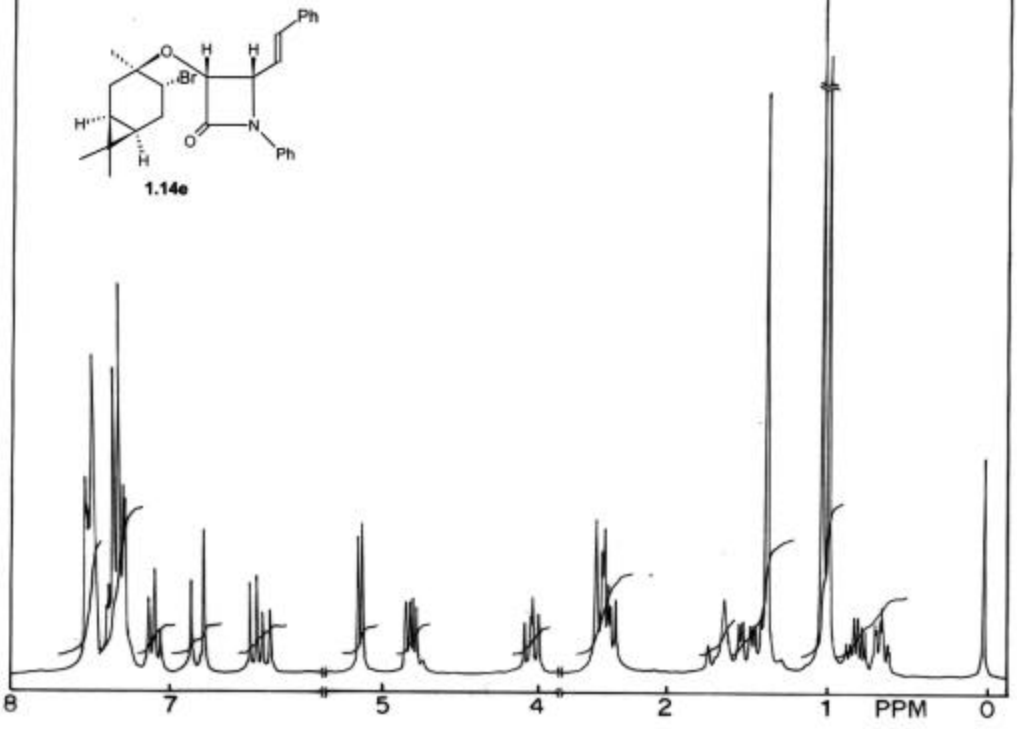

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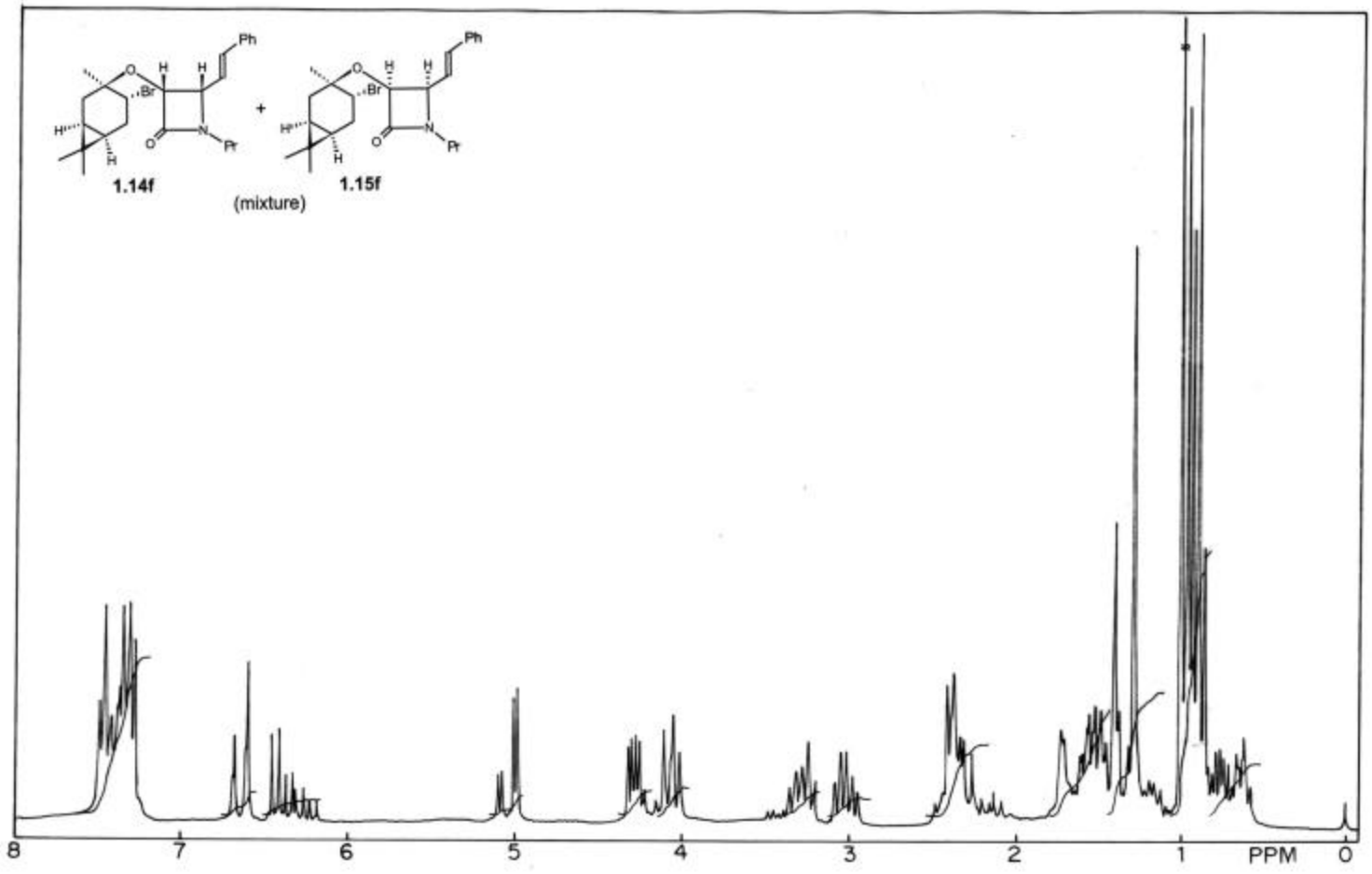
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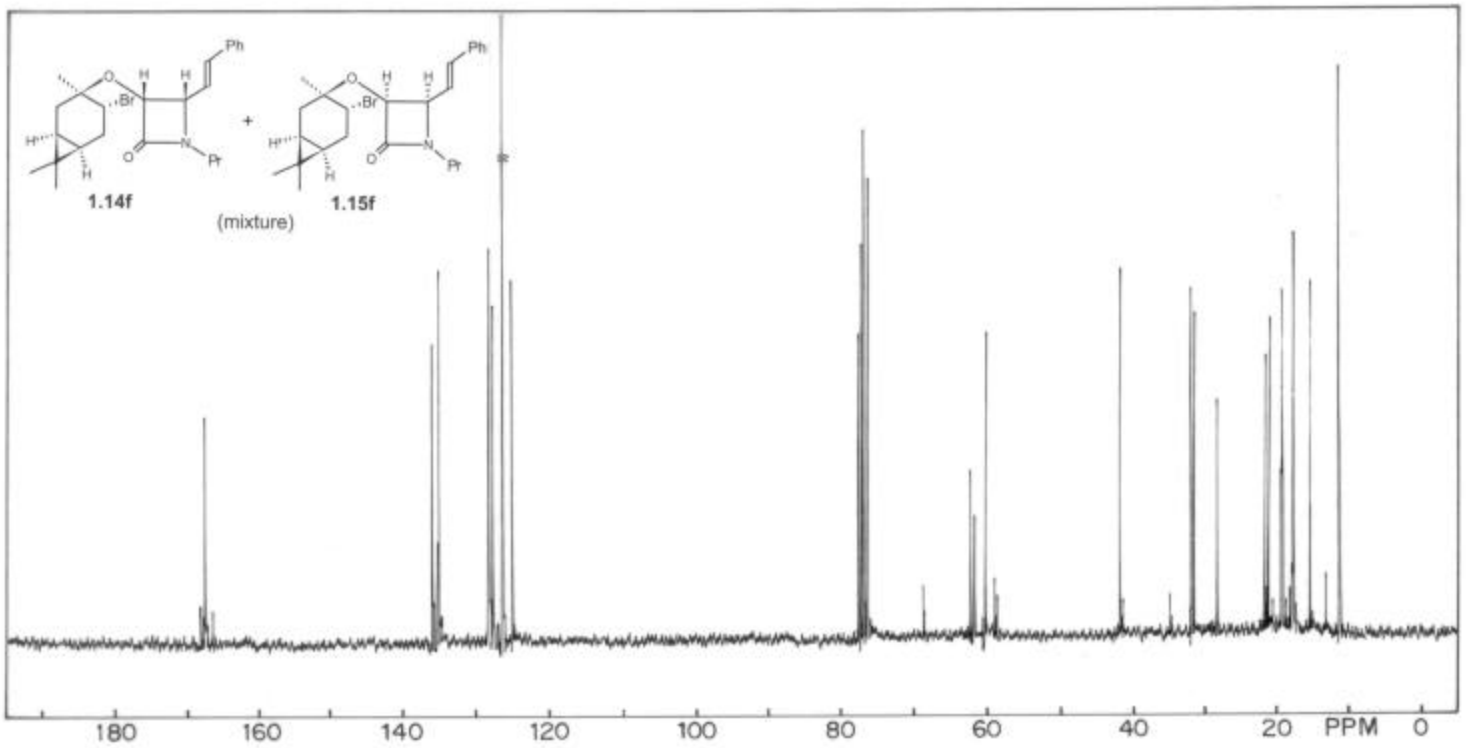
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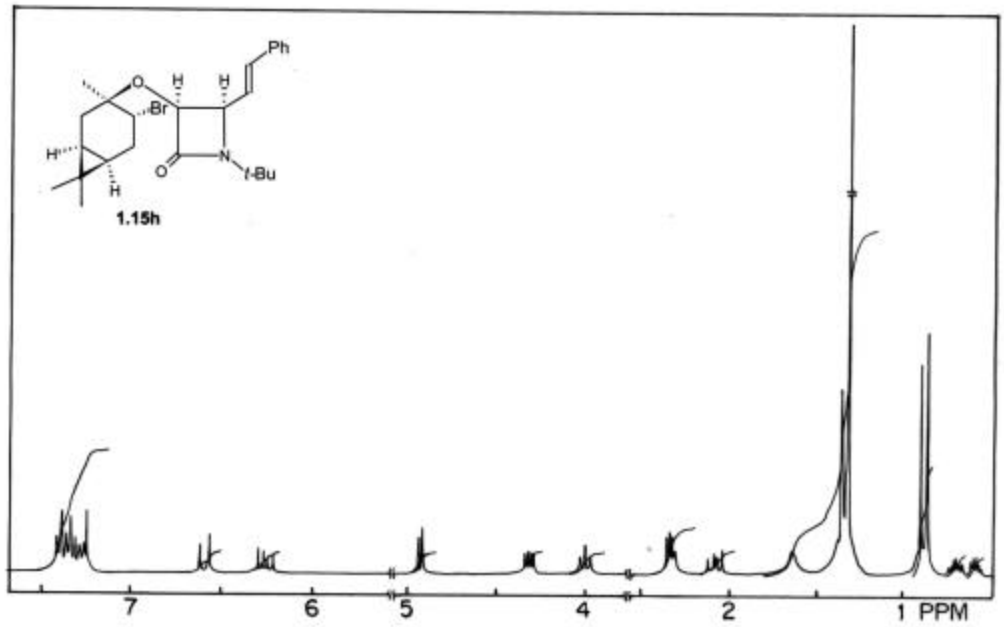

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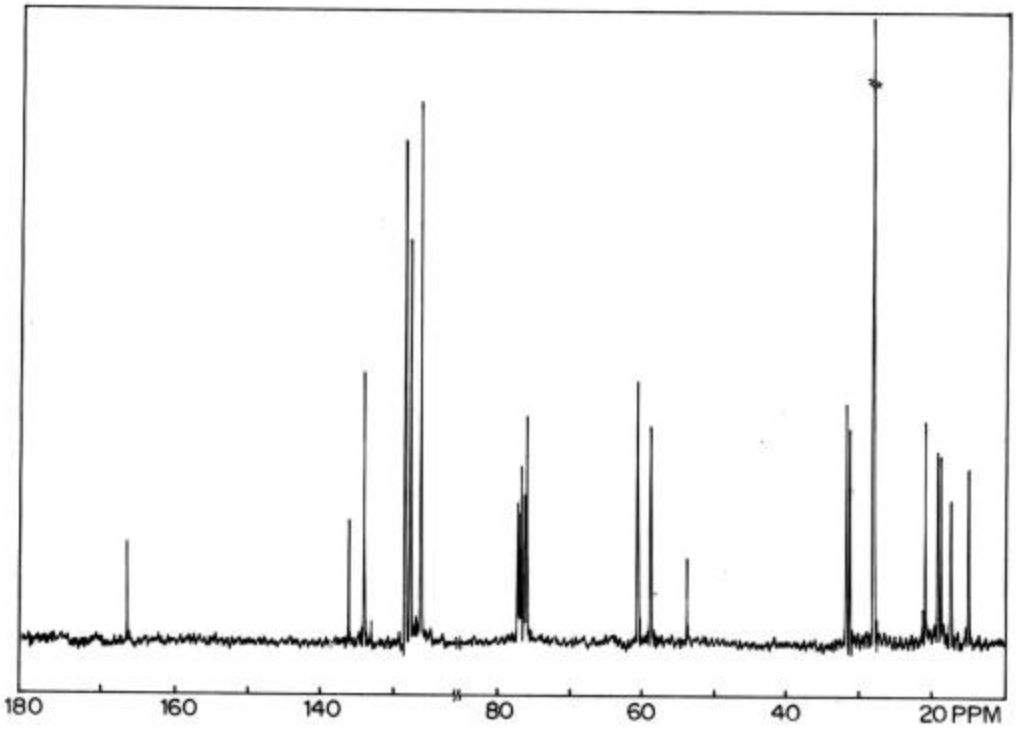

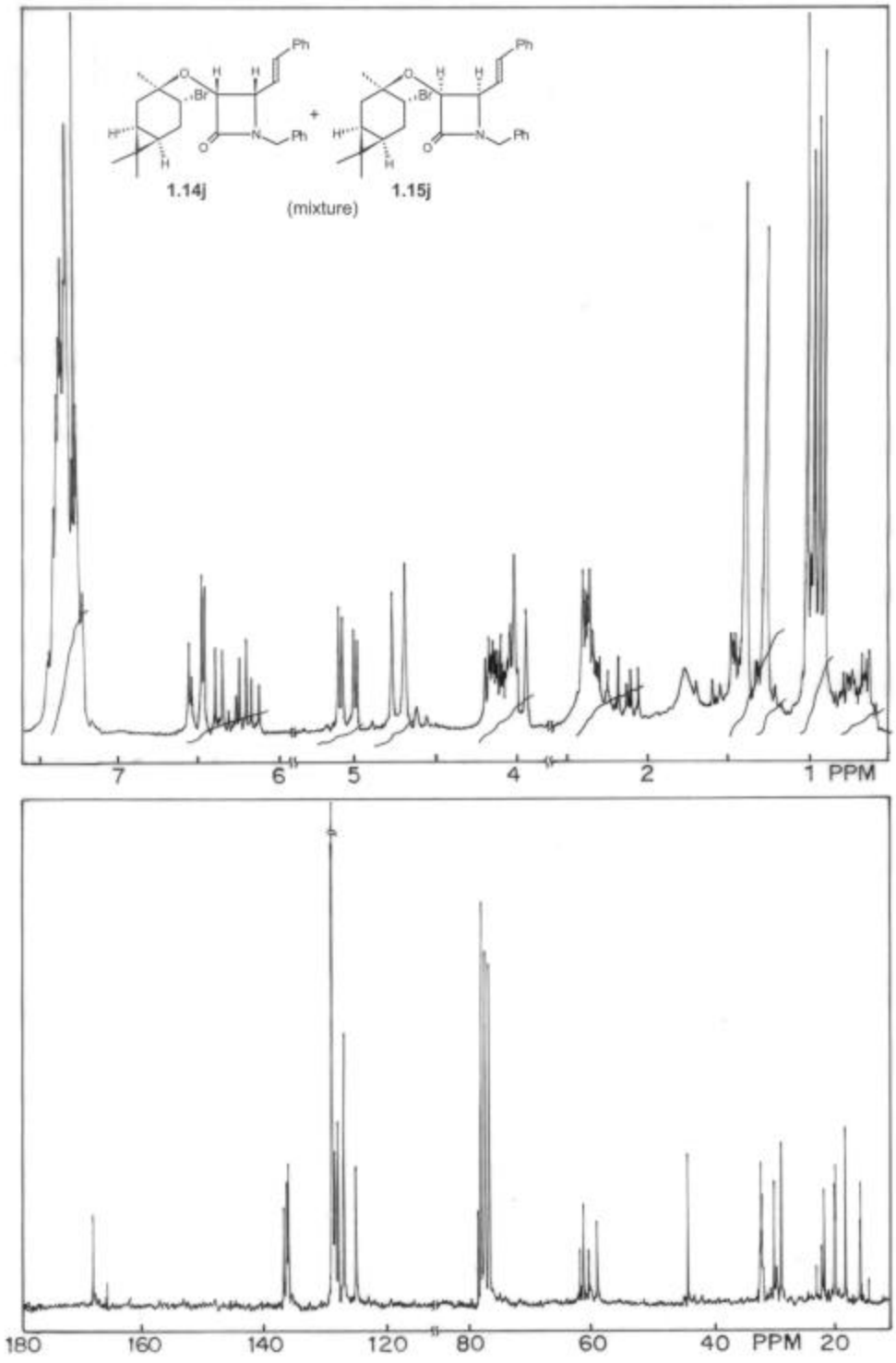
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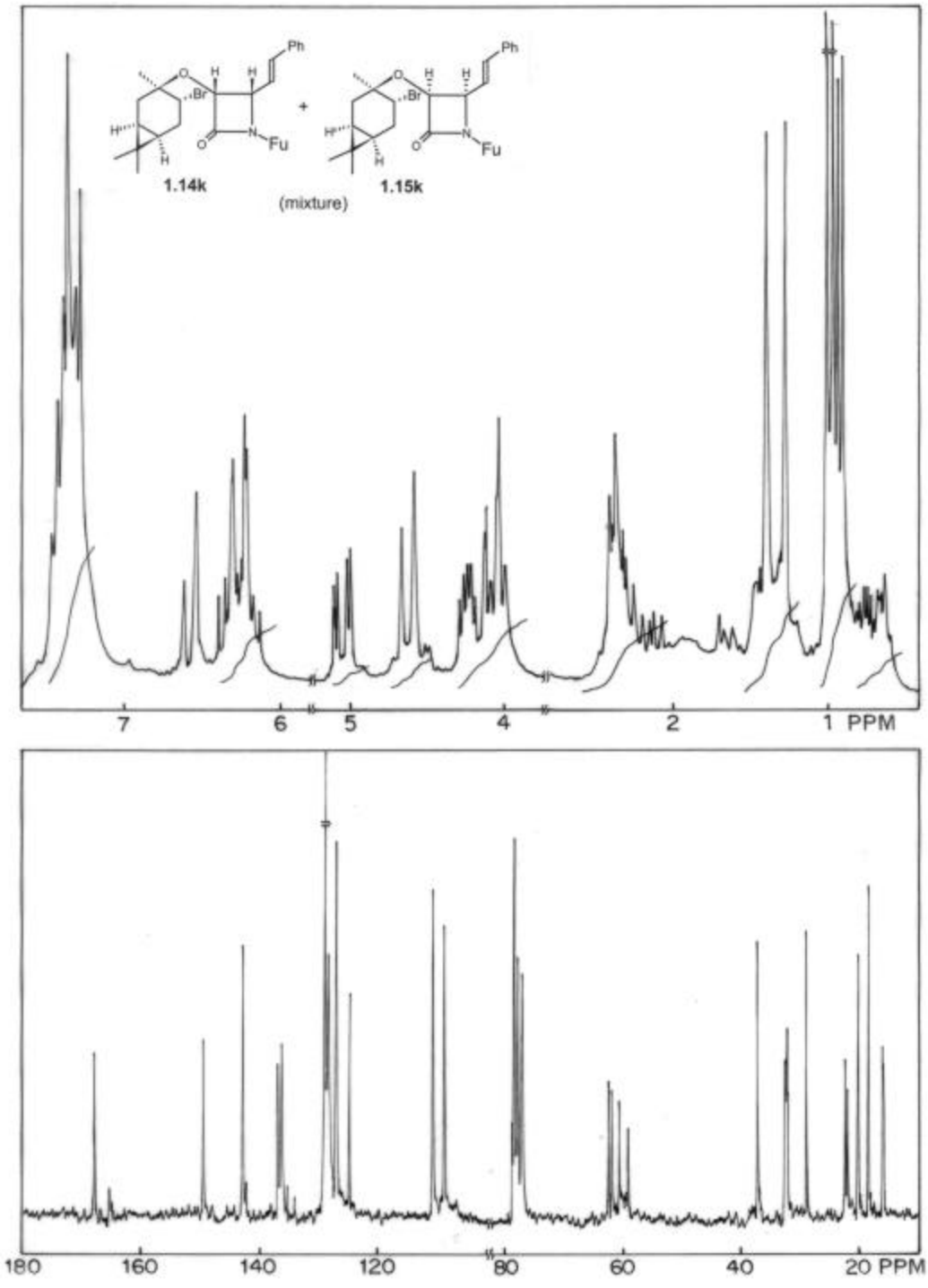
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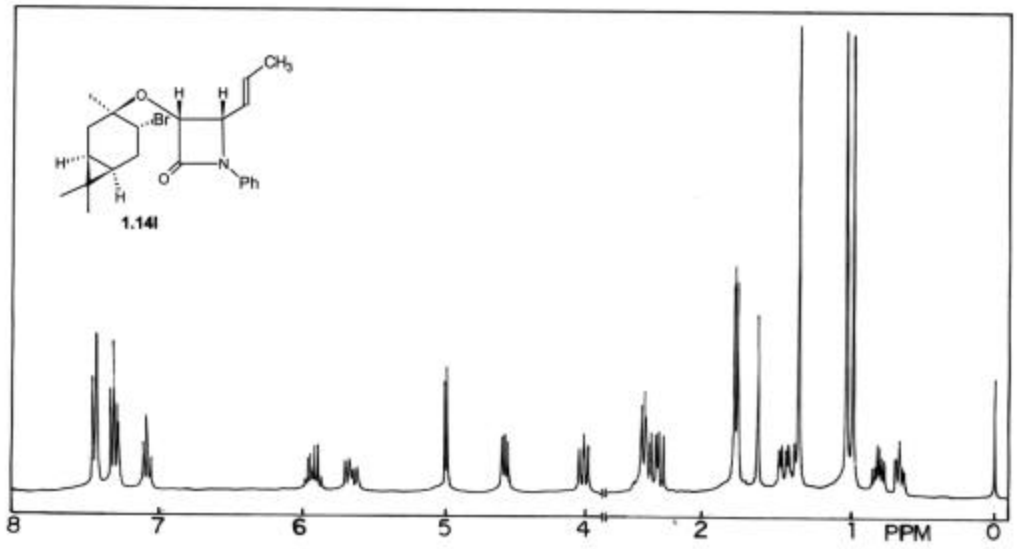
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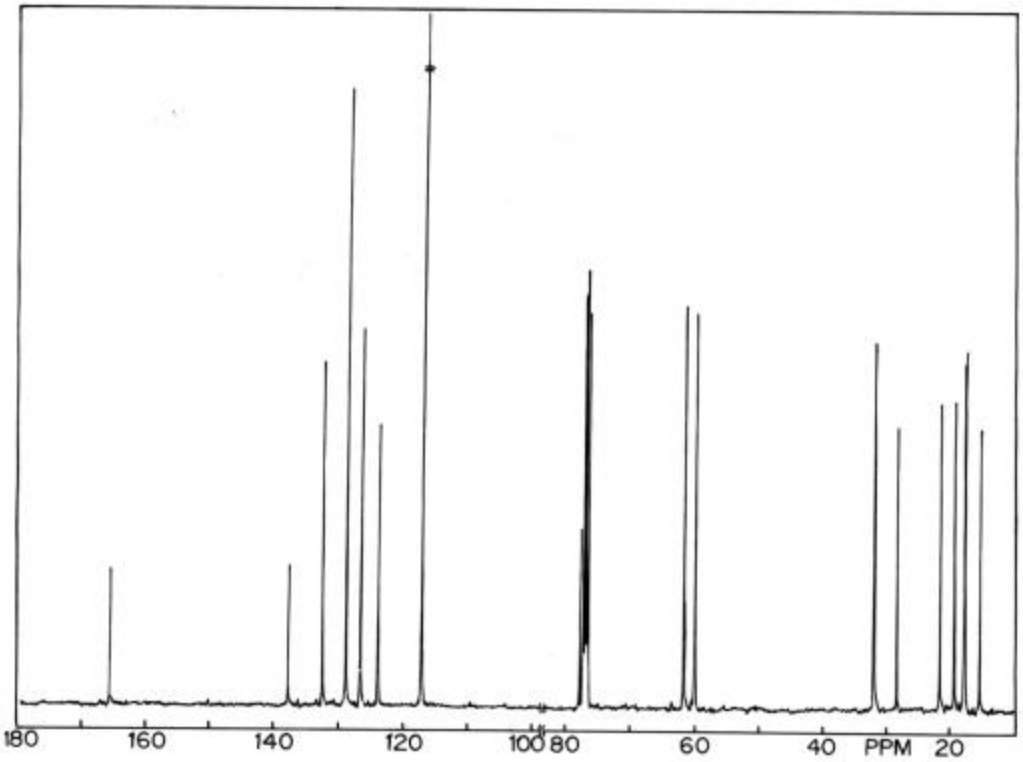
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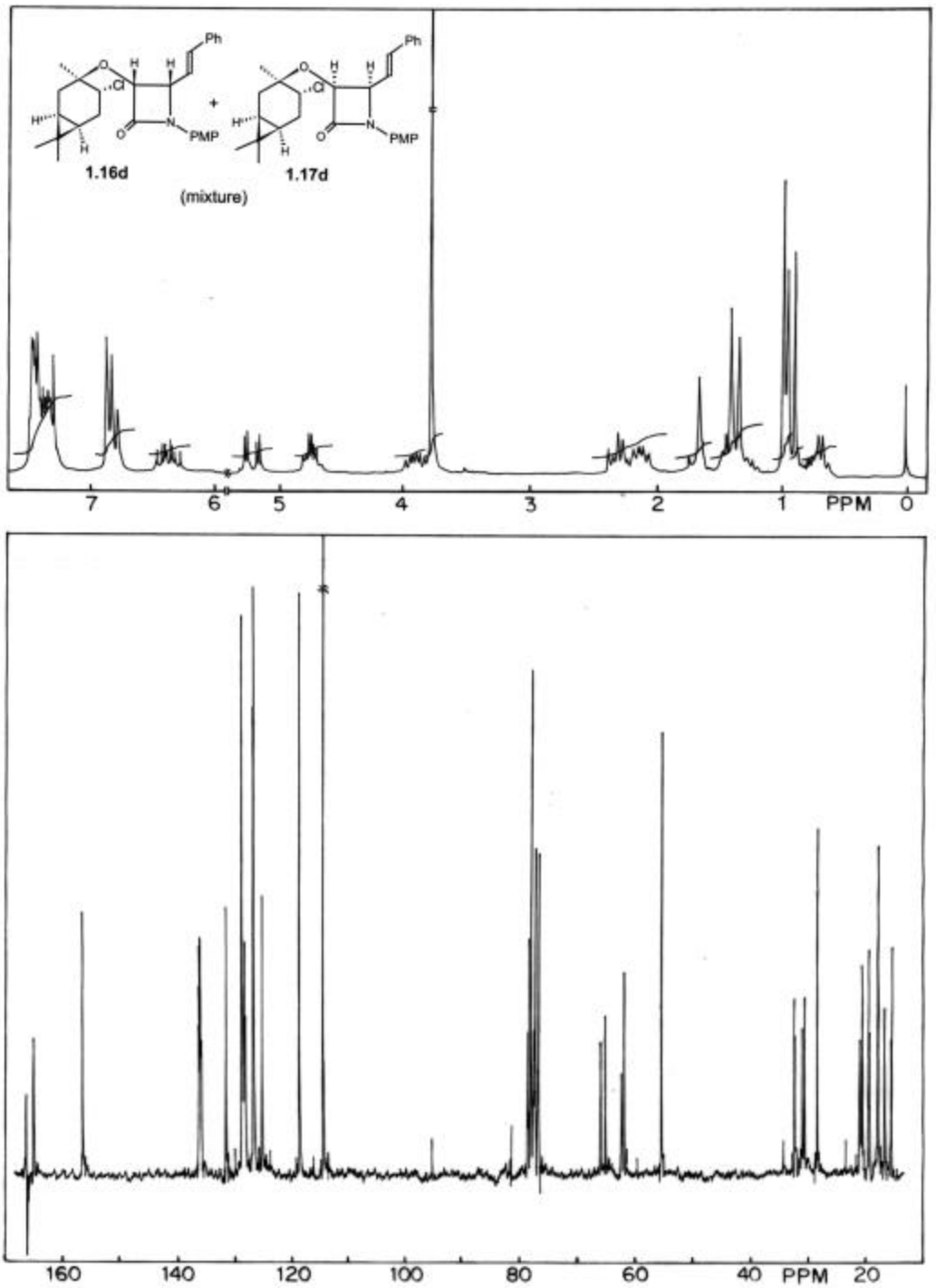
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N
PMP
1.16d
+
1.17d
(mixture)
7
6
5
4
3
2
1
PPM
0
160
140
120
100
80
60
40
PPM
20

Chapter II

Practical Synthesis of Optically Pure 3-Hydroxy *b*-Lactams by Zinc Induced Removal of Chiral Auxiliary

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Reality is merely an illusion, albeit a very persistent one.

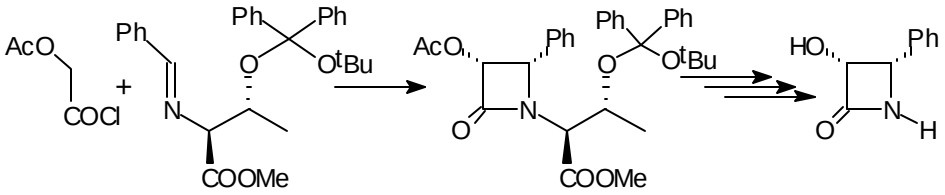
Albert Einstein

2.1 : Introduction

Besides being used for the synthesis of a variety of *b*-lactam antibiotics,[1] the *b*-lactam skeleton has been recognized as a useful precursor for various non-*b*-lactam derivatives (*b-lactam synthon approach*).[2] It has been shown that a suitably substituted 3-hydroxy-*b*-lactam can serve as a synthetic equivalent for the phenylisoserine,[3] a side chain of taxol or can be directly coupled with baccatin III[4] to give taxol. The syntheses of suitably substituted (3*R*, 4*S*) 3-hydroxy-*b*-lactams by diastereoselective cycloaddition reaction,[3-6] borohydride reduction[7] of 3-ketoazetidinones and resolution[8] of (±)-3-hydroxy-*b*-lactams have been reported.

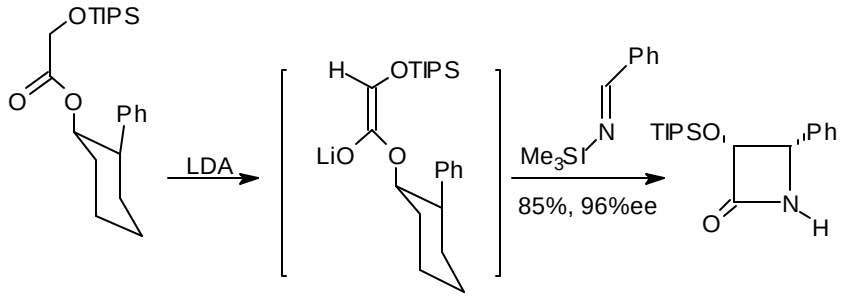
The major use of 3-hydroxy-*b*-lactams is in the asymmetric synthesis of taxol side chain.[9] Farina's approach[10] involves the use of bulkier amine as a chiral component in the Staudinger reaction (*Scheme 1*).

Scheme 1



Ojima[11] et. al. have used ester enolate-imine approach in which silyl protected lithium ester enolate is used effectively (*scheme 2*)[11a] to give required 3-hydroxy *b*-lactam.

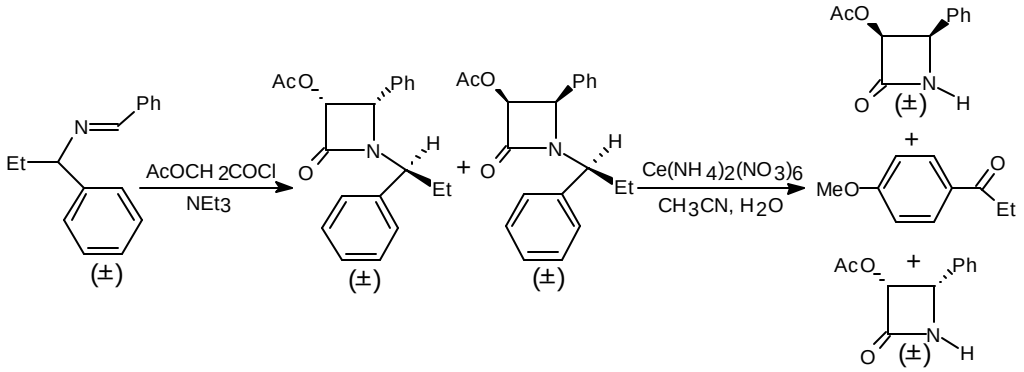
Scheme 2



As ester enolate-imine cyclocondensation approach involves the use of moisture sensitive enolates and unstable silylimines, it limits the applicability as well as the practical usefulness of this methodology.

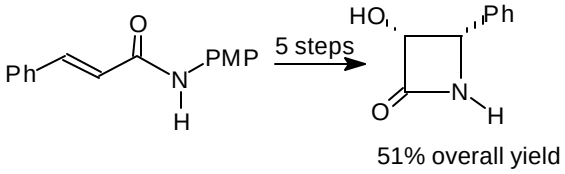
Brown[12] has recently reported asymmetric synthesis of 3-acetoxy-*b*-lactam, which involve the use of 1-(*p*-methoxyphenyl)propylamine as a chiral amine *(Scheme 3)*.

Scheme 3



Intramolecular cyclisation of N-(*p*-methoxyphenyl)-(2*S*, 3*R*)-2-acetoxy-3-bromo-3-phenylpropionamaide was used as a new synthetic route for the preparation of 3-hydroxy-4-phenylazetidinone (*Scheme 4*).[13] The key steps included catalytic asymmetric dihydroxylation of N-(*p*-methoxyphenyl)-*trans*-cinnamide followed by bromoacetylation. The overall yield of the reaction was 51%.

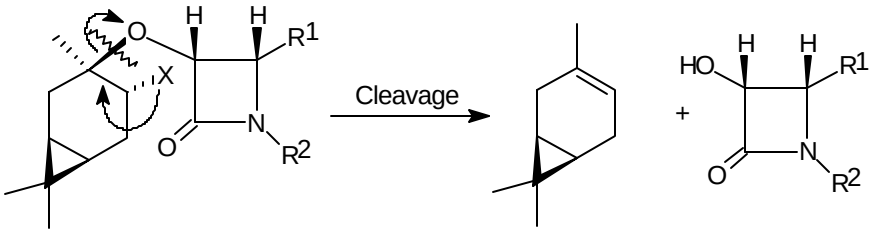
Scheme 4



2.2 : Present Work

The Chapter-1 dealt with the use of carane bromo acid **1.11a** effectively as a chiral ketene precursor in the asymmetric synthesis of novel *b*-lactam derivatives. It was necessary to recover (+)-3-carene, a chiral pool auxiliary from the *b*-lactam

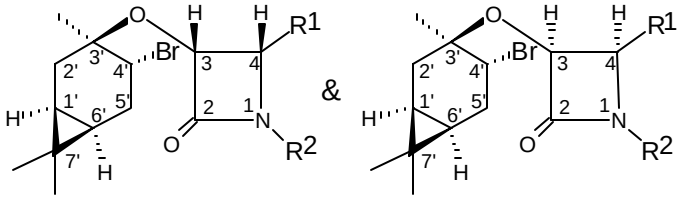
derivatives. We envisioned that a 2-halo-ether linkage could be a useful handle to remove the chiral auxiliary from the system. Present chapter describes our attempts towards the development of methodology to get enantiomerically pure 3-hydroxy-*b*-lactams, one of them is an advanced intermediate for taxol side chain as shown in the following scheme.



2.3 : Results & Discussion

***Attempted Cleavage of* 1.14 & 1.15**

The halo series of *b*-lactams **1.14** & **1.15** (section B, chapter 1) were obtained as diastereomeric mixtures with rather low diastereoselectivity. However, in most of the cases, it was possible to separate these diastereomers either by fractional crystallization or by flash column chromatography.



1.14 **1.15**

The initial attempts were concentrated on the cleavage of halo ether linkage, O-C3′-C4′-Br. The α-Br at C4′ (equatorial) was poised in such a way that it could not be removed easily by elimination. The yields of the eliminated products were low and a number of side products were invariably obtained.

The literature reports on the use of alkali metals like Na,[14] Mg,[15] Li[16] for the cleavage of haloether linkages prompted us to try these metals as a reagent of choice. However, removal of chiral auxiliary from **1.14** & **1.15** using sodium or activated magnesium under reflux conditions in dry ether or dry THF, was unsuccessful. In most

of the cases either starting material was recovered or polymerized products were obtained.

We came across a report on the use of Zn/acetic acid (*Boord Reaction)* for the cleavage of haloether linkage. *Boord reaction*[17] is a useful reaction applicable for the cleavage of haloether linkages. This reaction is generally a clean and high yielding reaction. We applied this reaction to the halo derivatives of *b*-lactams and it was possible to cleave the bromo-ether linkage from the system in almost quantitative yield.

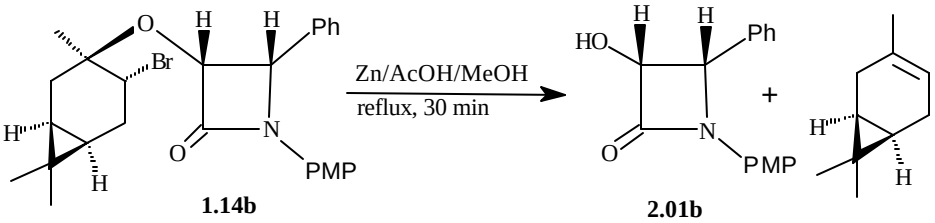
The typical Boord reaction conditions involve heating of haloethers in alcohol with Zn, with small amount of acetic acid used as a catalyst. One of the products of this reaction is olefin, which is generally a low boiling, volatile liquid. Excellent reproducibility, high yields, use of easily available reagents and simple experimental conditions mark the salient features of this reaction.

Cleavage of* 1.14 & 1.15 *Using Boord Reaction Conditions

In most of the cases the diastereomers **1.14** & **1.15** (chapter 1, section B) were obtained as crystalline solids, which could be separated by fractional crystallization.

The *b*-lactam **1.14b** was reacted with activated Zn in presence of catalytic amount of acetic acid under methanol reflux conditions *(Scheme 5)*. The reaction was over within half an hour. The crude reaction mixture was a white solid, which was purified by crystallization.

Scheme 5

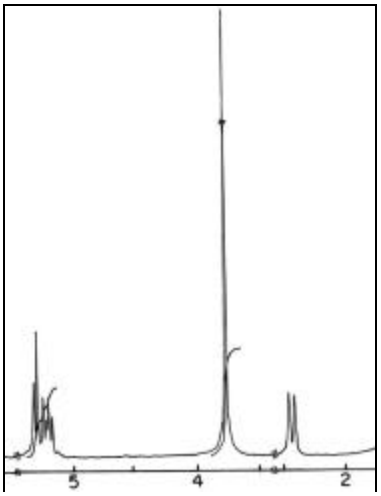


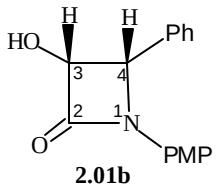
1.14b **2.01b**

2.01b was obtained as a crystalline solid with mp 200-201°C. The IR spectrum of the product **2.01b** showed a peak at 1716 cm^{-1}, typical of *b*-lactam amide. A broad peak at 3328 cm^{-1} indicated presence of hydroxyl group.

The ^{1}H NMR spectrum of the product **2.01b** was simplified, as the peaks corresponding to the carane ring system (between 1-3 δ) were absent. This clearly indicated the fact that the haloether linkage has been cleaved during the reaction.

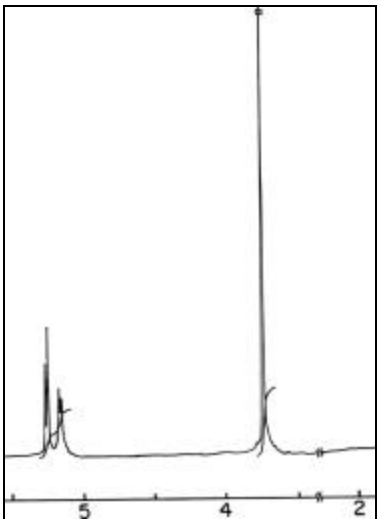
A singlet at 3.75 corresponding to the OMe group was present. The *b*-lactam proton H-3 appeared as a doublet at 5.30 with J = 5.4 Hz and the other *b*-lactam proton H-4 appeared at 5.20 as a dd with coupling constant J = 5.4 & 8.8 Hz. The high coupling constant indicated the presence of *cis* stereochemistry of *b*-lactam ring protons. The aromatic protons appeared as multiplets in the region 6.80-7.60. The optical rotation was found to be +177.4^o (c 0.33, $CHCl_3$).

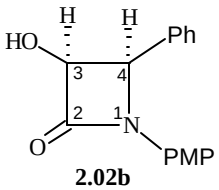




2.01b

In another reaction, **1.15b** was subjected to the above conditions. The product **2.02b** obtained was a crystalline solid with mp 197-199°C. The IR spectrum was identical to the **2.01b**. The ^{1}H NMR was also identical to **2.01b**, which showed a singlet at 3.75 for methoxy group of PMP moiety. Two doublets at 5.15 (J = 5.2 Hz) & 5.25 (J = 5.2 Hz) were assigned to H-3 & H-4 of the *b*-lactam ring. Aromatic protons were seen as multiplets in the region 6.80-7.50. The optical rotation for **2.02b** was −177.4 ^{o} (c 1.0, $CHCl_3$). The optical rotation as well the other physical properties clearly showed that **2.01b** & **2.02b** were enantiomers





2.02b

The generality of this cleavage reaction was established by applying it to the distereomers **1.14a-d** & **1.15a-d** and the results are listed in Table 1.

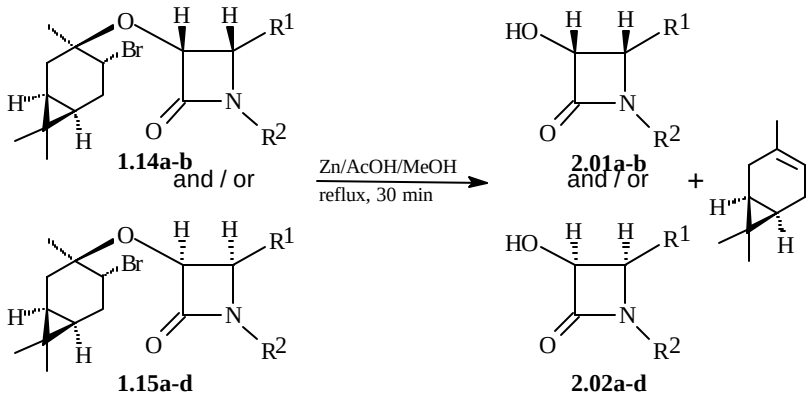


Table 1. Synthesis of 3-hydroxy-*cis*-*b*-lactams **2.01a-b** or **2.02a-d** from optically pure diastereomers **1.14a-b** or **1.15a-d**.

Prod.	R^1	R^2	Yield (%)[a]	mp (^oC)	$[\alpha]_D$ (conc. In g/100 ml)	Config
2.01a	Ph	Ph	96	217-218	+190.9^o (c 0.7, $CHCl_3$)	3*R*, 4*S*
2.02a	Ph	Ph	96	216-217	-188.7^o (c 0.39, $CHCl_3$)	*3S, 4R*
2.01b	Ph	PMP	95	197-198	+177.4^o (c 0.33, $CHCl_3$)	3*R*, 4*S*
					lit.[9] +176^o (c 1, $CHCl_3$)	
2.02b	Ph	PMP	95	200-201	-177.4^o (c 1.0, $CHCl_3$)	3*S*, 4*R*
					lit.[8b] –179^o (c 1, $CHCl_3$)	
2.02c	PMP	PMP	98	132-133	-181.90^o (c 0.93, $CHCl_3$)	*3S, 4R*
2.02d	Styryl	PMP	96	156	-236^o (c 0.01, MeOH)	*3S, 4R*
					lit.[6e] –237^o (c 0.01, MeOH)	

In all the cases, 3-hydroxy-*b*-lactams (**2.02** & **2.03**) were obtained in almost quantitative yields. The isolation and purification of the products was simple as no side products were formed during the reaction. In some of the cases (**2.02b**, **2.02d** & **2.01b**), optical rotation & physical properties were compared with the literature values of the reported compounds & they were in full agreement (Table 1). From the optical rotation it was possible to assign the absolute configuration of the 3-hydroxy-*b*-

lactams. The absolute configuration of *3R, 4S* was assigned to **2.01a-b** while *3S, 4R* absolute configuration was assigned to **2.02a-d**.

Isolation of Chiral Auxiliary

The isolation of 3-hydroxy-*b*-lactams posed no problems. However, isolation of the (+)-3-carene needed more attention. Since (+)-3-carene is a highly volatile liquid, it could be lost easily under the experimental conditions used. Since isolation of a chiral auxiliary is an important step in an asymmetric synthesis, it became essential to modify the experimental set up with the aim to isolate (+)-3-carene formed in the reaction mixture.

In a modified experimental procedure, the methanolic solution of **1.14b** containing catalytic amount of acetic acid was continuously distilled rather than refluxed over activated zinc. The distilled methanol was partitioned between water and pet ether. (+)-3-Carene, which being soluble in pet. ether was isolated by the distillation of the pet ether layer. The (+)-3-carene was isolated in about 90% yield. It was chemically and optically pure as confirmed by comparison with the data known for the authentic specimen of (+)-3-carene.

2.4 : Summary

The *b*-lactams with 4′-bromocarane chiral auxiliary were successfully cleaved by refluxing their methanolic solution in the presence of Zn/acetic acid system. The bromoether linkage on cleavage offered optically pure 3-hydroxy-*b*-lactams in almost quantitative yields along with (+)-3-carene as the only other product. Optical purity of the 3-hydroxy-*b*-lactams was used to assign the absolute configuration of both, the parent *b*-lactam as well as the 3-hydroxy-*b*-lactams. A practical procedure was developed for the isolation and recovery of (+)-3-carene, the side product of the reaction, which could be recovered in about 90% yield.

2.5 : Experimental

***Procedure for the Preparation of (3S, 4R) 3-Hydroxy-1-(4′-methoxyphenyl)-4-phenyl-cis-b-lactam* 2.02b**

To a solution of *b*-lactam **1.15b** (5 g, 10.35 mmol) in methanol (150 mL), activated Zn (6.35 g, 100 mmol) and glacial acetic acid (2.5 mL) was added with stirring. The reaction mixture was then heated at 80°C with continuous removal of methanol over a period of 3 h.

Isolation of (+)-3-carene

The distilled methanol from reaction mixture was diluted with ice-cold water (500 mL) and extracted with pet. ether (4x100 mL). The combined pet. ether extracts was washed with satd. $NaHCO_3$ (50 mL), water (50 mL) and finally with brine (50 mL) and dried over sodium sulphate. The solvent was removed by distillation and residue was purified by Kugelrohr distillation to give 1.26 g (90%) of pure (+)-3-carene. The IR, NMR, and optical rotation were identical with the authentic (+)-3-carene sample.

***Isolation of b-Lactam* 2.02b**

The residue from the reaction mixture was treated with dichloromethane (100 mL) and filtered, the solid was washed with dichloromethane (3x25 mL). The filtrate was successively washed with dil. HCl (5%, 50 mL), satd. $NaHCO_3$ (2x30 mL), water (2x40 mL), brine (20 mL)) and dried over anhydrous Na_2SO_4. The removal of solvent gave 2.50 g (90%) of **2.02b** as a white crystalline solid.

M.P.	:	200-201°C.
$[\alpha]^{D}_{25}$	:	–177.4° (c 1, $CHCl_3$).
IR (cm^{-1})	:	1716, 3328.
^{1}H NMR	:	δ 2.45 (d, *J* = 8.5 Hz, 1H), 3.75 (s, 3H), 5.20 (dd, *J* = 5.4, 8.8 Hz, 1H), 5.30 (d, *J* = 5.4 Hz, 1H), 6.80 (d, *J* = 9 Hz, 2H), 7.15-7.60 (m, 7H).
Microanalysis	:	M. F. $C_{16}H_{15}NO_3$.

Calculated	C : 71.36	H : 5.61	N : 5.20
Obtained	C : 70.84	H : 5.86	N : 5.02

Preparation of (3R,4S)-1-(4-Methoxyphenyl)-4-phenyl-3-hydroxyazetidin-2-one 2.01b

A mixture of **1.14b** (0.483 g, 1mmol) and activated Zn (0.635 g, 10 mmol) with acetic acid (0.25 mL) was refluxed in methanol (15 mL) for 1 h so as to provide **2.01b** (0.256 g, 96%) as a white solid.

M.P. : 197-199°C.

$[\alpha]^{D}_{25}$: +178.2° (c 0.33, $CHCl_3$).

IR (cm^{-1}) : 1716, 3328.

^{1}H NMR : δ 3.75 (s, 3H), 5.15 (d, *J* = 5.2 Hz, 1H), 5.25 (d, *J* = 5.2 Hz, 1H), 6.80 (d, *J* = 9 Hz, 2H), 7.15-7.50 (m, 7H).

Microanalysis : M. F. $C_{16}H_{15}NO_3$.

: Calculated	C : 71.36	H : 5.61	N : 5.20
Obtained	C : 71.65	H : 5.80	N : 5.49

***Preparation of (3S,4R)-1,4-Diphenyl-3-hydroxyazetin-2-one* 2.02a**

A mixture of **1.15a** (0.453 g, 1mmol) and activated Zn (0.635 g, 10 mmol) with acetic acid (0.25 mL) was refluxed in methanol (15 mL) for 1 h so as to provide **2.02a** (0.229 g, 96%) as a white solid.

M.P. : 216-217°C.

$[\alpha]^{D}_{25}$: -188.7° (c 0.39, $CHCl_3$).

IR (cm^{-1}) : 1716, 2852, 3328.

^{1}H NMR : δ 5.15 (d, *J* = 5.4 Hz, 1H), 5.20 (d, *J* = 5.4 Hz, 1H), 6.80-7.55 (m, 10H).

Microanalysis : M. F. $C_{15}H_{13}NO_2$.

: Calculated	C : 75.30	H : 5.48	N : 5.85

Obtained C : 75.68 H : 5.65 N : 6.10

***Preparation of (3R,4S)-1,4-Diphenyl-3-hydroxyazetidin-2-oneb* 2.01a**

A mixture of **1.14a** (0.453 g, 1mmol) and activated Zn (0.635 g, 10 mmol) with acetic acid (0.25 mL) was refluxed in methanol (15 mL) for 1 h so as to provide **2.01a** (0.229 g, 96%) as a white solid.

M.P. : 217-218°C.

$[\alpha]^{D}_{25}$: +190.9° (c 0.7, $CHCl_3$).

IR (cm^{-1}) : 1740, 2852, 3350.

^{1}H NMR : δ 5.15 (d, *J* = 5.4 Hz, 1H), 5.18 (d, *J* = 5.4 Hz, 1H), 6.90-7.50 (m, 10H).

Microanalysis : M. F. $C_{15}H_{13}NO_2$.

: Calculated C : 75.30 H : 5.48 N : 5.85

Obtained C : 75.14 H : 5.43 N : 5.89

***Preparation of (3S,4R)-1,4-Di-(4-methoxyphenyl)-3-hydroxyazetidin-2-one* 2.02c**

A mixture of **1.15c** (0.513 g, 1mmol), activated Zn (0.635 g, 10 mmol), acetic acid (0.25 mL) and methanol (15 mL) was refluxed for 1 h so as to provide **2.02c** (0.293 g, 98%) as a white solid.

M.P. : 132°C.

$[\alpha]^{D}_{25}$: –181.9° (c 0.93, $CHCl_3$).

IR (cm^{-1}) : 1726, 2852, 3301.

^{1}H NMR : δ 3.75 (s, 3H), 3.80 (s, 3H), 5.15 (dd, *J* = 5.4, 8 Hz, 1H), 5.25 (d, *J* = 5.4 Hz, 1H), 6.80 (d, *J* = 8 Hz, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.20-7.40 (m, 4H).

Microanalysis : M. F. $C_{17}H_{17}NO_4$.

: Calculated C : 68.21 H : 5.72 N : 4.68

	Obtained	C : 68.06	H : 5.98	N : 4.55

***Preparation of (3S,4R)-3-Hydroxy-1-(4-methoxyphenyl)-4-(2-phenylethenyl)azetidin-2-one* 2.02d**

A mixture of **1.15d** (0.509 g, 1mmol), activated Zn (0.635 g, 10 mmol), acetic acid (0.25 mL) and methanol (15 mL) was refluxed for 1 h so as to provide **2.02d** (0.283 g, 96%) as a white solid.

M.P. : 156-157°C.

$[\alpha]^{D}_{25}$: –236° (c 0.01, CH_3OH).

IR (cm^{-1}) : 1737, 3340.

^{1}H NMR : δ 3.75 (s, 3H), 4.85 (dd, *J* = 5.2, 7.4 Hz, 1H), 5.15 (bd, *J* = 5.2 Hz, 1H), 6.40 (dd, *J* = 8.1, 16.1 Hz, 1H), 6.65-7.00 (m, 3H), 7.20-7.65 (m, 7H)

Microanalysis : M. F. $C_{18}H_{17}NO_3$

:	Calculated	C : 73.20	H : 5.80	N : 4.74
	Obtained	C : 73.59	H : 6.02	N : 5.00

2.6 References

1. (a) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (b) Thomas, R.C. In *Recent Progress in Chemical Synthesis of Antibiotics;* Lukas, G.; Ohno, M., Eds.; Springler-Verlag: Berlin, 1990; p 553. (c) Palomo, C. In *Recent Progress in Chemical Synthesis of Antibiotics;* Lukas, G.; Ohno, M., Eds.; Springler-Verlag: Berlin, 1990; p 565. (d) Van der Steen, F. H.; Van Koeten, G. *Tetrahedron* **1991**, *47*, 7503. (e) Durckheimer, W.; Blumbach, J.; Latrell, R.; Sheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.

2. (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 699. (b) Ojima, I. In *The chemistry of b-lactams*; Georg, G. I., Ed.; VCH: New York, 1993; p 197. (c) Ojima, I. *Acc. Chem. Res*. **1995**, *28*, 383.

3. Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681.

4. Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vander Velde, D. G.; Himes, R. H. *J. Org. Chem.* **1996**, *61*, 2664 and references cited therein.

5. (a) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. (b) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467. (c) Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C. M.; Park, Y. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2479.

6. (a) Manhas, M. S.; Amin, S. G.; Chawla, H. P. S.; Bose, A. K. *J. Heterocycl. Chem.* **1978**, *15*, 601. (b) Nagao, Y.; Kumageri, T.; Takao, S.; Abe, T.; Ochiai, M.; Inoue, Y.; Taga, T.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 4737. (c) Wagle, D. R.; Garai, C.; Chiang, J.; Montleone, M. G.; Kurys, B. E.; Strohmeyer, T.W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227. (d) Palomo, C.; Cossio, P. P.; Cuevas, C. *Tetrahedron Lett*. **1991**, *32*, 3109. (e) Borer, B. C.; Balogh, D. W. *Tetrahedron Lett.* **1991**, *32*, 1039.

7. (a) Holton, R. A.; Liu, J. A. *Bioorg. Med. Chem. Lett.* **1993**, *11*, 2475. (b) Palomo, C.; Arrieta, A.; Cossio, P. P.; Aizpura, J. M.; Mielgo, A. I.;

Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6425, 6429.

8. (a) Basak, A.; Mahato, T.; Bhattaacharya, G.; Mukherjee, B. *Tetahedron Lett.* **1997**, *38*, 643. (b) Brieva, R.; Crish, J. Z.; Sih, C. J. *J. Org. Chem*. **1993**, *58*, 1068.

9. Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5585.

10. Farina, V.; Hauck, S. I.; Walker, D. J. *Synlett* **1992**, 761-763.

11. (a) Ojima, I., Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985-7012. (b) Ojima, I.; Habus, I.; Zhao, M. *J. Org. Chem.* **1991**, *56*, 1681-1683.

12. Brown, S.; Jordan, A. M.; Lawrence, N. J.; Pitchard, R. G. *Tetrahedron Lett*. **1998**, *39*, 3559-3562.

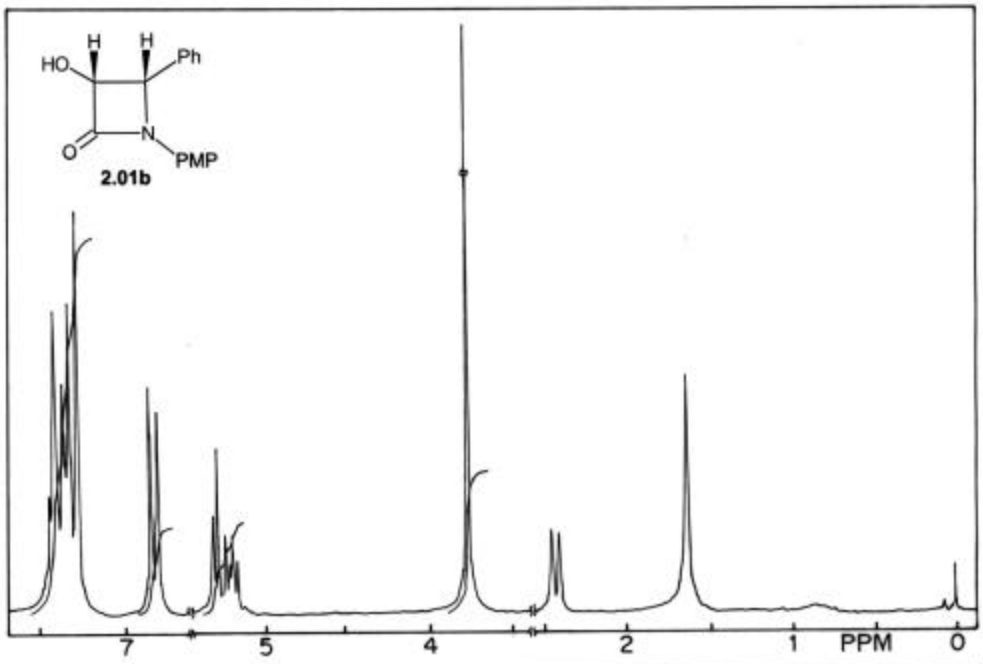
13. Song, C. E.; Lee, S. W.; Roh, E. J.; Lee, S. –G, Lee, W. –K. *Tetrahedron Asymm.* **1998**, *9*, 983.

14. (a) Brandon, R. C.; Derfer, J. M.; Boord, C. E. *J. Am. Chem. Soc.* **1950**, *72*, 2120. (b) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 182. (c) Schlessinger, R. H., Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (d) Crombie, L., Harper, S. H. *J. Chem. Soc., Chem. Commun.* **1950**, 1707, 1715.

15 (a) Swallen, Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 651, 3396. (b) Tallman, R. C. *J. Am. Chem. Soc.* **1934**, *56*, 126.

16. Amstutz, E. D. *J. Org. Chem.* **1944**, *9*, 310.

17. For references on the Boord reaction, see: (a) Dykstra, H. B.; Lewis, J. F.; Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 651, 3396. (b) Shoemaker, B. H., Boord, C. E. *J. Am. Chem. Soc.* **1931**, *53*, 1505.


H
H
HO
Ph
O
N
PMP
2.01b
7
5
4
2
1
PPM
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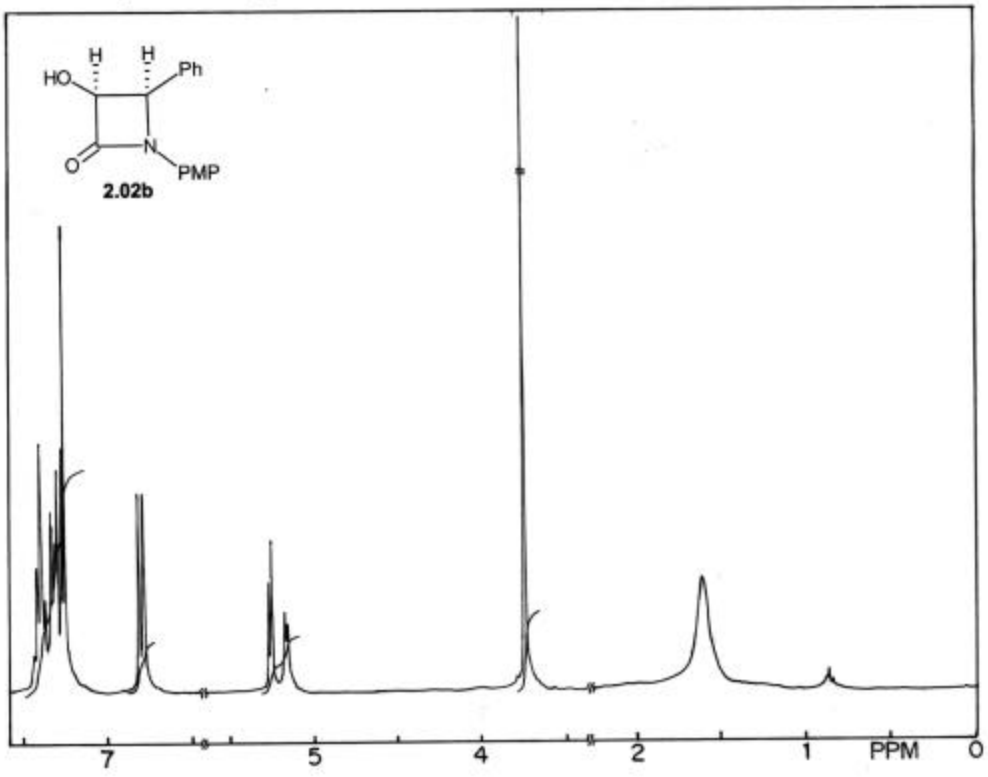
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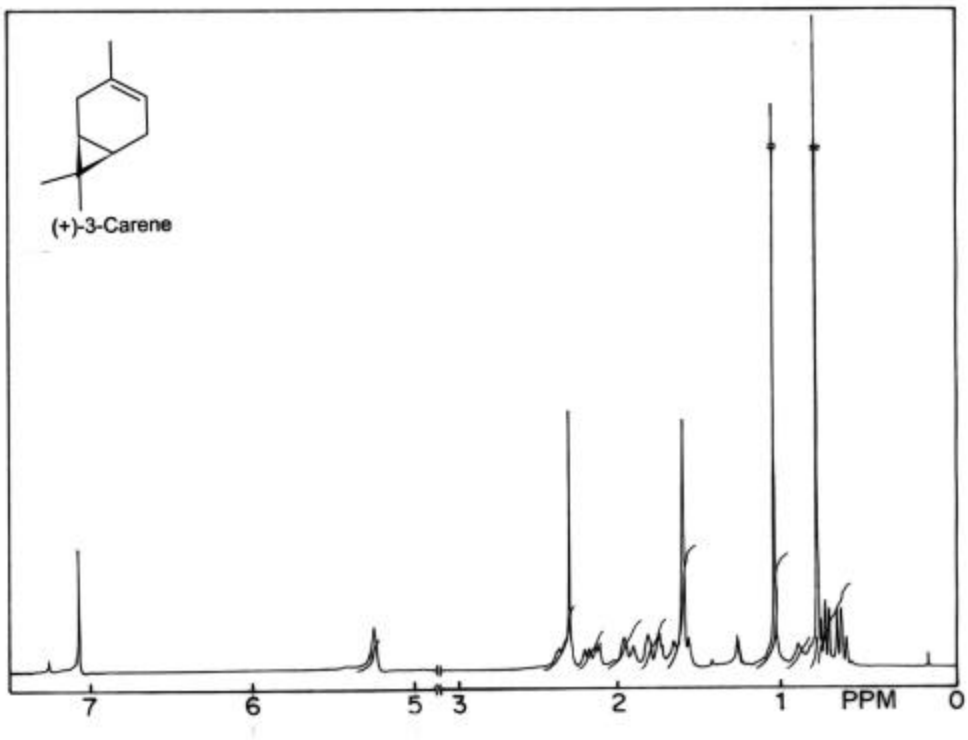
(+)-3-Carene
7
6
5
3
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1
PPM
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Chapter III

Diastereoselective Synthesis of Tetracyclic *b*-Lactams Using Radical Cyclization

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No great discovery was ever made without a bold guess.

Isaac Newton

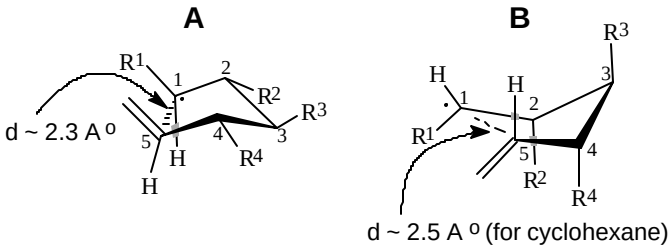
3.1 : Introduction

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

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

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

Scheme 1



Beckwith's Transition state model for hexenyl radical cyclisation

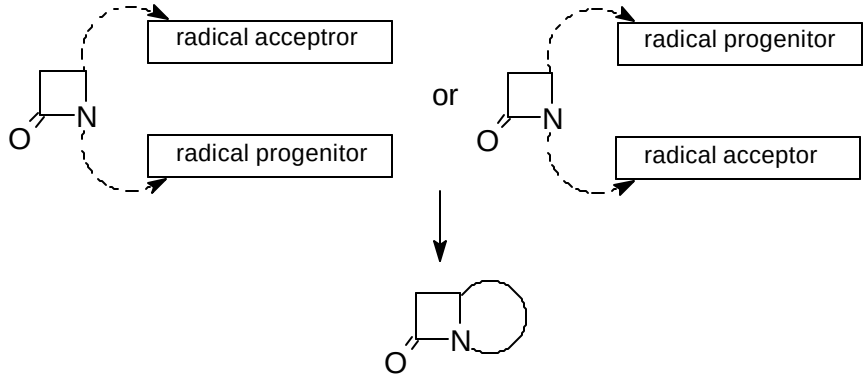
This model invokes a transition state in hexenyl radical cyclisation, which has a long incipient bond (d~2.3Å), which is not much different from that between C_1 & C_5 in cyclohexane (ca. 2.5 Å).

Radical Chemistry of b-Lactams

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

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

Scheme 2

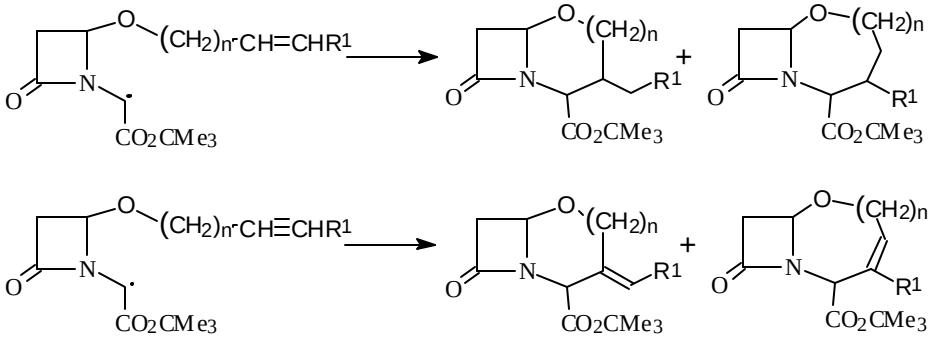


The molecular appendages in the form of substituted double bond attached to the nitrogen or C-4 carbon of the *b*-lactam ring acts as a radical acceptor while functional groups like halo, phenylseleno, phenylthio or acetylenic triple bond acts as a radical progenitor species.

Synthesis of Oxacephams, Oxapenams and Oxabicyclo b-Lactam Derivatives

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

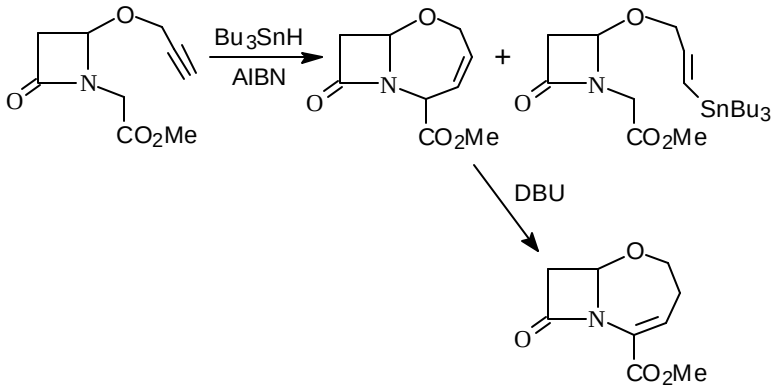
Scheme 3



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

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

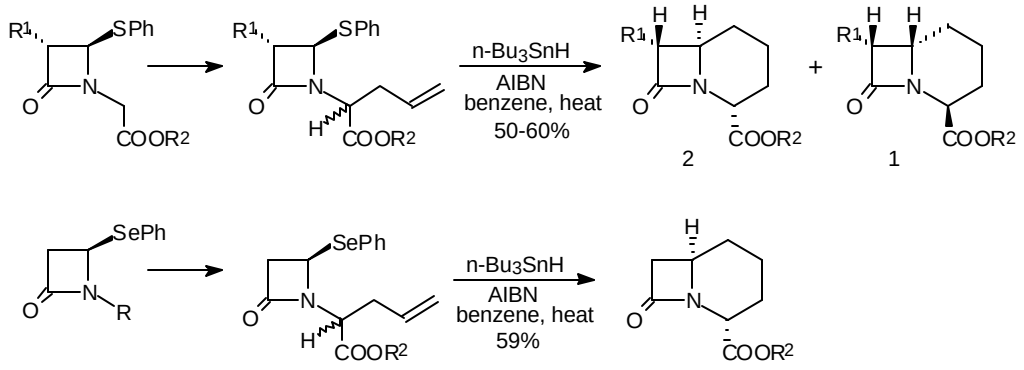
Scheme 4



Carbacephems, Carbapenems and their Derivatives

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

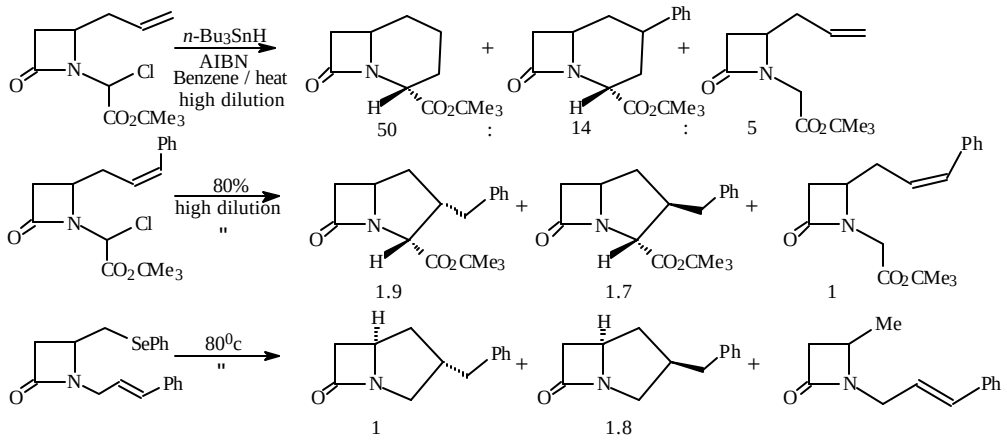
Scheme 5



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

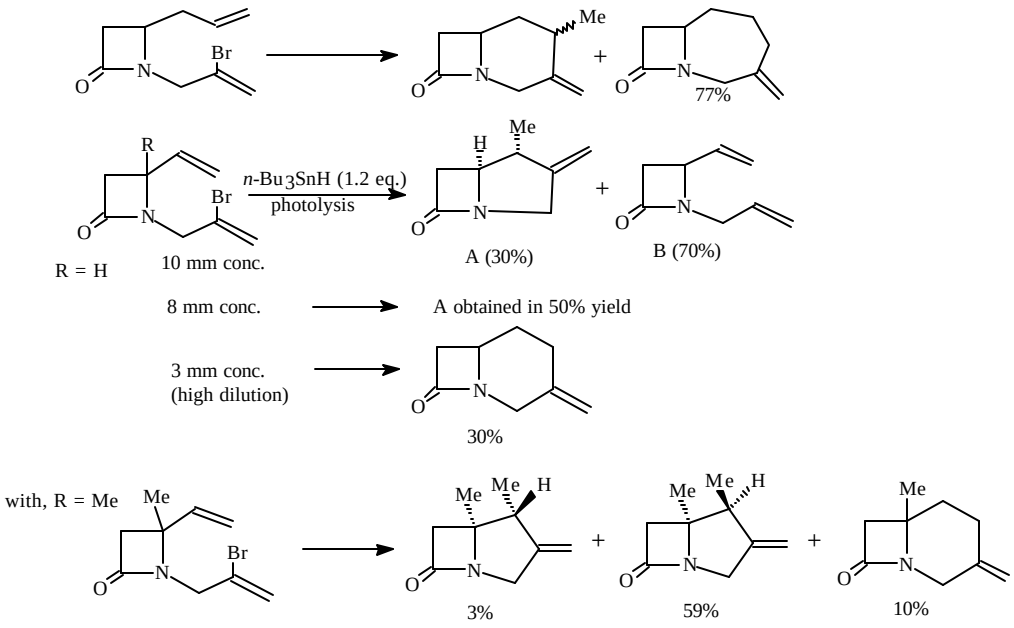
Interestingly, a cyclized product with the incorporation of Ph group from benzene, used as a solvent was also obtained in 14% *(Scheme 6)*.[20]

Scheme 6



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

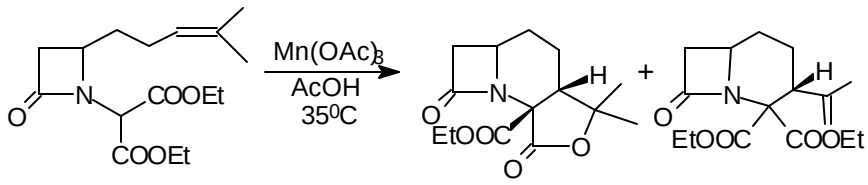
Scheme 7



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

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

Scheme 8

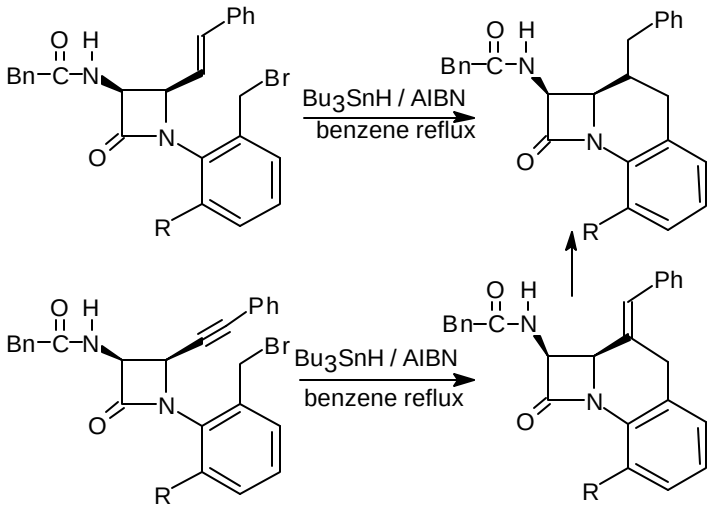


Synthesis of Bezocarbapenems and Benzocarbacephems

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

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

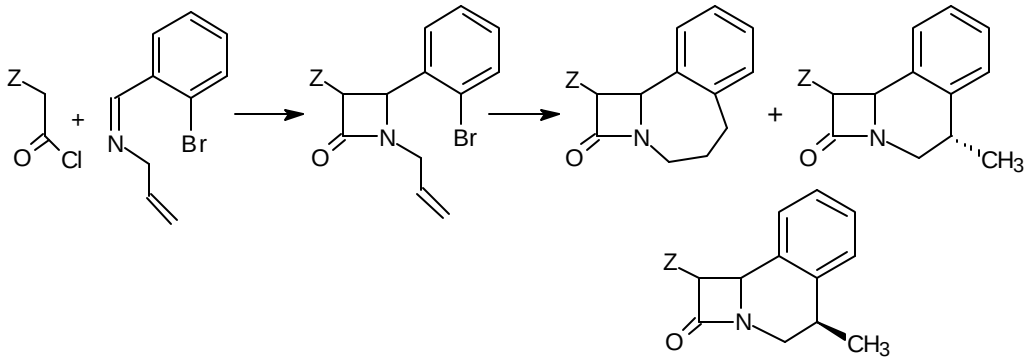
Scheme 9



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

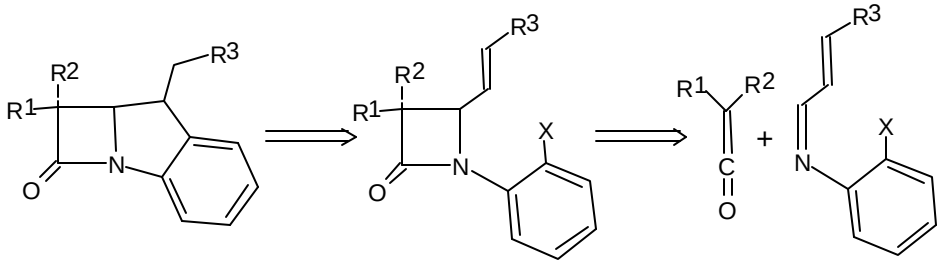
Bose & Manhas used aryl radical cyclization strategy to prepare benzocarbacephems. The use of properly substituted imine, obtainable from o-bromobenzaldehyde and allyl amine was the key step in this methodology. This imine on cycloaddition with acid chlorides afforded *b*-lactams with ideal functionalities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

Scheme 10



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

Scheme 11

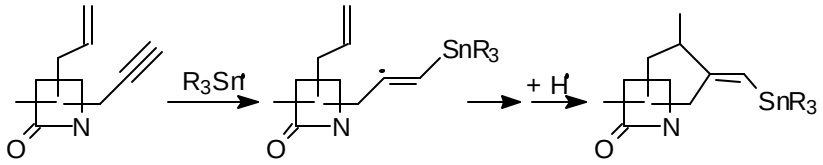


Recently, Alcaide[28] has reported a novel cyclisation and rearrangement process based on aryl-aryl coupling methodology.

The regio and stereocontrolled radical cyclisation of enyne *b*-lactams to furnish tin functionalised *b*-lactams is reported by using of enynes as radical progenitors.

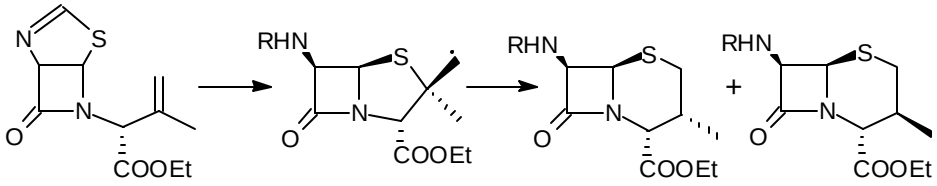
Proteiodestanylation followed by ozonolysis was used to convert these *b*-lactams into the corresponding oxo derivatives *(Scheme 12)*.[29]

Scheme 12



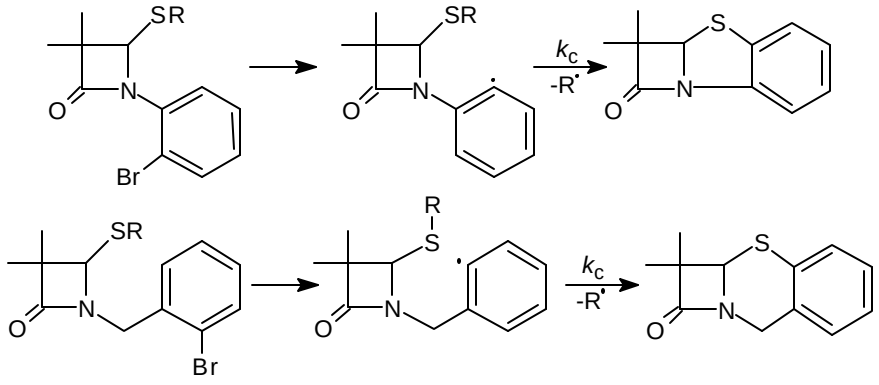
In another approach, 4-thiyl radical addition onto a substituted N-allyl double bond using Fe (III) and Mn (II) salts is studied. The primary radical formed initially by 5-exo cyclisation, rearranges to give 6-membered ring, a cephem derivative in poor to moderate yield *(Scheme 13)*.[30]

Scheme 13



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

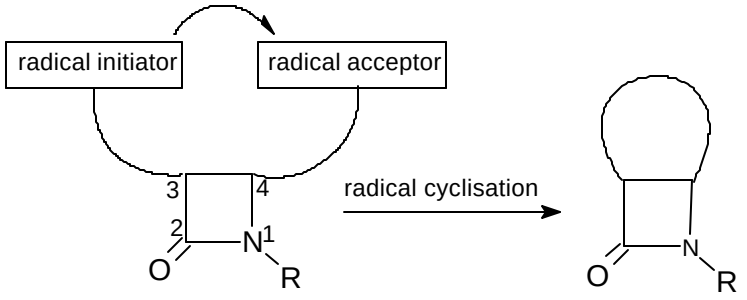
Scheme 14



3.2 : Present Work

The radical chemistry of *b*-lactams is mainly used as a methodology for the synthesis of bicyclic antibiotics. This involves the use of radical generator either attached at the C3 carbon or at the nitrogen of the *b*-lactam ring. However, the radical cyclisation involving styryl double bond as a radical acceptor and the radical generator at the C-4 of the azetidinone ring *(Scheme 15)* are rarely addressed.

Scheme 15



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

3.3 : Results & Discussion

***Radical Cyclisation of C-4 Styryl Substituted b-Lactam Derivatives: Cyclisation of* 1.13d-l *&/or* 1.14d-l**

The unique feature associated with all the *b*-lactam derivatives **1.14d-i** & **1.15d-i** is the presence of bromine at C′-4 centre and presence of styryl or crotyl double bond attached at the C-4 centre of the central azetidinone nucleus. This system

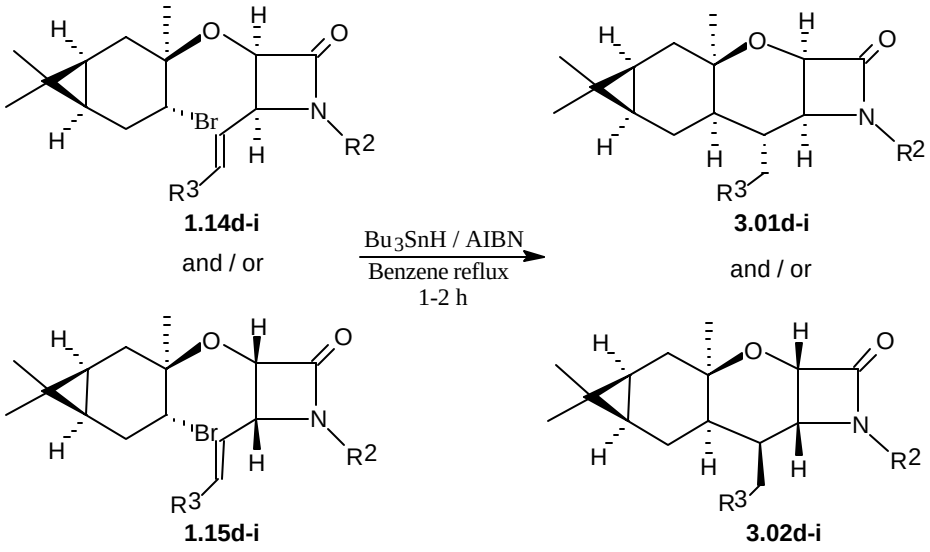
was ideal system for a radical cyclization and it was interesting to study the efficiency of such kind of cyclization.

In a typical procedure, to a refluxing solution of *b*-lactam in benzene was added tin hydride, in the presence of AIBN as a radical initiator. No high dilution condition or syringe pump technique was used. In most of the cases the reaction was over within 1h as could be judged from the TLC as well as the analysis of ^{1}H NMR of the crude reaction mixture.

The product could be easily purified by flash column chromatography and the removal of tin impurity was never a problem. It was not necessary to treat the reaction mixture with KF solution and the products obtained were sufficiently pure as could be analyzed from the ^{1}H NMR or the microanalysis of the product (**3.01d-i** & **3.02d-I**).

The ^{1}H NMR of the product revealed that it was a mixture of two diastereomers *(Scheme 16).*

Scheme 16



d R3 = Ph, R2 = PMP
e R3 = Ph, R2 = Ph
f R3 = Ph, R2 = propyl
g R3 = Ph, R2 = cyclohexyl
h R3 = Ph, R2 = tert. butyl
i R3 = Ph, R2 = (R)-(+)-Ph(Me)CH

Table 1 summarises the results of radical cyclisation for the diastereomeric mixtures.

Table 1. Radical cyclization of the diastereomeric mixture of *b*-lactams

Reactant No.	R^1	R^2	Product no.	Time (h)	Yield (%)
1.14d & **1.15d**	Ph	PMP	**3.01d** & **3.02d**	1/2	96
1.14e & **1.15e**	Ph	Ph	**3.01e** & **3.02e**	1	83
1.14f & **1.15f**	Ph	*n*-propyl	**3.01f** & **3.02f**	1	60
1.14g & **1.15g**	Ph	Cyclohexyl	**3.01g** & **3.02g**	2	72
1.14h & **1.15h**	Ph	*t*-Butyl	**3.01h** & **3.02h**	1	87
1.14i & **1.15i**	Ph	(+)-R-α-methylbenzyl	**3.01i** & **3.02i**	2	72

As shown in the Table 1, the diastereomeric mixture was highly efficient radical system and reacted smoothly under normal conditions of radical cyclisation. In a typical reaction, Bu_3SnH was added over 2-3 minutes to the refluxing solution of the starting material in benzene containing catalytic amount of AIBN. There was no need to use high dilution conditions or syringe pump techniques. Interestingly there was no product observed arising from the reduction of the starting material.

Table 2 shows the selected data for cyclised products obtained from the radical cyclisation of diastereomeric mixture or single diastereomer.

Table 2. Selected data for the cyclised produts

Product no.	R^1	R^2	Yield (%)[a]	m.p. (°C)	$[\alpha]_D$ (conc. In g/100 ml)
3.02d	Ph	PMP	96	197	+22.60 (c 1.28, CH_2Cl_2)
3.02e	Ph	Ph	80	186-188	+20.53 (c 0.76, CH_2Cl_2)
3.01f + **3.02f**	Ph	*n*-propyl	65	-	+20.14 (c 1.44, CH_2Cl_2)
3.01g + **3.02g**	Ph	Cyclohexyl	70	-	+29.10 (c 1.02, CH_2Cl_2)
3.02h	Ph	*t*-Butyl	90	132-134	+21.79 (c 0.78, $CHCl_3$)
3.02i	Ph	(+)-R-α-methylbenzyl	76	208	+24.07 (c 0.55, CH_2Cl_2)

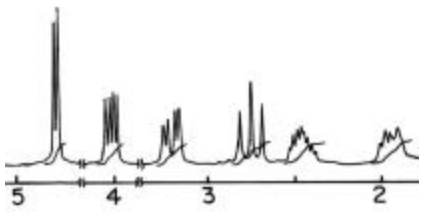
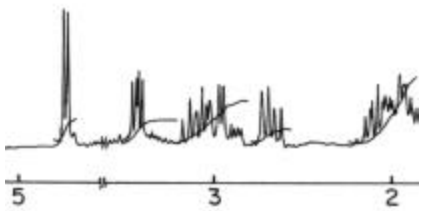
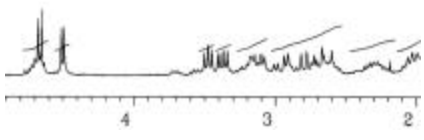
A general problem associated with the radical reactions is the removal of tin impurities formed in the reaction mixture. A further treatment with saturated KF solution is generally needed. But in case of the cyclized products **3.01d-i** & **3.02d-i**,

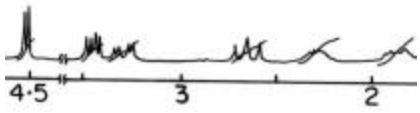
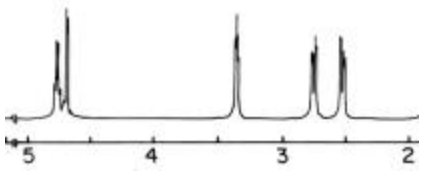
KF treatment was not required for the removal of tin impurities and the products could be easily purified by flash column chromatography.

In all the cases, IR spectra of the cyclized products showed a typical amide carbonyl peak around 1740-1750 cm^{-1}. The mass spectra showed a molecular ion peak in most of the cases.

The ^1H NMR of the crude reaction mixture obtained from the cyclisation of diastereomeric mixture showed presence of only two cyclized products, arising one from each diastereomer. Absence of any peaks in the region 6.0-6.50 (that of styryl double bond) clearly indicated that there was no formation of any reduced product. The formation of 6-membered ring was further confirmed from the typical pattern of the benzylic protons.

Table 3. Characteristic ^1H NMR data for the cyclised products

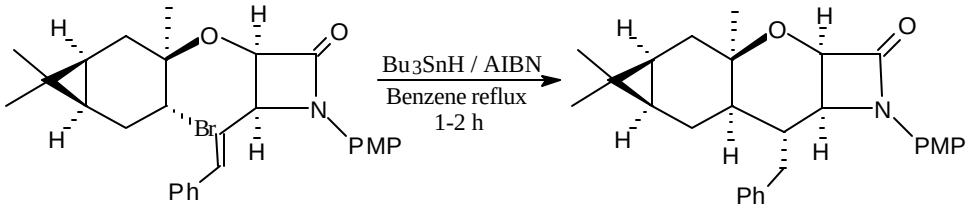
Comp No.	H	^1H NMR signal (δ ppm) & coupling constants (Hz)	Portion of the ^1H NMR spectrum
3.02e	H-2a H-7a Ph-CH2	4.78 (d, *J* = 4.9 Hz) 4.02 (dd, *J* = 4.9, 9.3 Hz) 2.75 (t, *J* = 13.2 Hz) 3.20 (dd, *J* = 4.9, 13.2 Hz)	
3.01f & **3.02f**	H-2a H-7a Ph-CH2	4.75 (d, *J* = 4.0 Hz) 3.43 (dd, *J* = 4, 8 Hz) 2.68 (dd, *J* = 8, 14 Hz) 3.10 (dd, *J* = 8, 14 Hz)	
3.01g & **3.02g**	H-2a H-7a Ph-CH2	4.5 (d, *J* = 4.3 Hz) 4.77 (d, *J* = 4.8 Hz) 3.38 (dd, *J* = 4.3, 6.8 Hz) 3.48 (dd, *J* = 4.8, 5.3 Hz) Multiplet	

3.02h	H-2a H-7a Ph-CH2	4.51 (d, *J* = 4.4 Hz) 3.44 (dd, *J* = 4.4, 8.8 Hz) 2.65 (dd, *J* = 12.8, 13.6 Hz) 3.28 (dd, *J* = 4.4, 13.6 Hz)	
3.02i	H-2a H-7a Ph-CH2	4.51 (d, *J* = 5.0 Hz) 3.38 (dd, *J* = 5, 6.9 Hz) 2.53 (dd, *J* = 5.5, 14.5Hz) 2.76 (dd, *J* = 5.5, 14.5 Hz)	

***Synthesis of* 3.01d**

The diastereomeric mixture of **1.14d** & **1.15d** was separated by fractional crystallization to obtain the individual diastereromers in the pure form. The diastereomer **1.14d** was subjected to the typical conditions of radical cyclisation *(Scheme 17)*. The reaction was over within ½ h (TLC).

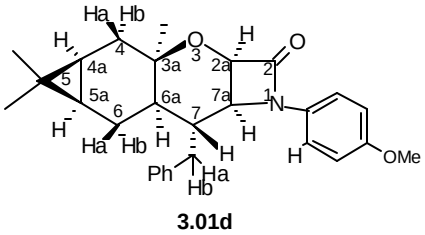
Scheme 17



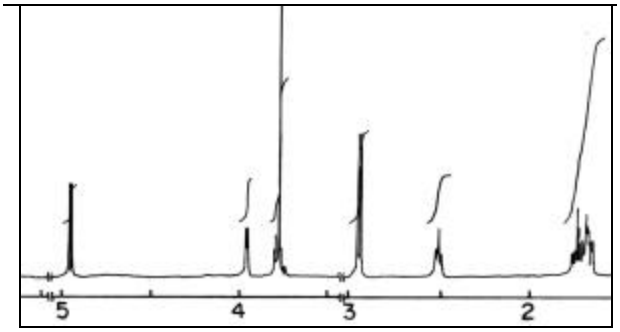
1.14d **3.01d**

The product obtained after work up was purified by flash column chromatography. The tin impurity was removed easily by elution with pet ether. The pure product was obtained from repeated flash column chromatography as a foamy solid (**3.01d**).

The IR of **3.01d** showed a peak at 1740 cm^{-1} indicating presence of *b*-lactam amide carbonyl. The mass spectrum showed a molecular ion peak at 431.



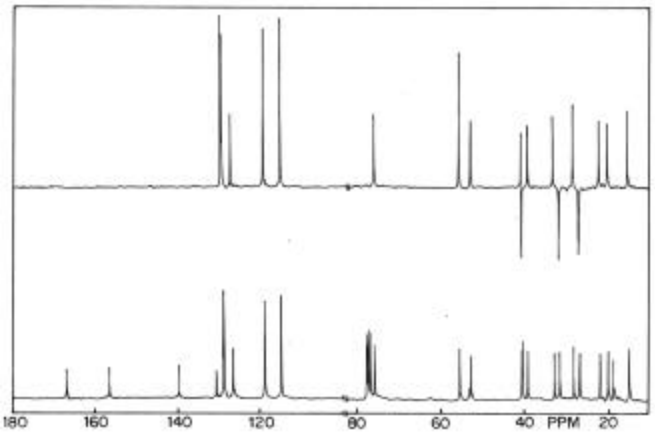
3.01d



^{1}H NMR of **3.01d**

The ^{1}H NMR spectrum showed absence of any peaks in the region of 6-6.75 (corresponding to the styryl double bond) which ruled out the possibility of reduced product being formed. Two multiplets in the region 0.35-0.50 could be assigned to the two-cyclopropyl methine protons H-4a & H-5a. The two singlets at 0.95 & 1.0 could be assigned to the two *gem*-dimethyl protons. The protons H-4, H-6 & H-6a attached to the carane ring were seen as multiplets in the region 1.0-1.70. The benzylic protons were observed as a doublet with J = 8 Hz. A singlet at 3.78 was due to the methoxy protons of the PMP group. The *b*-lactam proton H-7a was seen as dd at 3.95 with J = 1.7 & 5.6 Hz and other *b*-lactam proton H-2a was seen as a doublet at 4.94 with J = 5.6 Hz. The aromatic protons appeared as multiplets in the region 6.80-7.40.

The ^{13}C NMR spectrum showed peak at 18.51 that of the tertiary carbon C-5. Methylene carbons C-4 & C-6 were seen at 26.59 & 31.37. The benzylic carbon appeared at 40.13. The *b*-lactam carbons C-7a and C-2a appeared at 52.46 and 75.43 respectively. Methoxy carbon of PMP was seen at 55.13. Quaternary carbon C-3a was seen at 77.04.



^{13}C NMR of **3.01d**.

Aromatic carbons appeared at 114.35, 118.47, 126.25, 128.41, 128.65, 130.38, 139.58 & 156.22. The amide carbonyl carbon of the *b*-lactam ring was seen at 166.43.

The additional support for this structural assignment was obtained from the COSY NMR of **3.01d** (Fig 1).

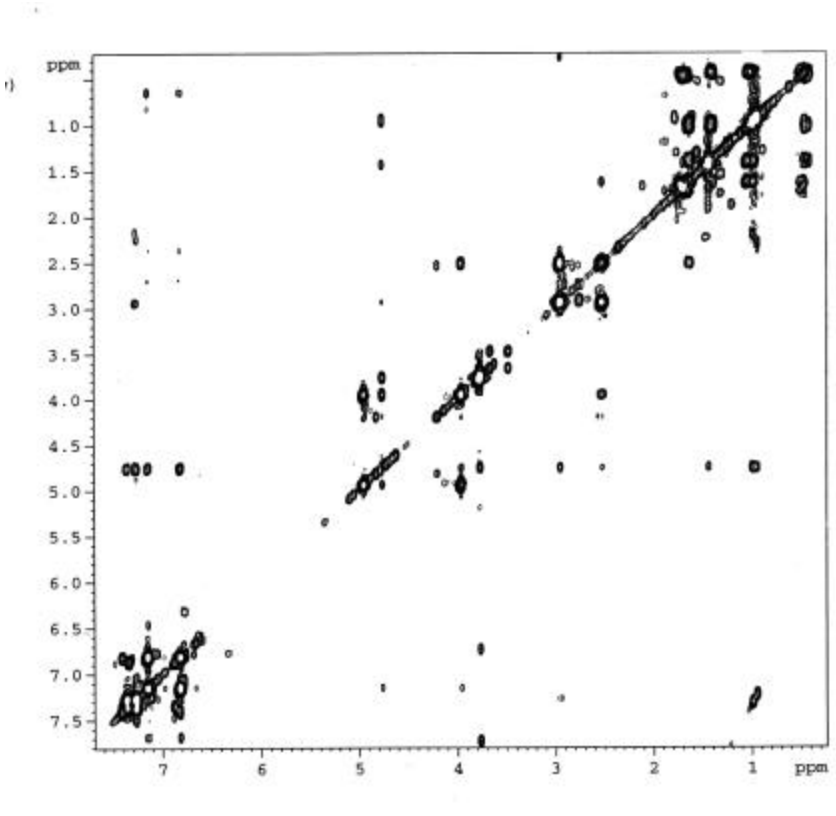
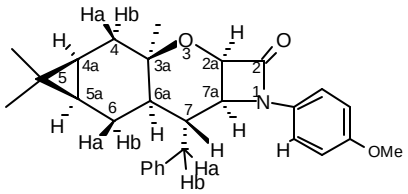


Fig. 1. COSY NMR of **3.01d**.

Table 4. Important COSY connectivities for **3.01d**

Proton no.	Chemical shift (multiplicity)	COSY connectivity
H-2a	4.95 (d)	H-7a
H-7a	3.95 (dd)	H-2a, H-7
H-7	2.43-2.55 (m)	H-6a, H-7a, -CH_2Ph
H-6a	1.63-1.70 (m)	H-7, Ha-6, Hb-6
Ph-CH_2-	2.95 (d)	H-7



3.01d

In the COSY NMR spectrum (Table 4), the benzylic protons showed strong coupling with H-7.

The proton H-7 was further connected with the *b*-lactam proton H-7a and the ring junction proton, H-6a. The H-6a further showed connectivity with methylene protons of the carane ring, Ha-6 & Hb-6. These two protons were further attached to the cyclpropyl methine protons in the region 0.45-0.50. From the further connectivity pattern of these cyclpropyl methine protons it was possible to assign the position of other methylene protons Ha-4 & Hb-4 which were seen at 1.66 & 1.73.

To decide the absolute stereochemistry of the compound, ROESY NMR of **3.01d** was recorded (Fig. 2).

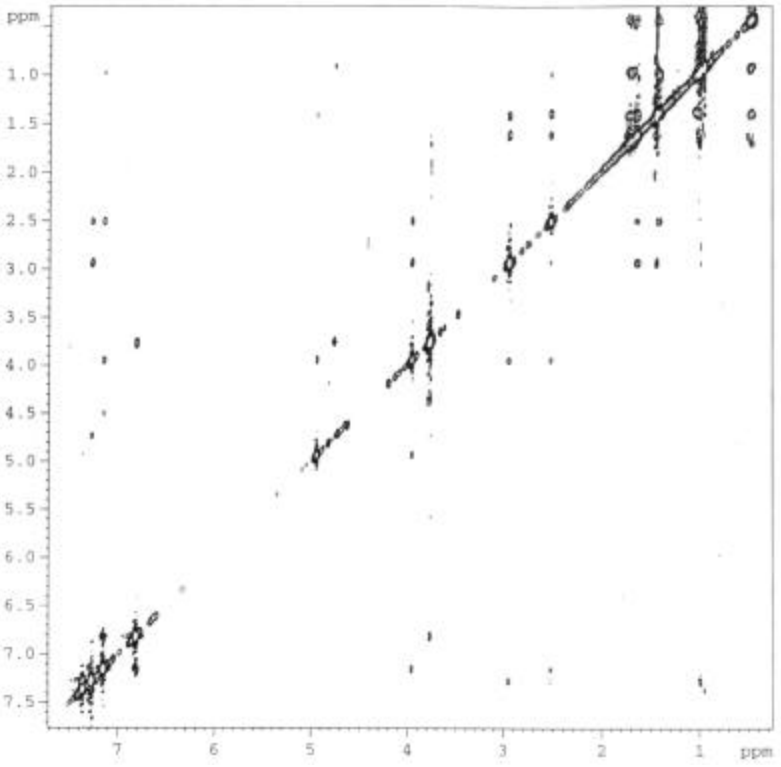
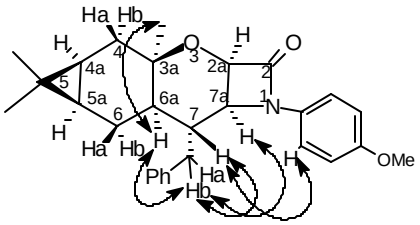


Fig. 2. ROESY NMR of **3.01d**.

Table 5. Important ROESY correlations for **3.01d**

Proton no.	Chemical shift (multiplicity)	ROESY connectivity
H-7a	3.95 (dd)	-CH_2-Ph
H-7	**2.43-2.55 (m)**	**-CH_2Ph, PMP**
H-6a	1.63-1.70 (m)	-CH_2Ph, CH_3(3a)
Ph-CH_2-	2.95 (d)	H-6a, **CH_3(3a)**, H7, H7a



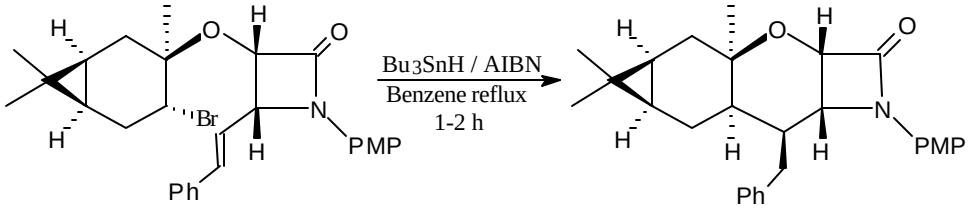
3.01d

As shown above (Table 5) a strong connectivity existed between benzylic proton and the angular methyl at C-3a which clearly indicated towards the possibility of benzyl group at C-7 to be *'a'*. The H-7 showed spatial connectivity with both, benzylic proton as well as the aromatic protons from PMP group. This is possible only if the proton H-7 is 'β'. The spatial connectivity between the H-7 & *b*-lactam proton H-7a further supported this conclusion. This led to the assignment of *2aR, 3aR, 4aS, 5aR, 6aR, 7R, 7aS* as the absolute stereochemistry at **3.01d**.

Radical Cyclisation of* 1.15d *(Synthesis of* 3.02d*)

The other diastereomer, **1.15d**, was also subjected to the optimized conditions of radical cyclisation independently. The reaction was over within ½ h (TLC). The product was purified by flash column chromatography *(Scheme 18)*.

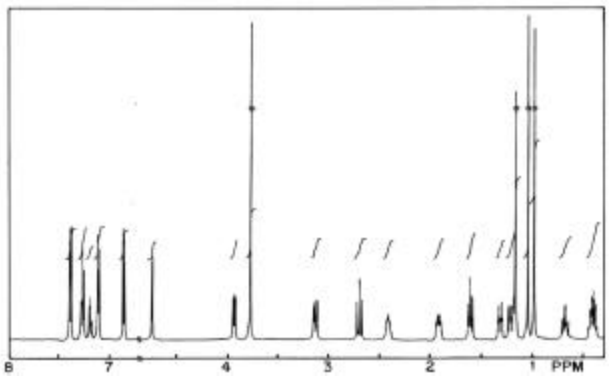
Scheme 18

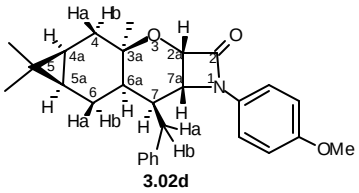


1.15d **3.02d**

The purified product was a crystalline solid with mp 197°C. The IR showed a typical amide peak at 1740 cm^{-1}. The mass spectrum showed a significant molecular ion peak at 431(38%).

In the ^{1}H NMR spectrum of **3.02d**, the cyclopropyl methine protons H-4a & H-5a were seen as a multiplet in the region 0.35-0.75. Singlets at 1.0 & 1.06 accounted for gem dimethyls at C-5, while singlet at 1.18 was due to the tertiary methyl at C-3a. The multiplets in the region 1.20 to 2.0 were due to the methylene protons at C-4 & C-6. H-7 resonated as a multiplet at 2.40-2.45.





3.02d

Fig. 3. ^{1}H NMR of **3.02d**.

The benzylic protons were diastereotopic and resonated as a dd at 2.70 (J = 12.5, 13.5 Hz) & dd at 3.13 (J = 4.5, 12.5 Hz). The methoxy peak was seen as a singlet at 3.78. The *b*-lactam proton H-7a appeared as a dd, with J = 4.6 & 9.4 Hz. The other proton

H-2a resonated as a doublet at 4.75 with coupling constant J = 4.6 Hz, a high coupling constant indicating the presence of *cis b*-lactam. The aromatic protons resonated in the region 6.80-7.50.

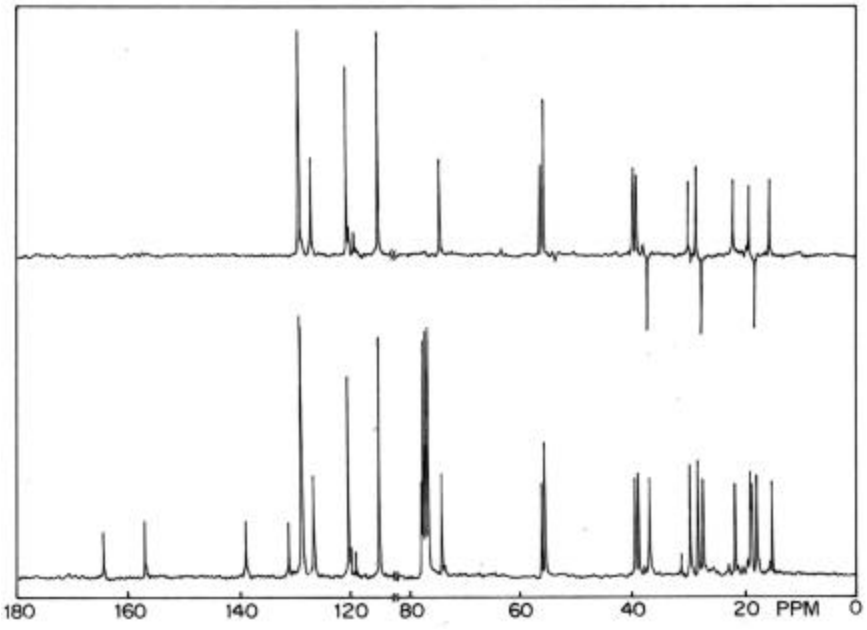
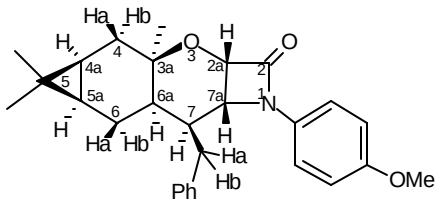


Fig. 4. ^{13}C NMR of **3.02d**

The ^{13}C NMR (Fig. 4) spectrum showed peaks at 17.61 & 27.14 that of C-4 & C-6. The tertiary carbon C-5 was seen at 18.67. The benzylic carbon resonated at36.73 while, the *b*-



3.02d

lactam carbon G7a and the methoxy group appeared at 55.33 & 55.89. The other *b*–lactam carbon C-2a appeared at 74.03, while the tertiary carbon C-3a appeared at 77.66. The aromatic carbons resonated in the region 115 to 160 as 8 peaks. The *b*-lactam amide carbonyl resonated at 163.99.

To decide the connectivity among different protons a COSY NMR of **3.02d** was recorded (Fig. 5).

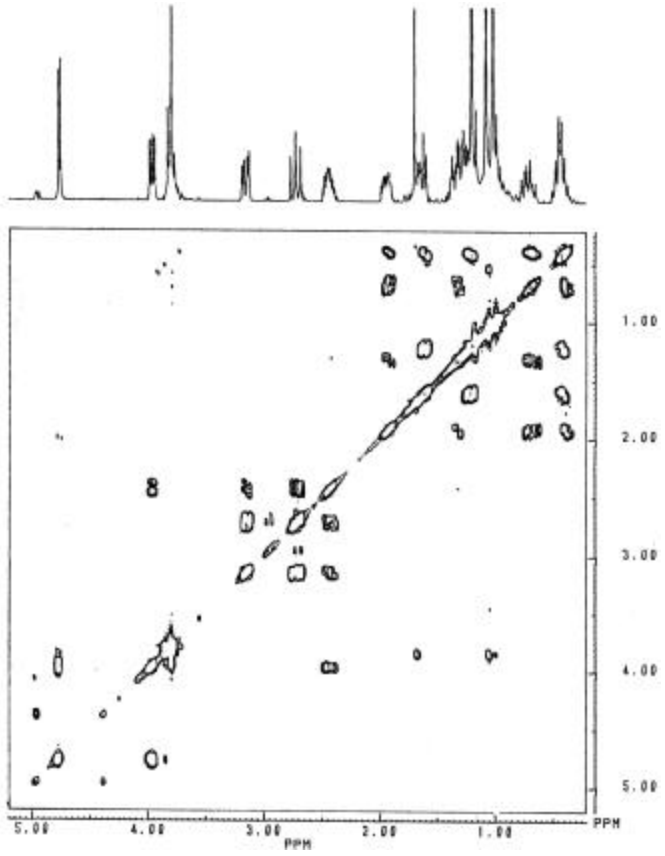
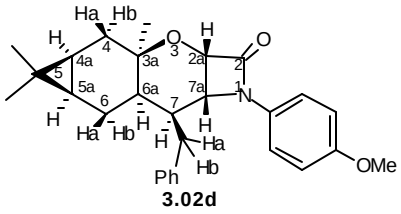


Fig 5. COSY NMR of **3.02d**.

Table 6. Important COSY connectivities for **3.02d**

Proton no.	Chemical shift (multiplicity)	COSY connectivity
H-2a	4.75 (d)	H-7a
H-7a	3.94 (dd)	H-2a, H-7
H-7	2.40-2.45 (m)	H-6a (weak), H-7a, Ph-CHa & Ph-CHb
H-6a	1.30-1.35 (m)	H-7, Ha-6, Hb-6
Ph-CHa-	3.13 (dd)	H-7, Ph-CHb
Ph-CHb-	2.70 (t)	H-7, Ph-CHa



3.02d

The COSY NMR spectrum showed that the diastereotopic benzylic protons (Ha & Hb) coupled with each other as well as with the proton H-7, which appeared at 2.42. The H-7 proton showed strong connectivity with *b*-lactam proton H-7a as well as the benzylic protons. But showed very weak coupling with H-6a. This indicated dihedral angle H-C7-C6a-H to be around 90°. H-6a further coupled with Ha-6 (axial) at 0.71 & Hb-6 (equatorial) at 1.91. The cyclopropyl protons at H-4a showed connectivity with

Ha-4 (axial) at 1.21 & Hb-4 (equatorial) at 1.60. The *b*-lactam proton H-2a showed strong connectivity with H-7a. This confirmed the two dimensional structure of the compound **3.02d**.

The compound **3.02d** was a crystalline solid. Suitable crystals, for X-ray analysis were obtained by the crystallization of **3.02d** from pet ether/dichloromethane system. Fig. 6 shows ORTEP digram for **3.02d**.

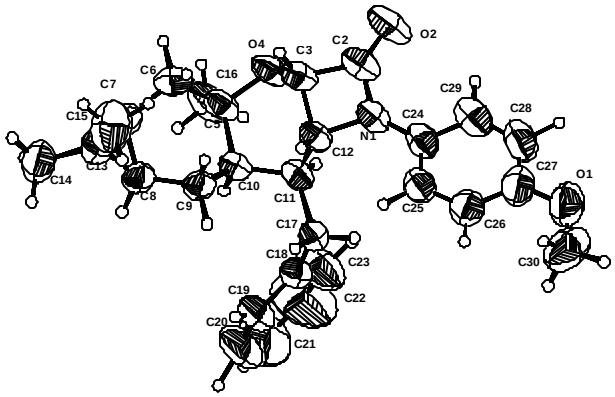


Fig. 6. *ORTEP* diagram of **3.02d**.

***X-ray Data for* 3.02d**

$C_{28}H_{33}rNO_3$, M_r = 431.55, a = 6.830 (2), b = 19.400 (4), c = 18.439 (4) Å, $\alpha = 90^0$, $\beta = 90^0$, $\gamma = 90^0$, V = 2443.2 (10) Å 3, Z = 4, ρ_{calcd} = 1.173 Mg m^{-3}, Rw = 0.1968, T = 293 (2) K, GOF = 0.966.

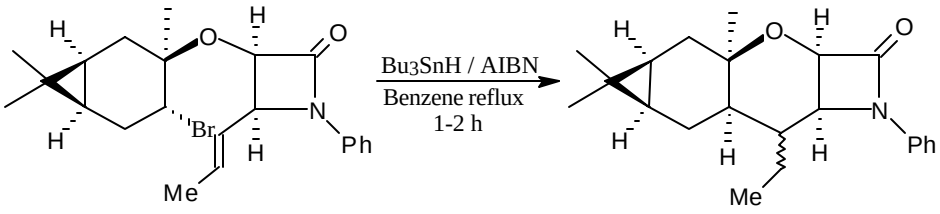
The Data for **3.02d** were collected on Enariuf Nonius CAD-4 single crystal X-ray diffractometer using Cu-Kα radiation (λ = o.70930 Å) and ω-2θ scan mode to a θ range of 1.52 to 24.88^0. The structure was solved by direct positional and anisotropic thermal parameters for non hydrogen atom converged to Rw = 0.1764 R1 = 0.0691 for 4240 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference fourier which was held fixed during the refinement. The refinements were carried out using SHELEX-97[11]

From the single crystal X-ray analysis the absolute stereochemistry of the molecule was determined. The benzyl group attached to the C-7 was 'β' and the absolute stereochemistry of the system was assigned as *2aS, 3aR, 4aS, 5aR, 6aR, 7S, 7aR.*

***Radical Cyclisation of* 1.14l**

In most of the cases studied, styryl double bond at C-4 was used as a radical acceptor. To examine the efficiency of other olefinic double bonds as radical acceptors, we decided to use crotyl double bond at C-4, as a radical acceptor. The *b*-lactam 1.14l, obtained as a crystalline solid was subjected to the optimized conditions of radical cyclisation *(Scheme 19)*.

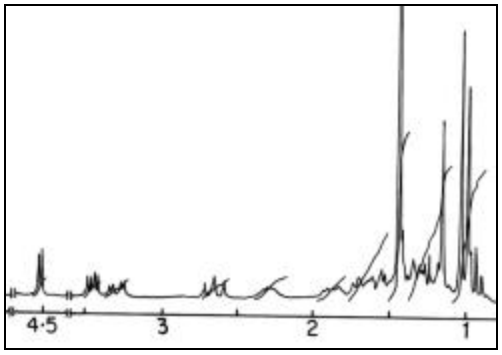
Scheme 19

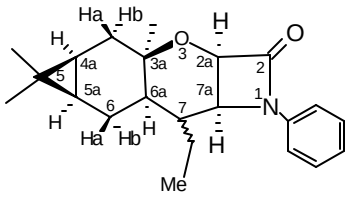


1.14l **3.01l**

The reaction was over within two hours (TLC). The crude product could be separated by flash column chromatography. The pure product **3.01l** was isolated in 91% yield as a white solid, mp 116-118°C.

The IR spectrum of the product showed typical *b*-lactam amide peak at 1770 cm^{-1}. A significant molecular ion peak at 339 (25%) was seen in the mass spectrum of **3.01l**. The ^{1}H NMR spectrum was conclusive. The cyclopropyl methine protons were seen as a multiplet in the region 0.35-0.65. The gem dimethyl groups appeared as two singlets at1.0 & 1.02, while the other methyl at C-3a appeared at 1.36. The rest of the protons resonated as multiplets in the region 0.75-2.0. The *b*-lactam proton H-7a appeared as a triplet (merged dd) at





3.01l

4.11 with J = 5.8 & 6.2 Hz. The other *b*-lactam proton H-2a appeared as a doublet at 4.93, with J = 5.3 Hz. The aromatic protons were seen as a multiplet in the region 7.0 to 7.6.

In the ^{13}C NMR spectrum of **3.01l**, the carbons from carane skeleton appeared in the region 9 to 55. The *b*-lactam carbon C-7a resonated at 53.51 while the other carbon, C-2a appeared at 74.62. The tertiary carbon C-3a, appeared at 77.75. The aromatic carbons appeared as 4 peaks at 124.38, 128.95, 129.11 & 137.53. The *b*-lactam amide carbonyl was seen at 166.07.

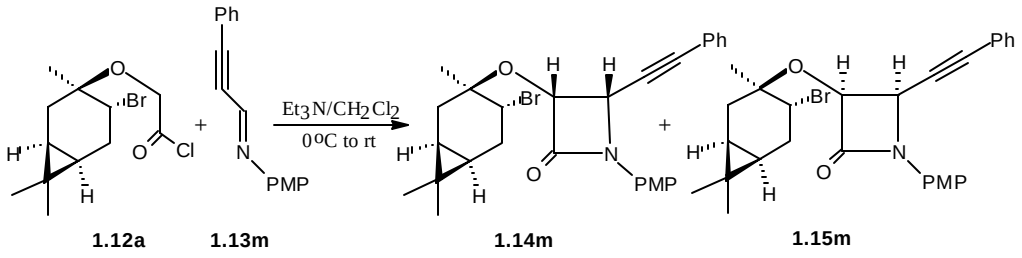
It was not possible to decide the absolute configuration at C-7 and so the absolute stereochemistry of **3.01l** was not determined.

***Radical Cyclisation of* 1.15m : *Preparation of* 3.02m**

So far we had used only olefinic double bond at C-4 as a radical acceptor. The effective cyclisation was thus a 6-exo trig type of radical cyclisation. In order to study the analogous 6-exo dig type of radical cyclisation, a *b*-lactam derivative with triple bond in the form of phenyl acetylene at C-4 was used.

Imine **1.13m** on treatment with acid chloride **1.12a** in the presence of Et_3N underwent cycloaddition reaction to give a diastereomeric mixture of *b*-lactams **1.14m** & **1.15m** in the ratio 55:45*(Scheme 20).*

Scheme 20



The polar diastereomer **1.15m** was obtained as a crystalline solid by fractional crystallization of diastereomeric mixture of **1.14m** & **1.15m** from pet. ether/dichloromethane. The absoltue stereochemistry of **1.15m** was determined from the single crystal X-ray analysis (Fig. 7).

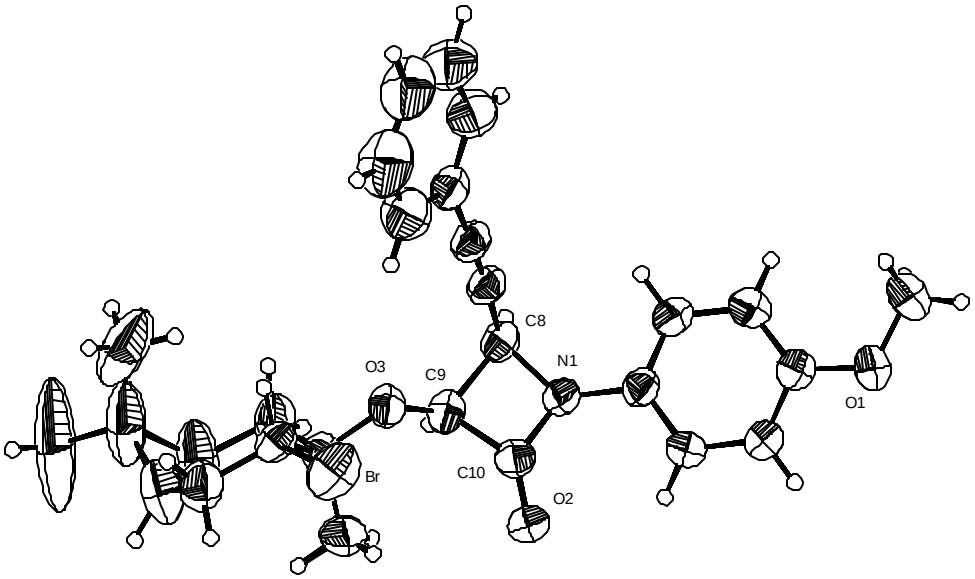
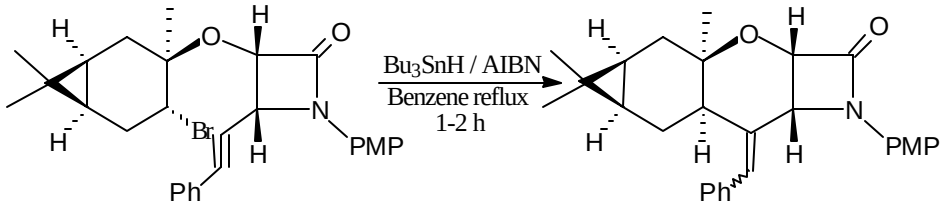


Fig. 7. *ORTEP* diagram of the crystals of **1.15m**.

***The Radical Cyclization of* 1.15m**

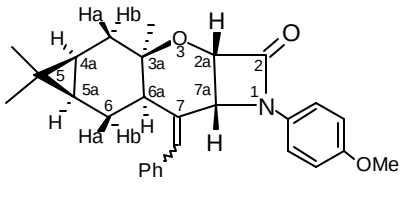
1.15m was subjected to the optimized conditions of radical cyclization. Benzene was used as a solvent, and the of Bu_3SnH was added over 5 minutes *(Scheme 21)*.

Scheme 21

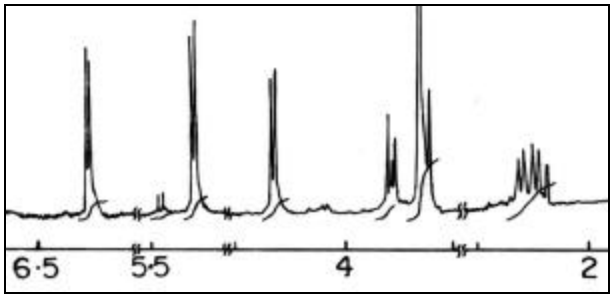


1.15m **3.02m**

As expected, the reaction was sluggish and the ^1H NMR of the crude reaction mixture showed formation of small amount of cyclized product. The major product observed was the reduced product obtained by simple reduction of the halide which was easily notified by the absence of any peaks in the olefinic portion corresponding to the cyclised product in the ^1H NMR spectrum.



3.02m

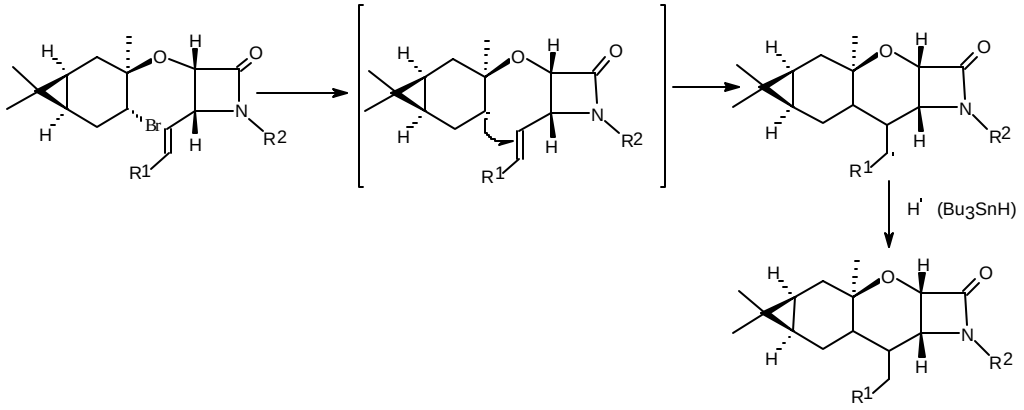


Under modified conditions, in which the Bu_3SnH in benzene was added by syringe pump over 5h, the reaction was completed in 5 h (TLC). The ^1H NMR spectrum of the product **3.02m** showed a small amount of product arising from the reduction of bromide. The major product was cyclized product, which showed a doublet at 6.28 (J = 2.5 Hz) due to the olefinic proton of the cyclized system. The *b*-lactam proton H-2a, appeared as a doublet at 5.32 (J = 3.9 Hz). The proton H-7a appeared at 2.28 as a dd with J = 4.8 & 13.2 Hz. The gem dimethyl as well as other methyl appeared as 3 singlets at 0.99, 1.06 & 1.14 respectively. The rest of the carane ring proton appeared as multiplets in the region 0.40-2.0. The aromatic protons were seen as multiplets in the region 6.75-7.60. Attempts to purify the compound failed, and a small amount of reduced product, obtained as a side product, couldn't be separated from the mixture.

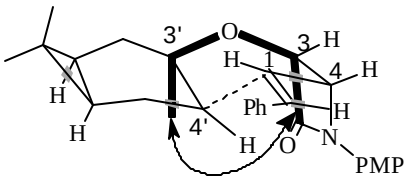
Discussion Regarding Possible Mechanism

A typical radical cyclization involves generation of a radical at proradical site. A radical trap quenches the radical and it again generates a second radical. This radical, in turn, is reduced by hydride supplied by tin hydride and the process terminates *(Scheme 22).*

Scheme 22



A very high diastereoselectivity in this cyclisation is intriguing. The stereochemical insights into the radical system reveal that the 3C-O-3′O bond is highly flexible and can attain variable torsion angle. The central substituted hydropyran ring also can take a variable conformation. When the styryl double bond is 'β' with respect to the radical center (Fig. 8), a system attains a conformation in which the central hydropyran has a boat T.S.



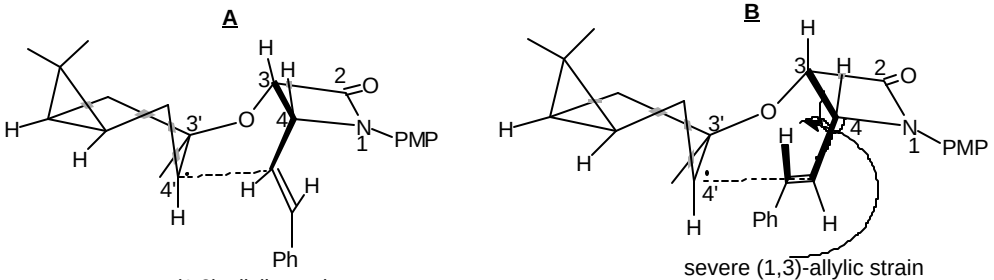
strong 1,3 diaxial interactions
energetically unfavorable conformation

Fig. 8

Also, the *b*-lactam ring and the 4′-Me attain energetically unfavorable 1, 3 diaxial positions. In all, these factors make the total system energetically unfavorable and is not a preferred route for the radical cyclization.

In other case, the styryl double bond can be oriented as shown *(Scheme 23)*.

Scheme 23



no (1,3)-allylic strain
energetically favorable T. S.

severe (1,3)-allylic strain
highly strained T. S.
energetically unfavorable T. S.

With the styryl double bond inwards (T. S. **B**), there exists a strong 1,3-angle strain among the *b*-lactam ring (C3-C4 bond) and the H of the styryl double bond. In other case, i. e. with outwards orientation of the styryl double bond (T. S. **A**), the double bond is far away from the plane of the *b*-lactam ring. There exists no steric interactions and energetically is a favorable transition state.

This leads to the attack in 6-exo fashion. The conformational constraints imposed by the system are strong enough to allow only one product to be formed under the radical conditions.

3.4 : Summary

A series of novel *b*-lactams with 4-styryl substituents were successfully used as precursors for the free radical cyclisation. On treatment with Bu_3SnH in refluxing benzene they smoothly cyclized diastereospecifically by *6-exo-trig*, heptenyl cyclisation in excellent yields. The products were multicyclic *b*-lactams with *3 : 6 : 6: 4* backbone. In almost all the cases the products were separated from the tin impurity easily by column chromatography. The major and minor diastereomers were cyclised separately and the stereochemical outcome of the cyclization was studied. The absolute stereochemistry of the tetracyclic ring system (3 : 6 : 6 : 4) thus synthesized was determined from the single crystal X-ray analysis as well as the spatial connectivity pattern of the ROESY NMR.

3.5 : Experimental

***General Procedure for the Radical Cyclisation of* 1.14d-i, l *& / or* 1.15d-i, l**:

***Preparation of* 3.01d-i, l** *& / or* **3.02d-i, l**

Bu_3SnH (0.40 mL, 1.5 mmol) was added over 5 minutes to a refluxing solution of *b*-lactam (1 mmol) and AIBN (15 mg, 0.09 mmol) in benzene (15 mL). The reaction mixture was further refluxed for 1-2 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate) to give pure cyclized products **3.01d-i, l** &/or **3.02d-i, l**.

***Preparation of (2aR, 3aR, 4aS, 5aR, 6aR, 7R, 7aS) 7-Benzyl-1-(4-methoxyphenyl)-3a,5,5-trimethyl-perhydrocyclopropa[6,7]chromeno[3,2-b]azet-2-one* 3.01d**

b-Lactam **1.14d** (0.508 g, 1 mmol) on reaction with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol), for ½ h, furnished *b*-lactam **3.01d** (0.410 g, 95%) as a foamy solid.

M.P. : 58-59°C.

$[\alpha]^D_{25}$: -8.75° (c 6.16, CH_2Cl_2).

IR (cm^{-1}) : 1740.

^1H NMR : δ 0.35-0.50 (m, 2H), 0.95 (s, 3H), 1.0 (s, 3H), 1.0-1.05 (m, 1H), 1.35-1.42 (m, 1H), 1.43 (s, 3H), 1.55-1.75 (m, 3H), 2.43-2.55 (m, 1H), 2.95 (d, *J* = 7.8 Hz, 2H), 3.78 (s, 3H), 3.95 (dd, *J* = 1.70, 5.60 Hz, 1H), 4.94 (d, *J* = 5.60 Hz, 1H), 6.82 (dd, *J* = 2, 9 Hz, 2H), 7.15 (dd, *J* = 2, 9 Hz, 2H), 7.26-7.28 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR : δ 14.77, 18.51, 19.84, 21.85, 26.59, 27.98, 31.37, 32.61, 38.95, 40.13, 40.35, 52.46, 53.13, 55.13, 75.43, 77.04, 114.35, 118.47, 126.25, 128.41, 128.65, 130.38, 139.58, 156.22, 166.43.

MS [m/z (%)] : 432 (M+1, 2), 431 (M^+, 5), 93 (100).

Microanalysis : M.F. $C_{28}H_{33}NO_3$.

Calculated	C : 77.91	H : 7.71	N : 3.25
Obtained	C : 77.98	H : 7.60	N : 3.43

Preparation of (2aS, 3aR, 4aS, 5aR, 6aR, 7S, 7aR) 7-Benzyl-1-(4-methoxyphenyl)-3a,5,5-trimethyl-perhydrocyclopropa[6,7]chromeno[3,2-b]azet-2-one **3.02d**

b-Lactam **1.15d** (0.508 g, 1 mmol) on reaction with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for ½ h, furnished *b*-lactam **3.02d** (0.410 g, 95%) as a white solid.

M.P. : 197°C.

$[\alpha]^{D}_{25}$: +22.6° (c 1.25, CH_2Cl_2).

IR (cm^{-1}) : 1740.

^1H NMR : δ 0.35-0.47 (m, 2H), 0.65-0.75 (m, 1H), 1.0 (s, 3H), 1.06 (s, 3H), 1.18 (s, 3H), 1.20-1.25 (m, 1H), 1.30-1.35 (m, 1H), 1.59-1.63 (m, 1H), 1.89-1.94 (m, 1H), 2.40-2.45 (m, 1H), 2.70 (dd, *J* = 12.5, 13.5 Hz, 1H), 3.13 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.78 (s, 3H), 3.94 (dd, *J* = 4.6, 9.4 Hz, 1H), 4.75 (d, *J* = 4.6 Hz, 1H), 6.87 (dd, *J* = 2, 9 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 7.18-7.28 (m, 3H), 7.38 (d, *J* = 9 Hz, 2H).

^{13}C NMR : δ 14.87, 17.61, 18.49, 18.67, 21.49, 27.14, 28.12, 29.49, 31.06, 36.73, 38.69, 39,32, 55.53, 55.89, 74.03, 77.66, 119.84, 126.21, 128.24, 128.41, 130.87, 138.57, 156.55, 163.99.

MS [m/z (%)] : 432 (M^++1, 11), 431 (M^+, 38), 165 (100).

Microanalysis : M.F. $C_{28}H_{33}NO_3$.

Calculated	C : 77.91	H : 7.71	N : 3.25
Obtained	C : 77.88	H : 7.84	N : 3.47

Preparation of (2aS, 3aR, 4aS, 5aR, 7R, 7aR) 7-Benzyl-3a,5,5-trimethyl-1-1-phenyl)-perhydrocyclopropa[6,7]chromeno[3,2-b]azet-2-one **3.02e**

b-Lactam **1.15e** (0.479 g, 1 mmol) on reaction with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for 1h, furnished *b*-lactam **3.02e** (0.321 g, 80%) as a white solid.

M.P. : 186-188°C.

$[\alpha]^{D}_{25}$: +20.53° (c 0.76, CH_2Cl_2).

IR (cm^{-1}) : 1379, 1598, 1755, 3018.

^1H NMR : δ 0.25-0.55 (m, 2H), 0.55-0.82 (m, 1H), 1.0, 1.07 (2s, 6H), 1.20-1.40 (m, 1H), 1.52-1.75 (m, 1H), 1.85-2.05 (m, 1H), 2.35-2.55 (m, 1H), 2.75 (dd, *J* = 12.7, 13.2 Hz, 1H), 3.20 (dd, *J* = 4.9, 13.2 Hz, 1H), 4.02 (dd, *J* = 4.9, 9.3 Hz, 1H), 4.78 (d, *J* = 4.9 Hz, 1H), 7.0-7.6 (m, 10H).

^{13}C NMR : δ 14.95, 17.68, 18.75, 21.52, 27.22, 28.19, 29.56, 36.92, 38.69, 39.43, 55.76, 74.07, 77.77, 118.15, 124.57, 126.32, 128.31, 128.52, 129.05, 137.73, 138.60, 164.50.

MS [m/z (%)] : 401 (M^+, 12), 191 (100), 95 (46), 91 (33).

Microanalysis : M.F. $C_{27}H_{31}NO_2$.

Calculated	C : 80.76	H : 7.78	N : 3.49
Obtained	C : 80.51	H : 7.53	N : 3.65

(2aS, 3aR, 4aS, 5aR, 7S, 7aR) & (2aS, 3aR, 4aS, 5aR, 7S, 7aR) 7-Benzyl-3a,5,5-trimethyl-1-propyl-perhydrocyclopropa[6,7]chromeno[3, 2-b]azet-2-one **3.01f** & **3.02f**

A diastereomeric mixture of **1.14f** & **1.15f** (0.445 g, 1 mmol) on refluxing with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for 1h, furnished diastereomeric mixture of **3.01f** & **3.02f** (0.239 g, 65%) as a gum.

$[\alpha]^{D}_{25}$: +20.14° (c 1.44, CH_2Cl_2).

IR (cm^{-1}) : 1215, 1743, 2873, 3018.

^1H NMR : δ 0.35-0.65 (m, 2H), 0.75 (t, *J* = 8 Hz, 3H), 1.03, 1.04 (s, 6H), 1.32 (s, 3H), 0.65-2.20 (m, 9H), 2.67 (dd, *J* = 8, 14 Hz, 1H), 2.80-3.25 (m, 3H), 3.43 (dd, *J* = 4, 8 Hz, 1H), 4.75 (d, *J* = 4 Hz, 1H), 7.1-7.5 (m, 5H).

^{13}C NMR : δ 11.22, 14.80, 18.75, 19.82, 20.91, 21.37, 25.14, 28.23, 28.72, 31.56, 39.21, 41.47, 42.22, 43.26, 55.88, 74.47, 78, 126.49, 128.39, 128.63, 129.18, 139.50, 167.94.

MS [m/z (%)] : 369 (M^++2, 0.1), 367 (M^+, 0.1), 191 (48), 95 (88), 91 (100).

Microanalysis : M.F. $C_{24}H_{33}NO_2$.

:	Calculated	C : 78.43	H : 9.05	N : 3.81
	Obtained	C :	H :	N :

(2aR, 3aR, 4aS, 5aR, 7R, 7aS) & (2aS, 3aR, 4aS, 5aR, 7R, 7aR) 7-Benzyl-1-cylco-hexyl-3a,5,5-trimethylperhydrocyclopropa[6,7]chromeno[3,2-b]azet-2-one **3.01g** *&* **3.02g**

A diastereomeric mixture of **1.14g** & **1.15g** (0.486 g, 1 mmol) on refluxing with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for 2h, furnished diastereomeric mixture of **3.01g** & **3.02g** (285 g, 70%) as a gummy solid.

$[\alpha]^{D}_{25}$: +29.01° (c 1.02, CH_2Cl_2).

IR (cm^{-1}) : 1495, 1741, 3163.

^1H NMR : δ 0.3-0.7 (m, 2H), 0.98, 1.02, 1.04 (3s, total 6H), 1.18, 1.32 (2s, total 3H), 0.80-2.10 (m, 15H), 2.15-2.50 (m, 1H), 2.50-3.05 (m, 2H), 3.38 & 3.48 (dd, *J* = 4.3, 9.3 Hz & dd, *J* = 4.8, 5.3 Hz respect. total 1H), 4.5 & 4.77 (d, *J* = 4.3 Hz & d, *J* = 4.8 Hz respect. total 1H), 7.05-7.5 (m, 5H).

^{13}C NMR : δ 14.88, 17.69, 18.44, 18.55, 18.69, 19.79, 21.27, 21.87, 25.03, 25.12, 25.17, 25.30, 25.98, 27.22, 28.21, 29.52, 29.73, 30.78, 30.81, 31.07, 31.59, 31.94, 36.54, 39.32, 39.63, 39.66, 41.25, 42.99, 53.44, 53.67, 54.49, 55.74, 73.52, 73.92, 76.89, 77.42, 126.42, 128.37, 128.63, 128.80, 129.07, 139.0, 139.67, 166.31, 168.04.

MS [m/z (%)] : 409 (M^++2, 2), 408 (M^++1, 0.05), 407 (M^+, 0.05), 191 (100).

Microanalysis : M.F. $C_{27}H_{37}NO_2$.

Calculated	C : 79.56	H : 9.15	N : 3.44
Obtained	C : 80.01	H : 8.90	N : 3.18

***Preparation of (2aS, 3aR, 4aS, 5aR, 6aR, 7S, 7aR) 7-Benzyl-1-(tert butyl)-3a,5,5-trimethylperhydrocyclopropa[6,7]chromeno[3, 2-b]azet-2-one* 3.02h**

b-Lactam **1.15h** (0.459 g, 1 mmol) on reaction with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for 1h, furnished *b*-lactam **3.02h** (0.305 g, 80%) as a white solid.

M.P. : 132-134°C.

$[\alpha]^{D}_{25}$: +21.79° (c 0.78, $CHCl_3$).

IR (cm^{-1}) : 1727.

^1H NMR : δ 0.25-0.80 (m, 3H), 0.97 (s, 3H), 1.04 (s, 3H), 1.16 (s, 3H), 0.89-1.78 (m, 3H), 1.44 (s, 9H), 1.78-1.96 (m, 1H), 2.17-2.40 (m, 1H), 2.65 (dd, *J* = 12.8, 13.6 Hz, 1H), 3.28 (dd, *J* = 4.4, 13.7 Hz, 1H), 3.44 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 7.12-7.43 (m, 5H).

^{13}C NMR : δ 14.95, 17.76, 18.56, 18.79, 21.48, 27.67, 28.21, 28.81, 29.35, 36.15, 38.59, 39.26, 53.77, 56.03, 73.16, 77.34, 126.34, 128.26, 128.61, 139.17, 166.54.

MS [m/z (%)] : 383 (M^++2, 1.5), 382 (M^++1, 1), 191 (100), 173 (30), 95 (65), 91 (53).

Microanalysis : M.F. $C_{25}H_{35}NO_2$.

Calculated	C : 78.70	H : 9.25	N : 3.67
Obtained	C : 78.34	H : 9.01	N : 3.40

***Preparation of (1¢R, 2aR, 3aR, 4aS, 5aR, 6aR, 7R, 7aS) & (1¢R, 2aS, 3aR, 4aS, 5aR, 6aR, 7S, 7aR) 7-Benzyl-3a,5,5-trimethyl-1-(1¢-phenylethyl)perhydrocyclopropa[6,7]-chromeno[3, 2-b]azet-2-one* 3.01i** & **3.02i**

The diastereomeric mixture of *b*-lactams **1.14i** & **1.15i** (0.507 g, 1 mmol) on treatment with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for 2h, furnished a diastereomeric mixture of *b*-lactams **3.01i** & **3.02i** (0.326 g, 76%) as a white solid. One of the diastereomers **3.02i** was separated by fractional crystallization. The data for which is given below:

(1′R, 2aS, 3aR, 4aS, 5aR, 6aR, 7S, 7aR) 7-Benzyl-3a,5,5-trimethyl-1-[1′-phenylethyl]-perhydrocyclopropa[6,7]chromeno[3, 2-b]azet-2-one **3.02i**

It was isolated as a white solid.

M.P. : 208°C.

$[\alpha]^{D}_{25}$: +24.07° (c 0.55, CH_2Cl_2).

IR (cm^{-1}) : 1760.

^{1}H NMR : δ 0.4-0.55 (m, 2H), 0.67-0.80 (m, 1H), 0.98 (s, 6H), 1.23 (s, 3H), 1.14-1.32 (m, 2H), 1.69 (dd, *J* = 2.5, 7.0 Hz, 3H), 1.65-1.82 (m, 2H), 1.83-1.93 (m, 1H), 2.53 (dd, *J* = 5.5, 14.5 Hz, 1H), 2.76 (dd, *J* = 5.5, 14.5 Hz, 1H), 3.38 (dd, *J* = 5, 6.9 Hz, 1H), 4.7 (d, *J* = 5.0 Hz, 1H), 4.79 (q, *J* = 7 Hz, 1H), 6.78 (dd, *J* = 2, 7 Hz, 2H), 7.12-7.5 (m, 8H).

^{13}C NMR : δ 14.83, 18.66, 19.70, 20.28, 21.11, 25.58, 28.20, 29.24, 31.55, 37.56, 40.77, 42.20, 53.43, 54.81, 74.08, 77.23, 126.71, 126.98, 127.59, 128.30, 128.83, 129.30, 138.78, 140.62, 168.32.

MS [m/z (%)] : 431 (M^++2, 0.1), 191 (100), 105 (30), 95 (28).

Microanalysis : M.F. $C_{29}H_{35}NO_2$.

Calculated	C : 81.08	H : 8.21	N : 3.26
Obtained	C : 80.79	H : 8.45	N : 3.52

Preparation of (2aR, 3aR, 4aS, 5aR, 6aR, 7S, 7aR) 7-Ethyl-1-phenyl-3a,5,5-trimethylperhydrocyclopropa[6,7]chromeno[3,2-b]azet-2-one **3.01l**

b-Lactam **1.14l** (0.417 g, 1 mmol) on reaction with Bu_3SnH (0.40 mL, 1.5 mmol) in the presence of AIBN (16 mg, 0.1 mmol) for ½ h, furnished *b*-lactam **3.01l** (0.309 g, 91%) as a white solid.

M.P. : 116-118°C.

$[\alpha]^{D}_{25}$: +79.80°(c 0.99, CH_2Cl_2).

IR (cm^{-1}) : 1400, 1520, 1620, 1770, 2950, 3040.

^{1}H NMR : δ 0.35-0.65 (m, 2H), 0.65-1.20 (m, 5H), 1.0, 1.02 (2s, 6H), 1.20-2.00 (m, 6H), 1.36 (s, 3H), 4.11 (dd, *J* = 5.8, 6.2 Hz,

1H), 4.93 (d, *J* = 5.3 Hz, 1H), 7.05-7.55 (m, 5H).

^{13}C NMR : δ 9.52, 14.83, 18.73, 19.96, 20.95, 23.22, 24.60, 28.25, 29.87, 31.40, 38.89, 40.94, 53.51, 74.62, 77.45, 124.38, 128.95, 129.11, 137.53, 166.07.

MS [m/z (%)] : 341 (M^++2, 13), 340 (M^++1, 36), 339 (M^+, 25), 311 (100), 283 (47), 267 (65), 220 (61), 191 (63), 175 (95), 135 (49), 121 (52), 95 (71), 57 (81).

Microanalysis : M.F. $C_{22}H_{29}NO_2$.

Calculated	C : 77.84	H : 8.61	N : 4.13
Obtained	C : 77.58	H : 8.32	N : 3.85

***Preparation of* 1.14m & 1.15m**

Imine **1.13m** (0.235 g, 1 mmol) on reaction with acid chloride **1.12a** (0.617 g, 2 mmol) in the presence of base Et_3N (0.84 mL, 6 mmol) in dichloromethane (20 mL) provided a diastereomeric mixture of *b*-lactams **1.14m** & **1.15m**. One of the diastereomers **1.15m** was isolated in pure form by fractional crystallization from pet ether/dichloromethane. The spectral and analytical data for which is given below.

***(3S,4R,1¢S,3¢R,4¢R,6¢R) 3-[4-Bromo-3,7,7-trimethylbicyclo[4.1.0]hept-3-yloxy]-1-(4-methoxyphenyl)-4-(2-phenyl-1-ethynyl)-2-azetanone* 1.15m**

M.P. : 169°C.

$[\alpha]^{D}_{25}$: -156.74°(c 0.43, CH_2Cl_2).

IR (cm^{-1}) : 1723, 2234.

^{1}H NMR : δ 0.60-0.80 (m, 2H), 0.95 & 0.97 (2s, 6H), 1.53 (s, 3H), 1.67 (dd, *J* = 4, 14 Hz, 1H), 2.28 (dd, *J* = 9.50, 14 Hz, 1H), 2.35-2.47 (m, 2H), 3.79 (s, 3H), 4.15 (t, *J* = 9 Hz, 1H), 4.92 (d, *J* = 4.4 Hz, 1H), 5.31 (d, *J* = 4.4 Hz, 1H), 6.88 (d, *J* = 8 Hz, 2H), 7.2-7.57 (m, 7H).

^{13}C NMR : δ 15.46, 17.92, 18.62, 19.57, 21.37, 28.43, 31.81, 32.40, 51.70, 55.45, 59.57, 77.53, 80.37, 82.72, 89.05, 114.41, 118.60, 122.16, 128.38, 128.85, 130.69, 131.87, 136.50, 163.59.

MS [m/z (%)] : 509 (M^++2, 1.5), 508 (M^++1, 2), 507 (M^+, 3), 236 (100), 93 (45), 134 (48).

Microanalysis	:	M.F. $C_{28}H_{30}BrNO_3$.			
		Calculated	C : 66.14	H : 5.95	N : 2.75
		Obtained	C : 66.01	H : 6.11	N : 3.01

***Preparation of* 3.02m**

Bu_3SnH (0.54 mL, 1.5 mmol) in toluene (10 mL) was added by syringe pump, to a refluxing solution of β-lactam **1.15m** (0.430 g, 1 mmol) and AIBN (15 mg, 0.09 mmol) in toluene (15 mL) over 5 h. The reaction mixture was further refluxed for 1-2 h. After the completion of reaction (TLC) solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate) to get **3.02m** (0.300 g, 70%) as a foamy solid.

M.P.	:	79-81°C.
$[\alpha]^D_{25}$	:	+8.88°(c 1.74, $CHCl_3$).
IR (cm^{-1})	:	1512, 1755, 2937, 3018.
^{1}H NMR	:	δ 0.40-0.67 (m, 2H), 0.99 & 1.06 (2s, 6H), 1.14 (s, 3H), 0.85-1.90 (m, 4H), 2.28 (dd, *J* = 4.8, 13.2 Hz, 1H), 3.65 (s, 3H), 4.32 (d, *J* = 3.9 Hz, 1H), 5.32 (d, *J* = 3.9 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 2.9, 8.3 Hz, 1H), 7.0-7.55 (m, 8H).

3.6 References

1. Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.
2. For some references on the work of Kharasch, see: (a) Kharasch, M. S.; White, P. C.; Mayo, F. R. *J. Org. Chem.* **1938**, *3*, 33. (b) Kharasch, M. S.; Margolis, E.; White, P. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1937**, *59*, 1405. (c) Kharasch, M. S., Berkman, M. G. *J. Org. Chem.* **1941**, *6*, 810.
3. For references, see: (a) Julia, M. *Pure Applied Chem.* **1974**, *40*, 553. (b) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
4. Lamb, R. C.; Ayers, P. W.; Toney, M. K. *J. Am. Chem. Soc.* **1963**, *85*, 3483.
5. Beckwith, A. L. J.; Ingold, K. C. In *Rearrangments in Ground and Excited States*; Mayo, P. de., Ed.; Academic: New York, 1980; Vol. 1, p 161.
6. Walling, C. In *Free Radicals in Solution;* Wiley: New York, 1957.
7. Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
8. Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.
9. (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. (c) Giese, B.; Kopping, B.; Göbel, J.; Dickhaut, G.; Thoma, G.; Trach, F. *Org. React. (NY)* **1996**, 48, 301.
10. Jasprese, C. P.; Curran, D. P.; Feviz, T. L. *Chem. Rev.* **1991**, 91, 1237.
11. For references, see: (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Easton, J. C.; Lawrence, Serelis, A. K. *Aus. J. Chem.* **1983**, *36*, 545.
12. For recent references on bacterial resistance, see: (a) Hook, V. *Chem. Br.* 1997, 33, 34. (b) Nicoolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333. (c) Spratt, B. G. *Science* **1994**, *264*, 388-393.
13. Mustafi, D.; Makinen, M. W. *J. Am. Chem. Soc.* **1995**, *117*, 6739.
14. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689.
15. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2693.
16. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1982**, *23*, 2505.
17. Bosch, E.; Bachi, M. D. *J. Org. Chem.* **1993**, *58*, 5581.
18. For a review on Syntheses, stabilities, and bioactivities of carbacephems, see: Cooper, R. D. G. In *The Chemistry of Beta-Lactams*; Page, M. I., Ed.; Chapman

and Hall: London, 1992; Chapter 8.

19. Kametani, T.; Shih, D. C.; Itoh, A.; Maeda, S.; Honda, T. *Heterocycles* **1988**, *27*, 875.
20. Bachi, M. D.; Demesmaeker, A.; Stevenart-Demesmaeker, N. *Tetrahedron Lett.* **1987**, *28*, 2637.
21. Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 78.
22. Crocker, P. J.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 6176-6179.
23. (a) Joyeau, R.; Yadav, L. D. S.; Wakselman, M. J. *J. Chem. Soc., Perkin Trans-I* **1987**, 1899-1907. (b) Gilchrist, T. L.; Graham, K.; Coutton, S. *Tetrahedron Lett.* **1995**, *36*, 8693-8696.
24. Finkelstein, J.; Holden, K. G.; Perchonock, C. C. *Tetrahedron Lett.* **1978**, *19*, 1629.
25. Just, C.; Sacripante, G. *Can. J. Chem.* **1987**, *65*, 104.
26. Banik, B. K.; Subbaraju, G. V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363-1366.
27. Alcaide, B.; Moreno, A. M.; Rodriguez-Vicente, A.; Sierra, M. A. *Tetrahedron Asymm.* **1996**, *7*, 2203.
28. Alcaide, B.; Rodriguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 6589-6592.
29. Alcaide, B.; Rodriguez-Campos, I. M.; Rodriguez-Lopez, J.; Rodriguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377-5387.
30. Cabri, W.; Candiani, I.; Bedeschi, A. *Tetrahedron Lett.* **1992**, *33*, 4783-4786.
31. Beckwith, A. L. J.; Boate, D. R. *J. Org. Chem.* **1988**, *53*, 4339-4348.

Chapter IV

Heterocyclic Ring Formation Using Radicals Derived From Aromatic System

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"I think and think for months and years. Ninety-nine times, the conclusion is false. The hundredth time I am right."

Albert Einstein

4.1 : Introduction

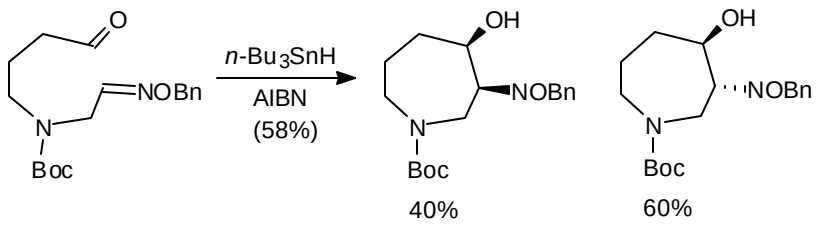
The radical chemistry has continued to attract research interests of organic chemists over the years. However, it has been mostly concentrated around the carbon-based radicals.[1] The studies mostly revolve around the examination and utilisation of carbon centered radicals and their interactions with related carbon based unsaturated systems and alkenes. Heteroatomic acceptors such as carbonyl groups, imines, nitriles, and related systems have received much less scrutiny.[2] After the accumulation of kinetic data and the detailed studies in such type of cyclizations, where heteroatomic acceptors like imines, hydrazones, oxime ethers are used, the picture has started changing dramatically. This is evidenced by a rapidly increasing number of publications, where heteroatomic radical traps are used as a key step in the construction of multicyclic skeletons.[1,2]

The major drawback associated with classical radical cyclisation precursors is the net loss of participating functional groups. This problem does not arise with heteroatomic acceptors, instead, products are generated that retain synthetically useful functionality for subsequent manipulations. If desired, the nitrogen can be removed to afford carbocyclic systems. Among the heteroatomic acceptors, the imines,[3] oxime ethers,[4] hydrazones[5] and nitrile[6] are the most useful and frequently used acceptors.

This strategy is effectively used in the total synthesis of a number of natural products like (-)-balanol,[7] tetrodotoxin,[8] (+)-7-deoxypancratistatin,[9] and opium alkaloids like morphine.[10]

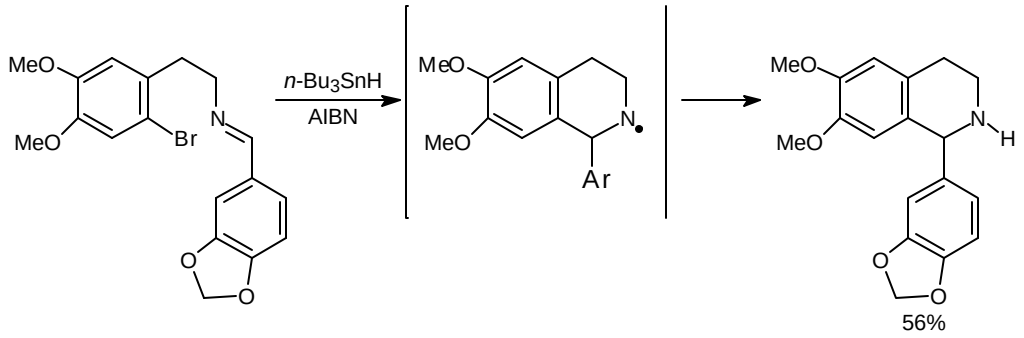
Naito and coworkers have reported both, *cis* as well as *trans* isomers of (-)-balanol. *(Scheme 1).*[7] The use of oxime ether as a radical acceptor was the key step in their strategy.

Scheme 1



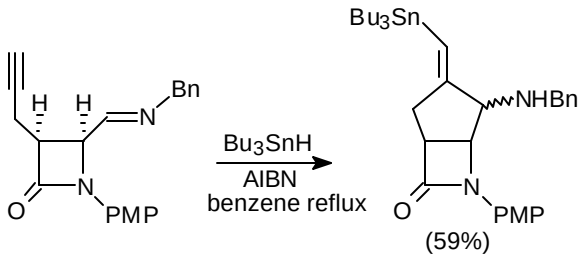
Radical cyclisation involving imine double bond was the key step in the synthesis of cryptostyline alkaloids with isoquinoline skeleton *(Scheme 2)*.[3a]

Scheme 2



Radical cyclisation, in which the appendages to the *b*-lactam core, in the form of heterolytic bonds are used as radical acceptors, is very rare. Recently Alcaide has used the imines derived from 4-formyl-*b*-lactams as radical acceptors in the synthesis of amino bicyclic *b*-lactams (S*cheme 3*).[11] There are very few reports of concise and elaborated work in this area.

Scheme 3



4.2 : Present Work

Generally 6-exo radical cyclisations are not among facile and reactive types of annulations known in the radical chemistry. The 5-exo type of cyclisation is kinetically controlled and thus highly efficient process than the 6-exo cyclisation. Our observation of a highly efficient 6-exo radical cyclisation in case of (+)-3-carene derived *b*-lactams with bromine atom of carane part as a radical generator and styryl double bond as a

radical acceptor was intriguing and promising (which is discussed in detail in earlier Chapter-III).

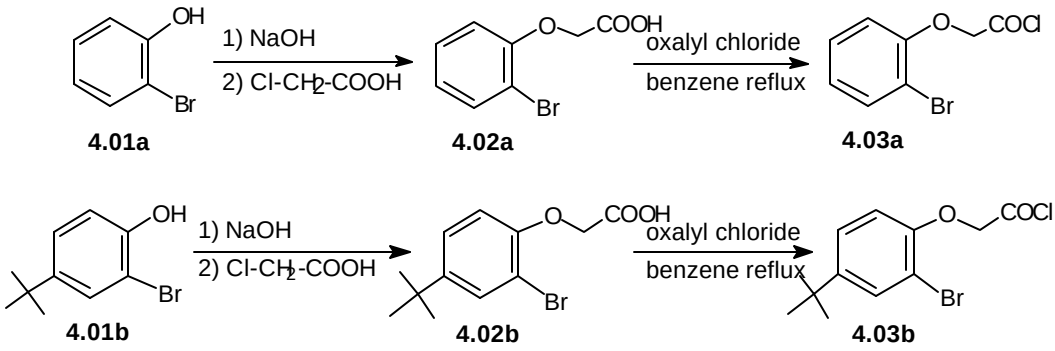
These results prompted us to use an aryl system in place of carane skeleton to get polycyclic ring frame anchored on aromatic ring. This chapter describes preparation of required *b*-lactam systems with appropriate radical generator and acceptor, using analogous aromatic halo acids by ketene-imine cycloaddition reaction. These systems were used to study the regioselectivity as well as efficiency of their radical cyclisation, which eventually led to the development of methodology for the synthesis of multicyclic ring systems. The other aim was to use and examine the efficiency of imino double bond as a radical trap in place of styryl double bond.

4.3 : Results & Discussion

***Preparation of acid chlorids* 4.03a-b**

o-Bromo phenol **4.01a** on treatment with chloroacetic acid in the presence of NaOH led to the formation of **4.02a** in around 60% yield (*Scheme 4*).

Scheme 4

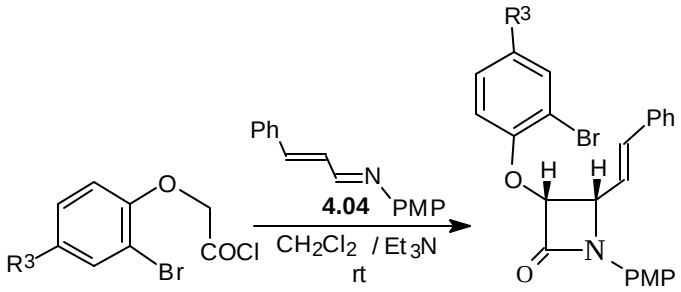


In another reaction, 4-tert-butylphenol on reaction with Br_2 in $CHCl_3$ was selectively brominated at ortho position to give 2-Bromo-4-tert-butylphenol (**4.01b**) in good yield. The phenol **4.01b** on treatment with chloroacetic acid, similarly got converted to the corresponding acid derivative **4.02b** in moderate yield. The acids **4.02a,b** on refluxing with oxalyl chloride in benzene for 2 h gave corresponding acid chlorides **4.03a** & **4.03b**. These acid chlorides were used as such without further purification.

***Preparation of* 4.05a,b**

The acid chlorides **4.03a,b** on cycloaddition with imine (**4.04**) in the presence of Et_3N offered *cis*-*b*-lactams **4.05a,b** in almost quantitative yields (*Scheme 5*).

Scheme 5



4.03a,b

4.03a, R3 = H

4.03b, R3 = t-butyl

(±)- **4.05a,b**

4.05a, R3 = H

4.05b, R3 = t-butyl

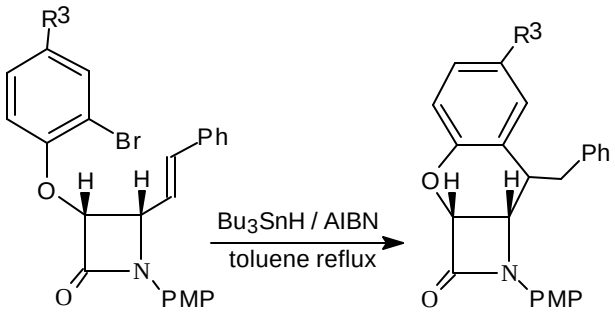
In the IR spectrum, the *b*-lactam **4.05a** showed a peak at 1752 cm^{-1}, typical of amide carbonyl. Molecular ion peak was present in the mass spectrum at 449 (0.1%). The ^1H NMR of **4.05a** showed a singlet corresponding to the methoxy peak of *p*-anisyl group at 3.79. A dd at 5.02 (J = 4.9, 8.3 Hz) and a doublet at 5.51 (J = 4.9 Hz) could be assigned to the H-4 & H-3 of the *b*-lactam respectively. A dd at 6.48 was due to the olefinic proton from the styryl double bond, while the aromatic protons and one of the olefinic protons from the styryl double bond resonated as multiplets between the region 6.7 to 7.7.

In case of **4.05b**, IR showed a *b*-lactam peak at 1745 cm^{-1}. The ^1H NMR showed a *b*-lactam proton H-3, at 5.48 as a doublet (J = 5.4 Hz) & H-4 at 5.0 as a dd (J = 5.4, 8.8 Hz). *tert*-Butyl group appeared as a singlet at 1.25.

Radical Cyclisation of the 4-Styryl b-Lactams

The addition of a solution of Bu_3SnH and catalytic AIBN in toluene by syringe pump to the refluxing solution of the bromo-substituted *b*-lactams **4.05a** & **4.05b** in toluene (*Scheme 6*) gave cyclic product in good yields.

Scheme 6



(±)- **4.05a,b** (±)- **4.06a,b**

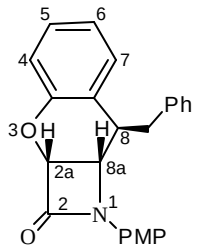
4.05a, R3 = H **4.06a**, R3 = H

4.05b, R3 = t-butyl **4.06b**, R3 = t-butyl

The product obtained from the cyclisation of **4.05a** was purified by crystallization from pet ether/dichloromethane system. A small amount of reduced product (5%) was also obtained as a side product, which showed a dd at 6.5 in ^{1}H NMR, typical of styryl double bond.

The cyclized product **4.06a** was obtained as a crystalline solid, with mp 146-148°C. The molecular ion peak of the cyclized product was observed at 371 (4%) in the mass spectrum. The IR spectrum showed a peak at 1751 cm^{-1}, which confirmed the presence of *b*-lactam ring.

The ^{1}H NMR spectrum showed benzylic protons of the cyclized ring as a doublet at 2.95, with J = 8.3 Hz. The secondary proton H-8 adjacent to the benzylic proton, appeared at 3.65 as a triplet with J = 8.3 Hz, indicating almost no coupling with the H-8a proton of the *b*-lactam ring. The *b*-lactam proton H-8a, resonated as a doublet at 4.55, with J = 5.3 Hz. The other *b*-lactam proton H-2a, resonated as a doublet at 5.40, with J = 5.3 Hz. The methoxy proton of the *p*-anisyl group appeared as a singlet at 3. 85. The aromatic protons appeared in the region 6.6 to 7.6.

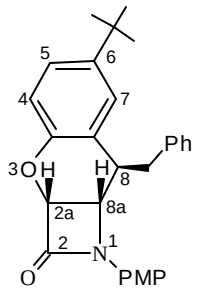


(±)- **4.06a**

To establish the 2D connectivity among the protons, Decoupling Experiments were carried out. The *b*-lactam protons as well as the benzylic and the ring junction protons were decoupled and from the ^{1}H NMR pattern the connectivity was confirmed.

The cyclized product **4.06b**, was a solid. However, it was difficult to remove the tin impurities from it, after repeated crystallization. The IR spectrum showed a peak at 1747 cm^{-1}, typical of *b*-lactam ring. The molecular ion peak at 427 (4%), was observed in the mass spectrum.

The ^1H NMR spectrum showed a singlet at 1.12 corresponding to the 9H of the *tert*-butyl group at C-6. The benzylic protons were diastereotopic and appeared at 2.90 (dd, J = 8.3, 13.5 Hz) & 3.0 (dd, J = 8.3, 13.5 Hz). The proton H-8 appeared as a triplet (merged dd) at 3.5 with J = 8.3 Hz. A singlet at 3.75 was seen due to the methoxy group of the PMP moiety. The *b*-lactam proton H-2a appeared as a doublet at 4.57 with J = 5.4 Hz, typical of *cis b*-lactam. The other *b*-lactam proton H-8a appeared at 5.4 as a doublet, with J = 5.4 Hz. Aromatic protons resonated in the region between 6.56-7.4.



(±)- **4.06b**

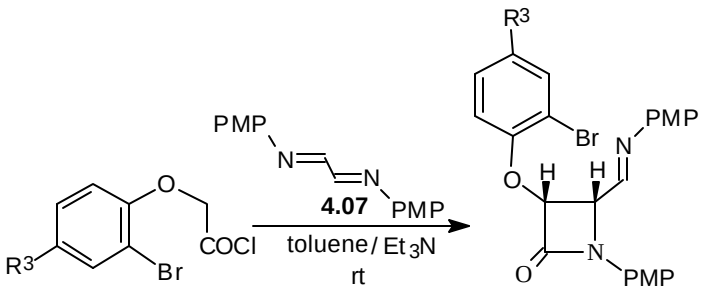
Decoupling Experiments were carried out to establish the connectivity among adjacent protons. When the *b*-lactam proton H-8a, at 5.4 was decoupled, the doublet due to the H-2a collapsed into a singlet, however, there was no effect on the triplet at 3.5, due to H-8. When the triplet at 3.5 from H-8 was decoupled, the multiplet due to the benzylic protons changed to two doublet, but there was no change in the doublet at 4.57 due to the H-8a. Finally, when the benzylic protons were decoupled, the triplet due to the H-8 changed to bs. All these experiments confirmed the fact that the *b*-lactam proton H-8a and the H-8 proton are not coupled. This indicated t a *syn* relation between H-8a & H-8, which was supported by the literature reports on the similar types of system.

Preparation of Imino b-Lactams

So far we have discussed most of the work using of 4-styryl double bond as a radical acceptor. We thought that it will be interesting to study the use imino group as a heteroatomic radical acceptor in place of styryl double. Therefore, corresponding radical cascades in the form of 4-imino *b*-lactams were synthesized.

The bromo acid chlorides **4.03a** & **4.03b** on treatment with bisimine **4.07** in the presence of Et_3N, reacted smoothly to furnish the imino *cis-b*-lactams **4.08a** & **4.08b** in excellent yields *(scheme 7)*.[12]

Scheme 7



4.03a,b

4.03a, R3 = H

4.03b, R3 = t-butyl

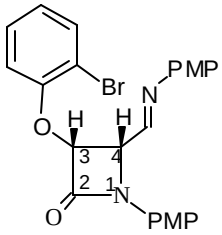
(±) - **4.08a,b**

4.08a, R3 = H

4.08b, R3 = t-butyl

The IR spectrum of **4.08a** showed a peak at 1751 cm^{-1} typical of *b*-lactam amide. A molecular ion peak was present at 480 (2%) in the mass spectrum.

The ^1H NMR spectrum showed two singlets at 3.78 and 3.80 for the two-methoxy groups of the *p*-anisyl moieties. The H-3 and H-4 of the *b*-lactam appeared at 5.6 (d, J = 5.3 Hz) and 5.1 (dd, J = 5.3 & 6.18 Hz) respectively. A high coupling constant indicative of a *cis b*-lactam ring. The aromatic protons appeared as multiplets in the region 6.6 to 7.75. The doublet due to the imine proton resonated at 8.1 with coupling constant J = 6.8 Hz.



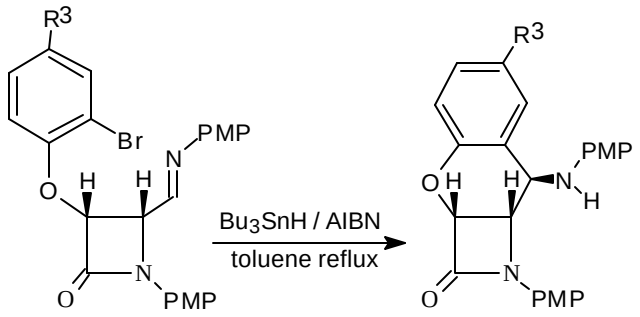
(±)- **4.08a**

The IR spectrum of **4.08b** showed a typical *b*-lactam carbonyl peak at 1759 cm^{-1}. The ^1H NMR spectrum showed a singlet at 1.28 for the three-methyl groups from the *tert-b*utyl moiety, accounting for 9H. Two singlets at 3.78 and 3.81 could be assigned to the two methoxy groups of the *p*-anisyl. The H-3 of the *b*-lactam appeared as a doublet at 5.58 with J = 5.4 Hz, typical of *cis b*-lactam. The H-4 of the *b*-lactam appeared as a dd at 5.07 with J = 5.4 & 7.3 Hz. The aromatic protons were located as multiplets between 6.75-7.60. The imine proton was seen as a doublet at 8.1 with J = 7.3 Hz.

The Radical Cyclisation of Imino b-Lactams

A toluene solution of Bu_3SnH containing catalytic amount of AIBN was slowly added to the refluxing solution of the imino *b*-lactams **4.08a,b** in benzene over 4 h *(Scheme 8).* The reaction was sluggish and most of the unreacted starting material was recovered. However, slow addition of Bu_3SnH using syringe pump improved the yield of cyclized product upto 50% with the recovery of rest of the unreacted starting material. In an interesting variation, when AIBN was used in the 1:1 molar ratio with the starting material (added in small portions), the reaction was over within 4 h and there was no unreacted starting material (TLC, ^{1}H NMR). The imino *b*-lactams were subjected to these modified conditions of radical cyclization and the results were analyzed.

Scheme 8



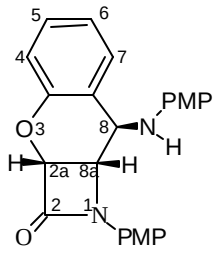
(±)- **4.08a,b** (±) - **4.14a,b**

4.08a, R3 = H **4.14a**, R3 = H

4.08b, R3 = t-butyl **4.14b**, R3 = t-butyl

The crude product obtained from the cyclisation of **4.08a** was purified by flash column chromatography to get a crystalline solid **4.14a**. The IR spectrum of **4.14a** showed a peak at 1751 cm-1 typical of *b*-lactam carbonyl.

The ^{1}H NMR spectrum of **4.14a** showed two singlets at 3.75 & 3.78, assigned to the two-methoxy groups from the two p-anisyl units. A dd at 4.80, with coupling constant of 49 Hz & 1.5 Hz could be accounted to the H-8a of the *b*-lactam. The secondary proton H-8, of the newly formed tetrahydropyran ring appeared as a doublet at 4.85, with J = 1.5 Hz. The doublet at 5.37 (J = 4.9 Hz) was due to the H-2a



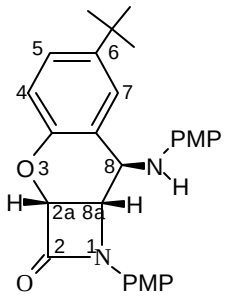
(±)- **4.14a**

of the *b*-lactam ring. A high coupling constant was indicative of *cis* stereochemistry of *b*-lactam. The aromatic protons appeared in the region of 6.6-7.5.

The connectivity among adjacent protons was further established from the Decoupling Experiments. When the doublet at 5.37 was decoupled, the signal at 4.80 changed to a broad singlet. The irradiation at 4.80 affected dd at 5.37 and it was changed to a singlet.

The *b*-lactam **4.14b** was obtained as a gummy liquid in 62% yield. The IR showed a typical amide carbonyl peak at 1750 cm^{-1}.

^{1}H NMR spectrum showed a singlet at 1.2 integrating for 9 H due to tertiary butyl group. Two singlets at 3.78 & 3.82 were due to the two methoxy groups of the *p*-anisyl moiety. The proton H-8 of the substituted pyran ring was seen at 4.84 as a doublet with J = 1.5 Hz. The *b*-lactam proton H-8a appeared at 4.80 as a dd with J = 1.5 & 4.9 Hz. The other *b*-lactam proton H-2a appeared as a doublet, with J = 4.9 Hz at 5.41. A high coupling constant again confirmed the presence of *cis* *b*-lactam. The aromatic protons resonated between 6.60-7.45 region.



(±)- **4.14b**

In the Decoupling Experiments, the irradiation of doublet at 5.41 (H-2a) showed no appreciable effect on H-8, while the dd due to H-8a collapsed into a singlet. The two protons H-8 & H-8a were too close and it was not possible to decouple them selectively. These two protons on simultaneous irradiation changed the doublet due to H-2a to a broad singlet.

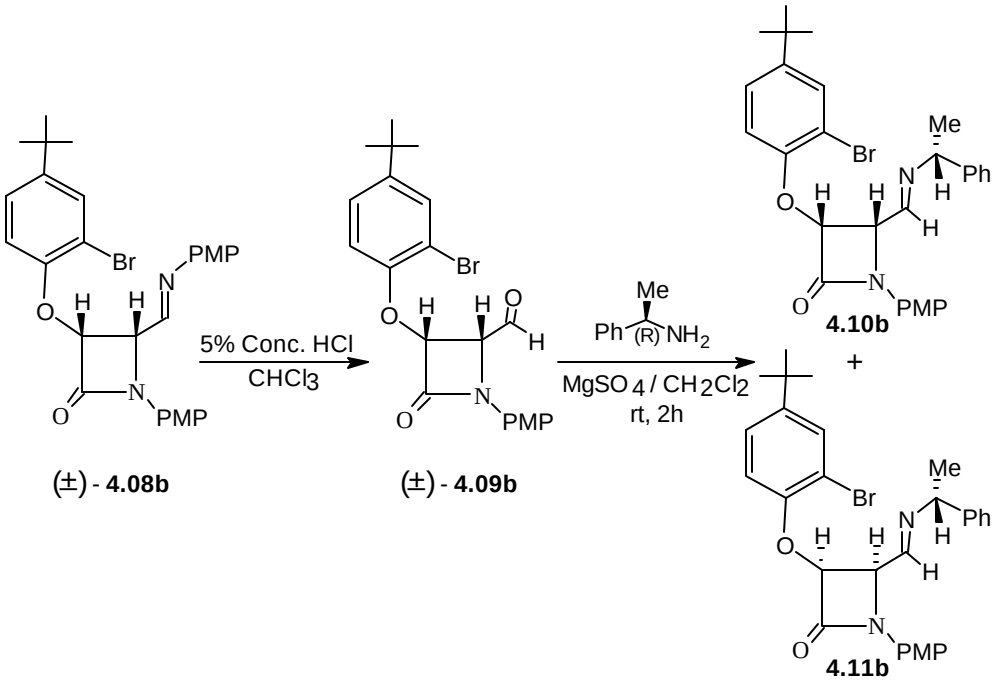
The radical cyclisation with 4-oximo ether derivative of the *b*-lactam was also attempted. However, the yield of cyclized product was very poor and most of the unreacted starting material was recovered.

***Synthesis of* 4.10 & 4.11b**

The *b*-lactam **4.08b** was hydrolyzed by treating with 5% aq. HCl in chloroform. The 4-formyl-*b*-lactam **4.09b** was obtained as a crystalline solid. The 4-formyl-*b*-lactam **4.09b** on reaction with (R)-α-methyl benzylamine in presence of $MgSO_4$ yielded diastereomeric mixture of 4-imino-*b*-lactams **4.10b** & **4.11b** *(Scheme*

9). It was not possible to separate the diastereomers **4.10b** & **4.11b** from the diastereomeric mixture.

Scheme 9

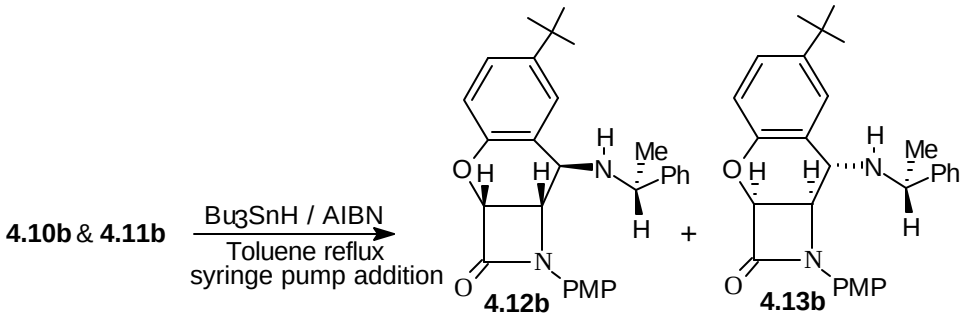


(±) - **4.08b** (±) - **4.09b**

***Radical Cyclisation of* 4.10b & 4.11b**

The diastereomeric mixture of **4.10b** & **4.11b** was subjected to the optimized conditions of radical cyclisation *(Scheme 10)*.

Scheme 10

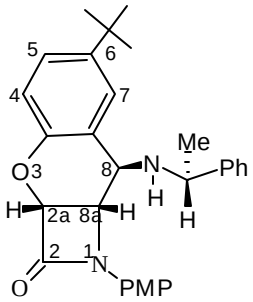


A mixture of Bu_3SnH and AIBN in toluene was added by syringe pump to the refluxing solution of **4.10b** & **4.11b** in toluene. AIBN was used in 1:1 molar ratio and was added in small portions over a period of 4 h. The reaction was over within 6 h &

the crude product was obtained as a gummy liquid which was purified by flash column chromatography.

The ^{1}H NMR spectrum of the crude reaction mixture showed presence of only two diastereomers. The two diastereomers were separated by flash column chromatography to get **4.12b** & **4.13b**. The nonpolar product **4.12b** ($[\alpha]^{D}_{25}$ = -3.98°, c 1.86, $CHCl_3$), showed a *b*-lactam carbonyl peak at 1751 cm^{-1} in its IR spectrum.

The ^{1}H NMR spectrum showed a singlet at 1.23 for the *tert-b*utyl group and a doublet at 1.30 (*J* = 6.3 Hz) for the methyl group from the amine component. The methoxy peak was seen as a singlet at 3.75. H-8 appeared as a singlet at 3.90 while the CH from the amine part appeared as a quartet in the region 3.75 to 3.95. The H-8a of the *b*-lactam was seen as a dd at 4.75, with *J* = 1.5 & 4.9 Hz while H-2a appeared as a doublet with *J* = 4.9 Hz at 5.42. The aromatic protons were seen in the region 6.70-7.50.

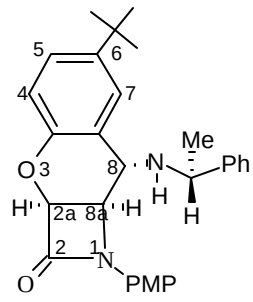


4.12b

The connectivity between the *b*-lactam protons was quite evident as the peak at 5.42 collapsed to a sharp singlet when the *b*-lactam proton H-8a, was decoupled. The bs around 4.10 (H-8) on irradiation, changed the dd of H-8a to a clean doublet with *J* = 4.9 Hz.

The polar diastereomer **4.13b** {$[\alpha]^{D}_{25}$ = +101.26° (c 1.43, $CHCl_3$)}was obtained as a gum, which showed a peak at 1751 cm^{-1} in the IR spectrum, typical of *b*-lactam amide carboyl.

The ^{1}H NMR spectrum showed a singlet at 1.25 for the *tert*-butyl group and a doublet at 1.45 (*J* = 6.9 Hz) for the α-methyl of group from the amine component. Methoxy peak appeared as a singlet at 3.75. The CH of methylbenzylamine part appeared as a quartet at 4.05 with *J* = 6.9 Hz. A bs at 4.12 could be assigned to the pyran ring proton, H-8. The H-8a of the *b*-lactam appeared at 4.76 as a dd, with *J* = 1.5 & 5.4 Hz. The H-2a appeared as doublet at 5.41 with coupling constant *J* = 5.4 Hz. The aromatic protons were seen in the region between 6.7-7.5.



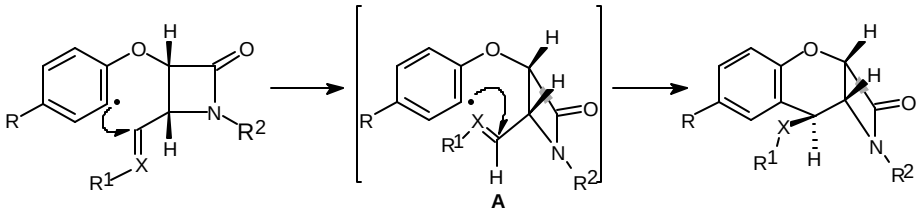
4.13b

In the Decoupling Experiments, when the doublet at 1.45 due to CH_3 was decoupled, the quartet at 4.05 was affected. The decoupling of the bs at 4.12 (H-8) affected the H-4, which was converted to a clean doublet with J = 4.9 Hz. when the dd at 4.76 (H-8a) was decoupled, the doublet at 5.41 (H-2a) was converted to a sharp singlet, while the a broad singlet at 4.12 (H-8) collapsed into a clean singlet. Again, a very low coupling constant (J = 1.5 Hz) between H-8a & H-8 was observed.

Mechanism

A low coupling constant (0-2 Hz) between *b*-lactam proton, H-4 & adjacent proton on the substituted tetrahydropyran ring indicates a trans relationship between them. It is well established fact that the stereochemistry of cyclization is governed by C-4 centre of *b*-lactam ring. As shown in the *Scheme 11*, the 4-imino or 4-styryl double bond is oriented in such a way that there is minimum interaction with *b*-lactam ring plane. The 1,3 diaxial interaction between *b*-lactam plane and X-R^1 are absent in TS-A.

Scheme 11



The other possible mode of cyclization (Fig. 1, TS-B) involves, a severe 1,3 diaxial interactions among *b*-lactam plane and the X-R^1 group.

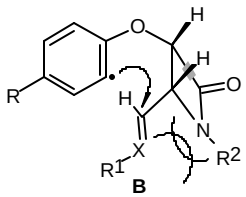


Fig. 1.

The TS – B is energetically unfavorable transition state and doesn't contribute to the formation of cyclized product.

4.4 : Summary

4-Styryl and 4-imino substituted *cis*-*b*-lactams were synthesized in high yields, using ketenes derived from aromatic bromo acids. These *b*-lactams underwent 6-exo-trig radical cyclization to give tricyclic (6:6:4) derivatives. In case of styryl substituted *b*-lactams it was difficult to purify the products from tin impurity. An asymmetric version of this strategy was also accomplished to get chiral, multicyclic *b*-lactams. Decoupling Experiments and ^{1}H NMR spectral pattern was used to confirm the structure of the products.

4.5 : Experimental

***Preparation of* 4.02a**

To a stirred mixture of *o*-bromophenol (0.87 g, 5 mmol) and 3.5 mL of 33% NaOH solution was added chloroacetic acid (2.5 mL, 50%). The flask was loosely corked and heated on a gently boiling water bath for 1 h. Then the reaction mixture was allowed to cool and water (10 mL) was added to it. It was acidified to Congo red with dil. HCl and extracted with ether (30 mL). The etheral extract was washed with water (10 mL) and then extracted with 5% Na_2CO_3 solution (25 mL). The Na_2CO_3 extract was acidified with conc. HCl to get the pure acid **4.02a** as a white solid (0.575 g, 50%).

M. P. : 138-139°C.

***Preparation of* 4.02b**

A procedure similar to **4.02a** was applied. **4.01a** (0.640 g, 5 mmol) was treated with chloroacetic acid (2.5 mL) to get **4.02b** (0.643 g, 45%) as a white solid.

M.P. : 110-111°C.

IR (cm^{-1}) : 1488, 1502, 1737, 2966, 3018, 3000-3500.

^1H NMR : δ 1.30 (s, 9H), 4.72 (s, 2H), 6.80 (d, J = 8 Hz, 1H), 7.20-7.35 (m, 1H), 7.57 (d, J = 2 Hz, 1H), 7.65-8.25 (bs, 1H).

***Preparation of acid chloride* 4.03a**

A solution of acid **4.02a** (1.61 g, 7 mmol) and oxalyl chloride (0.87 mL, 10 mmol) in benzene (25 mL) was refluxed under argon atmosphere for 2.5 h. The reaction mixture was then cooled and benzene removed under reduced pressure to get a crude acid chloride **4.03a**, which was used as such in the next step.

***Preparation of* 4.03b**

Similarly acid **4.02b** (2.86 g, 10 mmol) was treated with oxalyl chloride (1.51 g, 12 mol) to get a crude acid chloride **4.03b**, which was used as such without further purification.

General Procedure for the Preparation of 4-Styryl b-Lactams

To a stirred solution of imine (2 mmol) and Et_3N (1.05 mL, 7.5 mmol) in CH_2Cl_2 (30 mL), acid chloride (3 mmol) in CH_2Cl_2 (25 mL) was added drop-wise at 0°C over ½ h. The reaction mixture was allowed to stir further for 5 h. After completion of the reaction (TLC), the reaction mixture was diluted with CH_2Cl_2 (25 mL), and washed successively with satd. $NaHCO_3$ (2 x 20 mL), water (2 x 20 mL) and finally with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to furnish crude product, which was crystallized from pet ether/ dichloromethane.

***Preparation of 3-(2¢-Bromophenoxy)-1-(4¢¢-methoxyphenyl)-4-[2¢¢¢-phenyl-(E)-1¢¢¢-ethenyl]-2-azetanone* 4.05a**

Imine **4.04** (0.474 g, 2 mmol) on treatment with acid chloride **4.03a** (~0.745 g, 3 mmol) in the presence of Et_3N (1.12 mL, 6.0 mmol) furnished *b*-lactam **4.05a** (0.485 g, 96%) which was purified by crystallization to get a white solid.

M.P. : 140-142°C.

IR (cm^{-1}) : 1510, 1752, 3002.

^1H NMR : δ 3.79 (s, 3H), 5.02 (dd, *J* = 4.9, 8.3 Hz, 1H), 5.51 (d, *J* = 4.9 Hz, 1H), 6.48 (dd, *J* = 8.8, 15.6 Hz, 1H), 6.7-7.7 (m, 14 H).

MS [m/e (%)] : 449 (0.1, M^+), 451 (M+1, 0.1), 300 (15), 236 (18), 129 (100), 115 (29), 77 (17).

Microanalysis : M. F. $C_{24}H_{20}BrNO3$.

Calculated	C : 64.01	H : 4.48	N : 3.11
Obtained	C : 63.85	H : 4.72	N : 2.90

***Preparation of 3-[2¢-Bromo-4¢-(tert. Butyl)phenoxy]-1-(4¢¢-methoxyphenyl)-4-[2¢¢¢-phenyl-(E)-1¢¢¢-ethenyl]-azetan-2-one* 4.05b**

Imine **4.04** (0.474 g, 2 mmol) on treatement with acid chloride **4.03b** (~0.912 g, 2 mmol) in the presence of Et_3N (1.12 mL, 6 mmol) furnished β-lactam **4.05b** (0.97 g, 96%), which was purified by crystallization to get a white solid.

M.P. : 174-175°C.

IR (cm^{-1}) : 1463, 1500, 1745.

^{1}H NMR : δ 1.25 (s, 9H), 3.78 (s, 3H), 5.0 (dd, *J* = 5.4, 8.8 Hz, 1H), 5.48 (d, *J* = 5.4 Hz, 1H), 6.48 (dd, *J* = 8.8, 16.1 Hz, 1H), 6.75-7.70 (m, 13H).

Microanalysis : M. F. $C_{28}H_{28}BrNO_3$.

Calculated	C : 66.41	H : 5.57	N : 2.77
Obtained	C : 66.15	H : 5.29	N : 2.50

General Procedure for the Synthesis of 4-Imino-b-Lactams

To a stirred mixture of bisimine (2 mmol) and Et_3N (7.5 mmol) in toluene (25 mL) was added acid chloride (3 mmol) in toluene (10 mL) over ½ h at room temperature. The reaction mixture was allowed to stir at room temperature for 5 h. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (25 mL) and washed successively with satd. $NaHCO_3$ (2 x 20 mL), water (2 x 20 mL) and finally with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to furnish crude product, which was crystallized from pet ether/ dichloromethane to give pure 4-imino-β-lactam.

***Preparation of 3-(2′-Bromophenoxy)-1-(4′′-methoxyphenyl)-4-(4′′′-methoxyphenyl-iminomethyl)-2-azetanone* 4.08a**

Acid chloride **4.03a** (0.496 mg, 2 mmol) on treatment with bisimine **4.07** (0.804 g, 3 mmol) in the presence of Et_3N (1.05 ml, 7.5 mmol) provided the β-lactam **4.08a** as a white solid (0.749 g, 78%).

M.P. : 124-125°C.

IR (cm^{-1}) : 1512, 1751, 3016.

^{1}H NMR : δ 3.78 (s, 3H), 3.80 (s, 3H), 5.1 (dd, *J* = 5.3, 6.18 Hz, 1H), 5.6 (d, *J* = 4.9 Hz, 1H), 6.6-7.75 (m, 12H), 8.1 (d, *J* = 6.8 Hz, 1H).

MS [m/e (%)] : 482 (M+2, 2), 480 (M^+, 2), 309 (100), 281 (16), 252 (17), 174 (16), 134 (40), 77 (25).

Microanalysis : M. F. $C_{24}H_{21}BrN_2O_4$.

Calculated	C : 59.89	H : 4.40	N : 5.82
Obtained	C : 59.61	H : 4.10	N : 5.62

Preparation of 3-[2′-Bromo-4′-(tert. Butyl)phenoxy]-1-(4″-methoxyphenyl)-4-(4‴-methoxyphenyliminomethyl)-2-azetanone **4.08b**

Acid chloride **4.03b** (761 mg, 2.5 mmol) on treatment with bisimine **4.07** (536 mg, 2 mmol) in the presence of Et_3N (1.05 ml, 7.5 mmol) provided the β-lactam **4.08b** as a white solid (1.02 g, 95%).

M.P. : 134-135°C.

IR (cm^{-1}) : 1504, 1514, 1759, 3018.

^1H NMR : δ 1.28 (s, 9H), 3.78 (s, 3H), 3.81 (s, 3H), 5.07 (dd, *J* = 4.9, 7.3 Hz, 1H), 5.58 (d, *J* = 5.4 Hz, 1H), 6.75-7.60 (m, 11H), 8.1 (d, *J* = 7.3 Hz, 1H).

m/e (%) : 538 (M^++2, 1), 310 (20), 309 (100), 281 (20), 213 (29), 134 (93), 107 (31), 77 (43).

Microanalysis : M. F. $C_{28}H_{29}BrN_2O_4$.

Calculated	C : 62.58	H : 5.44	N : 5.21
Obtained	C : 63.30	H : 5.16	N : 5.01

Preparation of 3-[2′-Bromo-4′-(tert-butyl)phenoxy]-1-(4′-methoxyphenyl)-4-oxo-azetane-2-carbaldehyde **4.09b**

A stirred mixture of **4.08b** (0.538 g, 1mmol), $CHCl_3$ (25 mL) and 5% HCl (15 mL), at 0°C was stired at room temperature for 1.5 h. After completion of reaction the (TLC), the reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with water (20 mL), saturated $NaHCO_3$ and finally with brine. The organic layer was dried over Na_2SO_4 and the solvent was removed on rotary evaporator under reduced pressure. The crude product was purified by crystallization from pet ether/ethyl acetate to get a white solid **4.09b** (0.258 g, 60%).

M.P. : 149-150°C.

IR (cm^{-1}) : 1514, 1749, 2950, 3018.

^1H NMR : δ 1.28 (s, 9H), 3.80 (s, 3H), 4.75 (dd, *J* = 3.4, 5.4 Hz, 1H), 5.55 (d, *J* = 5.4 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.20-7.45 (m, 4H), 7.55 (d, *J* = 1.5 Hz, 1H), 9.95 (d, *J* = 3.4 Hz, 1H).

***Preparation of* 4.10b**

A mixture of **4.09b** (0.862 g, 2 mmol), (R)-(+)-methylbenzyl amine (0.22 mL, 1.8 mmol), CH_2Cl_2 (30 mL), and $MgSO_4$ (1 g) was stirred at 0°C. The reaction mixture was allowed to warm up to room temperature and further stirred for 2 h. After completion of the reaction (TLC), the reaction mixture was filtered through a sintered funnel to remove $MgSO_4$. The filtrate was concentrated under reduced pressure to get an oilly product **4.10b**, which was used without further purification in the next step.

General procedure for the radical cyclisation of 4-styryl-b-lactams

A toluene solution (10 mL) of Bu_3SnH (1.3 mmol) containing AIBN (30 mg, 0.18 mmol) was added by syringe pump over a period of 2 h, to a refluxing solution of β-lactam (1 mmol) in toluene (15 mL). The reaction mixture was allowed to reflux under argon atmosphere for 12 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate; 75 : 25).

***Preparation of 8-Benzyl-1-(4′-methoxyphenyl)-2, 2a, 8, 8a-tetrahydro-1H-chromeno-[3, 2-b]azet-2-one* 4.06a**

The *b*-lactam **4.05a** (0.449 g, 1mmol) on treatment with Bu_3SnH (0.4 mL, 1.5 mmol) in the presence of AIBN (30 mg, 0.18 mmol) underwent radical cyclisation to give *b*-lactam **4.06a** (0.334 g, 90%) as a white solid. A small amount of reduced proeduct (5%) was also formed along with the cyclised product but it was not possible to separate it from **4.06a** by crystallization or column chromatography. The spectral and physical data for **4.06a** is given below.

M.P. : 146-148°C.

IR (cm^{-1}) : 1512, 1751, 3016.

^1H NMR : δ 2.95 (d, *J* = 8.3 Hz, 2H), 3.56 (t, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 4.56 (d, *J* = 4.9 Hz, 1H), 5.41 (dt, *J* = 5.3, 20 Hz), 6.6-7.6 (m, 13H).

MS [m/e (%)] : 372 (M^++1, 1), 371 (M^+, 4), 149 (12.5), 131 (100), 91 (17), 77 (12).

***Preparation of 8-Benzyl-6-(tert. butyl)-1-(4-methoxyphenyl)-2,2a,8,8a-tetrahydro-1H-chromeno[3, 2-b]azet-2-one* 4.06b**

The *b*-lactam **4.05b** (0.505 g, 1mmol) on treatment with Bu_3SnH (0.4 mL, 1.5 mmol) in the presence of AIBN (30 mg, 0.18 mmol) underwent radical cyclisation to give *b*-lactam **4.06b** (0.384 g, 90%) as a white solid. It was not possible to remove the tin impurities completely from **4.06b** by crystallization or flash column chromatography. The spectral and physical data for **4.06b** is given below.

M.P. : 140°C.

IR (cm^{-1}) : 1514, 1747, 2962, 3018.

^1H NMR : δ 1.12 (s, 9H), 2.80-2.3.07 (m, 2H), 3.5 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 3H), 4.57 (d, *J* = 5.2 Hz, 1H), 5.4 (d, *J* = 5.2 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.75-7.4 (m, 12H).

^{13}C NMR : 13.22, 17.23, 26.50, 27.54, 31.00, 33.80, 39.83, 40.65, 55.17, 58.57, 79.30, 114.28, 117.49, 118.48, 124.07, 125.54, 126.33, 127.56, 128.20, 128.88, 138.43, 146.05, 150.00, 156.05, 162.50.

MS [m/e (%)] : 428 (M^++1, 1), 427 (M^+, 4), 187 (100), 172 (15), 157 (20), 134 (20), 91 (33), 77 (22), 57 (27).

General procedure for the radical cyclisation of 4-imino b-lactams

A toluene solution (10 mL) of Bu_3SnH (1.5 mmol) containing AIBN (0.08 g, 0.5 mmol) was added by syringe pump over a period of 5 h to the refluxing solution of β-lactam (1 mmol) in toluene (15 mL). To this refluxing reaction mixture AIBN (total 80 mg) was added in the small lots of 20 mg over a period of 4 h. The reaction mixture was allowed to reflux under argon atmosphere for 12 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and purified by flash column chromatography (Silica gel, petroleum ether/ethyl acetate; 75:25).

***Preparation of 6-(tert. Butyl)-8-(4′-methoxyphenyl)-2, 2a, 8, 8a-tetrahydro-1H-chromeno[3, 2-b]azet-2-one* 4.14a**

The *b*-lactam **4.08a** (0.480 g, 1mmol) on treatment with Bu_3SnH (0.53 mL, 2 mmol) in the presence of AIBN (total 0.164 g, 1 mmol) furnished β-lactam **4.14a** (0.241 g, 60%) as a white, crystalline solid.

M.P. : 163-164°C.

IR (cm^{-1}) : 1512, 1751, 3016.

^1H NMR : δ 3.75 (s, 3H), 3.78 (s, 3H), 4.80 (dd, *J* = 1.5, 4.9 Hz, 1H), 4.85 (d, *J* = 1.5 Hz, 1H), 5.37 (d, *J* = 4.9 Hz, 1H), 6.6-7.5 (m, 12H).

^{13}C NMR : 52.48, 55.22, 55.44, 57.75, 76.44, 76.69, 76.95, 79.34, 114.51, 114.92, 118.64, 118.89, 123.71, 129.339, 130.26, 130.32, 152.24, 156.71, 161.60.

MS [m/e (%)] : 403 (M^++1, 3), 402 (M^+, 16), 227 (99), 212 (25), 175 (95), 131 (100).

Microanalysis : M. F. $C_{24}H_{22}N_2O_4$.

Calculated	C : 71.63	H : 5.51	N : 6.96
Obtained	C : 71.45	H : 5.26	N : 6.70

***Preparation of 6-(tert. Butyl)-8-(4′-methoxyanilino)-1-(4″-methoxyphenyl)-2, 2a, 8, 8a-tetrahydro-1H-chromeno[3, 2-b]azet-2-one* 4.14b**

The β-lactam **4.08b** (0.530 g, 1mmol) on treatment with Bu_3SnH (0.53 mL, 2 mmol) in the presence of AIBN (total 0.164 g, 1 mmol) furnished β-lactam **4.14b** (0.284 g, 62%) as a gum.

IR (cm^{-1}) : 1750, 2985, 3055.

^1H NMR : δ 1.2 (s, 9H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (dd, *J* = 1.5, 4.9 Hz, 1H), 4.84 (d, *J* = 1.5 Hz, 1H), 5.41 (d, *J* = 4.9 Hz, 1H), 6.60-7.45 (m, 11H).

^{13}C NMR : 31.01, 33.99, 53.21, 55.47, 57.40, 79.14, 114.47, 114.87, 118.13, 118.69, 127.33, 117.45, 129.47, 146.54, 149.84, 156.66, 161.99.

MS [m/e (%)] : 459 (5), 458 (18), 283 (100), 268 (75), 187 (35), 157 (25), 134 (30).

***Preparation of* 4.12b & 4.13.**

The b-lactam **4.10b** (0.534 g, 1mmol) on treatment with Bu_3SnH (0.53 mL, 2 mmol) in the presence of AIBN (total 0.164 g, 1 mmol) furnished a mixture of β-lactams **4.12b** & **4.13b** (0.274 g, 60%). The diastereomers were separated by flash column chromatography to get the nonpolar diastereomer **4.12b** and polar diastereomer **4.13b**. The spectral and analytical properties of the diastereomers are given below:

The nonpolar diastereomer **4.12b** was isolated as oil.

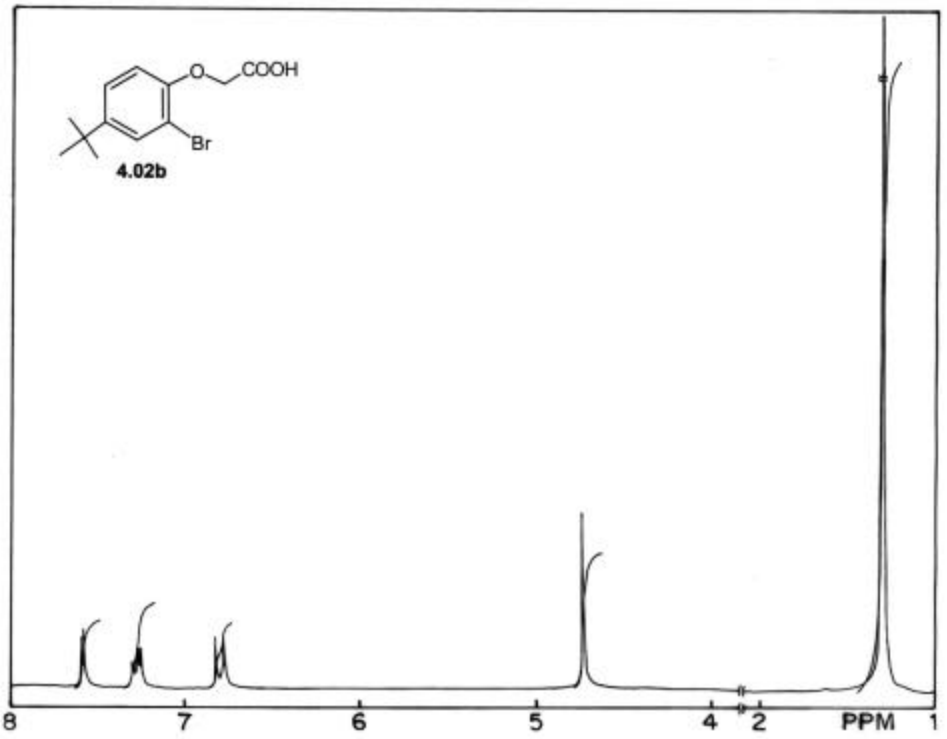
IR (cm^{-1})	:	1512, 1751, 2962, 3016.
^1H NMR	:	δ 1.23 (s, 9H), 1.30 (d, *J* = 6.3 Hz, 3H), 3.75 (s, 3H), 4.05 (q, *J* = 6.3 Hz, 1H), 3.90 (bs, 1H), 4.75 (dd, *J* = 1.5, 4.9 Hz, 1H), 5.42 (d, *J* = 4.9 Hz, 1H), 6.6-7.5 (m, 12H).
^{13}C NMR	:	25.32, 29.39, 31.13, 33.96, 51.71, 55.13, 55.62, 60.45, 79.11, 114.15, 117.96, 118.15, 124.10, 126.44, 126.87, 127.14, 128.52, 129.70, 114.63, 145.79, 149.51, 156.19, 161.82.
$[\alpha]^D_{25}$	:	-3.98° (c 1.86, $CHCl_3$).
MS [m/e (%)]	:	456 (2), 281 (100), 266 (40), 187 (40), 175 (40), 162 (55), 105 (42).

The polar diastereomer **4.13b** was isolated as oil.

IR (cm^{-1})	:	1512, 1751, 2962, 3016.
^1H NMR	:	δ 1.25 (s, 9H), 1.45 (d, *J* = 6.9 Hz, 3H), 3.75 (s, 3H), 4.05 (q, *J* = 6.9 Hz, 3H), 4.12 (bs, 1H), 4.76 (dd, *J* = 1.5, 5.4 Hz, 1H), 5.41 (d, *J* = 5.4 Hz, 1H), 6.65-6.80 (m, 3H), 6.90-7.10 (m, 3H), 7.20-7.60 (m, 6H).
^{13}C NMR	:	20.46, 23.72, 29.44, 31.10, 33.97, 51.49, 55.18, 55.71, 57.36, 78.90, 114.13, 118.04, 126.47, 126.50, 126.55, 128.54, 129.63, 144.38, 146.19, 149.69, 156.21, 162.34.
$[\alpha]^D_{25}$	:	+101.26° (c 1.43, $CHCl_3$).
MS [m/e (%)]	:	457 (2), 456 (5), 281 (100), 266 (50), 187 (36), 175 (40), 162 (45), 105 (55).

4.6 References

1. For recent reviews, see: (a) Fossey, J.; Lefort, D.; Sorba, J. In *Free Radicals in Organic Chemistry*; Translated by Lomas, J.; John Wiley & Sons Inc.: New York, 1995; p 151 and p 243. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (d) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulike, K. J.; Trach, F. *Org. React. (N. Y.)* **1996**, *48*, 301.
2. For a recent review on the radical cyclisation involving nitrogen, see: Fallis, A. F.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.
3. For examples of radical cyclisation on imines, see: (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chemistry Lett.* **1990**, 315. (b) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149.
4. Radical cyclisation involving oxime ether, see: (a) Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc.,Chem. Commun.* **1997**, 1789. (b) Miyabe, H.; Shibata, R,; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631.
5. For examples, see: Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882.
6. Radical cyclisation involving nitriile, see: Hegarty, P.; Mann, J. *Tetrahedron* **1995**, *51*, 9079.
7. Naito, T.; Torieda, M.; Tajiri, K.; Niniomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624.
8. Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745.
9. Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289.
10. Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628.
11. Alcaide, B.; Rodrigurz-Campos, I. M.; Rodriguez-Lopez, J.; Rodriguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377.
12. Alcaide, B.; Martin-Cantalejo, Y.; Perez-Castella, J.; Rodriguez-Lopez, J.; Sierra, M. A.; Monge, A.; Perez-Garcia, V. *J. Org. Chem.* **1992**, *57*, 5921.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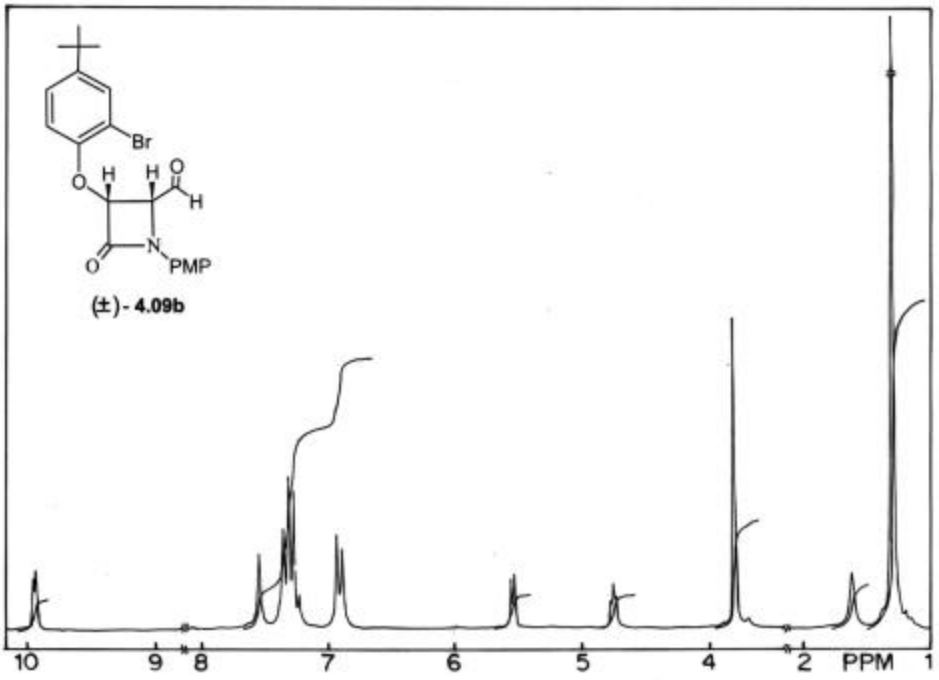
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(±) - 4.09b
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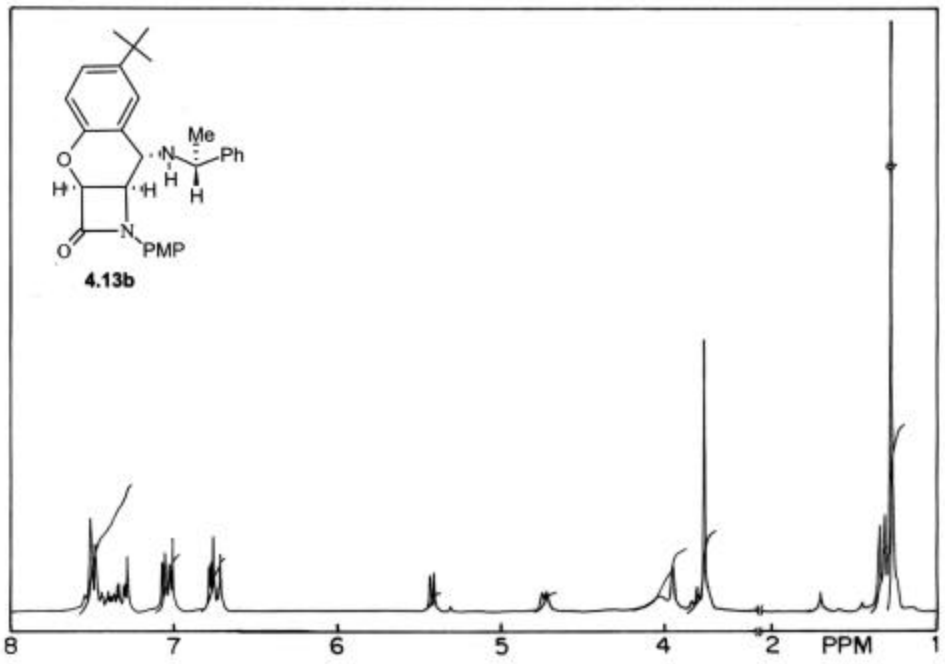
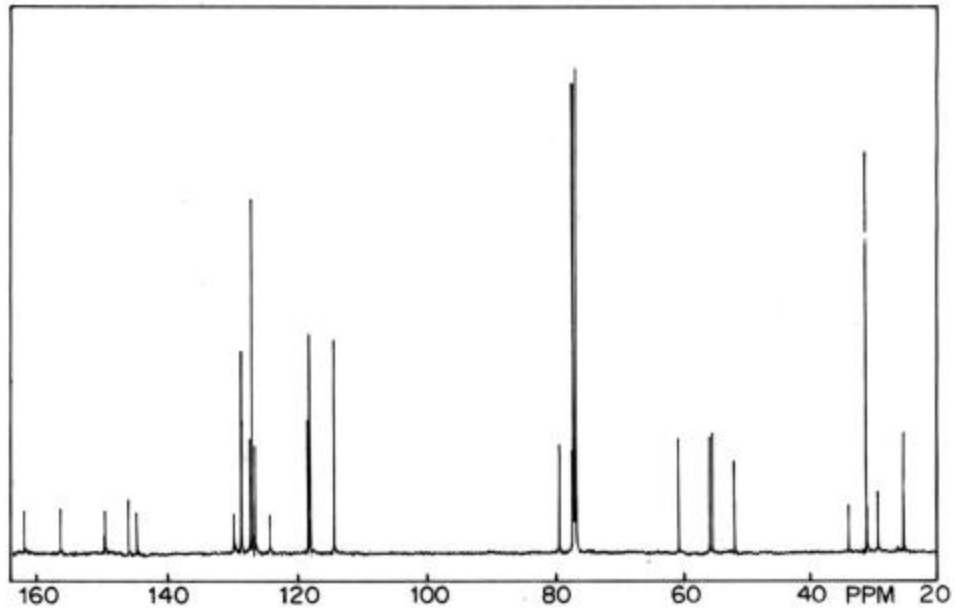
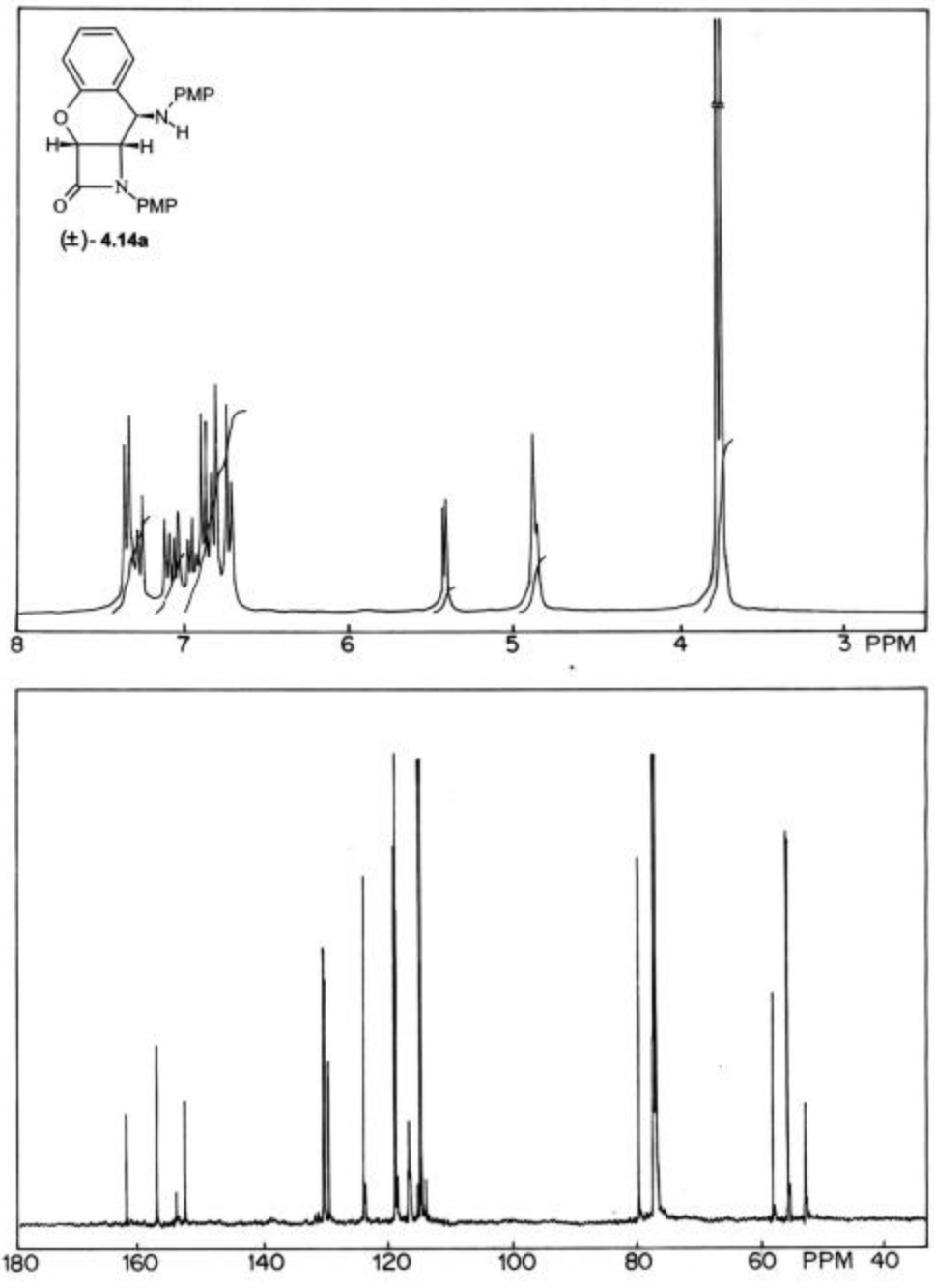


4.13b

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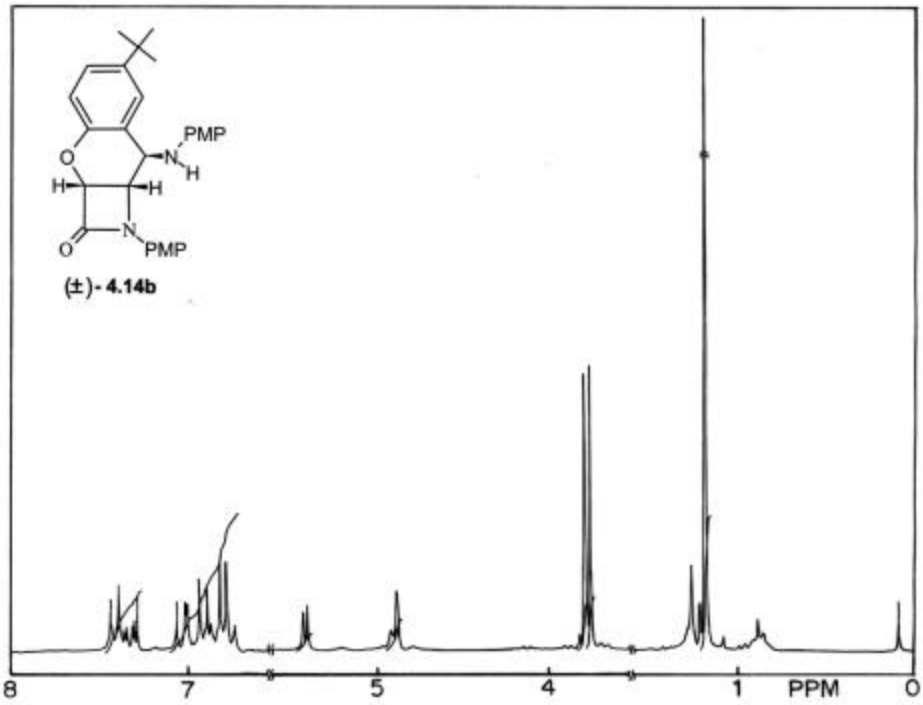
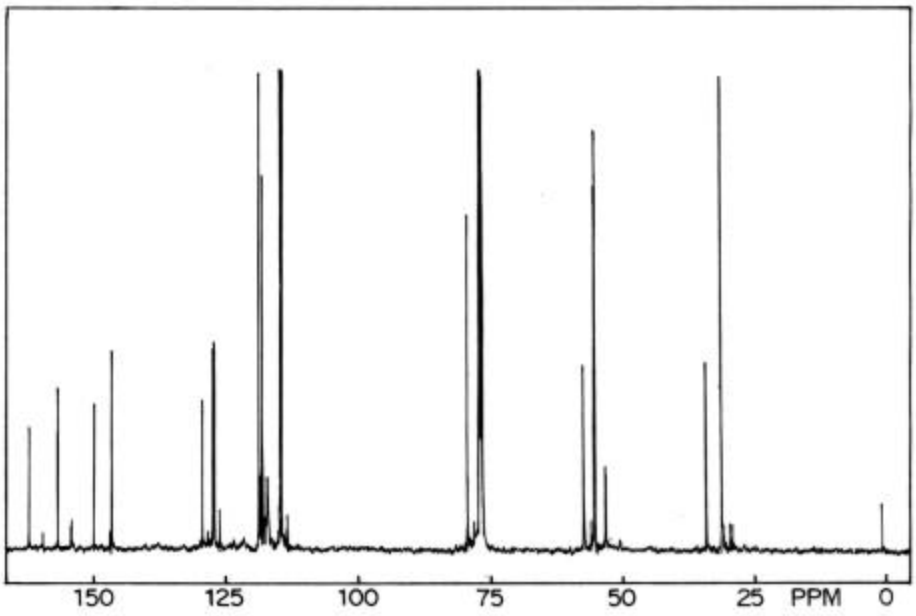


(±)- 4.14b



Chapter V

Tandem Radical Cyclization : Diastereoselective Synthesis of [3.6.6.7.4] Ring System

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There are only two ways to live your life. One is as though nothing is a miracle. The other is as though everything is a miracle.

Albert Einstein

5.1 : Introduction

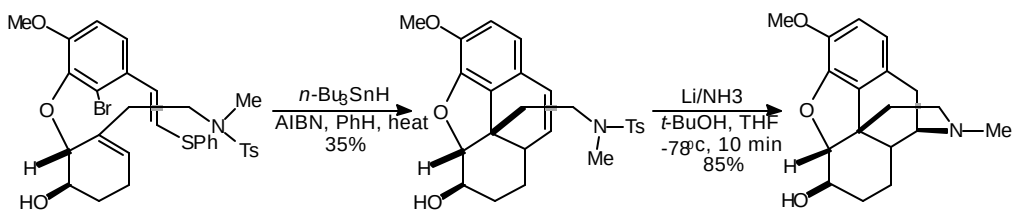
With the delineation of factors affecting the nature of chemical reactions, tandem reactions have become ubiquitous in nature. Tandem reactions[1,2] also called domino, sequential, consecutive, cascade, iterative, zipper reactions, link several transformations together in a single synthetic pathway. Typically, an initial reaction produces an intermediate that undergoes further transformations with strategically positioned reactive centers in the same molecule, with other compounds in the reaction mixture, or with additionally introduced after the initial transformation takes place. The increased applicability and widespread acceptance of these reactions is due to the increased synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. Furthermore, they frequently permit access to unique chemical structures and occasionally result in greater regio as well as stereoselectivity.

Among tandem reactions the radical reactions have become prevalent in organic synthesis.[3] The radicals are routinely generated from readily available halides (bromo, iodo, chloro etc), nitro, phenylthio, phenylselenyl compounds by the use of n-Bu_3SnH with a radical initiator (i.e., AIBN) in aromatic solvents. Additionally, redox procedures involving Mn (III) or Sm (II) can be employed to initiate tandem radical process.

The wide applications of the tandem cyclization are mainly exploited in the total synthesis of multicyclic targets. The use of properly substituted radical centers and the appropriately located radical traps are effective in converting an elegantly synchronized molecular system into biologically useful products.

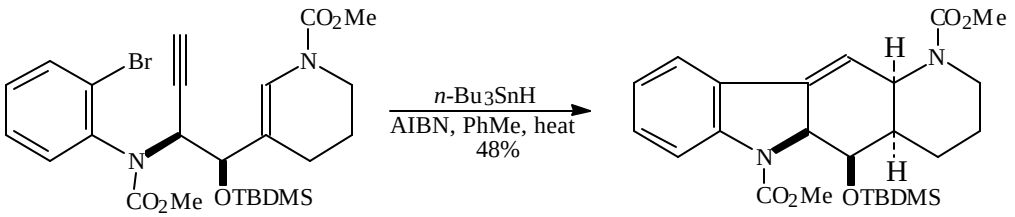
Tandem radical cyclisation of aryl radicals has been applied in the formal synthesis of racemic morphine (*Scheme 1*).[4]

Scheme 1



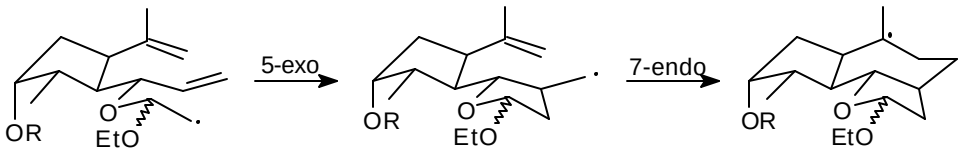
In an interesting reaction, Parsons et. al. used tandem radical cyclisation approach for the total synthesis of lysergic acid derivatives (*Scheme 2*).[5]

Scheme 2



Among the recent reports, there is an interesting example of *5-exo-trig-7-endo-trig* type of tandem radical cyclization (*Scheme 3*).[6]

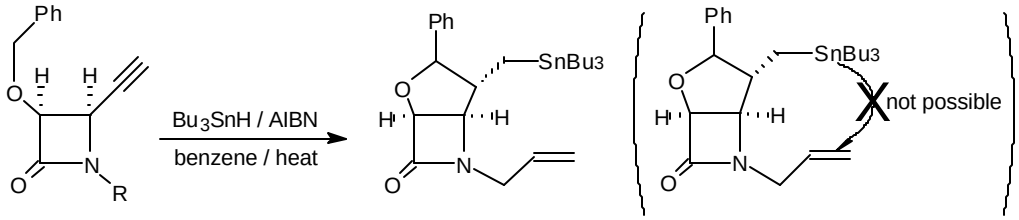
Scheme 3



The application of tandem radical cyclisation to the *b*-lactam chemistry are limited. Use of tandem radical cyclization in the construction of multicyclic *b*-lactam derivatives is not among very popular routes.

Recently Alcaide et. al. reported the use of enyne-2-azetidinones in the stereoselective synthesis of fused bicyclic *b*-lactams. In an interesting result, the benzyl radical was trapped by enyne triple bond, used as a radical acceptor, with the formation of 5-membered ring. However, it was not possible to quench the initially formed stanyl radical, with the use of N-allyl double bond as a second radical trap. Thus, the system couldn't be functionalised as an efficient radical machinery towards tandem radical cyclization (*Scheme 4*).[7]

Scheme 4



5.2 : Present Work

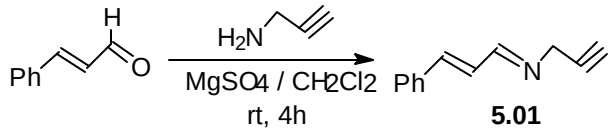
The exceptionally high efficiency of 6-exo heptenyl radical cyclisation in case of carane substituted *b*-lactams (Chapter III & IV) led us to think of the possibility of tandem radical cyclisation. Involvement of one more radical trap in the existing system, either in the form of vinyl or propargyl substituent attached to the nitrogen of the *b*-lactam gives, the right kind of molecular system ideal for tandem radical cyclisation. This chapter deals with the synthesis of radical cascade suitable for tandem radical cyclisation. The studies regarding behavior of these systems under tandem radical cyclisation conditions and subsequent formation of multicyclic ring systems using them, is also presented in this chapter.

5.3 : Results & Discussion

***Preparation of Imine* 5.01**

Propargyl amine and cinnamaldehyde were stirred in dichloromethane in the presence of anhydrous $MgSO_4$ for 4 hours to furnish the corresponding imine **5.01** quantitatively (*Scheme 5*).

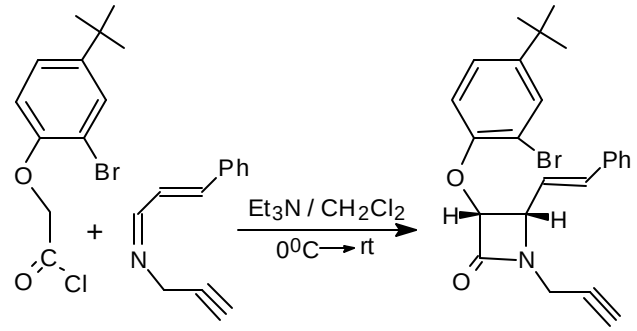
Scheme 5



***Preparation of* 5.02**

The acid chloride **4.03a** was added to the stirred mixture of imine **5.01**, and Et_3N in dichloromethane at 0°C over a period of 30 min. The usual ketene-imine cycloaddition reaction afforded the racemic *cis b*-lactam **5.02** in excellent yield (85%) *(Scheme 6)*.

Scheme 6



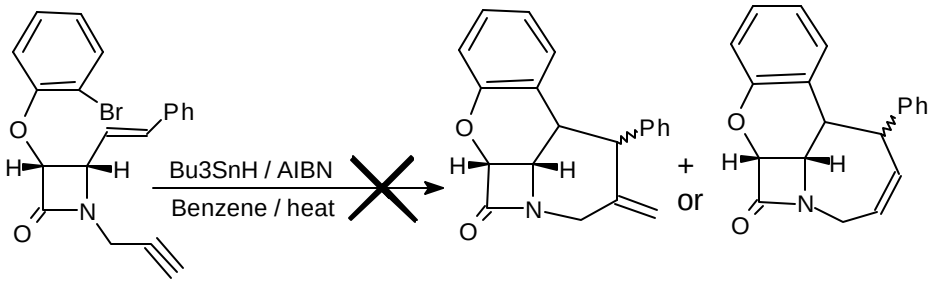
4.03a **5.01** **(±)- 5.02**

The IR of **5.02** showed a peak around 1750 cm^{-1}, typical for *b*-lactam amide. The ^1H NMR showed a dd at 4.70, with coupling constant *J* = 4.9 & 9.3 Hz, which belonged to the *b*-lactam proton H-4. The other *b*-lactam proton H-3 appeared at 4.9 as a doublet with coupling constant *J* = 4.9 Hz. A high coupling constant indicated a *cis* *b*-lactam. The terminal propargylic proton resonated as a triplet at 2.30 (*J* = 2.5 Hz). The methylene CH_2 protons from the propargylic group were diastereotopic and they appeared as two peaks at 3.85 (dd, *J* = 2.5, 18 Hz) and 4.35 (dd, *J* = 2.5, 18 Hz). The protons attached to the styryl double bond resonated at 6.4 (dd, *J* = 9, 16 Hz) and 6.80 (d, *J* = 16 Hz), confirming the presence of trans double bonded system. The aromatic protons appeared between 7.0 to 7.75.

***Attempted Radical Cyclisation of* 5.02**

The *b*-lactam **5.02** was subjected to the typical conditions of radical cyclisation. The mixture of tin hydride and AIBN were added by syringe pump over 4 hours to the refluxing solution of *b*-lactam in benzene *(Scheme 7)*. However, no reaction was observed even after prolonged heating (24 h).

Scheme 7



(±)- 5.02

This was confirmed by ^{1}H NMR spectrum of the reaction mixture, which showed the styryl as well as the propargyl protons in the respected region. The aromatic proton pattern was also similar to that of the starting material indicating the presence of bromide.

Synthesis of N-Vinyl Radical Cascades

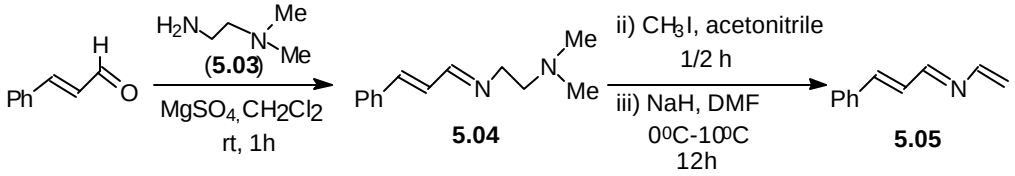
The failure to cyclize **5.02** led us to think of designing a new radical system with proper substituents. The failure of the reaction may not be due to ring size, as 6 - 6 tandem ring cyclization is entropically favored type of cyclization. The other obvious reason may be the strain developed in the system, which makes the total system energetically unfavorable. The rigidity of the aromatic ring, to which the bromine is attached was also one of the possible reasons.

To circumvent this problem we decided to use aliphatic bromide in place of aromatic bromide. Also we decided to use N-vinyl in place of N-propargylic group as a second radical trap.

***Preparation of Imine* 5.05**

The N-vinyl imine derivative **5.05** was prepared by using a reported procedure (Georg et. al.).[8] The imine **5.04**, prepared by using cinnmaldehyde and N,N'-dimethylethylenediamine, was further treated with iodomethane in acetonitrile to prepare the quarternary ammonium salt of the imine. The imine salt on further treatment with NaH in DMF yielded the product as N-vinyl imine **5.05** *(Scheme 8)*.

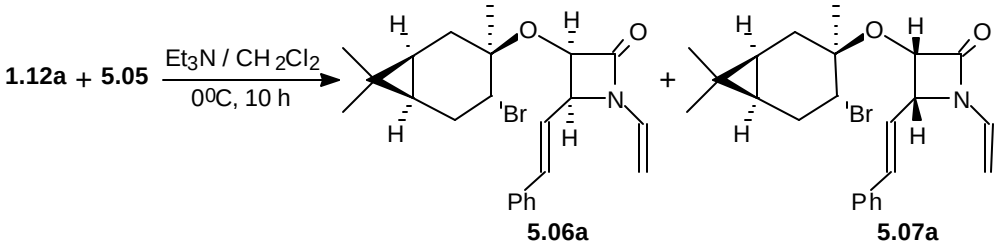
Scheme 8



***Synthesis of b-Lactams* 5.06a & 5.07a**

The imine **5.05** on treatment with the carane bromo acid chloride **1.12a** in the presence of triethylamine furnished a diastereomeric mixture of *b*-lactams in 45% yield *(Scheme 9)*.

Scheme 9



The ^{1}H NMR spectrum of the crude product showed moderate diastereoselctivity (60:40) in the *b*-lactam ring formation. The purification of crude reaction mixture by flash column chromatography could not separate the diastereromers.

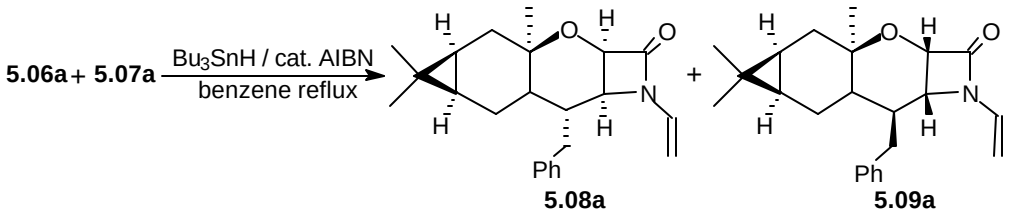
The IR spectrum of diastereomeric mixture of **5.06a** & **5.07a** showed a peak at 1757 cm^{-1}, typical of *b*-lactam amide carbonyl. The ^{1}H NMR spectrum showed *b*-lactam peaks as multiplets between 4.48-4.62 and doublets at 5.00 and 5.05 respectively. The terminal vinylic protons appeared as multiplets between 4.40-4.85 region. The vinylic proton attached to the nitrogen resonated between 6.60 and 6.80 as a multiplet. The styryl protons were seen as a dd at 6.35 (J = 9, 16 Hz) and multiplet between 6.60 and 6.80 respectively. The aromatic protons resonated as multiplets in the region 7.2 to 7.5.

The ^{13}C NMR showed peaks at proper positions.

***The Radical Cyclisation of* 5.06a & 5.07a**

Initially benzene was used as a solvent and the refluxing solution of the diasteromeric mixture of *b*-lactams **5.08a** & **5.09a** was reacted with Bu_3SnH in presence of cat. AIBN. The reaction was over within 2 hours (TLC). The product was separated from the tin impurities by using flash column chromatography *(Scheme 10).*

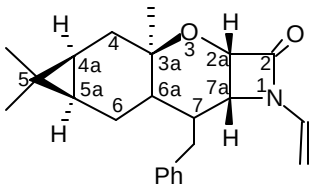
Scheme 10



The ^{1}H NMR showed that the column-purified product was a diastereomeric mixture, from which the nonpolar diastereomer **5.09a** could be obtained in the pure form by a flash column chromatography. The IR spectrum of **5.09a** showed a peak at 1750 cm^{-1}, typical of *b*-lactam carbonyl group. A molecular ion peak at 352 was observed in the mass spectrum.

^{1}H NMR (Fig. 1) showed absence of peaks related to the styryl double bond in the region from 6.0 to 6.6 indicating that it was not reduced but a cyclized product. The *b*-lactam proton H-7a appeared as a triplet at 3.7 (*J* = 4.7, 9.0 Hz) while the other *b*-lactam proton, H-2a, resonated as a doublet at 4.85 (*J* = 5.4 Hz). A high coupling constant clearly indicated a cis *b*- lactam ring being present. The diastereotopic

Fig. 1. ^{1}H NMR of **5.09a**.



5.09a

Protons from the benzyl group were seen as two peaks in the form of dd at 2.85 (*J* = 9, 14 Hz) & 2.95 (*J* = 6, 14 Hz). The additional peaks at 4.45 (d, J= 9.4 Hz) & 4.6 (d, *J* = 16 Hz) could be assigned to the terminal vinylic protons. The N-CH= protons from the vinylic portion appeared as a dd at 6.20 (*J* = 9, 16 Hz). The pattern of benzylic protons as well as the presence of vinylic peaks clearly indicated the formation of tetracyclic ring system by simple radical cyclisation and not by tandem cyclisation.

In another experiment toluene was used as a solvent, and AIBN was added in small portions over a period of time. In this case also the product obtained was found to be identical with the benzene experiment (formed by *6-exo*-heptenyl cyclisation) and no tandem cyclised product could be observed.

It is well known fact that N-vinylic double bond is not a good radical acceptor. The failure of the above system to undergo tandem radical cyclisation could be due to the inefficiency of N-vinylic double bond to act as a second radical trap. This prompted us to think of replacing vinylic group by some efficient radical scavenger, that could trap the benzylic radical formed after the first cyclisation. A *b*-lactam derivative with N-allyl group as a radical acceptor, was a promising candidate in this regard. But attempts to prepare such kind of radical system on practical scale proved

unsuccessful. This led us to think about the synthesis of *b*-lactam derivative with N-propargyl group as a radical acceptor.

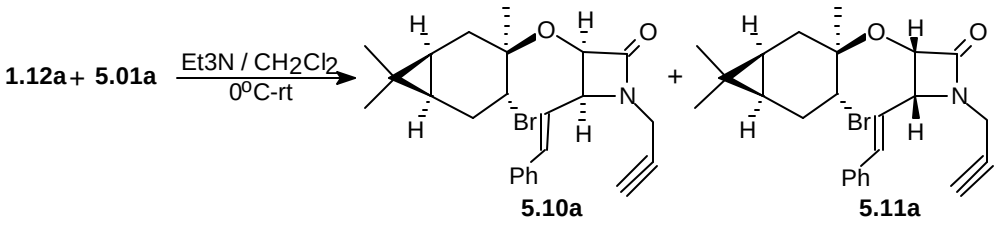
Synthesis of of b-Lactam Derivatives with N-Propargyl as a Radical Acceptor

The failure to synthesise N-allyl *b*-lactams led us to think of N-propargylic derivatives as a potential candidate. Alcaide[7] et.al. have reported the synthesis of enyne *b*-lactams and they have effectively used N-substituted acetylenic centre as an efficient radical progenitor. Compared to the olefinic double bond, enyne triple bond is a less efficient radical trap. Never the less it has been used in the synthesis of multicyclic natural products.

Synthesis of Enyne b-Lactam Using Carane Bromo Acid

The N-propargyl substituted *b*-lactam was synthesised by using Alcaide's procedure.[7] The imine **5.01** was condensed with the acid chloride **1.12a** in the presence of Et_3N used as a base. After overnight stirring and usual work up, the crude product was obtained as a gummy liquid in 48% yield. The column-purified material was a diastereomeric mixture (60:40, confirmed by ^1H NMR) *(Scheme 11).*

Scheme 11

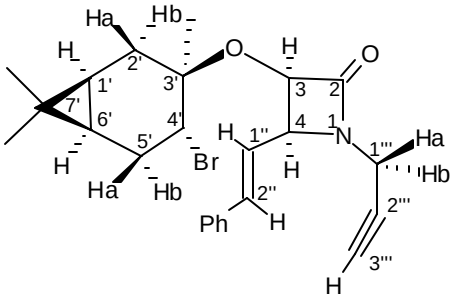


The Rf values of the diastereomers were very close (TLC), still, the polar diastereomer **5.10a** could be isolated in the pure form by flash column chromatography, in around 20% yield.

The IR of **5.10a** showed strong peak at 1755 cm^{-1} clearly indicating the presence of *b*-lactam amide carbonyl. The ^1H NMR of **5.10a** showed a typical spectrum (Fig. 2).

Two cyclopropyl methine protons H-1′ and H-6′ appeared as a multiplet between 0.50-0.85. The carane methylene protons at C-2′ & C-5′ gave multilplets in the region 1.25- 2.50. The gem dimethyls at C-7′ appeared as two singlets at 0.97 & 1.00. The methyl at C-3′ resonated as a singlet, at 1.30. The proton H-4′ appeared at

4.04 as a dd, with J = 9.2 & 10.5 Hz. The *b*-lactam proton H-3 appeared at 5.04 as a doublet (J = 4.4 Hz) while H-4, appeared at 4.45 as a dd, with J = 4.4 & 9.5



5.10a

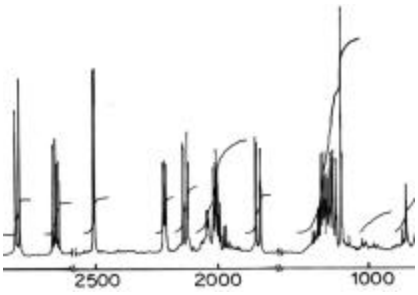


Fig. 2. ^{1}H NMR (**5.10a**, 500 MHz)

Hz. Again a high coupling constant indicated a *cis* *b*-lactam. The two protons Ha-1‴ & Hb-1‴ were appreciably diastereotopic and appeared as two dd, at 3.69 (J = 2.9, 17.5 Hz) & 4.29 (J = 2.2, 17.5 Hz). The terminal propargylic proton H-3‴ appeared as a triplet with a coupling constant J = 2.2 Hz. The styryl proton H-2″ appeared as a doublet while H-1″ appeared as a dd with J = 9.5 & 16 Hz.

The ^{13}C NMR (Fig. 3) was also satisfactory. The three-methylene carbons C-2′, C-5′ & C-1‴ were present at 29.3, 31.8 & 32.1. G4 & G-4′ were present at 60.3 & 61.8 The tertiary carbon C-3′ was present at 72.5, the acetylenic carbons C-2‴ & G-3‴ appeared at 77.8 & 78.0. The aromatic carbons and the styryl carbons appeared in the region 124-136. The amide carbonyl carbon appeared at 167.1.

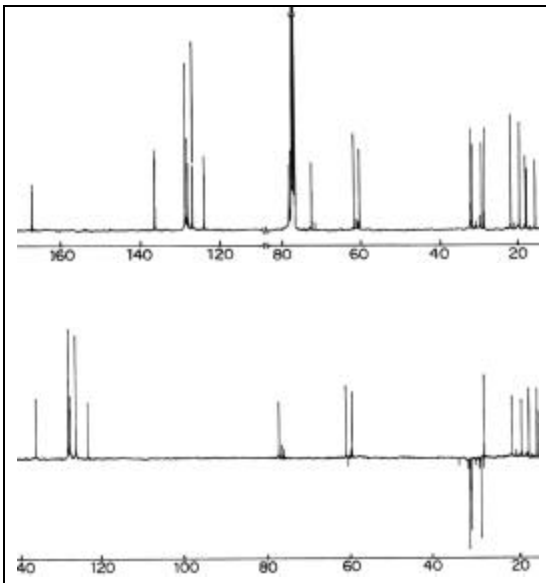


Fig. 3.^{13}C NMR of **5.10a**.

To determine the connectivity among adjacent protons and to establish the two dimensional structure of the radical system, COSY NMR spectrum of **5.10a** was recorded.

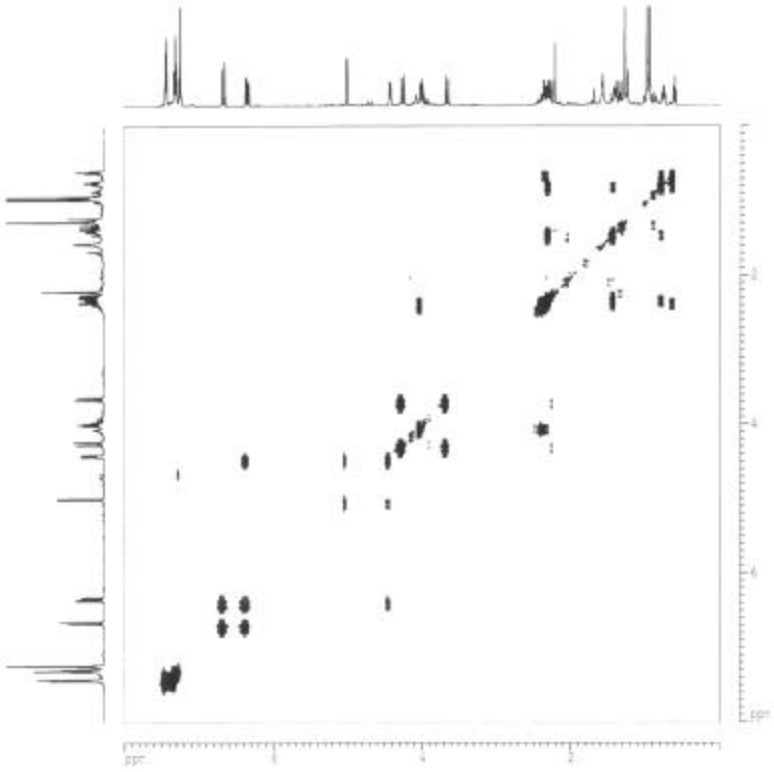
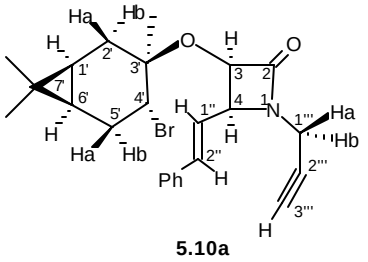


Fig. 4. COSY NMR spectrum of **5.10a** (selected region shown).

Table 1. Important connectivities in the COSY NMR of **5.10a**

Proton	δ (ppm)	J (Hz)	^{1}H-^{1}H connectivity
H-3	5.04 (d)	4.4	H-4
H-4	4.45 (dd)	4.4, 8.8	H-3, H-1″
H-1″	6.38 (dd)	9.5, 16	H-2″, H-4
H-2″	6.70 (d)	16	H-1″
Ha-1‴	3.69 (dd)	2.9, 17.5	Hb-1‴, H-3‴
Hb-1‴	4.29 (dd)	2.2, 17.5	Ha-1‴, H-3‴
H-3‴	2.25 (t)	2.2	Ha-1‴, H b1‴
H-4′	4.04 (dd)	9.2, 10.5	Hb-5″, Ha-5″



5.10a

From the COSY NMR, the connectivity among the cyclopropyl methine and the methylene protons at C-2′ & C-5′ was established. This further confirmed the positions of axial and equatorial protons at C-2′ & C-5′.

The spatial coupling among different protons was confirmed from the NOESY spectrum of **5.10a** (Fig. 5). The overall spatial connectivity picture of the molecule is shown in Fig. 6.

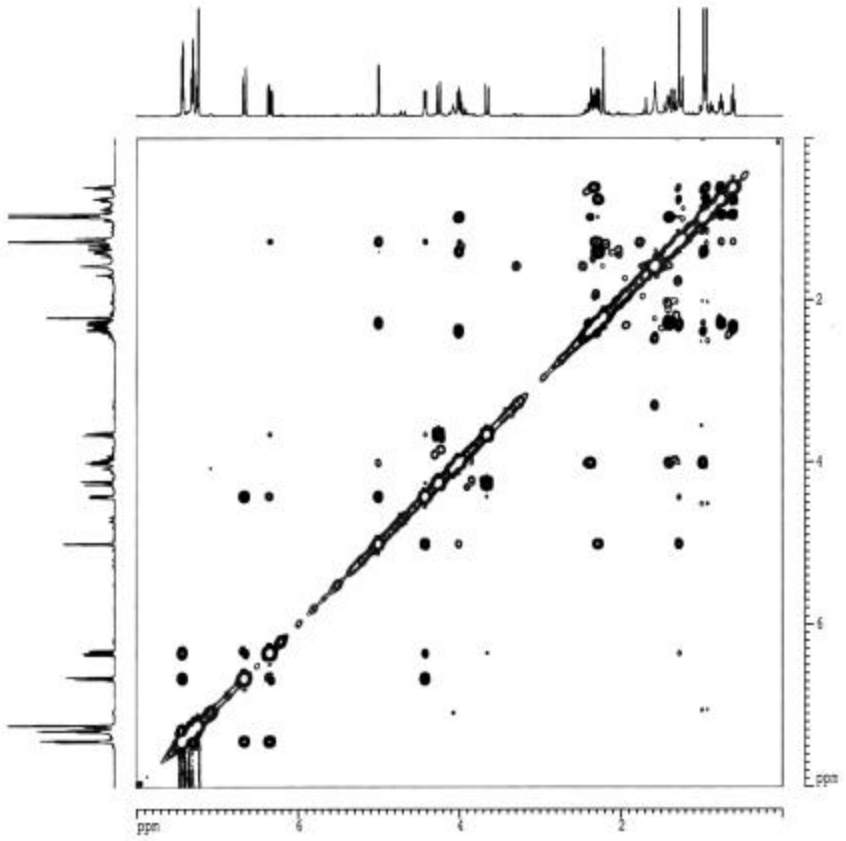


Fig. 5. NOESY spectrum of **5.10a** showing spatial correlations.

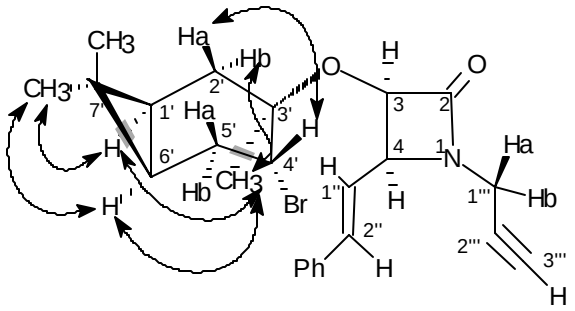


Fig. 6. The spatial correlation among protons as observed in the NOESY of **5.10a**.

The absolute configuration at the *b*-lactam protons was decided from the comparison of the ^{1}H NMR data of **5.10a**, with series of analogous derivatives

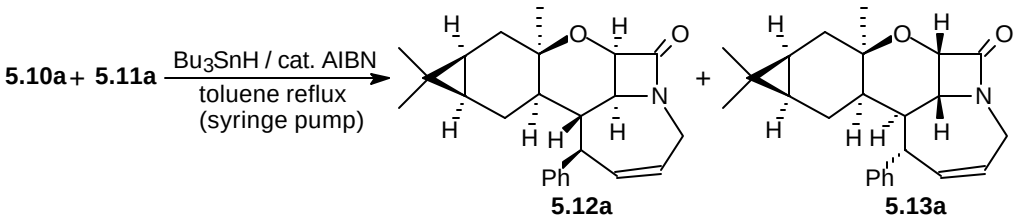
(Chapter I, Section B). From the above correlation, the absolute stereochemistry of **5.10a** was assigned to be 3*R*, 4*S* at the *b*-lactam ring centres.

***Radical Cyclisation of* 5.10a & 5.11a**

The diastereromeric mixture of **5.10a** & **5.11a** was subjected to the optimized conditions of radical cyclisation. The refluxing mixture of **5.10a** & **5.11a** in benzene was treated with Bu_3SnH in the presence of catalytic AIBN. There was no reaction (TLC & ^1H NMR of the crude reaction mixture).

In another experiment toluene was used as a solvent. The refluxing solution of the diastereomeric mixture (**5.10a** & **5.11a**) in toluene was reacted with a mixture of Bu_3SnH and catalytic AIBN by slow addition with syringe pump, over a period of 4 hours, under high dilution conditions (10 mL/5h). The reaction was over within 5 hours (TLC). The crude material was purified by flash column chromatography, where by tin impurities could be removed easily. The column-purified mixture of **5.12a** & **5.13a** was obtained in around 47% yield (*Scheme 12).*

Scheme 12

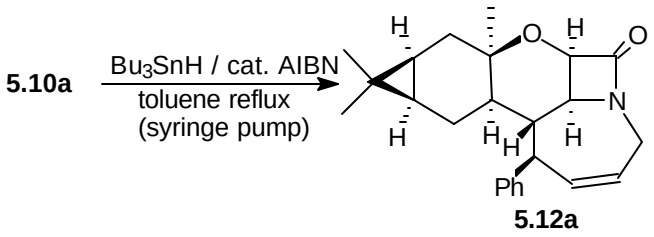


5.12a **5.13a**

The IR spectrum of the product showed a characteristic *b*-lactam carbonyl peak at 1756 cm^{-1}. The ^1H NMR spectrum showed absence of any peaks corresponding to the sryryl double bond in the region from 6.0-6.60, clearly negating the possibility of reduction. Absence of peaks corresponding to the propargylic unit, pointed towards the fact that propargylic unit is also involved in the cyclisation. The ^1H NMR of the diastereomeric mixture of **5.12a** & **5.13a** was complicated and showed presence of two products, alongwith a negligible amount of some uncharacterised side product. After repeated column chromatography it was possible to get a pure diastereomeric mixture.

In another experiment, the single diastereomer **5.10a** was subjected to the similar conditions of radical cyclisation (syringe pump technique). The reaction was over within 5 h *(Scheme 13)*.

Scheme 13

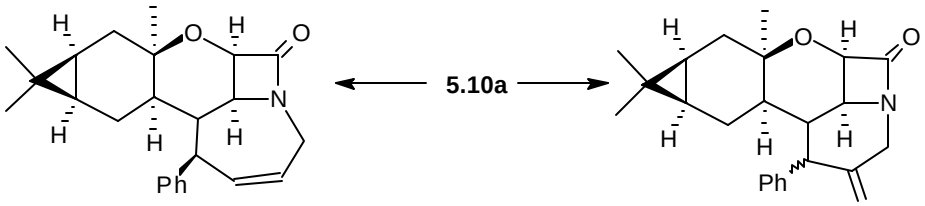


5.12a

^{1}H NMR spectrum of the crude reaction mixture showed formation of only one product.

***The Structure Elucidation of* 5.12a & 5.13a**

In the course of tandem cyclisation, there were two ways the cyclization could take place. It could be either *6exo-6exo* mode to give 3.6.6.4.6 type fused ring system; **B,** or it could be *6exo-7endo* annulation to give 3.6.6.4.7 type of fused system, **5.12a**.



5.12a *6 exo-7 endo*

B *6 exo-6 exo*

The possibility of formation of **B** was ruled out on the basis of ^{13}C NMR of the product. The structure **B** should have an additional terminal olefinic methylene group, therefore, 4 methylene carbons are expected in ^{13}C NMR spectrum of this compound. However, the decoupled ^{13}C NMR spectrum showed presence of only peaks corresponding to the 3 CH_2 groups. This led to he possibility of structure **5.12a** for the tandem cyclized product.

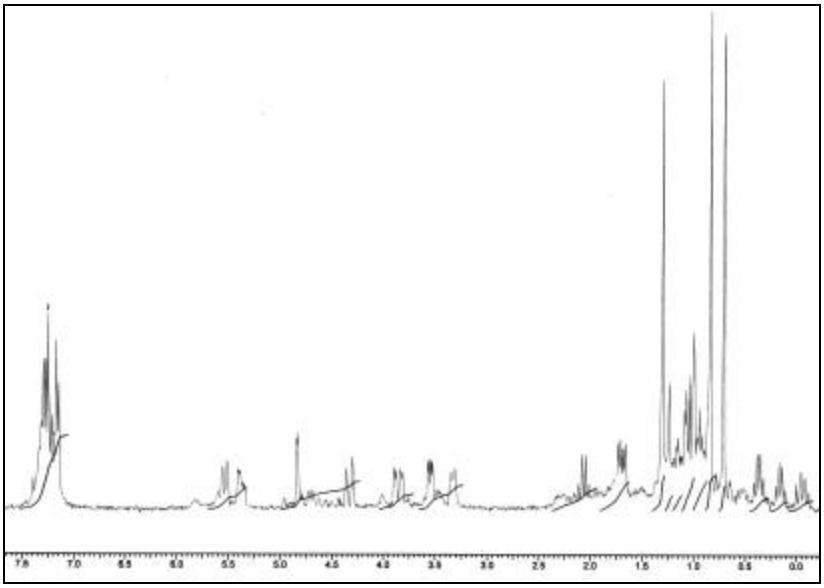
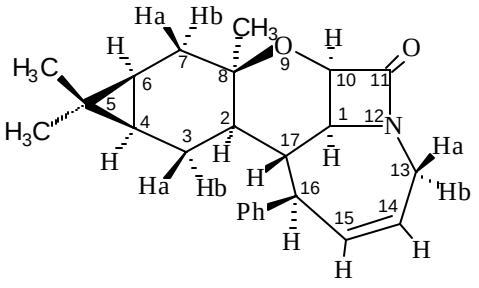


Fig. 7. ^{1}H NMR of **5.12a**

The ^{1}H NMR (Fig. 7) spectrum showed two singlets at 0.79 & 0.92 that could be accounted for the two gem-dimethyl protons at C-5. The methyl group at C-8 was seen at 1.38 as a singlet. Rest of the carane ring protons appeared between –0.1-2.2. The ring junction proton, H-17



5.12a

resonated as a ddd, with J =10, 10, 10 Hz. The benzylic proton H-16 appeared at 3.35 as a broad doublet with J = 10 Hz. The *b*-lactam proton H-1 resonated at 3.60, as a dd, with J = 4.4 & 9.6 Hz. The two geminal protons at C-13 appeared at 3.90 (ddd, J = 1.3, 6.0 & 18 Hz) & 4.35 (J = 2.7, 5.4 & 18 Hz). The other *b*-lactam proton H-10 was seen at 4.85 as a dd, with J = 1.2 & 4.4 Hz. The olefinic protons H-14 & H-15 resonated as two multiplets, in the region of 5.30-5.70. The aromatic protons appeared in the region 7.0-7.65 as multiplets.

The exact positions of different protons and the 2-dimensional structure of **5.12a** were further confirmed from the COSY NMR spectroscopy. (It was not possible to isolate enough amounts of pure diastereomers **5.12a** & **5.13a**. However, a diastereomeric mixture with **5.12a** major (**5.12a**/**5.13a** : 90/10) and **5.13a** major (**5.12a**/**5.13a** : 20:80) could be obtained from flash column chromatography, and was used for all special NMR experiments).

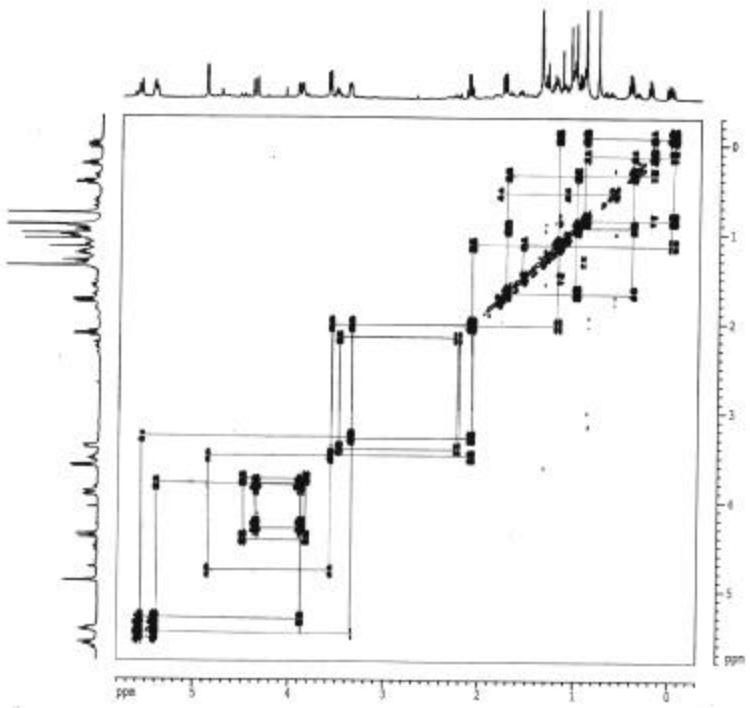


Fig. 8. COSY NMR of **5.12a** (small amount of **5.13a** also present)

Table 2. Connectivities among adjacent protons deduced from COSY NMR of **5.13a**

No.	δ ppm.	Proton No.	Multiplicity	Coupling constant *J* (Hz)	1H-1H (COSY)
1.	-0.1-0.1	Ha-3	m	-	Hb-3, H-4, H-2
2.	0.15-0.30	H-4	m	-	H-6, Ha-3, Hb-3
3.	0.4-0.5	H-6	m	-	H-4, Ha-7, Hb-7
4.	0.9	Hb-3	m	-	Ha-3, H-4
5.	0.95-1.15	Ha-7	m	-	H-6, Hb-7
6.	1.15-1.25	H-2	m	-	Ha, H-17
7.	1.75	Hb-7	m	-	H-6, Ha-7
8.	2.1	H-17	ddd	10, 10, 10	H-2, H-16, H-1
9.	3.35	H-16	dd	2, 10.4	H-15, H-17
10.	3.60	H-1	dd	4.2, 9.4	H-10, H-17
11.	3.90	Ha-13	ddd	2.8, 5.5, 18	Hb-13, H-14, H-15
12.	4.35	Hb-13	ddd	1.2, 6, 18	Ha-13, H-14, H-10
13.	4.85	H-10	dd	1.2, 4.1	Hb-13, H-1
14.	5.35-5.45	H-14	m	-	Hb-13, H-15
15.	5.55-5.70	H-15	dd	2.8, 13	H-14, H-16
16.	7.0-7.65	Arm.	m	-	-

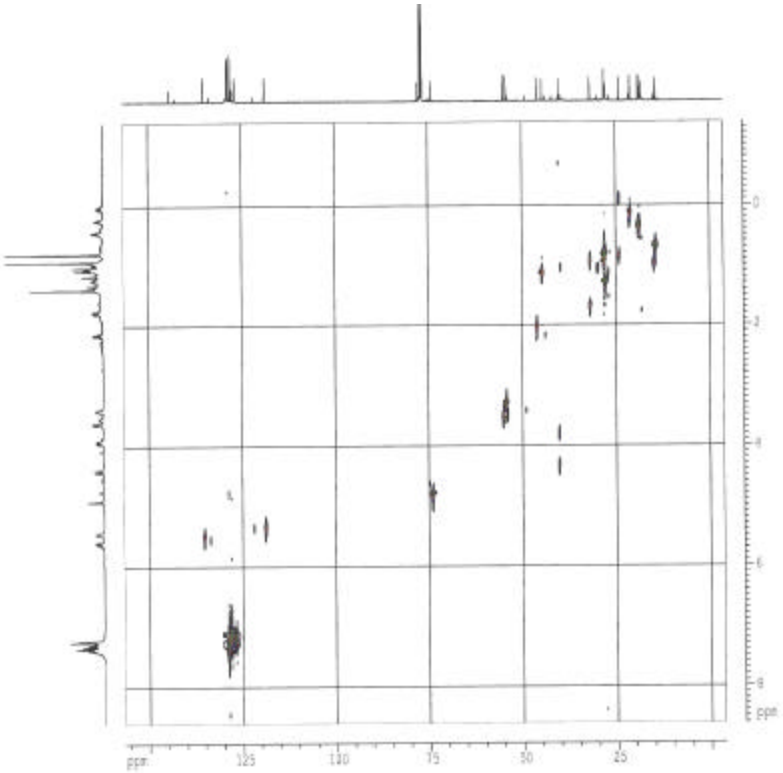
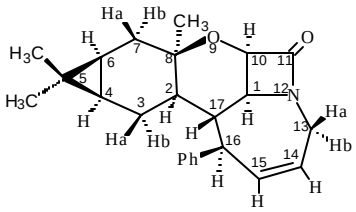


Fig. 9. HETCOSY NMR spectrum of **5.12a**.

Table 3. Important HETCOSY correlations for **5.12a**

No.	δ ppm. (H)	Proton No.	Carbon connectivity	δ ppm. (C)
1.	-0.1-0.1	Ha-3	C-3	24.1
2.	0.15-0.30	H-4	C-4	21.3
3.	0.4-0.5	H-6	C-6	18.7
4.	0.9	Hb-3	C-3	24.1
5.	0.95-1.15	Ha-7	C-7	31.7
6.	1.15-1.25	H-2	C-2	44
7.	1.75	Hb-7	C-7	31.7
8.	2.1	H-17	C-17	46
9.	3.35	H-16	C-16	54.2
10.	3.60	H-1	C-1	55.0
11.	3.90	Ha-13	C-13	40.2
12.	4.35	Hb-13	C-13	40.2
13.	4.85	H-10	C-10	74.0
14.	5.35-5.45	H-14	C-14	118.7
15.	5.55-5.70	H-15	C-15	135.1
16.	7.0-7.65	Arm.	-	-



5.12a

From the COSY & HET-COSY NMR of **5.12a**, it was possible to assign all the protons and the corresponding carbons for the cyclized product **5.12a**. A *trans* relationship between H-17 and rest of the adjacent protons were confirmed. Particularly informative was, a very high coupling constant among H-17 and the adjacent protons i. e. H-1, H-6 & H-2 (J = 10,

10, 10 Hz). To establish the structure unambiguously, NOESY spectrum of **5.12a** was recorded (Fig. 10).

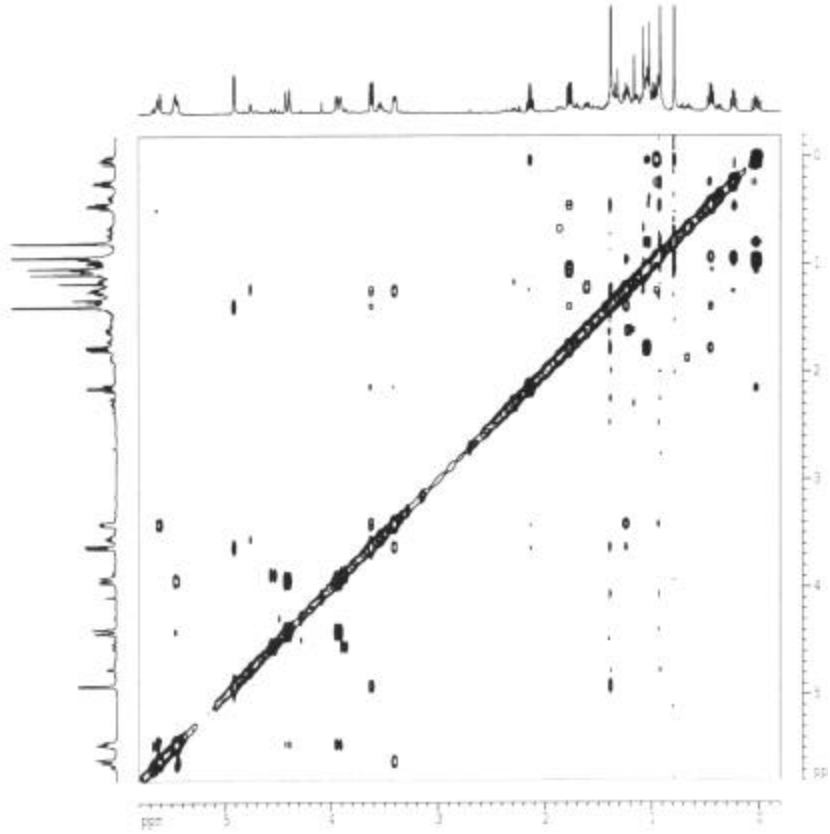


Fig. 10. NOESY specturm of **5.12a**.

The NOESY NMR spectrum of **5.12a** was important in the determination of structure. Absence of any spatial connectivity among H-17 and *b*-lactam protons H-1 & H-10 indicated that H-17 is β oriented. A strong interaction among benzylic proton H-16 with H-2 & H-1 could be possible only when the H-16 is α oriented. Particularly noticeable was a strong interaction among H-17 & H-3, which confirmed H-17 to be β. Thus, the absolute configuration at the newly formed asymmetric centers C-16 & C-17 was 16*R* & 17*S*. The assigned conformation was again consistent with the normal trend, as cyclisation generally favors a transition state

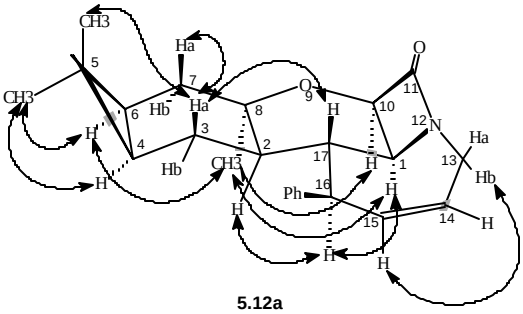


Fig. 11 Spatial correlations of protons observed in the NOESY spectrum of **5.12a**.

in which the *b*-lactam plane and the bulkier groups are away from each other. The stereochemistry of cyclisation is generally governed by C-4 center of the azetidinone.[7]

***Structure Elucidation of* 5.13a**

The structure determination of **5.13a** was carried out using spectral data of the ~80:20 diastereomeric mixture of **5.13a** & **5.12a**.

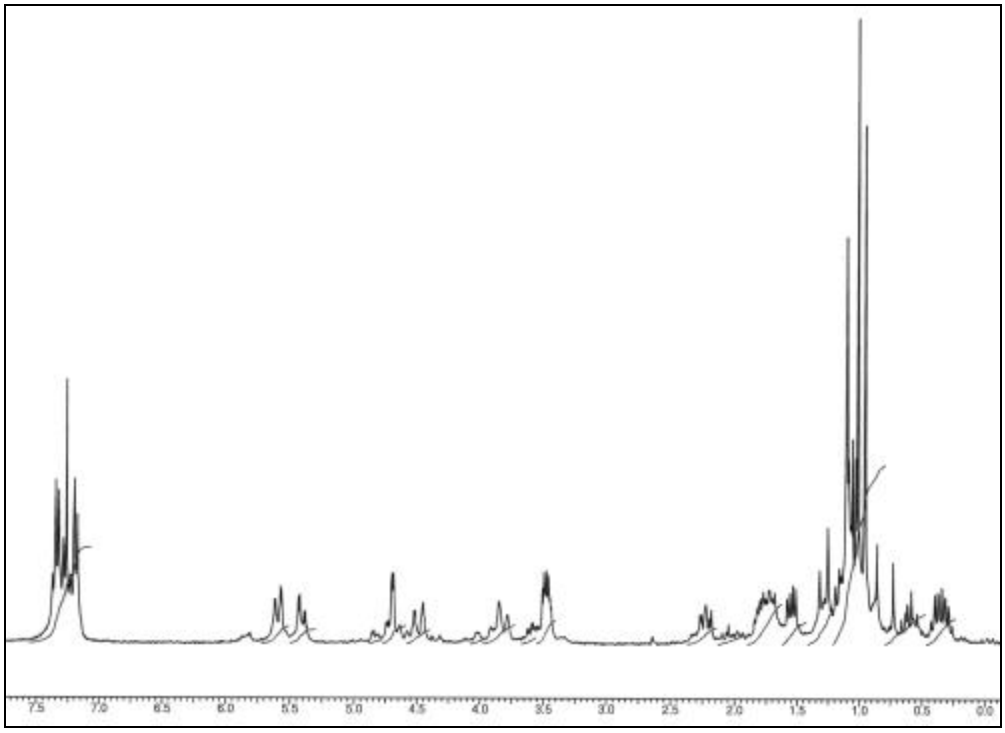
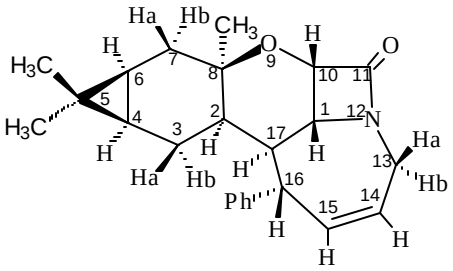


Fig. 12. ^{1}H NMR spectrum of **5.13a** (with small amount of **5.12a**).

In ^{1}H NMR spectrum, the three methyl groups at C-8 & C-5 appeared as three singlets at 0.95, 1.0 & 1.10. The carane ring protons were seen as multiplets between 0.2 to 2.5. A multiplet in the region between 3.4 to 3.6 could be accounted for H-16 & H-1. The two



5.13a

diastereotopic protons at G13 appeared as a multiplet between 3.80-4.0 & a doublet at 4.5. Other *b*-lactam proton, H-10 appeared as a broad doublet at 4.80. The olefinic protons H-14 & H-15 appeared as two doublets at 5.45 & 5.6. The aromatic protons appeared as multiplets in the region 7.0-7.7. To decide the connectivity among adjacent protons and to establish the molecular backbone of the compound, a COSY NMR spectrum of **5.13a** (Fig. 12) was recorded.

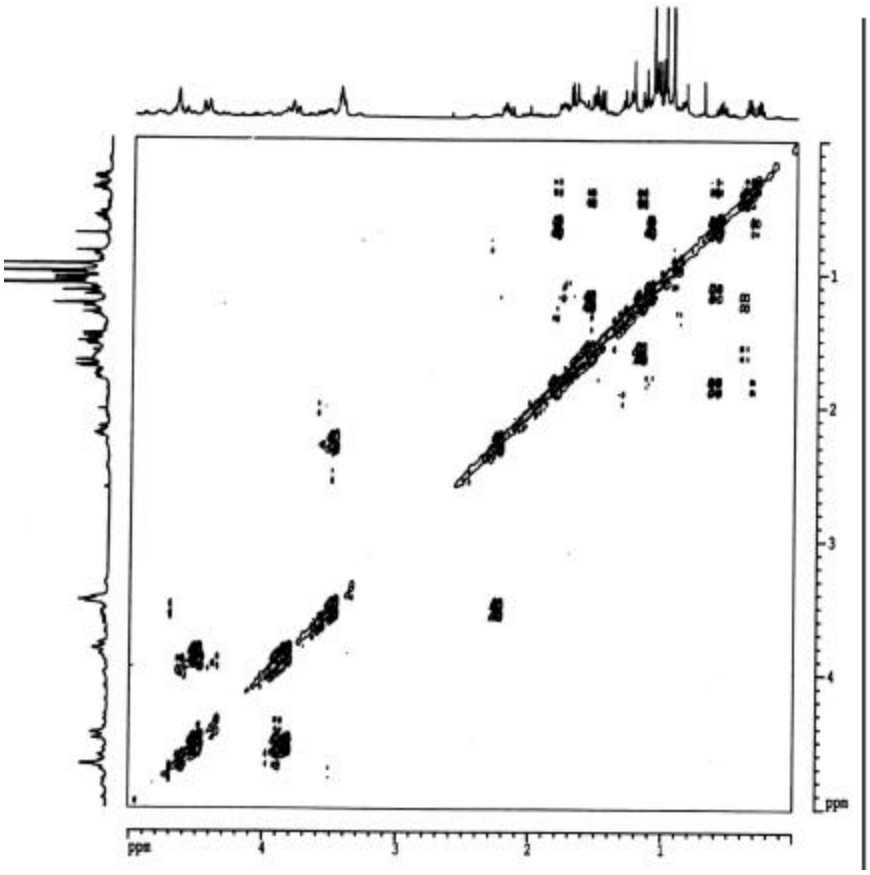


Fig. 13. Selected region of COSY NMR, **5.13a**.

Table 4. COSY NMR spectral data of *b*-lactam **5.13a**

No.	δ ppm	Proton No.	Multiplicity	Coupling constant *J* (Hz)	1H-1H (COSY)
1.	0.25-0.35	H-4	m	-	Ha-3, Hb-3, H-6
2.	0.35-0.45	H-6	m	-	H-4, Ha-7, Hb-7
3.	0.5-0.8	H-6	m	-	H-4, Ha-7, Hb-7
4.	1.1-1.2	Ha-3	m	-	Ha-3, H-4
5.	1.2-1.25	Ha-7	m	-	Hb-6, H-6
6.	1.5-1.65	Hb-7	m	-	Ha-7, H-6
7.	1.70-1.80	Hb-3	m	-	Ha-3, H-4
8.	2.25	H-17	ddd	2.2, 3.7, 4.4	H-2, H-16, H-1
10.	3.85	Ha-13	d	19.5	Hb-13, H-14
11.	4.50	Hb-13	dd	2.8, 19.5	Ha-13, H-14
12.	4.70	H-10	d	4.4	H-1
13.	5.4	H-14	ddd	1.2, 6, 18	Ha-13, H-14, H-10
14.	5.6	H-16	dd	1.2, 4.1	Hb-14, H-16 (w)

The structure for **5.13a** was assigned based on the ^{1}H NMR, ^{13}C NMR & COSY NMR spectral analysis. The assigned structure for **5.13a** was further confirmed unambiguously from its NOESY spectral data (Fig. 13).

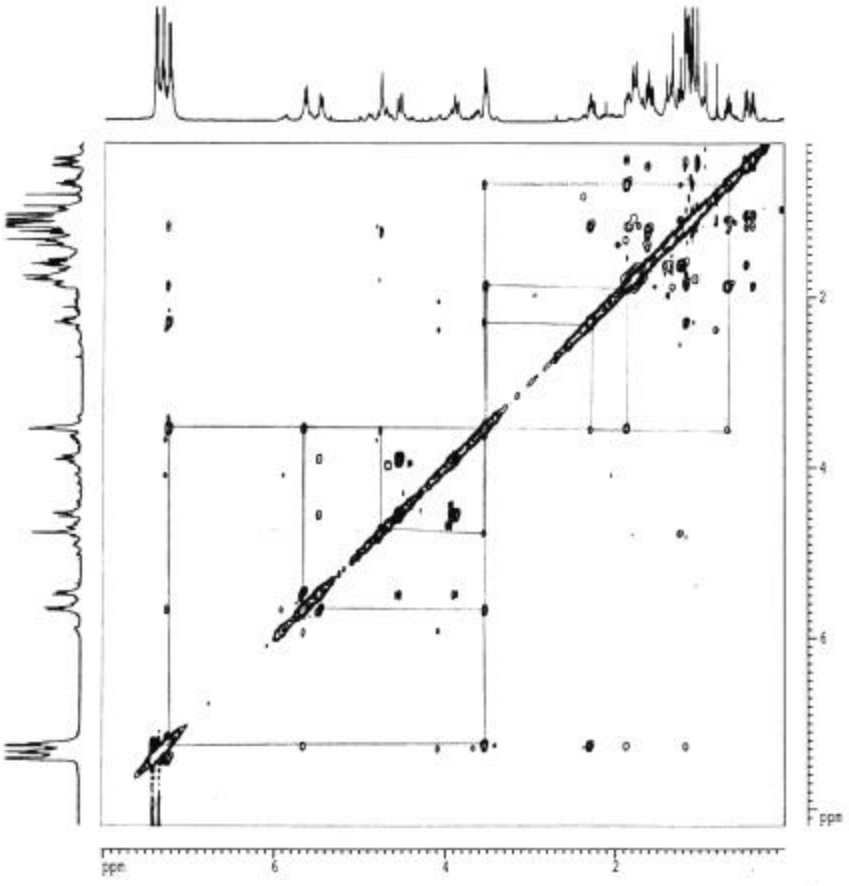
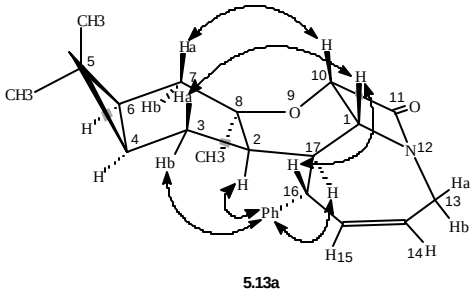


Fig. 14. NOESY NMR of **5.13a**.

The NOESY NMR spatial coupling pattern was highly decisive. Among the important signals, the benzylic proton H-16 & β-lactam proton H-1 appeared at 3.5. A careful identification of protons and their interaction pattern suggested



5.13a

that a strong interaction of H-1 with axial proton Ha-3. The benzylic proton H-16 has interaction with Hb-3. The aromatic protons of phenyl group at C-16 interact with H-2, Hb-3 & H-17. This observation strongly suggested that the β'orientation for H-16 and equatorial disposition of phenyl group in the structure. A strong interaction among H-17 and methyl at C-8 confirmed 'α' orientation of H-17. Based on this NOE spectral

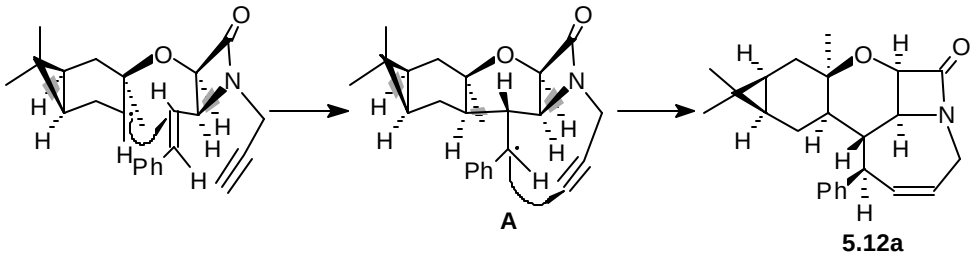
analysis the relative stereochemistry was assigned for **5.13a** and the absolute stereochemistry of newly formed centers was established as 16*S*,17*S*.

Mechanism of Tandem Radical Cyclisation

Mechanistically the tandem radical cyclisation is believed to be a stepwise one. The radical obtained from the cyclisation of the first sequence generates a second radical, which undergoes further quenching by a second radical trap. On the similar line, in case of the above cyclisation the secondary radical generated from bromine is quenched by the styryl double bond in a typical *6-exo trig* cyclisation mode. To avoid the interactions in the form of 1, 3 angle strain, with the β-lactam plane, the styryl double bond is oriented in such a way that the bulkier phenyl group remains opposite to the plane of the β-lactam ring. The benzylic radical thus formed acts as a second generation radical, which is trapped by the propargyl triple bond.

In case of **5.12a**, the benzylic radical (A) prefers to attack the terminal triple bond of the propargylic system from bottom of the triple bond, as benzylic group is α' oriented as shown in *Scheme 14*.

Scheme 14

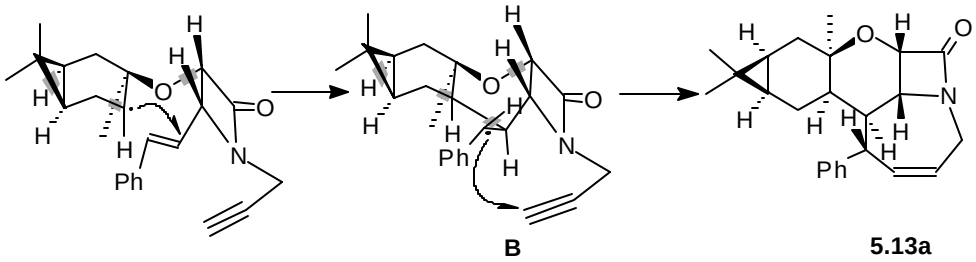


The structure A in which the phenyl group and propargylic group are away from each other and will have minimum steric interactions. Since Ph is at the apex of a 7 membered transition state, a conformation in which Ph occupies equatorial position. Therefore, a low energy transition state (**A**) will lead to the formation of tandem cyclized product **5.12a**.

In case of **5.13a**, benzylic group is β' oriented and benzylic radical will attack from the top of the propargylic triple bond (*Scheme 15*). A TS-**B**, accounts for energetically favorable conformation, in which the 'Ph' group and propargylic triple

bond are away from each other so as to avoid the steric interactions. Similarly, in this case also the tandem cyclization will lead to the formation of **5.13a** as the only isolable product.

Scheme 15



B **5.13a**

5.4 : Summary

The N-vinyl β-lactam derivative with bromo carane substituent was synthesized in good yield with low diastereoselectivity. The system failed to undergo tandem radical cyclisation so as to give [3.6.6.4.5] or [3.6.6.4.6] type of multicyclic ring system, instead, a tetracyclic [3.6.6.4] ring system was effected. The carane derived N-propargyl β-lactam was synthesized in good yield. When treated with Bu_3SnH in refluxing toluene it underwent tandem radical cyclisation to afford a pentacyclic ring system. The 6 *exo* trig – 7 *endo* dig cyclisation thus effected was highly diastereoselective and the structure of the mulicyclic product was determined by combined use of ^1H NMR, COSY, NOESY, HETCOSY spectral data.

5.5 : Experimental

***Preparation of* 5.01**

A solution of *E*-cinnamaldehyde (1.32 g,10 mmol), propargylamine (0.55 g, 10 mmol) in CH_2Cl_2 (10 mmol) was stirred overnight at room temperature over $MgSO_4$. The $MgSO_4$ was then filtered off and washed with an additional CH_2Cl_2 (15 mL). The resulting solution of imine **5.01** was cooled under argon and used as such for further reaction.

***Preparation of* 5.02**

To the cooled solution of imine **5.01** and Et_3N (4.16 mL, 30 mmol) in CH_2Cl_2 (15 mL), a solution of acid chloride **4.03a** (3.375 g, 15 mmol) in CH_2Cl_2 (15 mL) was added over ½ h at 0°C. The resulting mixture was stirred overnight at room temperature. After completion of the reaction (TLC), the reaction mixture was further diluted with CH_2Cl_2 (10 mL), and washed successively with satd. $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and finally brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to furnish **5.02** (90%, 3.93 g), which was purified by crystallization from pet ether/dichloromethane to get a white solid.

M. P.	:	106°C.
IR (cm^{-1})	:	1757.
^{1}H NMR	:	1.25 (s, 9H), 2.30 (t, *J* = 2.5 Hz), 3.80 (dd, *J* = 2.4, 17.6 Hz. 1H), 4.35 (dd, *J* = 2.4, 17.6 Hz, 1H), 4.7 (dd, *J* = 4.9, 8.8 Hz, 1H), 5.4 (d, *J* = 4.9 Hz, 1H), 6.4 (dd, *J* = 8.8, 16.1 Hz, 1H), 7.05-7.60 (m, 5H).

***Preparation of* 5.04**

To a solution of cinnamaldehyde (8 mL, 64 mmol) & N′,N′-dimethyl-ethylenediamine (13.9 mL, 127 mmol) in anhydrous ether (150 mL), was added anhydrous $MgSO_4$ (4 g). The mixture was stirred at room temperature for about 1 h. After completion of the reaction (^{1}H NMR of crude reaction mixture), the mixture was filtered to remove $MgSO_4$. The residue was rinsed with ether (3 x 15 mL) & the combined ethereal solution was concentrated under reduced pressure to provide a crude oil, which was distilled (95-100 °C, 1.5 torr) to get **5.04** as a light yellow oil. The spectral and analytical data for which was compared with the authentic sample.

***Preparation of* 5.05**

A solution of **5.04** (9.1 g, 45 mmol) and iodomethane (96 mmol) in CH_3CN (200 mL)was stirred at 25 °C for about ½ h. The precipitated quarternary ammonium salt was filtered, washed with dry ether and then dissolved in DMF (200 mL). NaH (2.72 g, 113 mL) was then added to the reaction mixture in several portions. After 12 h at 0-10 °C the reaction mixture was quenched with ice water. It was extracted with ethyl ether (3 x 150 mL) and the combined organic phase was washed with water (5 x 50 mL), dried over $MgSO_4$ and concentrated to get imine **5.05**, which was used as such without further purification in the next step.

***Preparation of (3R, 4S, 1′S, 3′R, 4′R, 6′R) & (3S, 4R, 1′S, 3′R, 4′R, 6′R) 3-[4′-bromo-3′,7′,7′-trimethyl-)-bicyclo[4.1.0]hept-3′-yloxy]-4-[2′′-phenyl-(E)-1′′-ethenyl]-1-vinyl-2-azetanone* 5.06 & 5.07**

A solution of acid chloride **1.12a** (0.617 g, 2 mmol) in CH_2Cl_2 (15 mL) was added drop-wise to a stirred solution of **5.05** (0.157 g, 1 mmol) and Et_3N (0.84 g, 6 mmol) in CH_2Cl_2 (20 mL) at 0°C, over a period of ½ h. The reaction mixture was allowed to warm up to room temperature and stirred further 12 h. It was then diluted with CH_2Cl_2 (10 mL), and washed successively with satd. $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and finally brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to furnish crude product, which was purified by flash column chromatography using pet ether/ethyl acetate to get diastereomeric mixture of **5.06a** & **5.07a** (0.257 g, 60%) as an oil.

$[\alpha]^{D}_{25}$	:	-35.92° (c 2.11, $CHCl_3$).
IR (cm^{-1})	:	1506, 1541, 1757, 3018.
^{1}H NMR	:	δ 0.55-0.85 (m, 2H), 0.88, 0.94, 0.96 & 0.98 (4s, total 6H), 1.31 & 1.40 (2s, total 3H), 1.30-2.5 (m, 4H), 3.9-4.1 (m, 1H), 4.4 (d, *J* = 8.9 Hz, 1H), 4.5-4.8 (m, 1H), 4.65 (d, *J* = 15.9 Hz, 1H), 5.02 & 5.10 (d, *J* = 5.0 Hz & d, *J* = 5.12 Hz respect. Total 1H), 6.21 & 6.6.31 (dd, *J* = 8.8 & 16 Hz for both, total 1H), 6.60-6.75 (m, 2H), 7.2-7.6 (m, 5H).
MS [m/z (%)]	:	216 (26), 158 (30), 135 (59), 115 (100), 93 (90), 91 (51), 79 (32).

***Preparation of* 5.08a & 5.09a**

Bu_3SnH (0.40 mL, 1.5 mmol) was added (5 min) to a refluxing solution of distereomeric mixture of β-lactams **5.06a** & **5.07a** (429 mg, 1 mmol) and AIBN (16 mg, 0.1 mmol) in benzene (10 mL). The reaction mixture was further allowed to reflux for ½ h. After completion of the reaction (TLC) the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and purified by flash column chromatography (Silica gel, petroleum ether / ethyl acetate ratio 92:10) to get a diastereomeric mixture of cyclized products **5.08a** & **5.09a** (211 mg, 60%). One of the diastereomers **5.08a** could be separated by using flash chromatography.

***The data for the diastereomer* 5.08a**

$[\alpha]^D_{25}$: -7.84° (c 2.5, $CHCl_3$).

IR (cm^{-1}) : 1635, 1757, 2867, 2933, 3016.

^1H NMR : δ 0.59 to 0.80 (m, 2H), 0.88, 0.94, 0.96, 0.98 (4s, total 6H), 1.31 & 1.40 (2s, total 3H), 1.40-1.46 (m, 1H), 2.24-2.42 (m, 3H), 3.94-4.04 (m, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.48-4.60 (m, 1H), 4.61 (d, *J* = 16 Hz, 1H), 5.02 & 5.10 (d, *J* = 5.0 Hz & d, *J* = 5.1 Hz, total 1H), 6.21 & 6.31 (dd, *J* = 8.8 & 15.8 Hz for both, total 1H), 6.58-6.85 (m, 2H), 7.2-7.5 (m, 5H).

m/e (%) : 216 (26), 158 (30), 135 (59), 115 (100), 93 (90), 91 (51), 79 (32).

***Preparation of* 5.10a & 5.11a**

To the stirred solution of imine **5.01** (0.169 g, 1 mmol) & Et_3N (0.84 ml, 6 mmol) in CH_2Cl_2 (15 mL) was added acid chloride **1.12a** (0.617 g, 2 mmol) in CH_2Cl_2 (15 mL) at 0°C over ½ h. The reaction mixture was allowed to stir further, at room temperature, for 12 h. After completion of the reaction (TLC) the reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with satd. $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and finally brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to furnish a crude product, which was purified by flash column chromatography (pet ether / ethyl acetate mixtures) to get **5.10a** & **5.11a** (0.257 g,

60%) as a gum. One of the diastereomers, **5.10a,** was obtained in pure the form by flash column chromatography of the diastereomeric mixture. The spectral & analytical data for **5.10a** is given below.

(3R, 4S, 1′S, 3′R, 4′R, 6′R) 3-[4′-bromo-3,7,7-trimethylbicyclo(4.1.0)hept-3′-yloxy]-4-[2″-phenyl-(E)-1″-ethenyl]-1-(2‴-propynyl)-azetan-2-one **5.10a**

Obtained as a gum.

$[\alpha]^{D}_{25}$	:	-17.75° (c 0.71, $CHCl_3$).
IR (cm^{-1})	:	1759, 2939, 3303.
^{1}H NMR	:	δ 0.55-0.70 (m, 1H), 0.70-0.85 (m, 1H), 0.95 (s, 3H), 1.00 (s, 3H), 1.30-1.50 (m, 1H), 2.30 (s, 1H), 2.25-2.50 (m, 3H), 3.70 (dd, *J* = 2.4, 17.6 Hz, 1H), 3.95-4.20 (m, 1H), 4.30 (dd, *J* = 2.4, 17.6 Hz, 1H), 4.45 (dd, *J* = 4.4, 8.8 Hz, 1H), 5.05 (d, *J* = 4.9 Hz, 1H), 6.4 (dd, *J* = 9.3, 16.1 Hz, 1H), 6.70 (d, *J* = 15.6 Hz), 7.20-7.60 (m, 5H).
^{13}C NMR	:	δ 15.7, 17.7, 18.0, 19.3, 19.5, 19.6, 21.8, 28.5, 29.3, 32.1, 32.3, 60.3, 61.8, 72.5, 77.8, 78.0, 124.0, 126.9, 127.8, 128.2, 128.7, 136.3, 136.4, 167.1.
m/e (%)	:	226 (43), 198 (30), 135 (66), 115 (100), 93 (90), 94 (65), 66 (30).
Microanalysis	:	M.F. $C_{24}H_{28}BrNO_2$.
	:	Calculated C : 65.16 H : 6.38 N : 3.17
		Obtained C : 64.87 H : 6.15 N : 2.95

Preparation of (1S, 2R, 4R, 6S, 8R, 10R, 16R, 17S) 5,5,8-trimethyl-16-phenyl-9-oxa-12-azapentacyclo[8.6.1.$0^{2,8}$. $0^{4,6}$.$0^{12,17}$]heptadec-14-en-11-one **5.12a**

A toluene solution (10 mL) of Bu_3SnH (0.40 mL, 1.5 mmol) containing AIBN (30 mg, 0.18 mmol) was added by syringe pump over a period of 5 h, to the refluxing solution of β-lactam **5.10a** (441 mg, 1 mmol) in toluene (20 mL). After the addition is over, again AIBN (10 mg, 0.06) in toluene (5 mL) was added and the reaction mixture was further refluxed for 1 h. After completion of the reaction (TLC) the solvent was removed on rotary evaporator under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column

chromatography (Silica gel, petroleum ether / ethyl acetate ratio 75 : 25), when the product was isolated (145 mg, 44%) as a gum.

$[\alpha]^{D}_{25}$	:	+21.93° (c 0.31, $CHCl_3$).
IR (cm^{-1})	:	1750.
^{1}H NMR	:	δ -0.1-0.1 (m, 1H), 0.15-0.30 (m, 1H), 0.4 –0.5 (m, 1H), 0.79 (s, 3H), 0.9 (d, 1H), 0.92 (s, 3H), 0.95-1.15 (m, 1H), 1.15-1.25 (m, 1H), 1.38 (s, 3H), 1.75 (dd, *J* = 7.5, 14.3 Hz, 1H), 2.1 (dd, *J* = 10.0, 10.0, 10.0 Hz, 1H), 3.35 (bd, *J* = 10.0 Hz, 1H), 3.60 (dd, *J* = 4.4, 9.6 Hz, 1H), 3.90 (broad dd, *J* = 6.0, 18.0 Hz, 1H), 4.35 (dd, *J* = 18 Hz, 1H), 4.85 (dd, *J* = 1.0, 4.4 Hz, 1H), 5.35-5.45 (m, 1H), 5.55-5.70 (m, 1H), 7.0-7.65 (m, 5H).
^{13}C NMR	:	δ 18.4, 18.7, 21.1, 21.3, 24.1, 28.0, 29.7, 31.7, 44.0, 46.0, 49.0, 54.2, 55.0, 74.9, 77.8, 118.7, 126.8, 127.5, 128.0, 128.7, 135.1, 144.2, 166.0.
m/e (%)	:	191 (16), 105 (30), 95 (100), 93 (80), 91 (68), 77 (32), 57 (48), 55 (42).
Microanalysis	:	M.F. $C_{28}H_{33}NO_3$.
	:	Calculated C : 77.91 H : 7.71 N : 3.25
		Obtained C : 77.68 H : 7.84 N : 3.47

5.6 References

1. For reviews on tandem radical cyclisation, see: (a) Ho, T., -L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Waldmann, H. *Natchr. Chem. Tech. Lab*. **1992**, *40*, 1133. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131. (d) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (e) Fukumoto, K. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 2.

2. (a) Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1332. (b) Ihara, M.; Fukumoto, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010. (c) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203.

3. For a recent review on tandem radical cyclisation see: Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

4. Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688.

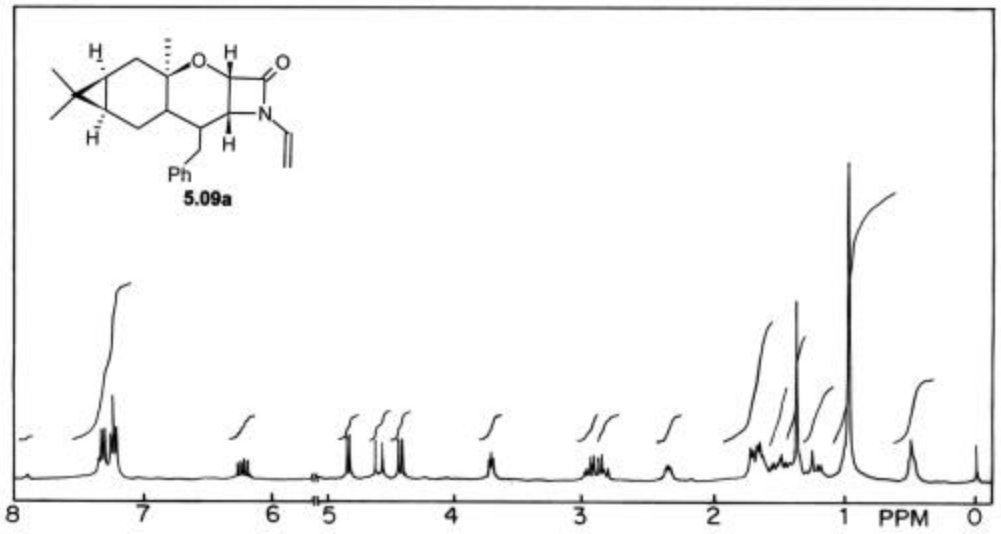
5. Jenkinson, J. J.; Parsons, P. J.; Eyley, S. C. *Synlett* **1992**, 679.

6. Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y. –S.; Kim, Y. K.; Yum, M.; Kim, S. *J. Am. Chem. Soc.* **1997**, *119*, 8391.

7. Alcaide, B.; Rodrigurz-Campos, I. M.; Rodriguez-Lopez, J.; Rodriguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377.

8. Georg, G. I.; He, P.; Kant, J.; Wu, Z. J. **1993**, *58*, 5771.

9. For mechanistic studies and application of MM2 calculations to the tandem radical cyclisation reactions, see: (a) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y. –S.; Kim, Y. K. *J. Am. Chem. Soc.* **1997**, *199*, 8391. (b) Tomida, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 2363. (c) Takahashi, T.; Katouda, W.; Sakamoto, Y.; Tomida, S.; Yamada, H. *Tetrahedron Lett.* **1995**, *36*, 2273. (d) Takahashi, T.; Tomida, S.; Sakamoto, Y.; Yamada, H. *J. Org. Chem,* **1997**, *62*, 1912.



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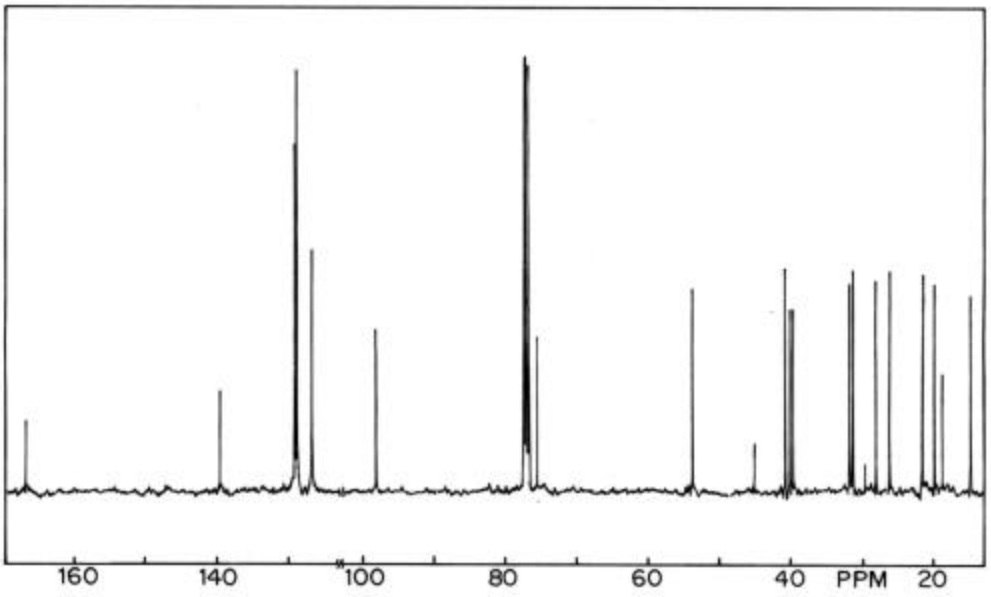

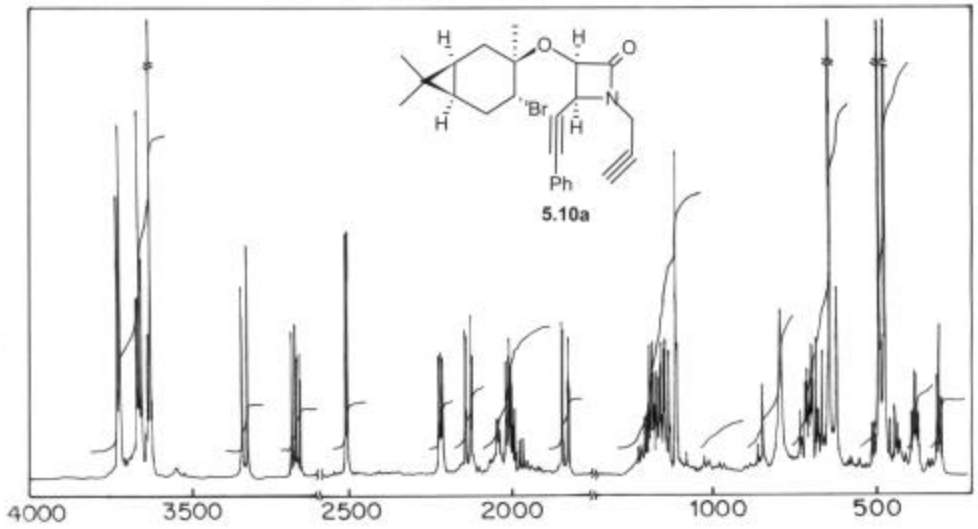
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Ph
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3500
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1000
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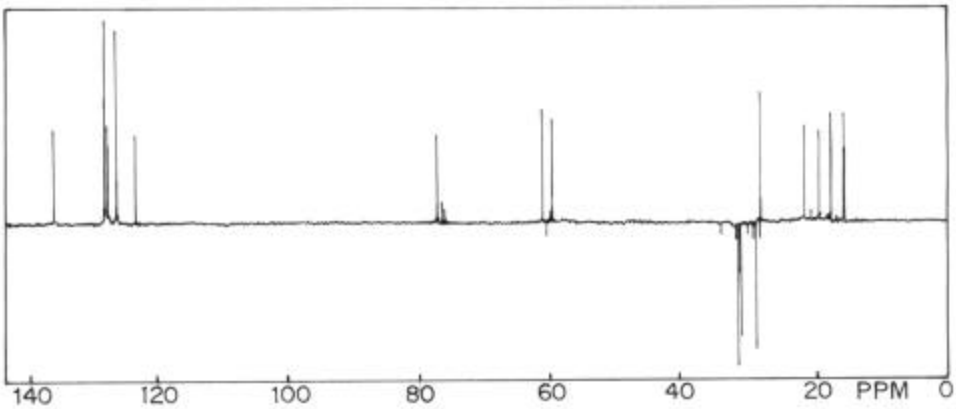
5.10a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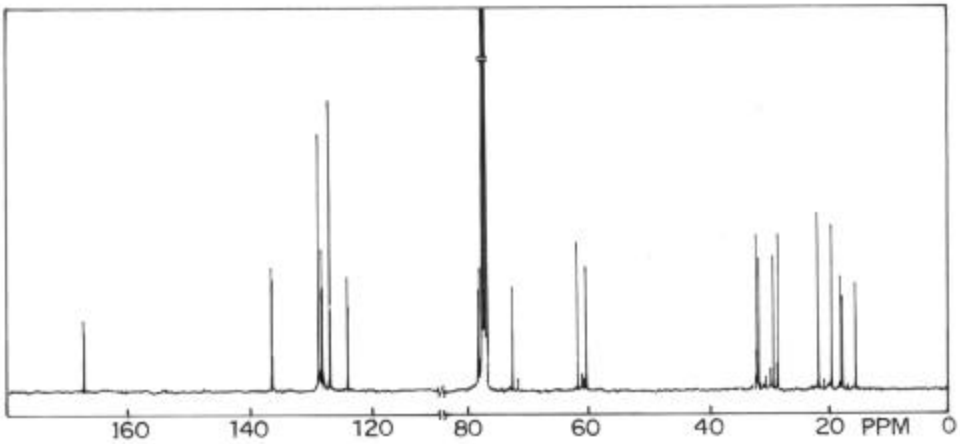
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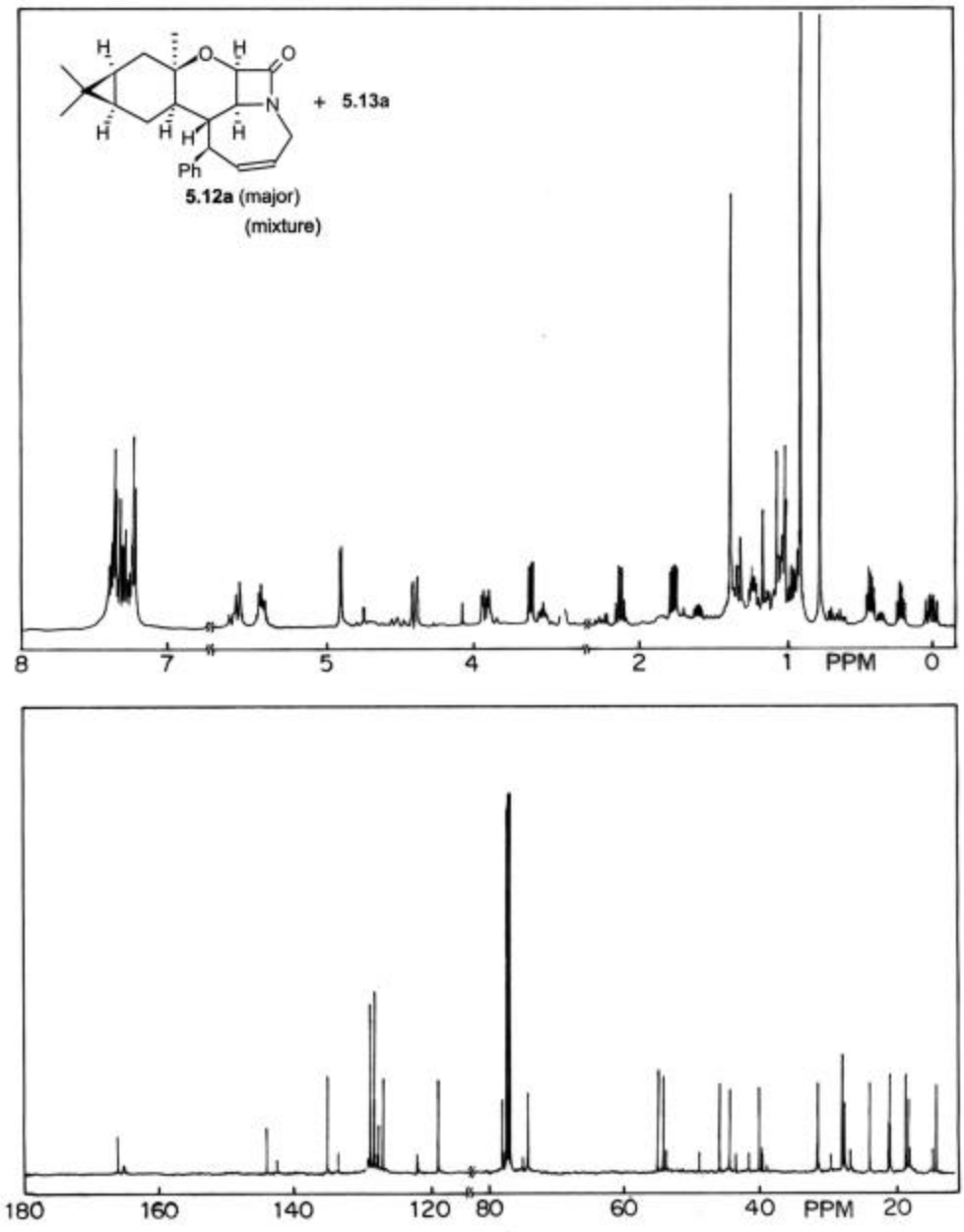
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(mixture)
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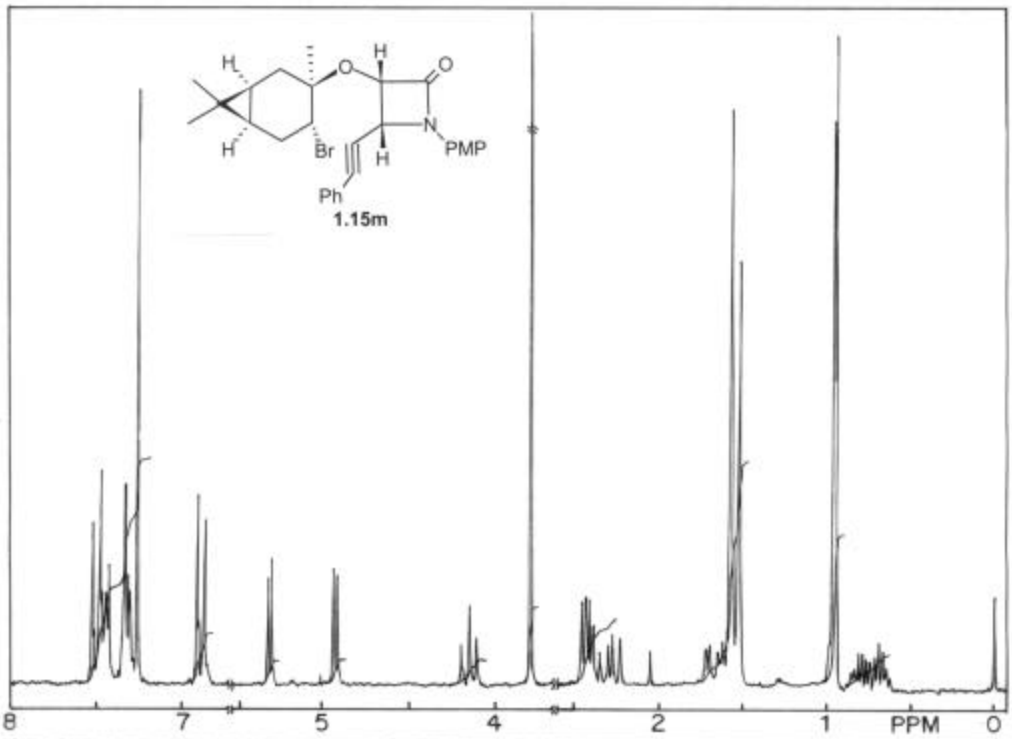
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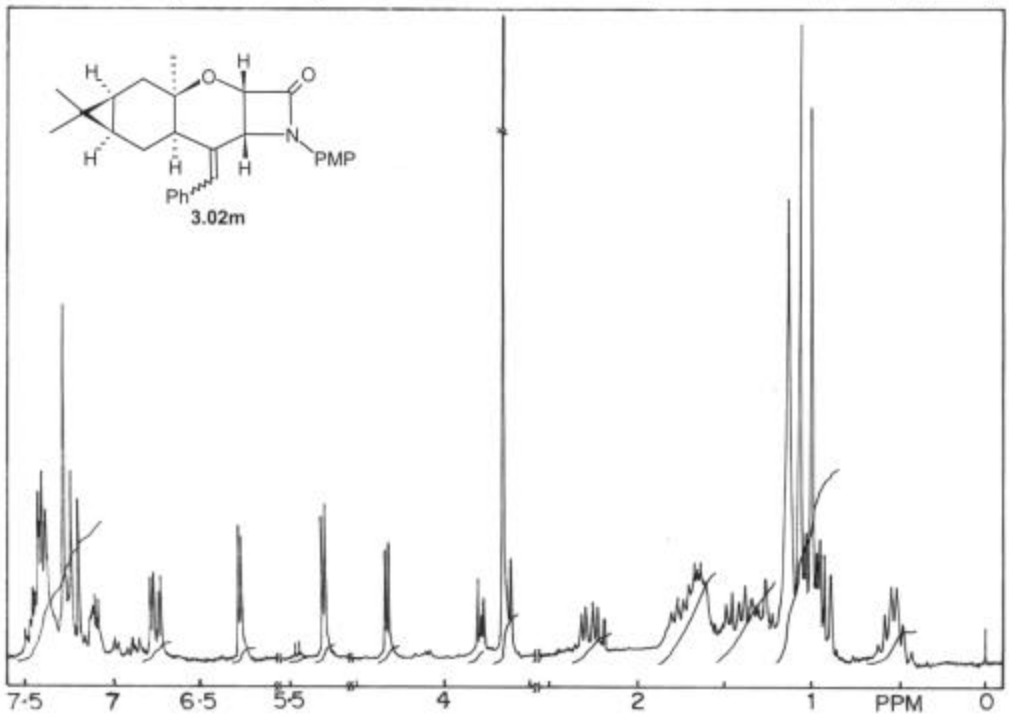
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Chapter VI

Stereoselective Synthesis of *cis*-*b*-Lactams Using Glucose Derived Chiral Aldehyde *via* Asymmetric Staudinger Reaction

---

Finally, one that is very apropos to us chemists:

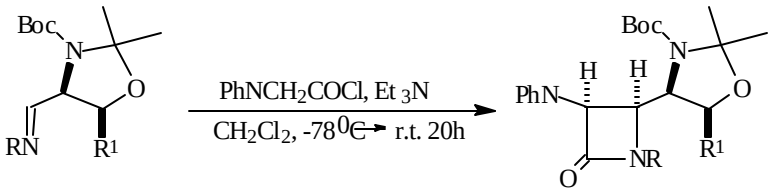
And as diamonds ere their season,
All is coal before it's light.
J. Marti

6.1 : Introduction

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

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

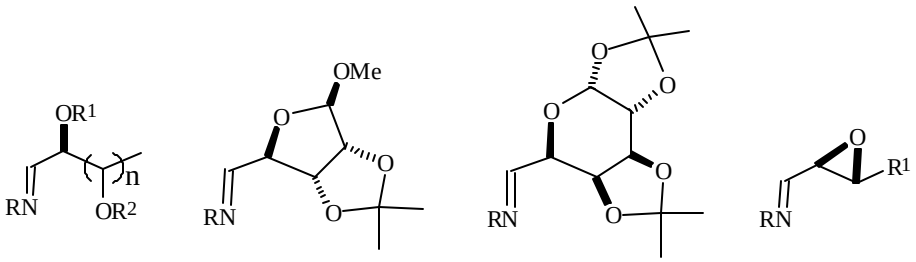
Scheme 1



R1 = H, Ph

The most common approaches in the Staudinger reaction involve the use of α-oxyaldehydes-derived imines, sugar derived imines and α,β-epoxyimines (*Chart 1*).[2]

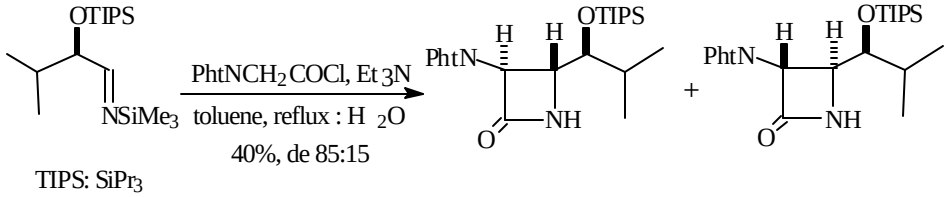
Chart 1



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

Recently, Panunzio and co-workers have reported a case of *trans*-stereoselectivity preference. The method involves the reaction of phthalimidoacetyl chloride with N-trimethylsilyl imines and trimethylamine under toluene reflux conditions (*Scheme 2*).[3]

Scheme 2



According to the proposed mechanism the cycloaddition step involved (fig. 1) intermediate like in Fig. 1.

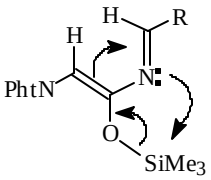


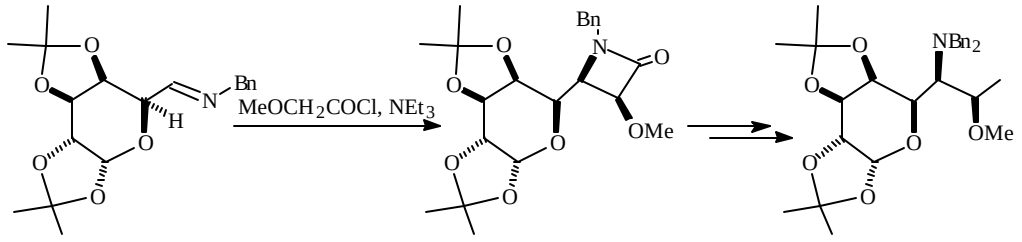
Fig. 1.

Carbohydrate derived chiral auxiliaries

Carbohydrates and related polyhydroxy compounds have attracted considerable attention and increasing interest as a chiral starting materials in the ex-chiral pool synthesis of chiral drugs and natural products.[4] Though carbohydrates contain upto five stereochemical centers with lots of stereochemical information, they are at the same time "overfunctionalised" by them to be successfully applicable as stereodifferentiating groups.

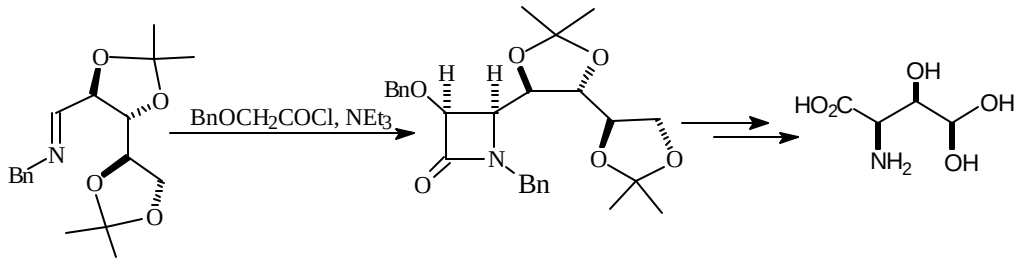
The use of carbohydrates in the asymmetric synthesis of *b*-lactams is now well known. It is Bose & Manhas,[2b,2e,5] who successfully introduced the use of chiral imines derived from carbohydrates in the asymmetric Staudinger reaction. They synthesized different chiral auxiliaries derived from sugars and successfully employed them as chiral imine components. The chiral imines proved to be extremely efficient and always a very high level of diastereoselectivity (de > 90%) was obtained. They mainly used it as chiral synthon rather than chiral pool, and utilized the carbohydrate skeleton in the synthesis of important natural products. A single *cis*-diastereomer was obtained, on reaction of carbohydrate based chiral imine with methoxyketene (*Scheme 3*). On further synthetic transformations this isomer was converted into 6-*epi*-lincosamine.[6]

Scheme 3



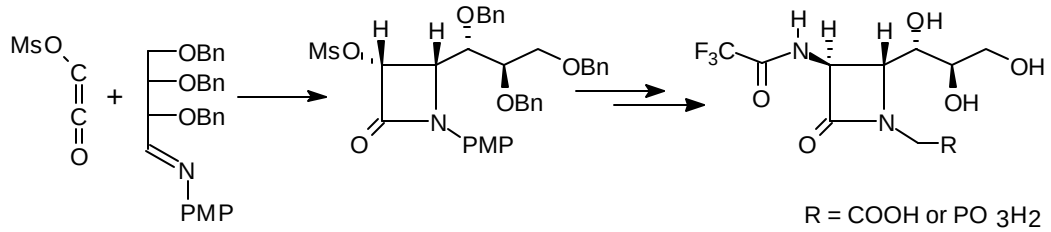
Similarly, the cycloaddition reaction of benzyloxyketene with the imine proceeded under complete control of diastereoselectivity to give a *cis-b*-lactam. On further chemical transformations it was possible to synthesize (-)-polyoxamic acid, a enantiomer of the component of the antifungal polyoxin antibiotic (*Scheme 4*).[7]

Scheme 4



Recently Stortz et. al. have reported the use of D-erythrose derived imines in the synthesis of 2,3-dideoxy-D-mannonoic acid derivatives (*Scheme 5*).[8]

Scheme 5



Mechanism

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

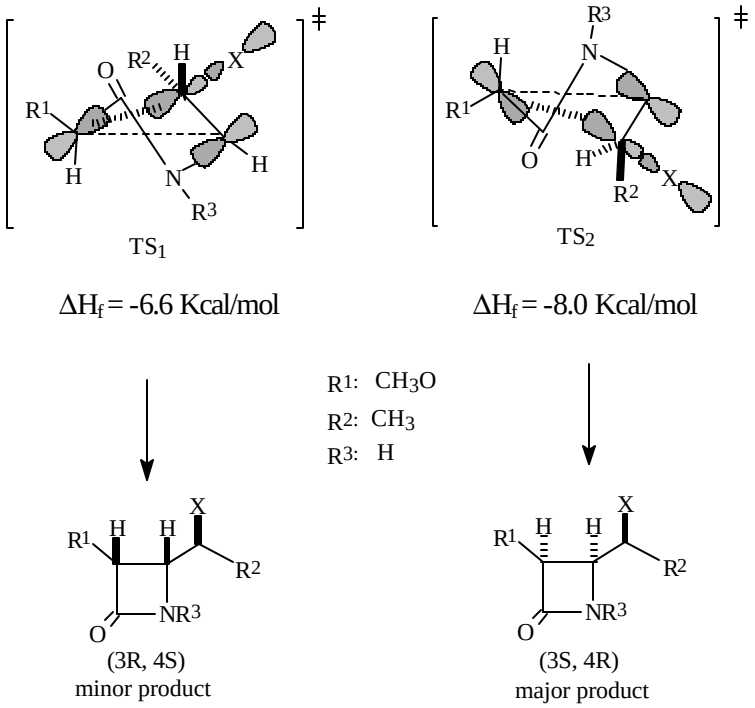


Fig. 2.

In case of TS_1, there is an angular arrangement between C3 and the exocyclic C-X bond, while linear arrangement exists between the same atoms in TS_2. So there is a steric interaction between the methyl group (R_2) and the *b*-lactam ring. Such kind of interaction is absent in the case of TS_2. As a result, there is effective HOMO-σ* stabilization and the product obtained is major one.

6.2 : Present Work

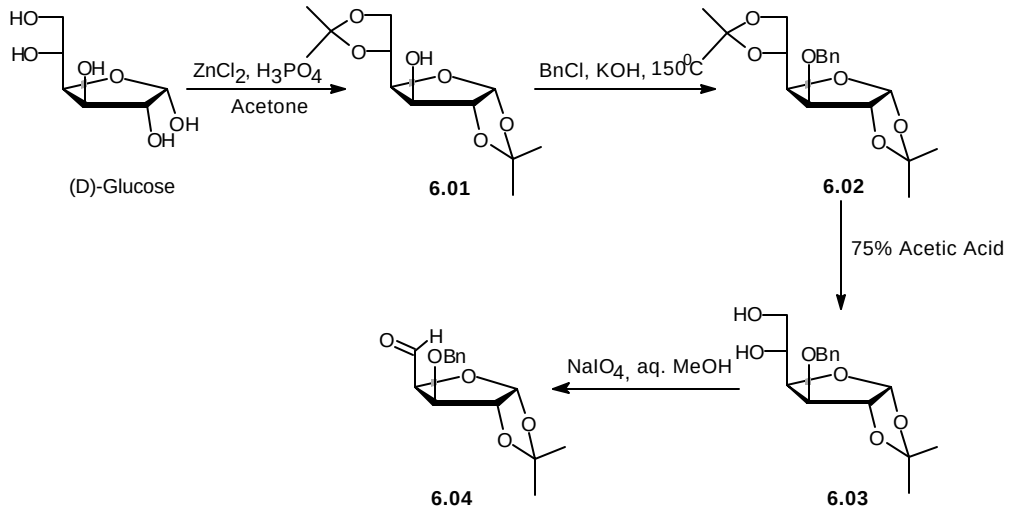
The use of carbohydrate derived chiral auxiliaries in the asymmetric synthesis of *b*-lactams is now well established. The literature reports indicated that the use of sugar derived chiral aldehydes is also popular one. Surprisingly, the use of D-glucose derived aldehyde, as chiral imine precursor is not well exploited. This prompted us to think about the use of D-glucose as a chiral auxiliary. The present chapter deals with the synthesis and structure determination of cis-*b*-lactams using D-glucose derived chiral aldehyde.

6.3 : Results & discussion

***Synthesis of* 6.01**

D-Glucose was transformed into aldehyde **6.04** in few synthetic steps. Acetone solution of D-Glucose was stirred with $ZnCl_2$ / H_3PO_4 to prepare the diacetonide **6.01** *(Scheme 6)*.

Scheme 6

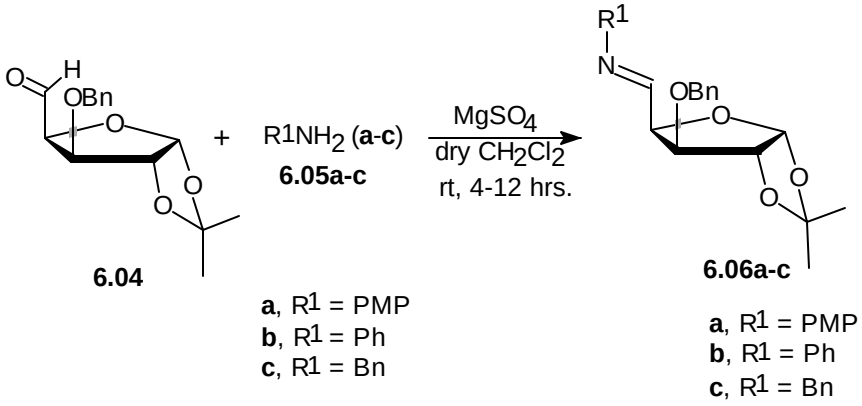


The benzyl protection of the diacetonide **6.01** was effected, by heating it with BnCl at 150°C, in the presence of KOH as a base. The diacetonide was selectively deprotected to glycol **6.03** by treating **6.02** with 75% aq. acetic acid. The glycol **6.03** on oxidative cleavage with $NaIO_4$ resulted in the formation of aldehyde **6.04** in good yield.

***Synthesis of imine* 6.06**

The analogous imines **6.06a-c** were synthesized by the reaction of aldehyde **6.04** with amines **6.05a-c** in the presence of $MgSO_4$ *(Scheme 7)*.

Scheme 7



***Synthesis of* 6.08a-d**

The chiral imines **6.06a-c**, when treated with acid chlorides **6.07a-c** in the presence of triethylamine, reacted smoothly to furnish the *b*-lactams **6.08a-d** stereospecifically as a single *cis* diastereomer in good yield *(Scheme 8)*.

Scheme 8

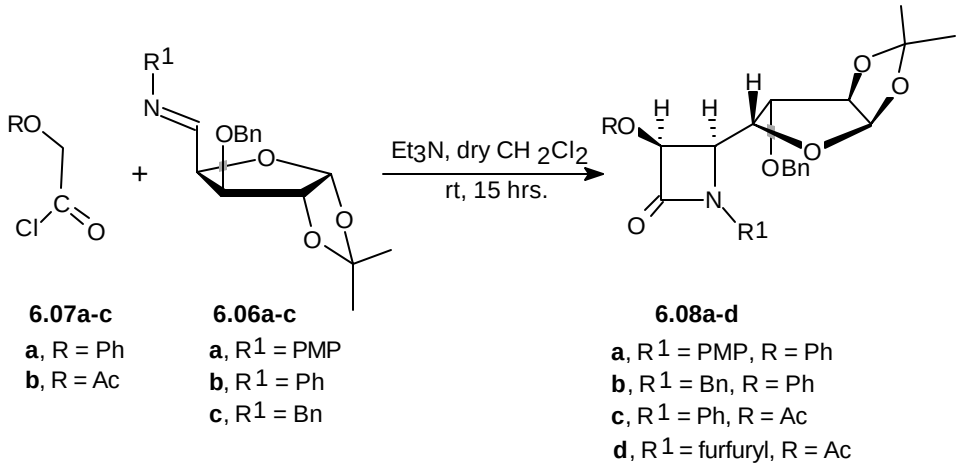


Table 1: Synthesis of **6.08a-d** from **6.06a-c**

Compound no.	R	R^1	Diastereoselectivity	Yield
6.08a	Ph	PMP	100%	70
6.08b	Ph	Bn	„	69
6.08c	Ac	Ph	„	72
6.08d	Ac	Furfuryl	„	65

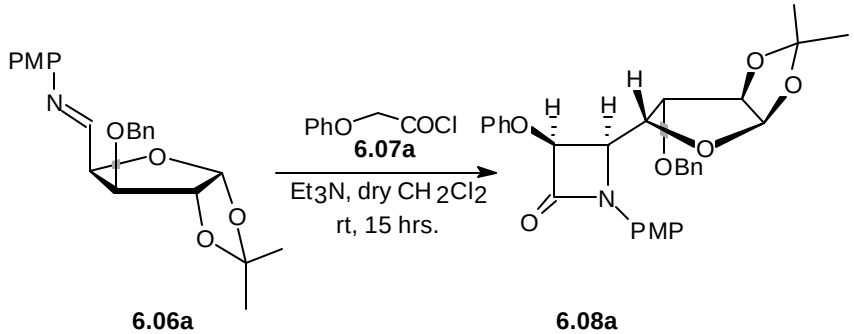
The chemical yields of the cycloaddition reaction were moderate to good and diastereoselectivity was excellent. The ^{1}H NMR showed presence of only one diastereomer. The compounds were easily purified by flash column chromatography or by fractional crystallization.

The *b*-lactam **6.08a** was selected for detailed discussion regarding the preparation and structural assignment, which is presented below:

***Synthesis of* 6.08a**

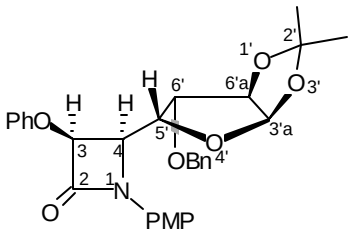
The imine **6.06a** on treatment with phenoxyacetyl chloride in the presence of triethylamine underwent ketene-imine cycloaddition reaction to give *b*-lactam **6.08a** in 70% yield. The NMR of the crude reaction mixture showed presence of peaks corresponding to only one diastereomer. The crude product was purified by column chromatography to get a solid, which was further purified by crystallization from dichlromethane/methanol *(Scheme 9)*.

Scheme 9



The crystallized product was a white solid with m.p. 148°C. The IR of **6.08a** showed peak at 1749 cm^{-1}, typical of *b*-lactam amide carbonyl. The mass spectrum showed presence of molecular ion peak at 517 (5%).

^{1}H NMR showed two singlets at 1.34 & 1.54 belonging to two methyl groups of acetonide. The OMe of PMP group resonated as a singlet at 3.78. One of the diastereotopic protons from the benzyl group resonated as a doublet at 4.3 with coupling constant 11.7 Hz. One of the ring Protons of the sugar skeleton, H-6′a appeared at 4.45 as a doublet



6.08a

with coupling constant J = 3.0 Hz. The signals due to *b*-lactam proton H-4, the other ring protons H-5′, H-6′ and one of the benzylic protons appeared as a merged multiplet in the region of 4.5-4.8. The other *b*-lactam proton H-3, appeared at 5.31 as a doublet with coupling constant 5.4 Hz. A high coupling constant indicated a *cis* stereochemistry among *b*-lactam ring protons. The H-3′a was seen downfield at 6.08, with coupling constant J = 3.9 Hz. The aromatic protons were seen as multiplets in the region of 6.80-7.70.

In the ^{13}C-NMR of **6.08a**, the dimethyl acetonide peaks at C-2′ appeared at 26.29 & 26.83. The *b*-lactam carbon at C-4 & the OMe from the PMP moiety appeared at 55.40 & 58.47. The rest of the carbons of the chiral backbone as well as the *b*-lactam i. e. C-6′, C-6, C-5′, C-3 & O-CH_2-Ph carbon appeared at 71.95, 79.14, 81.38, 81.86 & 83.14.

***X-ray crystallographic analysis of* 6.08a**

To determine the absolute stereochemistry of **6.08a**, a single crystal X-ray analysis of **6.08a** was carried out. Suitable Crystals for X-ray analysis were obtained by crystallization of **6.08a** from dichloromethane/methanol solvent system (Fig. 1).

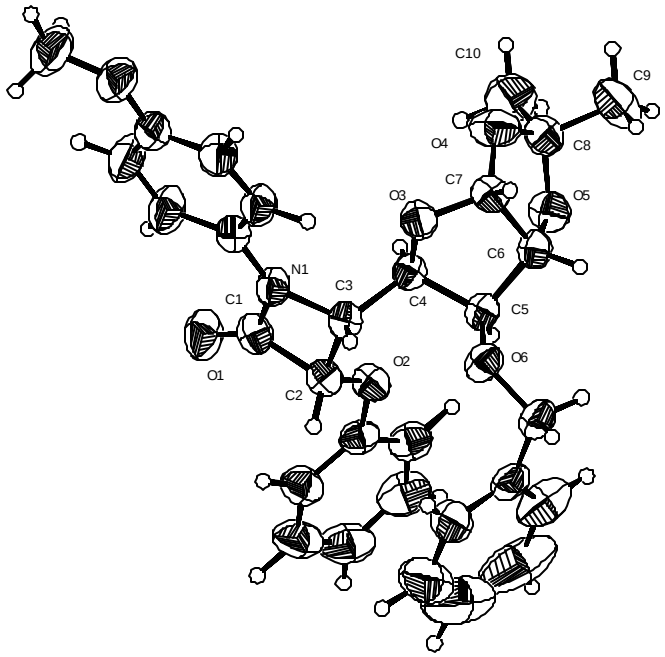


Fig. 3. *ORTEP* diagram of the crystals of **6.08a**.

The important X-ray data for **6.08a** is as follows.

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

The data were collected on Enariuf Nonius CAD-4 single crystal X-ray diffractometer using Cu-Kα radiation (λ = 1.54060 Å) and ω-2θ scan mode to a θ range of 3.89 to 59.82^0. The structure was solved by direct positional and anisotropic thermal parameters for non hydrogen atom converged to R*w* = 0.1235 R1 = 0.0575 for 2314 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference Fourier which was held fixed during the refinement. The refinements were carried out using SHELEX-97[11]

The X-ray analysis further confirmed the assigned structure to **6.08a**. The absolute stereochemistry of newly formed *b*-lactam ring centers were assigned as 3*S*, 4*R* based on the known absolute stereochemistry of sugar residue present in the molecule. The overall absolute stereochemistry of *b*-lactam **6.08a** was established as 3*R*, 4*R*, 3′a*R*, 5′*R*, 6′*S*, 6′a*R*.

6.4 : Summary

Chiral imines derived from D-glucose were used effectively in the asymmetric Staudinger rection. The corresponding *b*-lactams were obtained stereospecifically as a single *cis* diastereomers in good chemical yields. The absolute stereochemistry of the product was determined from the single crystal X-ray analysis of one of the compounds.

6.5 : Experimental

***Preparation of* 6.01**

To a stirred mixture of aldehyde **6.01** (3.33 g, 12 mmol), $MgSO_4$ and dichloromethane (40 mL), a solution of *p*-anisidine (1.23 g, 10 ml) in dichloromethane (5 mL) was added at 0°C. The reaction mixture was then allowed to stir at room temperature for 5 h. After completion of the reaction (TLC), the reaction mixture was filtered through sintered funnel to remove $MgSO_4$. The filtrate on removal of solvent at reduced pressure afforded imine **6.02** (3.45 g, 90%), as a pale yellow liquid. This crude imine was used as such without further purification in the next step.

***Preparation of 4-(6′-benzyloxymethyl-2′,2′-dimethylperhydrofuro[2, 3-d][1,3]dioxo-5′-yl)-1-(4″-methoxyphenyl)-3-phenoxy-(3S, 4R)-azetan-2-one* 6.03**

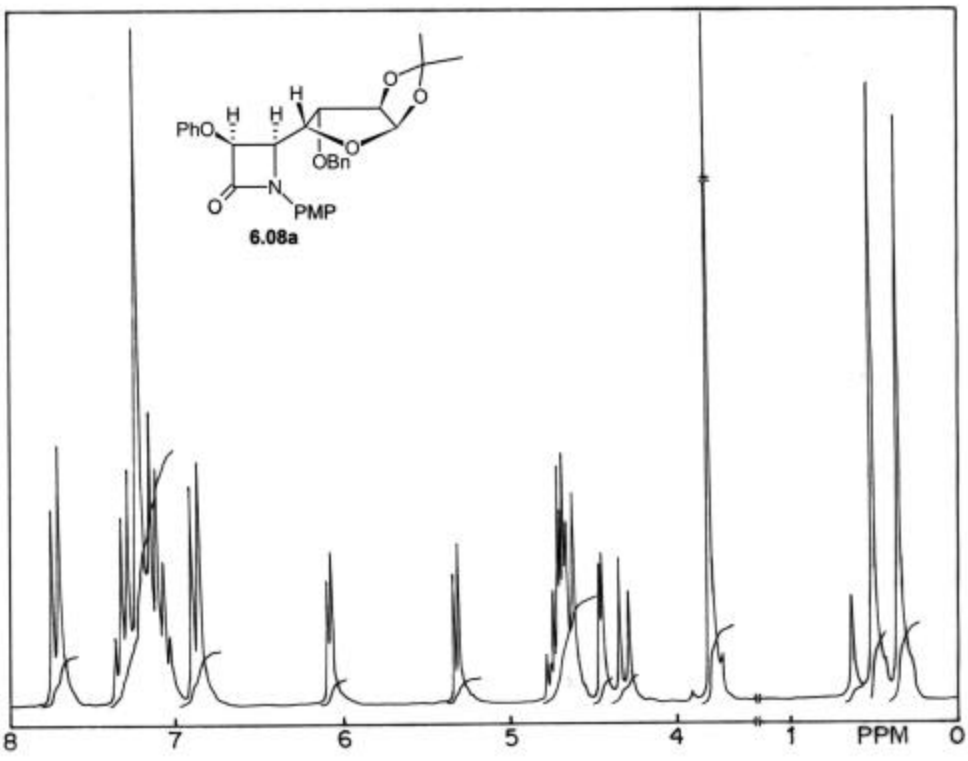
To a stirred solution of imine **6.02** (0.383 g, 1 mmol) and Et_3N (0.303 mL, 3 mmol) in dry dichloromethane (15 mL), a solution of phenoxyacetyl chloride (0.255 g, 1.5 mmol) in dry dichloromethane (5 mL) was added drop-wise at 0°C over a period of 1 h. The reaction mixture was allowed to warm-up to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (20 mL) and washed successively with water (25 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over anhyd. Na_2SO_4. The solvent was removed under vacuum and residue was purified by crystallization (pet ether/dichloromethane) to obtain **6.03** as a white crystalline solid.

M.P.	:	148°C
$[\alpha]^{D}_{25}$	:	-245° (c 1.85, CH_2Cl_2).
IR (cm^{-1})	:	1514, 1749, 3018.
^{1}H NMR	:	δ 1.34 (s, 3H), 1.54 (s, 3H), 3.78 (s, 3H), 4.3 (d, *J* = 1.7 Hz, 1H), 4.45 (d, *J* = 3.0 Hz, 1H), 4.5-4.8 (m, 4H), 5.31 (d, *J* = 5.4 Hz, 1H), 6.08 (d, *J* = 3.9 Hz, 1H), 6.87 (d, *J* = 8 Hz, 2H), 6.9-7.41 (m, 10H), 7.7 (d, *J* = 8 Hz, 2H).
$^{!3}$C NMR		δ 26.29, 26.83, 55.40, 58.47, 71.95, 79.14, 81.38, 81.86, 83.14, 104.96, 111.83, 113.94, 115.62, 119.79, 122.41, 127.57, 127.99, 128.46, 129.62, 131.21, 137.12, 156.55, 157.39, 163.44.

MS m/z (%)	:	517, (M^+, 5), 518 (M^++1, 1), 519 (M^++2, 0.1), 430 (2), 149 (41), 134 (15), 91 (100), 77 (12).			
Microanalysis	:	M. F. $C_{30}H_{31}NO_7$			
	:	Calculated	C : 70.04	H : 6.26	N : 2.63
		Obtained	C : 69.85	H : 6.01	N : 2.49

6.6 References

1. Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360-9369.
2. For Sugar derived aldehydes and α-Oxyaldehydes as chiral imine component in asymmetric Staudinger reaction, see: (a) Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta.* **1983**, *66*, 2206-2209. (b) Wagle, D. R.; Garai, G.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227-4236. (c) Brown, A. D.; Colvin, E. W. *Tetrahedron Lett.* **1991**, *32*, 5187-5190. (d) Saito, S.; Ishikawa, T.; Morikawe, T. *Synlett* **1993**, 139-140. (e) Wagle, D. R.; Garai, C.; Monteleone, M. G.; Bose, A. K. *Tetrahedron Lett.* **1988**, *29*, 1649-1652. (f) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065-5068.
3. Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Tetrahedron Lett.* **1996**, *37*, 4409-4412.
4. For a review on Carbohydrate derived chiral auxiliaries, see: Horst, K.; Ruck, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336-358.
5. For references, See: (a) Bose, A. K.; Manhas, M. S.; Hegde, V. R.; Wagle, D. R.; Bari, S. S. *J. Chem. Soc.; Chem. Commun.* **1986**, 181. (b) Manhas, M. S.; Van der veen, Wagle, D. R.; Hedge, V. R.; Sari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Indian J. Chem.* **1986**, *25B*, 1095.
6. Bose, A. K.; Mathur, C.; Wagle, D. R.; Nagui, R.; Manhas, M. S. *Heterocycles* **1994**, *39*, 491.
7. Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307.
8. Storz, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1999**, *82*, 2380.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H
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PMP
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PPM
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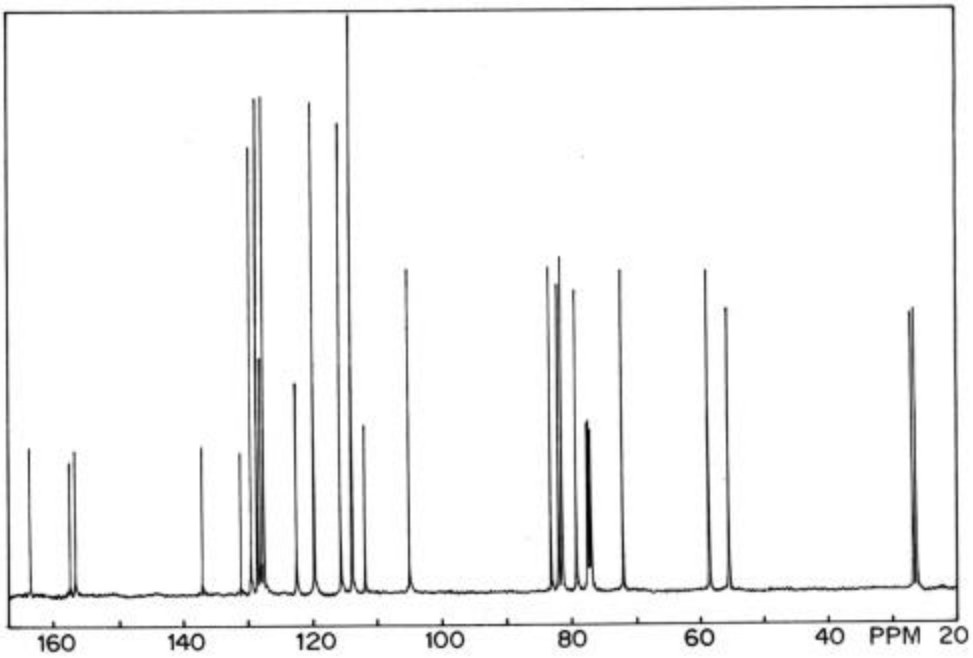
6.08a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