

DIASTEREOSELECTIVE SYNTHESIS OF β -LACTAMS

COMPUTERISED

A THESIS
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IN CHEMISTRY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "*Diastereoselective synthesis of β -lactams*" submitted by *Mr. V. Srirajan* was carried out by him under my supervision at National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date : 13-9-96

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TH-1058

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DEDICATED TO
MY PARENTS

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GENERAL REMARKS

- 1 All melting points (recorded on a Thermonik Campbell melting point apparatus) and are uncorrected.
- 2 IR spectra were recorded as films of nujol or chloroform solution, on a Perkin-Elmer Infracord Spectrophotometer Model 599-B using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
- 3 ^1H NMR spectra were recorded using tetramethylsilane as internal reference on AC-200 (Bruker 200 MHz FT NMR Spectrometer), ^{13}C NMR spectra were recorded on AC-200 (Bruker 200 MHz FT NMR Spectrometer) at 50 MHz frequency and Bruker 300 MHz instruments and the chemical shifts are recorded in parts per million (δ) relative to the center line of CDCl_3 (77.0 ppm). All spectra were recorded using CDCl_3 as solvent unless otherwise mentioned.
- 4 EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.
- 5 Elementary analyses (C, H, N, S) 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 the sodium line (5893 Å). Concentration is expressed in g/100 mL.
- 7 References pertaining to each chapter are given at the end of that particular chapter.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Compd.	Compound
CAN	Ceric ammonium nitrate
DCC	Dicyclohexylcarbodiimide
DMAP	N,N-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
de	Diastereomeric excess
ee	Enantiomeric excess
HMPT	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
LTA	Lead tetraacetate
LiHDMS	Lithium hexamethyldisilazide
NCS	N-Chlorosuccinamide
NBS	N-Bromosuccinamide
M. P.	Melting point
M. F.	Molecular formula
m-CPBA	<i>m</i> -Chloroperbenzoic acid
<i>p</i>	para
py	Pyridine
PTSA	<i>p</i> -Toluenesulfonic acid
Ph	Phenyl
PhthN	Phthalimido
PMP	<i>p</i> -Methoxyphenyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TBDMS	<i>tert</i> -butyldimethylsilyl

SYNOPSIS OF THE THESIS

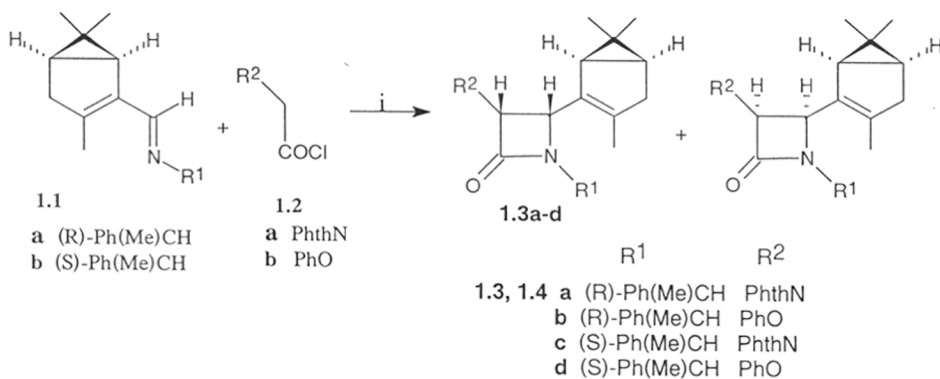
CHAPTER I : STUDY OF DIASTEREOSELECTIVITY IN β -LACTAM FORMATION

SECTION A : Use of a six-member [3.1.0] bicyclic aldehyde derived from (+)-3-carene

It has been shown in our group that the maximum diastereoselectivity of 80 : 20 could be achieved in β -lactam formation by using imines derived from chiral six member [3.1.0] bicyclic aldehyde and phthalimido ketene.

In order to probe the effects of two chiral components of imine (*double induction*) on the diastereoselectivity in 2+2 cycloaddition reactions (Staudinger reaction), we decided to use the optically pure [3.1.0] six member bicyclic aldehyde derived from (+)-3-carene and optically pure α -phenylethyl amine as the two chiral components of the imine moiety. The β -lactams **1.3** & **1.4 a-d** were obtained by using these chiral imines in excellent yields (Scheme 1.1). The maximum diastereoselectivity of 96 : 4 was obtained when phthalimido acetyl chloride (**1.2a**) and imine (**1.1a**) derived from (R)- α -phenylethyl amine and six member [3.1.0] bicyclic aldehyde were used. The diastereomers of the β -lactams were separated by column chromatography. The major diastereomer (**1.3a**) on treatment with $\text{NaIO}_4/\text{RuCl}_3$ in $\text{CH}_3\text{CN}/\text{water}$, gave diketo β -lactams in good yield.

Scheme 1.1 :



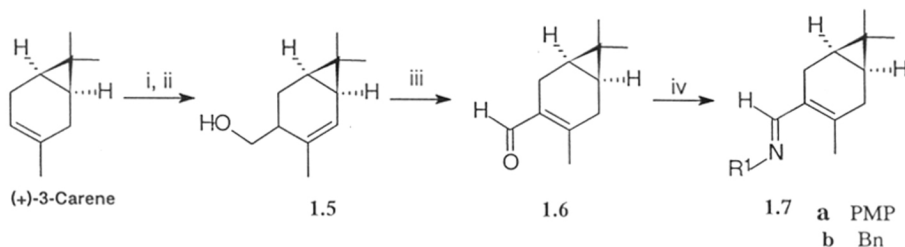
Reagents and conditions : i) $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, -78°C to r.t., 12 h.

SECTION B : Use of a seven-member [4.1.0] bicyclic aldehyde derived from (+)-3-carene : Effect of ring size

In order to study the steric effect of ring size and position of the chiral center from the reaction site on diastereoselectivity in the β -lactam formation, we selected imines (**1.7**) derived from seven

member chiral bicyclic aldehyde (1.6) in place of six member bicyclic aldehyde. The seven member aldehyde (1.6) was obtained from (+)-3-carene (Scheme 1.2). The aldehyde on treatment with amines offered imines (1.7) in very high yields.

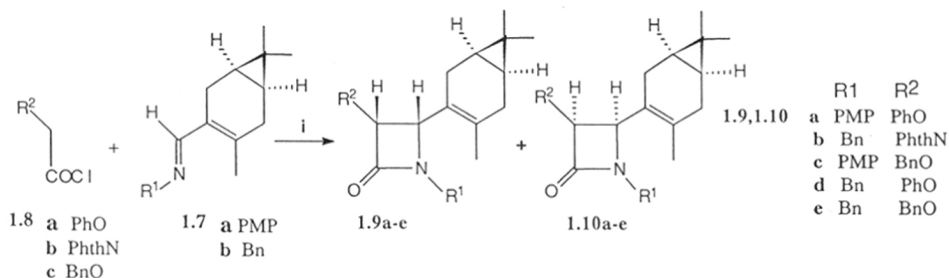
Scheme 1.2 :



Reagents and Conditions : i) $(\text{CH}_2\text{O})_n$ /AcOH/reflux, 48 h. ii) KOH/MeOH/reflux, 8 h. iii) DMSO/ $(\text{COCl})_2$ /Et₃N/ CH_2Cl_2 , -60°C to r.t. iv) R^1NH_2 / CH_2Cl_2 /MgSO₄, r.t., 4 h.

Treatment of these imines (1.7) with various acid chlorides (1.8) in presence of triethylamine gave a mixture of β -lactams (1.9 & 1.10) in moderate yields with poor diastereoselectivity. The mixture of diastereomers could not be separated by column chromatography. However, in one case, the major diastereomer (1.9a) was obtained in pure form by crystallization from the diastereomeric mixture.

Scheme 1.3 :



Reagents and Conditions : i) Et₃N/ CH_2Cl_2 , -23°C to r.t. 12 h.

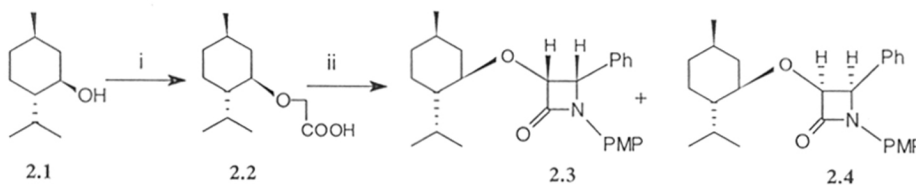
The poor diastereoselectivity in the β -lactam formation may be attributed to two factors :

- i) The steric bulk provided by the bicyclic moiety is not effective enough for the preferential attack of imine nitrogen on the ketene part in the Staudinger reaction.
- ii) The nearest chiral center of the six member bicyclic aldehyde is on the γ -carbon and two carbon away from the newly forming chiral center as compared to the five member bicyclic aldehyde in which the chirality resides on β -carbon.

CHAPTER II : SYNTHESIS OF TAXOL SIDE CHAIN

The optically active menthyloxyacetic acid (**2.2**) was selected as the chiral ketene precursor for diastereoselective synthesis of β -lactam. The alkylation of secondary alcoholic group of L-(-)-menthol (**2.1**) with chloroacetic acid using sodium metal in dry toluene under reflux condition gave menthylacetic acid (**2.2**) in good yield. The acid (**2.2**) on annulation reaction with imine using the phenoxy dichlorophosphate at 0 °C gave a diastereomeric mixture of β -lactams (**2.3** & **2.4**) in good yield (Scheme 2.1). However, the diastereoselectivity obtained in this reaction was very poor as confirmed by ^1H NMR spectral data of crude reaction mixture, which showed the presence of two diastereomers (**2.3** & **2.4**) in almost equal proportions. Moreover, these diastereomers (**2.3** & **2.4**) could not be separated by column chromatography or by crystallization.

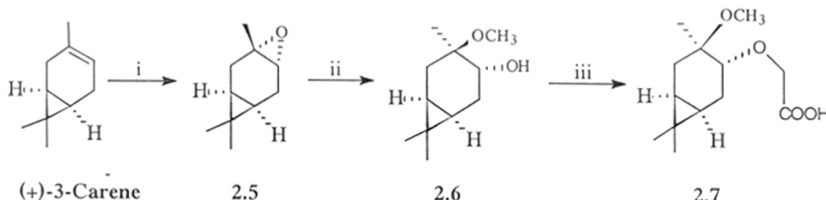
Scheme 2.1



Reagents and Conditions : i) $\text{Na}/\text{ClCH}_2\text{COOH}$, dry.Toluene ii) $\text{PhCH}=\text{N-PMP}/\text{Et}_3\text{N}/\text{PhO-P(O)-Cl}_2/\text{dry. CH}_2\text{Cl}_2$, 0°C to r.t.

In order to improve the diastereoselectivity, bicyclic acid derived from (+)-3-carene with gem dimethyl group on fused cyclopropane ring was selected as a ketene precursor for the synthesis of β -lactams. It was thought that the acid might provide the necessary steric requirement in facial discrimination of ketene. The (+)-3-carene was converted into carene epoxide (**2.5**) by known procedure. This carene epoxide (**2.5**) was opened with methanol in presence of PTSA at 0 °C to get methoxy alcohol (**2.6**). The secondary alcoholic group of (**2.6**) was alkylated under the similar condition as used for the menthol to give acid (**2.7**). (Scheme 2.2).

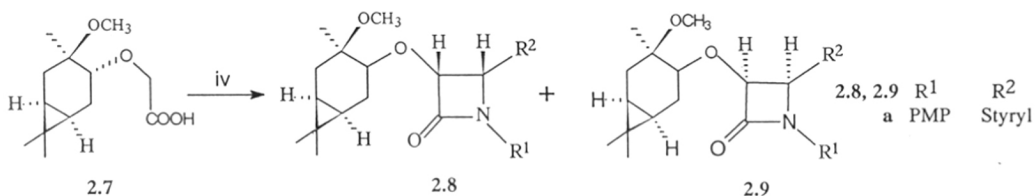
Scheme 2.2



Reagents and conditions: i) Ethyl orthoformate/ $\text{H}_2\text{O}_2/\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$, dry. CH_2Cl_2 ii) $\text{CH}_3\text{OH}/\text{PTSA}$. 2 h. iii) $\text{Na}/\text{ClCH}_2\text{COOH}$, dry.Toluene

The cycloaddition of imines (derived from cinnamaldehyde and *p*-anisidine) with acid (2.7) under Staudinger reaction conditions in presence of phenoxy dichlorophosphate, gave a mixture of β -lactams (2.8 & 2.9) in good yield with moderate diastereoselectivity (Scheme 2.3). The ratio of two diastereomers was determined by HPLC and ^1H NMR spectral analysis. The major isomer (2.8a) was obtained in pure form by crystallization.

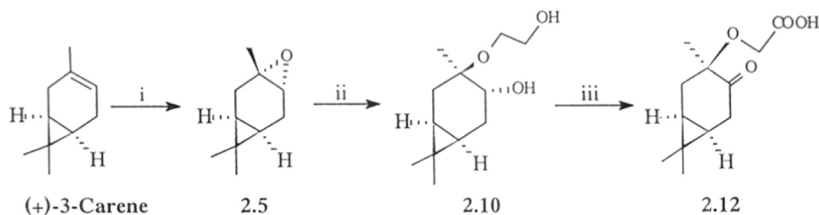
Scheme 2.3



Reagents and conditions: iv) R²CH=N-R¹/Et₃N/PhO-P(O)-Cl₂/dry. CH₂Cl₂, 0°C to r.t.

Similar reaction sequence was also tried using acid (2.12) derived from (+)-3-carene. Thus the epoxide (2.5) on treatment with ethylene glycol in presence of catalytic amount of PTSA gave diol 2.10 in quantitative yield. The diol 2.10 on oxidation with Jones' reagent gave keto acid 2.12 in good yield (Scheme 2.4).

Scheme 2.4

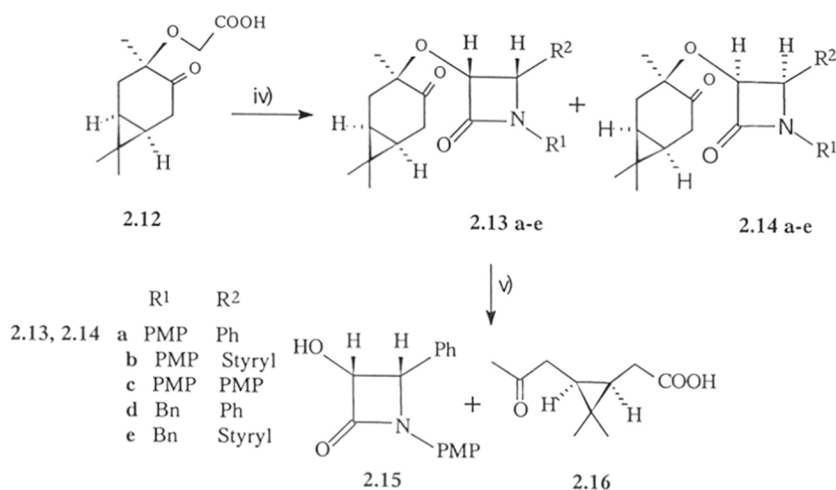


Reagents and Conditions : i) Ethyl orthoformate/H₂O₂/Na₃PO₄·12H₂O, dry. CH₂Cl₂ ii) HOCH₂CH₂OH/PTSA, 2 h. iii) Jones' reagent /0°C, 4 h.

Treatment of the acid (2.12) with imines in presence of triethylamine and phenoxy dichlorophosphate, gave a diastereomeric mixture of β -lactams (2.13 & 2.14) in good yield (Scheme 2.5). The ratio of two diastereomers was determined by HPLC and ^1H NMR spectral analysis of crude reaction mixture. A maximum diastereoselectivity of 70 :30 was obtained for β -lactams (2.13a & 2.14a), when the imine (2.17) derived from benzaldehyde and *p*-anisidine was used in the annulation reaction with keto acid (2.12). The major diastereomers 2.13a was separated by crystallization.

The protected β -lactam (2.13a) on treatment with *m*-CPBA underwent Baeyer-Villiger oxidation followed by hydrolysis to give 3-hydroxy-4-phenyl- β -lactam (2.15) along with keto acid (2.16) in very good yield. The structure of 3-hydroxy-4-phenyl- β -lactam (2.15) was confirmed from analytical and spectral data. The absolute configuration was assigned by comparing its optical rotation with values reported in the literature.

Scheme 2.5



Reagents and Conditions : iv) $R^2CH=NR^1$ / Et_3N / CH_2Cl_2 / $PhOP(O)Cl_2$ $0^\circ C$ - r.t. 15 h. v) *m*-CPBA / CH_2Cl_2 / r.t. 48 h.

The phenyl isoserine side chain at C-13 of the taxol molecule was proved to be very significant to exhibit the cytotoxicity. 3-Hydroxy-4-Phenyl- β -lactam have been used as a precursor for phenyl isoserine in taxol synthesis. Therefore, our strategy provides an easy access to 3-hydroxy-4-phenyl- β -lactam (2.15) starting from easily available (+)-3-carene.

CHAPTER III : ENANTIOSPECIFIC SYNTHESIS OF β -LACTAMS USING OPPOLZER SULTAM

The Oppolzer sultam (3.1) was prepared by the known procedure. The N-alkylation of sultam was carried out using NaH and ethyl bromoacetate in presence of Bu_4NI to give ester (3.2). The ester (3.2) on hydrolysis using MeOH/KOH at room temperature gave acid (3.3) in good yield (Scheme 3.1). The acid derivative of the sultam was converted into the acid chloride (3.4) using $SOCl_2$.

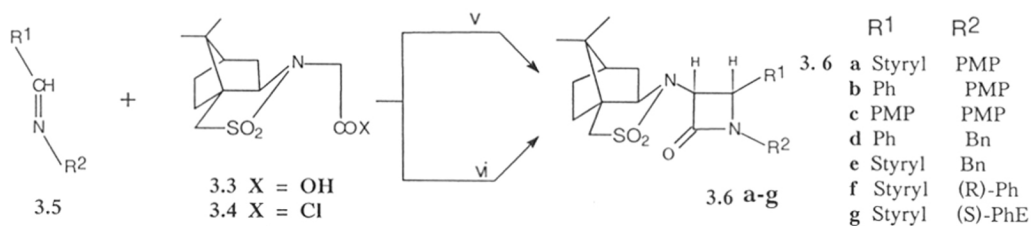
Scheme 3.1



Reagents and Conditions : i) NaH/dry THF, reflux, 1 h. ii) $\text{NBu}_4\text{I}/\text{BrCH}_2\text{COOEt}$, r.t., 3 h. iii) $\text{CH}_3\text{OH}/\text{KOH}$, r.t., 16 h. iv) SOCl_2 , reflux, 5 h.

The acid chloride (3.4) on Staudinger reaction with various Schiff's bases (3.5) in the presence of triethylamine at -23°C offered β -lactams (3.6a-g) in good yields. In an alternative method the acid 3.3 when subjected to Staudinger reaction with imines (3.5) using phenoxy dichlorophosphate as an acid activator at -23°C gave β -lactams (3.6a-g) in very good yield (Scheme 3.2).

Scheme 3.2



Reagents and Conditions : v) $\text{PhOP}(\text{O})\text{Cl}_2/\text{Et}_3\text{N}/\text{dry.CH}_2\text{Cl}_2$, -23°C to r.t. vi) $\text{Et}_3\text{N}/\text{dry.CH}_2\text{Cl}_2$, -23°C to r.t.

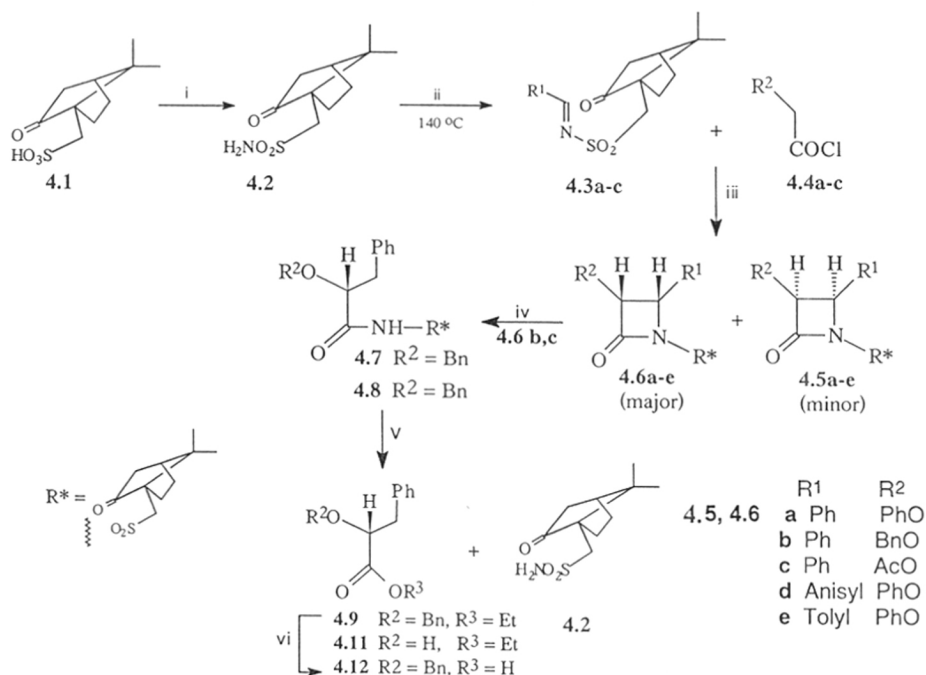
The HPLC and ^1H NMR analysis of the crude product obtained by both methods showed the presence of only one *cis* diastereomer (3.6). The absolute configuration was also determined by single crystal X-ray analysis. The configuration at C3 and C4 of the β -lactam was established as 3*R* and 4*S* based on the known absolute configuration of sultam moiety. All attempts made to cleave the chiral auxiliary by oxidative hydrolysis, acidic, basic hydrolysis or reductive techniques were unsuccessful.

CHAPTER IV : PREPARATION OF α -HYDROXY ESTERS via β -LACTAMS

The optically pure camphor-10-sulphonic acid (4.1) was converted into camphor-10-sulphonamide (4.2) by the reported procedure. This camphor-10-sulphonamide (4.2) on treatment with various protected acetals of aromatic aldehydes gave corresponding imines (4.3a-c) in quantitative yields. These imines (4.3a-c) on subsequent annulation with various acid chlorides (4.4a-c) in the presence of

triethylamine at -23°C , yielded the β -lactams (**4.5** & **4.6**) in good diastereoselectivity (Scheme 4.1). The diastereoselectivity was determined by HPLC and ^1H NMR spectral analysis of the crude reaction mixture. In all the cases the major diastereomer (**4.6**) was obtained in pure form by crystallization. The absolute configuration of the major diastereomer (**4.6b**) has been established from its single crystal X-ray analysis. The configuration at C3 and C4 of the β -lactam **4.6b** was assigned as $3R$ and $4S$ respectively on the basis of the known absolute configuration $1'S$ of camphor-10-sulphonyl moiety.

Scheme 4.1



Reagents and Conditions: i) $\text{SOCl}_2/\text{NH}_3$ ii) $R^1 \text{CH}(\text{OEt})_2$, 140°C . iii) $\text{RCH}_2\text{COCl}/\text{Et}_3\text{N}/\text{dry. CH}_2\text{Cl}_2$, -23°C to r.t. iv) $\text{H}_2/\text{Pd-C}$, EtOH , reflux, 12 h. v) HCl/EtOH , reflux, 8 h. vi) KOH/MeOH , r.t., 8 h.

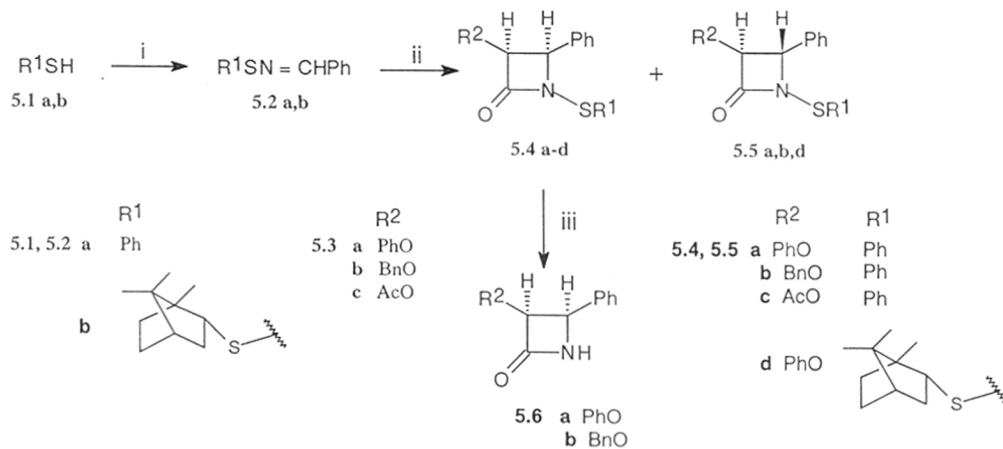
The N1 - C4 bond cleavage was effected by refluxing ethanolic solution of the major isomers (**4.6b,c**) in presence of Pd/C in EtOH for about 28 h to give N-protected amides **4.7** & **4.8**. The amides **4.7** & **4.8** on hydrolysis with EtOH/HCl under reflux for 8 h gave α -hydroxy esters **4.9** & **4.11** in good yields along with camphor-10-sulphonamide (Scheme 4.1). The pure α -hydroxy esters **4.9** & **4.11** and camphor-10-sulphonamide (**4.2**) were isolated by column chromatography. The ester **4.9** on hydrolysis in methanolic KOH offered α -hydroxy acid **4.12** in quantitative yield. The absolute configuration of these

esters (4.9 & 4.11) and acid (4.12) were assigned by comparing the optical rotation of these compounds with reported values.

CHAPTER V : PREPARATION OF N-UNSUBSTITUTED β -LACTAMS

Thiols were treated with NCS in liq NH_3 and the sulfenamide formed were reacted with benzaldehyde to give imines (5.2a) in quantitative yields. These imines on subsequent treatment with various acid chlorides (5.3a-c) in the presence of triethylamine at -23°C yielded the mixture of *cis* and *trans* β -lactams (5.4a-c & 5.5a,b) in excellent yields. The mixture of *cis-trans* β -lactams (5.4a,b & 5.5a,b) was separated by column chromatography. The *cis* isomer of the β -lactams (5.4a,b) on treatment with thiophenol in pyridine for 2 h gave the unsubstituted β -lactams (5.6a,b) in quantitative yield. The same methodology was extended to imine derived from optically active thioisoborneol. Thus, thioisoborneol was prepared from optically pure isoborneol by using reported procedure. The sulfenimine (5.2b) was prepared using NCS in liq NH_3 and condensing it with benzaldehyde. The imine (5.2b) on treatment with acid chloride (5.3a) in the presence of triethylamine at room temperature gave the β -lactam (5.4d & 5.5d) in good yield. The *cis-trans* mixture was separated by column chromatography.

Scheme 5.1



Reagents and Conditions: i) NCS/Liq. NH_3 / PhCHO; ii) $\text{R}^2\text{CH}_2\text{COCl}$ (5.3a-c) / Et_3N , CH_2Cl_2 ; iii) PhSH/Pyridine.

CHAPTER I

STUDY OF DIASTEREOSELECTIVITY IN β - LACTAM FORMATION

Part of this work has been published in
Tetrahedron, 1996, 52, 3741

1.1 INTRODUCTION

Although the first synthesis of a β -lactam was reported by Staudinger in 1907,¹ the importance of the β -lactam has come to light only after the discovery of penicillin² by Fleming in 1923 and its structural confirmation by X-ray crystallography.³ Even though the invention of penicillin was a boon to the human race, the resistive property of this drug for many pathogenic bacteria, stresses the need for more effective microbial agents. Of the thousands of penicillin derivatives known so far, very few are reported to be as active as penicillin. The second drug of this class of β -lactam antibiotics was cephalosporin.⁴ The discovery of 7- α -methoxy cephalosporin from *Streptomyces* in 1971, stimulated researchers to discover novel β -lactam antibiotics. The recent result of the immense efforts made by chemists led to the successful discovery of carbapenem,⁵ monocyclic nocardicin,⁶ monobactams⁷ and clavulanic acid.⁸ The β -lactams can be classified into several groups according to their structural framework.

- * Penicillin
- * Cephalosporin
- * Cephameycin
- * Oxacephems
- * Penems
- * Oxapenems like Clavulanic acid
- * Carbapenems like Thienamycin
- * Nocardicin
- * Monobactam

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

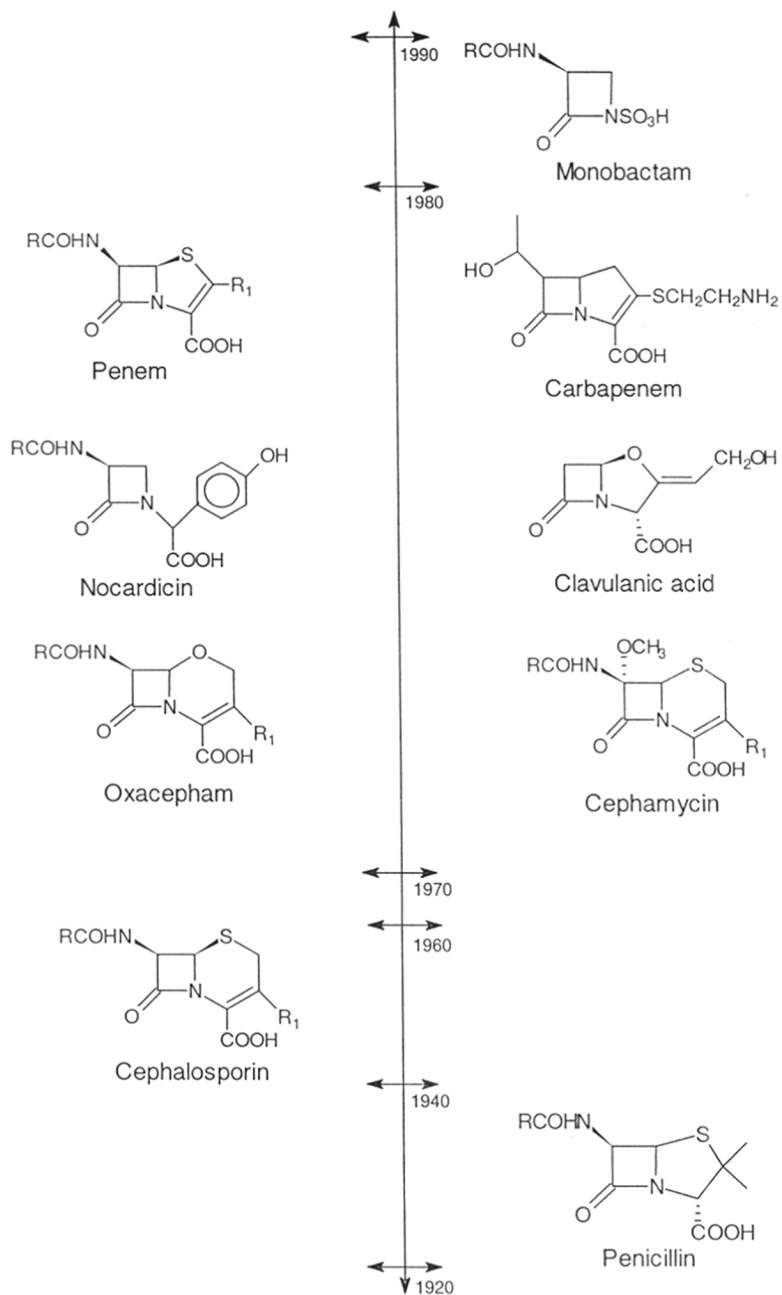


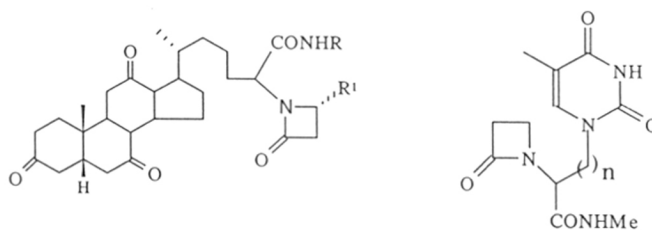
Fig. 1

The structural diversity of these β -lactams requires an extensive and sophisticated study on the Structure Activity Relationship.⁹

The properly substituted β -lactam can be used for the construction of bicyclic β -lactam antibiotics¹⁰ and as a starting material for several naturally occurring and biologically active non β -lactam molecules.¹¹ Therefore, many efforts have been made for the stereoselective construction of β -lactam ring with appropriate substituents in proper positions.¹² An extensive report by Ojima¹³ on the use of β -lactams as synthons for natural products has appeared recently.

Recently, a new class of compounds was reported in the β -lactam family in which the antibiotic property of β -lactams and the antiviral property of nucleosides were incorporated together to afford dual properties of the drug.¹⁴ Kehagia et al¹⁵ reported a new class of β -lactams in which a steroidal and a β -lactam units were coupled together via Ugi reaction in a one-step process.

Scheme 1.01

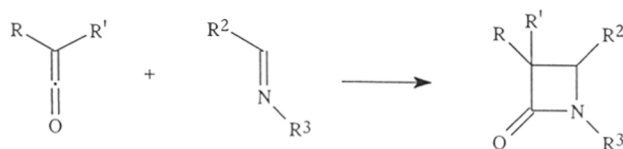


1.1.1 Methods for Constructing β -Lactam ring

Staudinger Reaction :

The first synthesis of a β -lactam was achieved by Staudinger¹ in 1907 by the 2 + 2 cycloaddition of ketene and imine. This reaction is called as Staudinger or Ketene-Imine cycloaddition reaction. An excellent review on the Staudinger reaction has appeared recently.¹⁶ In the modified Staudinger reaction, acid chlorides or activated carboxylic acids were used in the presence a base as a ketene precursor.

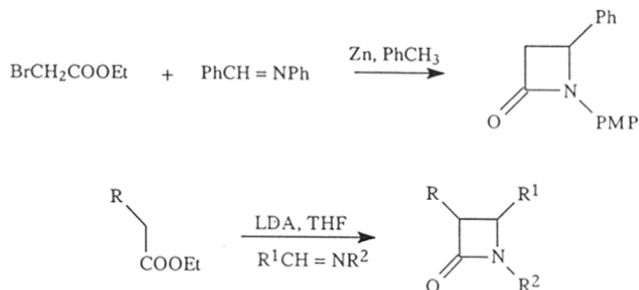
Scheme 1.02



Enolate-Imine Condensation :

The first example of this type of reaction has been reported by Gilman and Speeter¹⁷ by the condensation of zinc enolate (Reformatsky reagent) with imines to give β -lactams. Other metal enolates have also been used in enolate-imine cycloaddition reaction to achieve diastereoselective synthesis of β -lactams.¹⁸

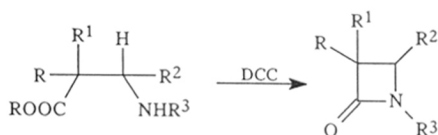
Scheme 1.03



Formation of N-C2 bond :

This methodology has been used by Sheehan and Henery-Logan¹⁹ for the synthesis of penicillin by the cyclisation of β -amino acids using dicyclohexylcarbodiimide (DCC) as a condensing agent.

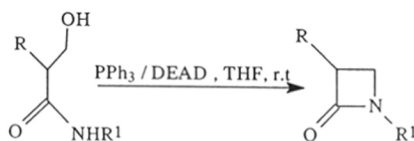
Scheme 1.04



Formation of N-C4 bond :

This methodology involves a $\text{S}_{\text{N}}2$ displacement of a good leaving group attached at β -carbon amide by an intramolecular amide nitrogen under basic condition. Miller has reported the synthesis of β -lactams by the cyclisation of β -hydroxy amides under Mitsunobu reaction conditions.²⁰

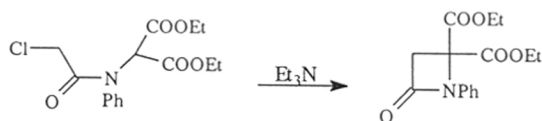
Scheme 1.05



Formation of C3-C4 bond :

The first example of this type of C3-C4 bond formation has been achieved by Sheehan and Bose²¹ by intramolecular cyclisation of haloacylamino malonate in presence of a base.

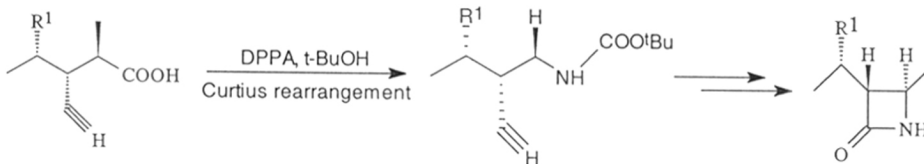
Scheme 1.06



Miscellaneous Methods :

Jacobi et al²² have used acetylenic carboxylic acid (Scheme 1.07) as a synthon for the preparation of β -lactam *via* Curtius rearrangement in a four step process.

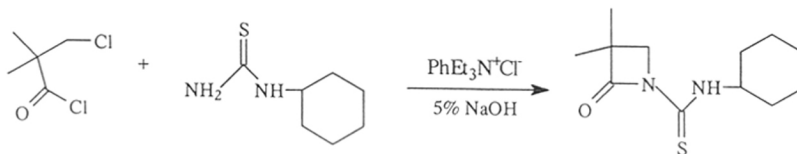
Scheme 1.07



DPPA = diphenylphosphorazidate

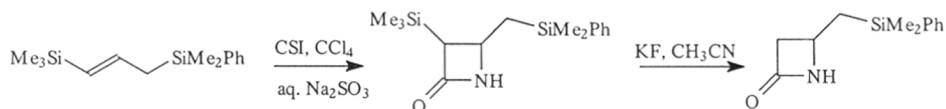
The condensation of a bis-electrophile with N-alkylthiourea to form azetidinone²³ has been reported to proceed *via* simultaneous or step-wise formation of two bonds at the N1 center.

Scheme 1.08



The addition of chlorosulfonyl isocyanate (CSI) to olefin is well documented for the preparation of β -lactams.²⁴ Colvin et al²⁵ have used CSI addition on allyl and allenyl silanes, which afforded a highly functionalised β -lactam (Scheme 1.09). The substituent on C3 position can also be cleaved to generate an useful β -lactam intermediate.

Scheme 1.09



1.1.2 Asymmetric Synthesis of β -Lactams

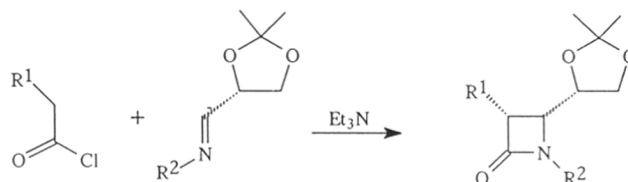
Asymmetric synthesis of β -lactams is of current interest and several reports have appeared during the last decade. The Staudinger reaction is the most widely used method for the asymmetric synthesis of β -lactams due to simplicity and predictability of the stereochemical outcome of the reaction. The approaches followed to induce asymmetry in ketene-imine cycloaddition are based on the use of a chiral auxiliary attached to either ketene precursors or imines (derived from chiral aldehydes or amine). The use of chiral ketene and chiral amine for the asymmetric synthesis of β -lactams has been discussed in Chapter III and Chapters IV & V respectively. Following is a brief review on use of imines derived from chiral aldehydes.

1.1.4 Chiral Aldehyde

The imines derived from chiral aldehydes have been reported to give better diastereoselectivity in the β -lactam formation than imines derived from chiral amines.

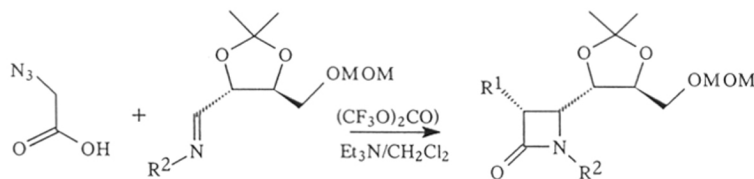
A diastereospecific synthesis of *cis*- β -lactams has been reported by using imines derived from D- and L-glyceraldehyde acetonides *via* ketene-imine cycloaddition reaction²⁶ (Scheme 1.10)

Scheme 1.10



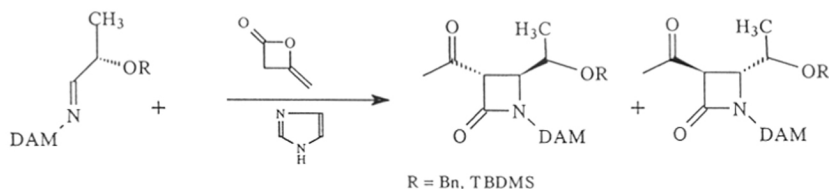
Ikota²⁷ has used 2,3-O-isopropylidene-L-threitol (Scheme 1.11) as the chiral aldehyde in the annulation reaction and reported the formation of only one *cis* diastereomer.

Scheme 1.11



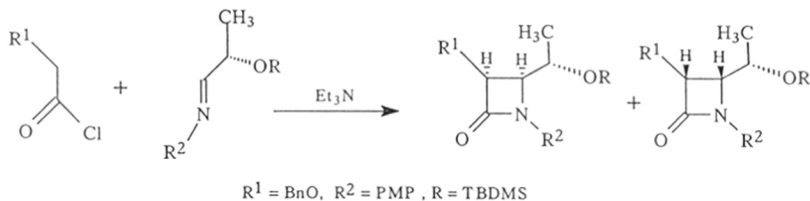
Ito et al²⁸ have used the diketene along with the imine derived from commercially available inexpensive (S)-ethyl lactate as the chiral aldehyde in the cycloaddition reaction (Scheme 1.12). Various levels of diastereoselectivity were obtained. The stereochemical course of the reaction was found to be solvent dependent and acetonitrile was the best one of choice, which gave a maximum diastereoselectivity of 10:1 obtained when R = Bn.

Scheme 1.12



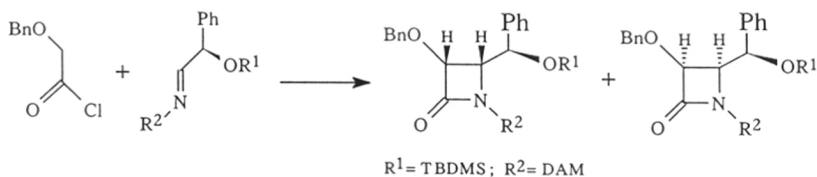
(S)-Ethyl lactate has also been used as a chiral auxiliary for the asymmetric synthesis of β -lactams by Palomo et al²⁹ and a maximum diastereoselectivity of 95 : 5 was obtained by using suitable protective groups (Scheme 1.13).

Scheme 1.13



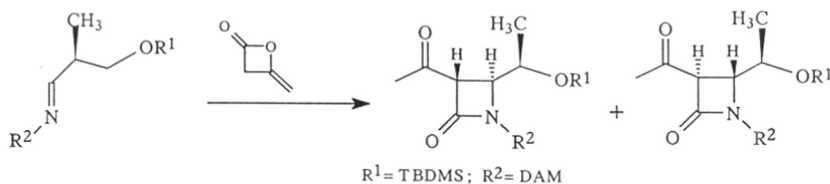
The cycloaddition reaction with imines derived from optically active mandelate has been reported (Scheme 1.14) to give the diastereoselectivity of 10 : 1 when the combination of TBDMS and DAM were used as a protective groups.³⁰

Scheme 1.14



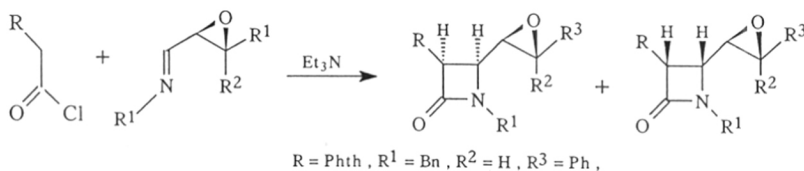
The imines derived from the (S)-methyl-3-hydroxy-2-methyl propionate afforded excellent diastereoselectivity (15 : 1) in the cycloaddition reaction³¹ (Scheme 1.15). They have shown that the protecting group of the hydroxyl moiety played a major role in determining the stereochemical course of the reaction.

Scheme 1.15



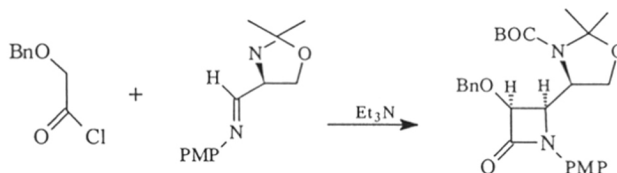
The imines derived from the α,β -epoxyaldehyde³² were also used in the cycloaddition reaction. The imines were synthesized from S-malic acid and (+)-tartaric acid (Scheme 1.16). These imines afforded enantiomerically pure *cis*- β -lactams in good yields.

Scheme 1.16



The imines derived from N,O-diprotected L-serinal on treatment with acid chloride in the presence of triethylamine afforded total diastereocontrol in the β -lactam ring formation³³ (Scheme 1.17).

Scheme 1.17



1.1.2 Mechanism of Ketene-Imine Reaction

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

The ketenes can be generated either thermally, photochemically or from activated acids or acid chlorides in the presence of a base. The *in situ* formation of the ketene in the reaction 3-hydroxybutyric acid chloride with an imine in the presence of a base has been proved by monitoring the course of the reaction with FT-IR.³⁴ A strong band corresponding to the ketene was observed at 2120 in the FT-IR. This indicates that the *in situ* generated ketene reacts with imine to form a zwitterionic intermediate (Scheme 1.10), which cyclises to a β-lactam. The possibility of acylation of imine with acid chloride under the reaction conditions has been ruled out as the acid chloride when reacted with imine in the absence of a base leads to a formation of amide instead of β-lactam.

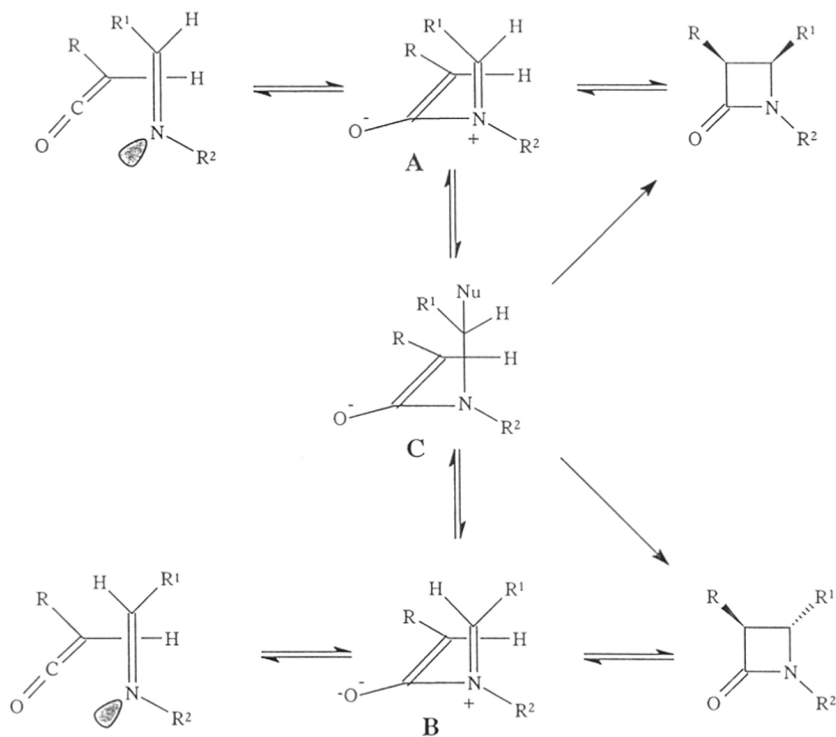
It has been postulated that the LUMO of the ketene carbonyl group lies coplanar with the other substituent of the ketene. The imine can attack from the least hindered side of the ketene orthogonally either from the top face or from the bottom face of the ketene and produce a zwitterionic intermediate in which the ketene and the imine lie perpendicular to each other.³⁵ The conrotatory ring closure of the dipolar species **A** will then generate the thermodynamically less stable *cis* β-lactam. This mechanism explains the formation of *cis* β-lactams from the reaction between many acyclic imines (*anti*) and ketenes. This mechanism also explains the well-known preference for the *trans* β-lactams with cyclic imines (*syn*). An orthogonal approach between

ketene and imine (*syn*) will produce the zwitterionic intermediate **C**, which on conrotatory electrocyclicization will generate *trans* isomer (Scheme 1.10).

This hypothesis was also supported by the semi-empirical molecular orbital calculation for the intermediate between the reaction of methyl ketene and N-methylimine.³⁶

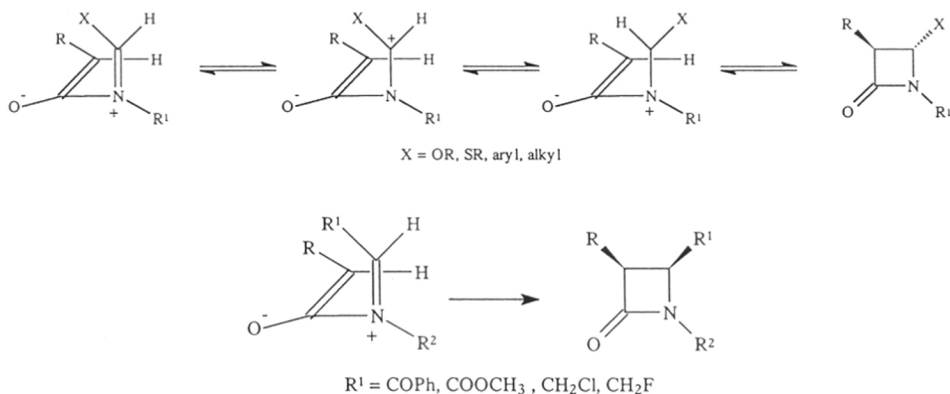
This mechanism also successfully explains the formation of a mixture of *cis* and *trans* isomers in ketene-imine reaction. A nucleophile can add to the iminium ion intermediate **A** or **B** to form an intermediate **C**. The loss of nucleophile from intermediate **C** after N - C bond rotation can result in the formation of a dipolar species **B** and the subsequent *trans*- β -lactam. The intermediate **C** can also revert back to **A** and form *cis*- β -lactam. Thus, the ratio of *cis* and *trans* isomers depends upon the formation and stability of the intermediate dipolar species **A** and **B**. It was also observed that the initially formed *cis* product can undergo base catalysed isomerisation to produce the more stable *trans* product (Scheme 1.18).³⁷

Scheme 1.18



The formation of *trans* isomer by using imidates, thioimidates and sometimes C-arylimines and potentially C-alkylimines can be explained by the ability of these groups to stabilize the positive charge of the zwitterionic intermediate by inductive or mesomeric effect. This allows the isomerization of *trans*-iminium ion to the sterically less crowded *cis*-iminium ion, which on ring closure will generate *trans*- β -lactam (Scheme 1.19). On the contrary, the imine possessing electron withdrawing substituents, like α -carbonyl group or α -halomethyl group, prevents the C-N bond rotation of the zwitterionic intermediate **A** and produces the *cis* isomer.

Scheme 1.19



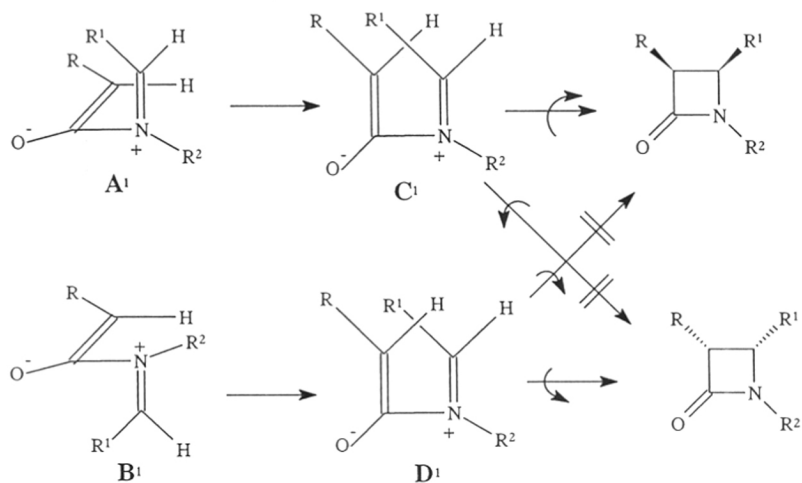
A detailed account of semiempirical calculation reported by Cossio et al³⁸ also supports the Ketene-Imine Mechanism.

1.1.3 Asymmetric Induction

The ketene can be approached by the imine either from the top face or bottom face to produce two possible zwitterionic intermediates **A**¹ and **B**¹ respectively (Scheme 1.20). Before the conrotatory ring closure can take place, the intermediates **A**¹ and **B**¹ have to undergo the 90° rotation around C-N bond to produce two more intermediates **C**¹ and **D**¹ respectively. The conrotatory ring closure of these intermediates **C**¹ and **D**¹, will produce *cis*- β -lactams and its enantiomer. This intermediates **D**¹ and **C**¹ can also be formed from **A**¹ and **B**¹ by rotating through 270° around C-N bond. According to the principle of least motion, the transformation of **A**¹ to **C**¹ and **B**¹ to **D**¹ is favoured as this transformation needs only 90° rotation.

It has been pointed out by Hegedus et al. that the conrotatory ring closure of intermediate C^1 can only occur clockwise³⁹ as the counterclockwise ring closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is of importance for chiral induction, because a counterclockwise rotation would generate the enantiomeric β -lactam. The opposite is true for intermediate D^1 , which can undergo only counterclockwise conrotatory ring closure.

Scheme 1.20



SECTION A

*Use of a six-member [3.1.0] bicyclic aldehyde
derived from (+)-3-carene*

SECTION A

1.2 PRESENT WORK

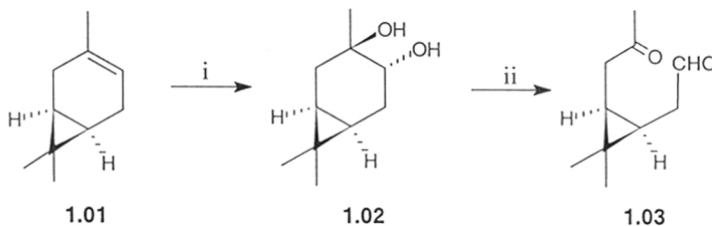
It has been established that a high level of diastereoselectivity can be achieved in the cycloaddition reaction by using imines derived from aldehyde having an α chiral carbon with a heteroatom attached to it. In the course of our investigation, it has been observed in our group that the diastereoselectivity in cycloaddition is controlled by a sterically demanding bicyclic aldehyde component even though the nearest chiral center was located at a β -carbon from the aldehydic group. A maximum diastereoselectivity of 80 : 20 has been achieved in β -lactam ring formation *via* ketene-imine cycloaddition using imines derived from five membered bicyclic aldehydes obtainable from abundantly available (+)-3-carene. We thought that the use of additional chiral component (double induction) in the form of amine should help in enhancing the diastereoselectivity in a cycloaddition reaction. This chapter deals with our results in the diastereoselective synthesis of β -lactams using imines derived from chiral aldehydes and amines.

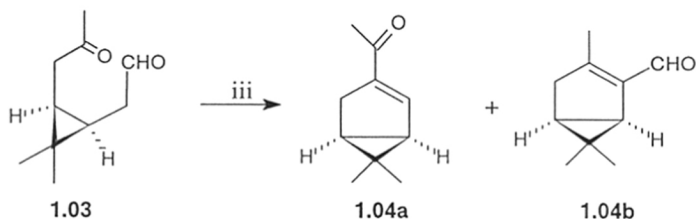
1.3 RESULTS AND DISCUSSION

Preparation of Aldehyde 1.04b.

The bicyclic aldehyde **1.04b**, bearing a β -chiral center, was chosen for our present investigation. The (+)-3-carene was converted into a bicyclic five-membered aldehyde (Scheme 1.21) using the reported procedure.⁴⁰

Scheme 1.21



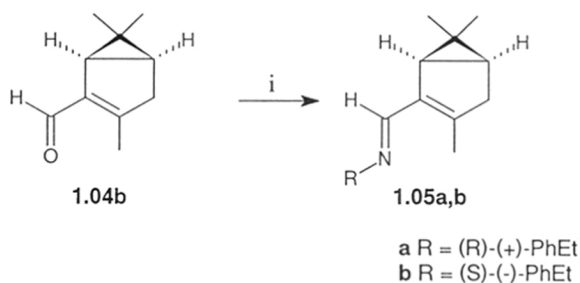


Reagents and conditions: i) $\text{HCO}_2\text{H}/\text{H}_2\text{O}_2$, $<30^\circ\text{C}$, 28 h. ii) $\text{NaIO}_4/\text{Acetone}/\text{Water}$ iii) $\text{Pipridine}/\text{AcOH}$ 3 h.

Preparation of the imine 1.05a,b.

The imines **1.05a,b** were prepared by treating the aldehyde **1.04b** with an optically active (R) & (S) phenylethyl amine in CH_2Cl_2 at room temperature for 30 minutes in the presence of anhydrous MgSO_4 (Scheme 1.22). After completion of the reaction (TLC), the reaction mixture was filtered and the filtrate was concentrated to provide the imines **1.05a,b** in 100% yield.

Scheme 1.22



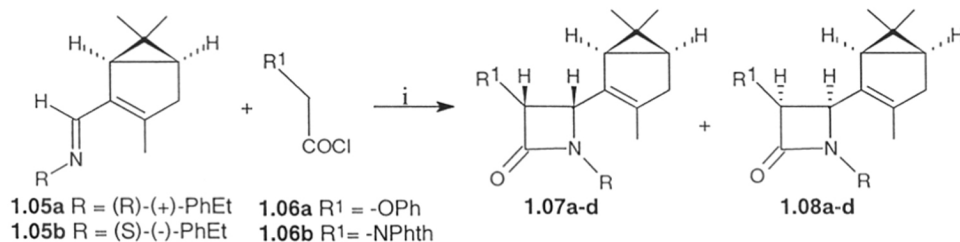
Reagents and conditions : i) $\text{R-NH}_2/\text{CH}_2\text{Cl}_2$, MgSO_4 .

Preparation of β -lactam 1.07a-d & 1.08a-d.

The imines **1.05a,b** were treated with acid chlorides **1.06a,b** in CH_2Cl_2 at -78°C under argon and the reaction mixture was stirred at room temperature for 12 h. The usual workup and purification by column chromatography, provided a diastereomeric mixture of β -lactams **1.07a-d** & **1.08a-d** in 65 to 94% yields (Scheme 1.23). The diastereomeric ratio of the β -lactams was determined by ^1H NMR and HPLC analysis. All the major and minor isomers were separated by column chromatography. In one case the major diastereomer **1.07a** was also obtained in pure form by single crystallization from pet. ether/acetone in 84% yield. A maximum diastereoselectivity of

96 : 4 was obtained when phthalimidoacetyl chloride and (R)-(+)-phenylethyl amine was used. These β -lactams provide a facile entry to a novel class of chemical entity that features a β -lactam moiety attached to a cyclopropane ring. These fascinating derivatives may combine the biological activity of the β -lactam and the pesticidal properties of the cyclopropane.

Scheme 1.23



Reagents and conditions : i) Et₃N/CH₂Cl₂, -78°C to r.t., 12 h.

Table 1. Synthesis of β -lactams **1.07a-d** & **1.08a-d** via cycloaddition reaction of imines **1.05a,b** with ketens derived from the acid chlorides **1.06a,b**.

Compd 1.07 & 1.08	R	R ¹	Yield (%)	Ratio of 1.07 : 1.08
a	(R)-(+)- Ph(Me)CH-	PhthN-	92	96 : 4
b	(R)-(+)- Ph(Me)CH-	PhO-	65	63 : 37
c	(S)-(-)- Ph(Me)CH-	PhthN-	86	72 : 28
d	(S)-(-)- Ph(Me)CH-	PhO-	94	55 : 45

The compound **1.07a** was selected as a representative of this series for the discussion and characterization by spectral analysis. The IR spectrum of this compound showed two sharp bands at 1760 and 1730 corresponding to the β -lactam carbonyl and phthalimido carbonyl groups. The ¹H NMR spectrum of **1.07a** showed the presence of two *gem* dimethyl groups at 0.75 and 0.80, integrating for three protons each. The cyclopropyl methine protons appeared as a multiplet in between 0.85 and 1.05. The vinylic methyl protons of the chiral aldehyde appeared as a sharp

singlet at 1.35 integrating for three protons. The methyl group of the chiral amine moiety appeared as a doublet at 1.7 ($J = 7$ Hz), integrating for three protons. The two methylene protons of the carene moiety appeared as a multiplet at 1.95-2.10. The C4 and C3 protons of the β -lactam ring appeared as doublets at 4.60 and 5.35 with the coupling constant value of 5 Hz. The geometry of these protons was assigned as *cis* from the coupling constant measurements of these protons. The methine proton of the chiral amine moiety appeared as a quartet at 5.0 with the coupling constant value of 7 Hz. The phenyl protons appeared in between 7.3 and 7.5 integrating for five protons. The other four aromatic protons appeared as multiplets in the region of 7.7 to 7.8.

The characteristic peaks for other compounds are given in the following table.

Table 2 : ^1H NMR data for β -lactam protons **1.07a-d** & **1.08b,c**

Compound No.	β -lactam protons		
	C4	C3	Coupling constants
1.07a	4.60 (d)	5.35 (d)	$J = 5$ Hz
1.07b	4.56 (d)	5.20 (d)	$J = 5$ Hz
1.07c	4.4 (d)	5.3 (d)	$J = 5$ Hz
1.07d	4.45 (d)	5.25 (d)	$J = 5$ Hz
1.08b	4.60 (d)	5.75 (d)	$J = 4.5$ Hz
1.08c	4.45 (d)	5.15 (d)	$J = 5$ Hz

The ^{13}C NMR spectrum of **1.07a** showed the presence of two sharp peaks at 166.8 and 164.7 corresponding to the β -lactam carbonyl and phthalimido carbonyl carbons. The two quaternary carbons of the aromatic ring appeared at 140.6 and 137.8. The other five aromatic carbons appeared at 134.4, 128.8, 127.6, 127.1, 123.5. The two olefinic carbons of the bicyclic moiety appeared at 131.7 and 130.1. The C3 and C4 carbons of β -lactam resonated at 57.7 and 57.0. The methine carbon of the chiral amine moiety appeared at 53.6. One of the methine carbons

of the cyclopropyl group appeared at 38.8. The methylene carbon of the bicyclic moiety was observed at 38.4. The other cyclopropyl methine carbon appeared at 26.1. The methyl carbon of the chiral amine moiety appeared at 25.6. The vinylic methyl carbon of the carene moiety appeared at 20.5. The quaternary carbon of the bicyclic carene moiety appeared at 19.7. The two *gem* dimethyl carbons appeared as two sharp peaks at 13.3 and 13.2.

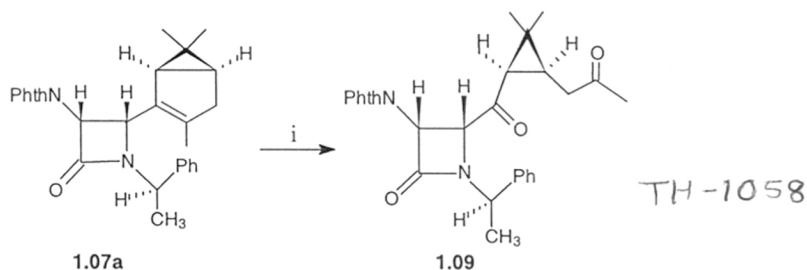
The above spectral data is in well agreement with the assigned structure to the β -lactam **1.07a**. This compound also gave satisfactory microanalysis.

The cleavage of the bicyclic moiety at the C4 position of the β -lactam **1.07a** was effected under mild oxidative conditions,⁴¹ hoping to get an intermediate which could be transformed into the bicyclic β -lactam.

Preparation of diketo β -lactam 1.09.

To a solution of the β -lactam in $\text{CH}_3\text{CN} : \text{CCl}_4 : \text{H}_2\text{O}$, powdered NaIO_4 was added followed by the addition of catalytic amount of RuCl_3 at 0°C and the reaction mixture was stirred for 3 h at this temperature. After the completion of reaction (TLC), the usual workup and purification by column chromatography provided diketo β -lactam **1.09** (Scheme 1.24) in 58% yield.

Scheme 1.24



Reagents and conditions : i) RuCl_3 , NaIO_4 / $\text{CH}_3\text{CN} : \text{CCl}_4 : \text{H}_2\text{O}$, 25°C , 3 h

The compound **1.09** was characterized by spectral analysis. The ^1H NMR spectrum of **1.09** showed the presence of two *gem* dimethyl groups as two singlets at 0.6 and 0.7. The cyclopropyl methine protons appeared as a multiplet in between 0.75 and 1.10. The methyl group of the chiral

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amine moiety appeared as a doublet at 1.7 ($J = 7.3$ Hz). The methyl group attached to the carbonyl group appeared as a singlet at 2.05 integrating for three protons. The methylene protons of the carene moiety were observed as a multiplet in between 2.55 to 2.85. The β -lactam ring protons at C4 and C3 appeared as doublets at 4.45 and 5.45 respectively. The geometry of these protons was found to be of *cis* from their coupling constant values ($J = 5.3$ Hz). The methine protons of the chiral amine moiety appeared as a quartet at 5.2 ($J = 7.3$ Hz). The aromatic protons were observed as multiplets in between 7.30 and 7.85, integrating for nine protons. The IR spectrum of **1.07a** showed sharp bands at 1760, 1740 and 1710.

Our attempts to cyclize the diketo β -lactam to form bicyclic β -lactam from diketone **1.09** failed.

1.4 SUMMARY

We have extensively studied the effect of the β -chiral center (remote stereocontrol) of an aldehyde component of the imine in the diastereoselective formation of the β -lactam *via* ketene-imine cycloaddition. A high level of diastereoselectivity (80 : 20) has been achieved in this reaction. The effect of two chiral components (double induction) on the diastereoselective formation of the β -lactam was studied by using imines derived from chiral aldehydes and as well as chiral amines. A maximum diastereoselectivity of 96 : 4 was obtained when phthalimidoacetyl chloride and imine derived from (R)-(+)-phenylethyl amine were used. The major isomer **1.07a** was converted into diketo β -lactam **1.09**. All attempts made to prepare the bicyclic β -lactams from diketone **1.09** failed.

SECTION B

*Use of a seven-member [4.1.0] bicyclic aldehyde derived from
(+)-3-carene : Effect of ring size*

SECTION B

1.5 PRESENT WORK

Our earlier studies revealed that, to achieve a very high diastereoselectivity in the formation of β -lactams, it is not mandatory that the α -chiral center of imine should be attached to a hetero atom. We also showed that the diastereoselectivity in the β -lactam formation was not fully controlled by the chiral amine (phenylethyl amine), when it has been introduced as the second chiral auxiliary in the cycloaddition. Our results showed that the high diastereoselectivity in the β -lactam formation could be achieved by selecting sterically demanding chiral groups. In our studies directed towards the diastereoselective synthesis of β -lactams using the chiral aldehydes derived from (+)-3-carene, we decided to see the effect of the chiral center located at the γ -carbon atom of the imine (remote stereo control).

1.6 RESULTS AND DISCUSSION

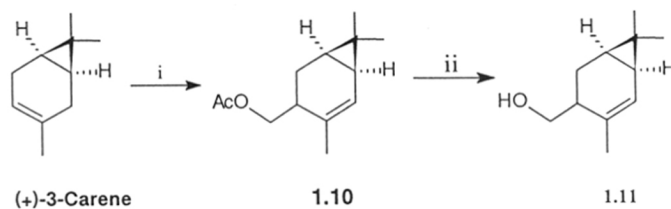
An aldehyde derived from the (+)-3-carene was used as the chiral auxiliary for the synthesis of β -lactams. This homochiral aldehyde **1.12** was prepared in three steps.

Preparation of prince alcohol 1.11.

The prince alcohol **1.11** was prepared from (+)-3-carene by a reported procedure⁴² as follows :

The (+)-3-carene was treated with paraformaldehyde in the presence of glacial acetic acid under reflux conditions for 48 h. After completion of the reaction, acetic acid was distilled out, the gummy reaction mixture was diluted with water and extracted with CHCl_3 . The organic layer was concentrated by distillation and the residue was purified by column chromatography to provide the prince acetate **1.10** as an oil in 38% yield. The acetate **1.10** was hydrolyzed by treating with methanolic KOH under reflux conditions for 8 h. Methanol was removed by distillation and the residue was diluted with water and extracted with CHCl_3 . The organic layer was concentrated and the residue was purified by column chromatography to provide the prince alcohol **1.11** in 78% yield (Scheme 1.25).

Scheme 1.25

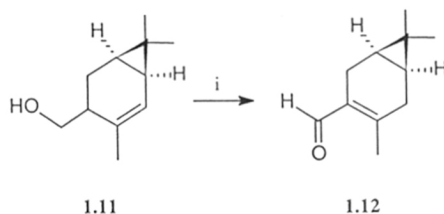


Reagents and Conditions : i) $(\text{CH}_2\text{O})_n$ /AcOH/reflux, 48 h. ii) KOH/MeOH/reflux, 8 h.

Preparation of homochiral aldehyde 1.12.

This aldehyde **1.12** was prepared by Swern oxidation reaction.⁴³ A solution of dimethyl sulfoxide in CH_2Cl_2 was added to a stirred solution of oxalyl chloride at -60°C under nitrogen atmosphere. A solution of alcohol **1.11** in CH_2Cl_2 was added dropwise over 10 minutes at -60°C and stirred for 15 minutes. The reaction mixture was warmed to -50°C , triethylamine was added over a period of 5 minutes and the reaction mixture was then slowly allowed to warmup to room temperature. After the usual workup, the aldehyde **1.12** was obtained (Scheme 1.26) as an oil, which was used as such for further reaction.

Scheme 1.26



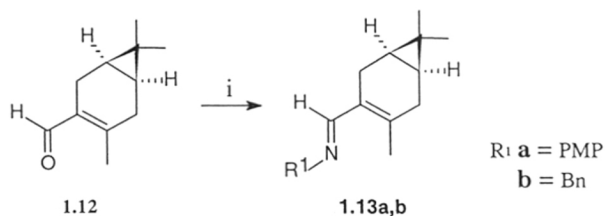
Reagents and Conditions : i) DMSO/ $(\text{COCl})_2$ / Et_3N / CH_2Cl_2 , -60°C to r. t.

Preparation of imines 1.13a,b.

To a solution of amine in CH_2Cl_2 , a solution of aldehyde **1.12** in CH_2Cl_2 was added drop by drop in the presence of anhydrous MgSO_4 at room temperature and the reaction mixture was stirred further for 12 h. After completion of the reaction, the reaction mixture was filtered and the

solid was washed with CH_2Cl_2 . The combined filtrate was concentrated to afford the imines in quantitative yields (Scheme 1.27). These crude imines were used as such for further reactions.

Scheme 1.27

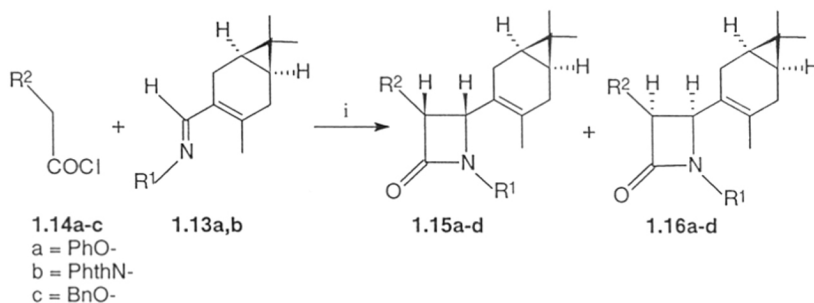


Reagents and Conditions : i) $\text{R}^1\text{NH}_2 / \text{CH}_2\text{Cl}_2 / \text{MgSO}_4$, r. t., 4 h.

*Preparation of β -lactams **1.15a-d** & **1.16a-d**.*

A solution of acid chloride **1.14a-c** in anhydrous CH_2Cl_2 was slowly added to a solution of imines **1.13a,b** and triethylamine in CH_2Cl_2 at -23°C . After completion of the addition, the reaction mixture was allowed to warmup to room temperature and stirred for 12 h. The reaction mixture after usual workup gave a crude product, which was purified by column chromatography (silica gel, acetone/pet. ether) to give a diastereomeric mixture of β -lactams (Scheme 1.18) **1.15a-d** & **1.16a-d**. The diastereomeric ratio was determined from ^1H NMR spectral data and HPLC analysis.⁴⁴

Scheme 1.28



Reagents and Conditions : i) $\text{Et}_3\text{N} / \text{CH}_2\text{Cl}_2$, -23°C to r. t. 12 h.

The diastereomeric mixture of β -lactam **1.15b** & **1.16b** was chosen as a representative of this series for spectral characterization and discussion.

Table 1. Synthesis of β -lactams **1.15a-d** & **1.16a-d** via cycloaddition reaction of imines **1.13a,b** with ketenes derived from the acid chlorides **1.14a-c**.

Compound 1.15 & 1.16	R ¹	R ²	Diastereomeric ratio	Yield (%)
a	PMP-	PhO-	54 : 46	46
b	Bn-	PhthN-	54 : 46	48
c	Bn-	PhO-	55 : 45	32
d	Bn-	BnO-	56 : 44	53

The ¹H NMR spectrum of the mixture of **1.15b** & **1.16b** showed two sets of signals, indicating the presence of two diastereomers in the mixture. One of the *gem* dimethyl protons of the bicyclic six membered ring appeared as two singlets at 0.50 and 0.95, integrating for a total of three protons. The diastereomeric ratio was found to be 54 : 46 from integrating ratio of these peaks. The other *gem* dimethyl group appeared as two separate singlets at 1.05 and 1.15, integrating for total three protons. The vinylic methyl protons appeared as two singlets at 1.45 and 1.55 with the diastereomeric ratio of 54 : 46 for the major and minor isomer respectively. Several multiplets appeared in between 0.8 and 3.45 corresponding to the methylene and methine protons of the bicyclic chiral auxiliary. One of the benzylic methylene protons appeared as doublets at 4.21 and 4.25, integrating for total one proton. The other benzylic methylene protons appeared as doublets at 5.10 and 5.21 (*J* = 14 Hz), integrating for total one proton. The C4 proton of the major and minor appeared as doublet at 4.61 and 4.68 respectively. The C3 proton of the minor and major appeared as doublet at 5.58 and 5.65 respectively with the *J* value of 4.8 Hz. The stereochemistry of the β -lactam at C3 and C4 was established as *cis* from the coupling constant measurements (*J* = 4.8 Hz). The aromatic protons appeared as several multiplets in between 7.20 and 8.00, integrating for a total of nine protons. The IR spectrum showed a band at 1760 for β -lactam carbonyl stretching, 1730 for phthalimido carbonyl stretching and 1600 for olefinic stretching.

The ^{13}C NMR spectrum of the mixture of **1.15b** & **1.16b** showed two sets of signals indicating the presence of two diastereomer. The *gem* dimethyl carbons of the major and minor isomer resonated at 10.4, 10.8, 14.4, 14.9. The quaternary carbon of the chiral auxiliary appeared at 21.87 and 22.0. The angular methyl carbon of the major and minor isomers appeared at 25.0 and 25.7 respectively. The methylene carbons of the chiral auxiliary appeared at 23.2 and 23.4. The methine carbon of the chiral auxiliary appeared at 32.4 and 32.6. The benzylic methylene carbon appeared at 47.5. The C4 and C3 carbons of the major and minor isomers appeared at 57.9, 58.3 and 59.3, 60.3 respectively. The aromatic carbons appeared in their usual region of 123.7 to 134.7. The two quaternary carbons of the aromatic group and the two olefinic carbons of the chiral auxiliary appeared at 147.4, 147.9 and 164.4, 164.8 respectively. The phthalimido carbonyl appeared at 166.8. The β -lactam carbonyl of the major and minor isomers appeared at 195.1 and 194.9 respectively.

The pure major isomer **1.15a** was obtained by crystallization from methanol. In other cases we could not separate the diastereomeric mixture either by column chromatography or by crystallization.

The ^1H NMR spectrum of **1.15a** showed two singlets at 1.0 and 1.2 for *gem* dimethyl protons of the carene moiety. A triplet appeared at 1.4 ($J = 7$ Hz) corresponding to the cyclopropyl methine proton. Several multiplets appeared in the region of 1.60 and 2.65, integrating for four protons of the chiral auxiliary. A doublet appeared at 2.85 was accounted for one proton of the chiral auxiliary. Two singlets appeared at 2.0 and 3.8, accounted for methyl protons of the chiral auxiliary and methoxy protons of the aromatic group. The C4 and C3 protons of the β -lactam ring appeared as doublets at 5.31 and 5.55 respectively. The stereochemistry at C3 and C4 centers was determined as *cis* from the coupling constant measurements ($J = 5$ Hz.). The multiplets was observed in between 6.90 - 7.15 integrated for five aromatic protons. The multiplets appearing in between 7.25 and 7.45 accounted for four aromatic protons. The IR spectrum showed a sharp band at 1750 for the β -lactam carbonyl stretching. This compound gave satisfactory microanalysis. These spectral analyses are in agreement with the assigned structure of β -lactam **1.15a**.

1.7 SUMMARY

The effect of γ -chiral center (remote stereocontrol) on diastereoselection in β -lactam ring formation has been studied by using imines derived from homochiral aldehydes in which the chiral center resides at γ -carbon. The range of diastereoselectivity obtained was very poor. Moreover, the separation of diastereomeric mixtures by column chromatography was unsuccessful. However, in one case the diastereomer **1.15a** was isolated in optically pure form by crystallization.

1.8 EXPERIMENTAL

SECTION A :

1.8.1 Synthesis of Diol 1.02.

In a 1 lit. round bottom flask formic acid (250 mL, 6.6 mmol) was taken and (+)-3-carene (55 g, 0.4 mol) was added to it dropwise with stirring. To the resulting mixture, H_2O_2 (82.5 mL) was added dropwise over a period of 1 h maintaining the temperature below 40°C and it was stirred overnight. A solution of sodium hydroxide (80 g) in water (200 mL) was then added dropwise without allowing the temperature to rise above 40°C . The reaction mixture was stirred for 1/2 h. and poured into a separating funnel. The upper formate ester layer was removed and the aqueous layer was again treated with a solution of NaOH (60 g) in water (150 mL). The second crop of formate ester obtained was separated. The combined formate ester was taken in a 1 lit. round bottom flask attached with a stirrer and a thermometer. Then it was treated with water (450 mL) followed by a dropwise addition of a solution of NaOH (20 g) in water (30 mL) without allowing the temperature to go above 40°C . The white crystalline solid separated out was filtered, washed with cold water and dried to give 34.5 g (50%) of diol 1.02.

1.8.2 Synthesis of Ketoaldehyde 1.03.

To a solution of diol 1.02 (27.5 g, 0.16 mol) in acetone (425 mL) and water (130 mL), powdered sodium periodate (55 g) was added in portions over a period of 1/2 h with stirring. After the addition, reaction mixture was stirred for 3 h and solid was filtered off. The filtrate was concentrated on a rotary evaporator. The residue was diluted with about water (100 mL) and extracted with benzene (3 x 100 mL). The combined organic layer was washed with water (2 x 50 mL), brine (30 mL) and dried over anhydrous sodium sulphate. The benzene solution of the ketoaldehyde 1.03 was concentrated to 200 mL and this solution was used as such for the next reaction.

1.8.3 Synthesis of Cyclic Aldehyde 1.04b.

To the above benzene solution of ketoaldehyde **1.03**, piperidine (2 mL) and acetic acid (2 mL) were added and the mixture was refluxed for 3 h with azeotropic removal of water. After the completion of the reaction, the reaction mixture was washed well with water (3 x 40 mL), dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to get a dark brown oil, which was then distilled under vacuum and the aldehyde **1.04b** (53%) was collected boiling at 60 - 63°C/1.5 mm and the cyclic ketone **1.04a** (35%) was collected at 90-95°C/1.5 mm.

1.8.4a Procedure for the preparation of imines 1.05a.

To a mixture of amine, (*R*)-(+)-phenylethyl amine (1.0 g, 8.2 mmol), CH₂Cl₂ (15 mL) and anhydrous MgSO₄ (1.0 g), the aldehyde **1.04b** (1.2 g, 8 mmol) in CH₂Cl₂ (10 mL) was added dropwise with stirring. The mixture was stirred for 1/2 h at room temperature. After the completion of the reaction (TLC), the reaction mixture was filtered and the filtrate on concentration gave 2.0 g (100%) of imines **1.05a**.

1.8.4b Procedure for the preparation of imines 1.05b.

The mixture of amine (*S*)-(-)-phenylethyl amine (0.850 g, 7 mmol), CH₂Cl₂ (15 mL) and anhydrous MgSO₄ (1.0 g), was treated the aldehyde **1.04b** (0.900 g, 6 mmol) in CH₂Cl₂ (10 mL) to provide 1.5 g (100%) of imine **1.05b**.

The above imines were used as such for further reaction.

1.8.5 General Procedure for the Preparation of β -lactams 1.07a-d & 1.08a-d.

A solution of the acid chloride (5 mmol) in dry CH₂Cl₂ (20 mL) was slowly added to a solution of imines **1.05a,b** (4 mmol) and triethylamine (15 mmol) in CH₂Cl₂ (20 mL) at -78°C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 12 h. It was then washed with water (30 mL), satd. NaHCO₃ (30 mL) and brine. The organic layer was dried (anhyd Na₂SO₄) and concentrated under reduced pressure to give a diastereomeric

mixture of β -lactams **1.07a-d** & **1.08a-d** in 65 - 92% yield. The major and minor diastereomers were separated by column chromatography (silica gel, 60-120 mesh, 10% EtOAc in pet. ether).

1.8.5a (3*R*,4*S*,1'*R*,5'*S*,1''*R*) 1-[1''-phenylethyl]-3-phthalimido-4-[3',6',6'-trimethylbi-cyclo (3.1.0)-hex-2'-en-2'-yl] azetidin-2-one 1.07a.

The imine **1.05a** (1.0 g, 4 mmol) on treatment with phthalimidoacetyl chloride (1.1 g, 5 mmol) at -78°C in the presence of triethylamine (1.5 g, 15 mmol), provided the β -lactam **1.07a** and **1.08a** (1.6 g, 92%) as a diastereomeric mixture. The pure diastereomer **1.07a** was isolated in 84% yield by single crystallization from pet. ether/acetone.

M. P. : 147-148°C.

¹H NMR : 0.75 (s, 3H, CH₃); 0.8 (s, 3H, CH₃); 0.85-1.05 (m, 2H, CH); 1.35 (s, 3H, CH₃); 1.70 (d, *J* = 7 Hz, 3H, CH₃); 1.95-2.10 (m, 2H, CH₂); 4.6 (d, *J* = 5 Hz, 1H, C4H); 5.0 (q, *J* = 7 Hz, 1H, CH); 5.35 (d, *J* = 5 Hz, 1H, C3H); 7.30-7.50 (m, 5H, Ar); 7.70-7.80 (m, 4H, Ar).

¹³C NMR : 13.2, 13.3, 19.7, 20.5, 25.6, 26.1, 38.4, 38.8, 53.6, 57.0, 57.7, 123.5, 127.1, 127.6, 128.8, 130.1, 131.7, 134.4, 137.8, 140.6, 164.7, 166.8.

IR : 3040, 1760, 1730, 1400.

MS (m/z) : 439 (M⁺ - 1).

[α]_D²⁵ : -26.12 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₈H₂₈N₂O₃

Calculated : C, 76.36; H, 6.36; N, 6.36.

Found : C, 76.10; H, 6.80; N, 6.50.

1.8.5b (3*R*,4*S*,1'*R*,5'*S*,1''*R*) and (3*S*,4*R*,1'*R*,5'*S*,1''*R*) 3-phenoxy-1-[1''-phenylethyl]-4-[3',6',6'-trimethylbicyclo (3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.07b & 1.08b.

The imine **1.05a** (1.0 g, 4 mmol) on treatment with phenoxyacetyl chloride (0.750 g, 4.4 mmol) at -78°C in the presence of triethylamine (1.3 g, 13 mmol), provided the β -lactam **1.07b** &

1.08b (0.990, 65%) as a diastereomeric mixture. The two diastereomers **1.07b** and **1.08b** were separated by column chromatography.

(3*R*,4*S*,1'*R*,5'*S*,1''*R*) 3-phenoxy-1-[1''-phenylethyl]-4-[3',6',6'-trimethylbicyclo (3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.07b.

The compound **1.07b** was isolated as an oil.

¹H NMR : 0.4 (s, 3H, CH₃); 0.95 (s, 3H, CH₃); 1.0 - 1.1 (m, 1H, CH); 1.5 (s, 3H, CH₃); 1.55 - 1.57 (m, 1H, CH); 1.8 (d, 3H, *J* = 7 Hz, CH₃); 2.2 - 2.3 (m, 2H, CH₂); 4.56 (d, *J* = 5 Hz, 1H, C4H); 4.59 (q, *J* = 7 Hz, 1H, CH); 5.2 (d, *J* = 5 Hz, 1H, C3H); 6.9 - 7.0 (m, 3H, Ar); 7.2 - 7.4 (m, 7H, Ar).

¹³C NMR : 13.5, 14.0, 19.5, 21.0, 26.5, 27.0, 38.0, 38.5, 53.5, 55.0, 82.0, 115.5, 122.0, 127.5, 128.0, 128.5, 129.0, 129.5, 141.0, 142.0, 159.2, 166.5.

IR : 1740.

[α]_D²⁵ : -3.10 (c 1, CH₂Cl₂).

(3*S*,4*R*,1'*R*,5'*S*,1''*R*) 3-phenoxy-1-[1''-phenylethyl]-4-[3',6',6'-trimethylbicyclo(3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.08b.

The compound **1.08b** was isolated as an oil.

¹H NMR : 0.70 (s, 3H, CH₃); 0.90 (s, 3H, CH₃); 0.95 - 1.25 (m, 2H, CH); 1.5 (s, 3H, CH₃); 1.6 (d, 3H, *J* = 7 Hz, CH₃); 1.9 - 2.05 (m, 2H, CH₂); 4.6 (d, *J* = 4.5 Hz, 1H C4H); 4.80 (q, *J* = 7 Hz, 1H, CH); 5.75 (d, *J* = 4.5 Hz, 1H, C3H); 6.85 - 7.00 (m, 3H, Ar); 7.15 - 7.35 (m, 7H, Ar).

¹³C NMR : 13.2, 13.3, 19.6, 20.2, 25.9, 26.0, 38.4, 52.9, 56.3, 80.6, 115.3, 121.6, 127.0, 127.6, 128.6, 129.0, 129.3, 129.7, 139.9, 140.0, 157.1, 165.6.

IR : 3010, 1740.

[α]_D²⁵ : +4.80 (c 1, CH₂Cl₂).

1.8.5c (3*R*,4*S*,1'*R*,5'*S*,1'*S*) and (3*S*,4*R*,1'*R*,5'*S*,1''*S*) 1-[1''-phenylethyl]-3-phthalimido-4-[3',6',6'-trimethyl bicyclo(3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.07c & 1.08c.

The imine **1.05b** (0.760 g, 3 mmol) on treatment with phthalimidoacetyl chloride (0.890 g, 4 mmol) at -78°C in the presence of triethylamine (1.2 g, 12 mmol), provided the β-lactam **1.07c** & **1.08c** (1.14 g, 86%) as a diastereomeric mixture. The two diastereomers **1.07c** and **1.08c** were separated by column chromatography.

(3*R*,4*S*,1'*R*,5'*S*,1''*S*) 1-[1''-phenylethyl]-3-phthalimido-4-[3',6',6'-trimethyl bicyclo(3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.07c.

The major compound **1.07c** was isolated as an oil.

¹H NMR : 0.75 (s, 3H, CH₃); 0.76 - 0.85 (m, 1H, CH); 1.0 (s, 3H, CH₃); 1.09 (d, *J* = 8 Hz, 1H, CH); 1.25 (s, 3H, CH₃); 1.80 (d, *J* = 15 Hz, 1H, CH₂); 2.0 (d, *J* = 7 Hz, 3H, CH₃); 2.05 - 2.20 (m, 1H, CH₂); 4.35 (q, *J* = 7 Hz, 1H, CH); 4.4 (d, *J* = 5 Hz, 1H, C4H); 5.3 (d, *J* = 5 Hz, 1H, C3H); 7.25 - 7.4 (m, 5H, Ar); 7.65 - 7.8 (m, 4H, Ar).

¹³C NMR : 12.7, 13.4, 20.1, 20.3, 25.7, 26.0, 37.8, 55.5, 56.3, 57.3, 123.1, 126.2, 127.4, 128.6, 129.5, 131.3, 134.1, 137.6, 141.6, 163.7, 166.4.

IR : 3020, 1730, 1220.

[α]_D²⁵ : -16.89 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₈H₂₈N₂O₃

Calculated : C, 76.36; H, 6.36; N, 6.36.

Found : C, 75.80; H, 6.10; N, 5.90.

(3*S*,4*R*,1'*R*,5'*S*,1''*S*) 1-[1''-phenylethyl]-3-phthalimido-4-[3',6',6'-trimethyl bicyclo(3.1.0)-hex-2'-en-2'-yl]azetidin-2-one 1.08c.

M. P. : 115-117 °C.

¹H NMR : 0.1 (s, 3H, CH₃); 0.6 (s, 3H, CH₃); 0.8 - 0.9 (m, 2H, CH); 1.75 (s, 3H, CH₃); 1.65 (d, *J* = 7 Hz, 3H, CH₃); 1.75 - 1.95 (m, 1H, CH₂); 2.23 (dd, *J* = 8 & 18 Hz, 1H, CH₂); 4.45 (d, *J* = 5 Hz, 1H, C4H); 5.15 (d, *J* = 5 Hz, 1H, C3H); 5.20 (q, *J* = 7 Hz,

1H, CH); 7.25 - 7.45 (m, 5H, Ar); 7.70 - 7.90 (m, 4H, Ar).

¹³C NMR : 12.7, 13.0, 18.0, 20.2, 25.5, 27.45, 38.0, 51.7, 54.3, 57.7, 123.4, 127.3, 127.8, 128.6, 128.9, 132.3, 134.3, 139.0, 143.4, 163.4, 166.1.

IR : 1730.

$[\alpha]_D^{25}$: +51.73 (c 1, CH₂Cl₂).

1.8.5d (3*R*,4*S*,1'*R*,5'*S*,1''*S*) and (3*S*,4*R*,1'*R*,5'*S*,1''*S*) 3-phenoxy-1-[1''-phenylethyl]-4-[3',6',6'-trimethylbicyclo (3.1.0)-hex-2'-en-2'-yl]azetidin-2-one **1.07d** & **1.08d**.

The imine **1.05c** (0.760 g, 3 mmol) on treatment with phenoxyacetyl chloride (0.680 g, 4 mmol) at -78°C in the presence of triethylamine (1.2 g, 12 mmol), provided the β-lactam **1.07d** & **1.08d** (1.1 g, 94%) as a diastereomeric mixture. The β-lactam **1.07d** was isolated from the diastereomeric mixture by column chromatography as an oil. The minor isomer **1.08d** could not be obtained in pure form.

(3*R*,4*S*,1'*R*,5'*S*,1''*S*) 3-phenoxy-1-[1''-phenylethyl]-4-[3',6',6'-trimethylbicyclo (3.1.0)-hex-2'-en-2'-yl]azetidin-2-one **1.07d**.

¹H NMR : 0.9 (s, 3H, CH₃); 1.10 (s, 3H, CH₃); 1.20 (d, *J* = 8 Hz, 1H, CH); 1.30 (m, 1H, CH); 1.45 (s, 3H, CH₃); 1.95 (d, *J* = 8 Hz, 3H, CH₃); 2.10 - 2.25 (m, 2H, CH₂); 4.15 (q, *J* = 8 Hz, 1H, CH); 4.45 (d, *J* = 5 Hz, 1H, C4H); 5.25 (d, *J* = 5 Hz, 1H, C3H); 6.85 - 7.05 (m, 3H, Ar); 7.10 - 7.45 (m, 7H, Ar).

¹³C NMR : 11.9, 13.2, 13.5, 14.11, 20.4, 20.8, 26.4, 29.8, 38.1, 38.6, 55.8, 56.1, 81.1, 115.6, 116.0, 121.9, 126.7, 129.0, 129.3, 129.5, 129.7, 141.4, 141.9, 157.5, 165.7.

IR : 3000, 1750, 1730, 1220.

$[\alpha]_D^{25}$: -27.77 (c 3, CH₂Cl₂).

1.8.6 Preparation of Diketone **1.09**.

To a solution of β-lactam **1.07a** (0.220 g, 0.5 mmol) CH₃CN:CCl₄:H₂O (2:2:3, 7 mL), powdered NaIO₄ (0.210 g, 1 mmol) was added followed by a catalytic amount of RuCl₃ (4 mg) at 0°C and the reaction mixture was stirred for 4 h at this temperature. After completion of the

reaction (TLC), the reaction mixture was diluted with water and extracted with CHCl_3 (2 X 20 mL). The combined organic extracts were dried and concentrated to give crude product, which on column purification (silica gel, 60-120 mesh, $\text{CHCl}_3/\text{EtOAc}$ mixtures) furnished the diketone (0.125 g) **1.09** as oil in 58 % yield.

IR : 1760, 1740 and 1710.

^1H NMR : 0.6 (s, 3H, CH_3); 0.7 (s, 3H, CH_3); 0.75 - 1.1 (m, 2H, CH); 1.7 (d, $J = 7.3$ Hz, 3H, CH_3); 2.05 (s, 3H, CH_3); 2.55 - 2.85 (m, 2H, CH_2); 4.45 (d, $J = 5.3$ Hz., 1H, C4H); 5.2 (q, $J = 7.3$ Hz., 1H, CH); 5.45 (d, $J = 5.3$ Hz., 1H, C3H); 7.30 - 7.85 (m, 9H, Ar).

$[\alpha]_{\text{D}}^{25}$: +32.18 (c 2.5, CH_2Cl_2).

SECTION B

1.8.7 Preparation of Alcohol 1.11.

In a 250 mL round bottom flask, a mixture of paraformaldehyde (18 g), glacial acetic acid (150 mL) and optically pure (+)-3-carene (27 g, 200 mmol) were taken. This reaction mixture was stirred under reflux for 48 h. The glacial acetic acid was removed by distillation and the residue was diluted with water (30 mL). It was then extracted with CHCl_3 (3 x 20 mL), washed with brine, dried over Na_2SO_4 and concentrated. The residue was fractionated to give 16.5 g (38%) of pure prince acetate **1.10** fraction boiling at 75 - 84°C/10 mm.

To this prince acetate (16 g, 90 mmol), a of potassium hydroxide (10 g) in CH_3OH (100 mL) was added drop by drop and stirred at room temperature for 8 h. The solvent was removed by distillation and the residue was diluted with water (30 mL). It was extracted with CHCl_3 (3 x 20 mL), washed with brine, dried over Na_2SO_4 . It was concentrated under reduced pressure and the residue was purified by column chromatography to afford 10 g (78%) of the pure alcohol **1.11**.

1.8.8 Preparation of Aldehyde 1.12.

A solution of dimethyl sulfoxide (24 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of oxalyl chloride (12 mmol) in CH_2Cl_2 (25 mL) over 30 minutes at -60°C under nitrogen atmosphere and stirred 30 minutes. A solution of alcohol **1.11** (1.8 g, 11 mmol) in CH_2Cl_2 (10 mL) was then added dropwise over 10 minutes at -60°C and stirred for 15 minutes. The reaction mixture was then warmed up to -50°C and triethylamine (55 mmol) was added over a period of 5 minutes and the reaction mixture was slowly allowed to warmup to room temperature. The reaction mixture was diluted with water (30 mL) were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 . It was then filtered and filtrate on concentration under reduced pressure gave crude aldehyde as an oil, which was used as such for the preparation of imines.

1.8.9a Procedure for the preparation of imines 1.13a.

To a solution of benzylamine (0.640 g, 6 mmol) in dry CH_2Cl_2 (20 mL), aldehyde 1.12 (0.900 g, 6 mmol) in CH_2Cl_2 (10 mL) was added in presence of anhyd MgSO_4 (1 g) and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered and the solid was washed with CH_2Cl_2 . The combined filtrates were concentrated to get imine 1.13b (1.4 g) in 92% yield.

1.8.9b Procedure for the preparation of imines 1.13b.

To a solution of *p*-anisidine (1.85 g, 15 mmol) in CH_2Cl_2 (20 mL) and anhydrous MgSO_4 (1.0 g), aldehyde 1.12 (2.2 g, 15 mmol) in CH_2Cl_2 (10 mL) was treated to provide the imine 1.13a in (3.4 g) 86% yield.

These imines 1.13a,b were used as such for further reaction without purification.

1.8.10 General Procedure for the Preparation of β -lactams 1.15a-d & 1.16a-d.

A solution of the acid chlorides (5.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was slowly added to a solution of imines (4.5 mmol) and triethylamine (16 mmol) in CH_2Cl_2 (20 mL) at -23°C . After the completion of addition, the reaction mixture was allowed to warmup to room temperature and stirred further for 12 h. The reaction mixture was then washed with water (30 mL), satd. NaHCO_3 (30 mL), brine (15 mL) and dried (anhyd Na_2SO_4). The removal of solvent at reduced pressure gave diastereomeric mixture of β -lactams 1.15a-d & 1.16a-d in 32 - 53% yields. The attempts to separate diastereomers by column chromatography were failed in all the cases. However, the major diastereomer 1.15a was separated by crystallization from methanol.

1.8.10a (3*R*,4*S*,1'*S*,6'*R*) 1-(*p*-Anisyl)-3-phenoxy-4-[3',7',7'-trimethylbicyclo(4.1.0)-hept-3'-en-4'-yl]azetidin-2-one 1.15a.

The imine 1.13a (1.2 g, 4.5 mmol) on treatment with phenoxyacetyl chloride (0.935 g, 5.5 mmol) at -23°C in the presence of triethylamine (1.6 g, 16 mmol), provided the β -lactam 1.15a &

1.16a (0.880 g, 46%) as a diastereomeric mixture. The major diastereomers **1.15a** was separated by crystallization from methanol.

M. P. : 179 - 181°C.

¹H NMR : 1.0 (s, 3H, CH₃); 1.2 (s, 3H, CH₃); 1.4 (t, *J* = 7 Hz, 1H, CH); 1.6 - 1.9 (m, 2H, CH₂ & CH); 2.0 (s, 3H, CH₃); 2.40 - 2.65 (m, 2H, CH₂); 2.85 (d, *J* = 17 Hz, 1H, CH₂); 3.8 (s, 3H, CH₃); 5.31 (d, *J* = 5 Hz, 1H, C4H); 5.55 (d, *J* = 5 Hz, 1H, C3H); 6.90 - 7.15 (m, 5H, Ar); 7.25 - 7.45 (m, 4H, Ar).

IR : 3020, 1750, 1230.

[α]_D²⁵ : +96.1 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₆H₂₉O₃N

Calculated : C, 77.39; H, 7.24; N, 3.47.

Found : C, 77.57; H, 7.20; N, 3.30.

1.8.10b (*3R,4S,1'S,6'R*) and (*3S,4R,1'S,6'R*) 1-(Benzyl)-3-phthalimido-4-[3',7',7'-tri-methyl bicyclo(4.1.0)-hept-3'-en-4'-yl]-azetidin-2-one **1.15b** & **1.16b**.

The imine **1.13b** (1.7 g, 7 mmol) on treatment with phthalimidoacetyl chloride (2.2 g, 10 mmol) at -23°C in the presence of triethylamine (3 g, 30 mmol), provided the β-lactam **1.15b** & **1.16b** (1.45 g, 48%) as the diastereomeric mixture. The two diastereomers could not be separated by column chromatography.

M. P. : 73 - 75°C.

¹H NMR : 0.5 & 0.95 (s, total 3H, CH₃); 0.8 - 1.1 (m, 1H, CH₂); 1.05 & 1.15 (s, total 3H, CH₃); 1.45 & 1.55 (s, total 3H, CH₃); 1.4-1.6 (m, 2H, CH₂); 2.3 - 2.6 (m, 2H, CH₂ & CH); 3.0 - 3.45 (m, 1H, CH); 4.21 & 4.25 (d, *J* = 14 Hz, total 1H, CH₂); 4.61 & 4.68 (d, *J* = 4.8 Hz, total 1H, C4H); 5.10 & 5.21 (d, *J* = 14 Hz, total 1H, CH₂); 5.58 & 5.65 (d, *J* = 4.8 Hz, total 1H, C3H); 7.20-7.55 (m, 5H, Ar); 7.65-8.00 (m, 4H, Ar).

¹³C NMR : 10.4, 10.8, 14.4, 14.9, 21.87, 22.0, 23.2, 23.4, 25.0, 25.7, 32.4, 32.6, 47.5, 57.9, 58.3, 59.3, 60.3, 123.7, 123.9, 128.6, 129.1, 129.2, 131.2, 132.9, 134.0, 134.4, 134.7, 147.4, 147.9, 164.4, 164.8, 166.8, 194.9, 195.1.

IR : 3020, 1760, 1730, 1600.

$[\alpha]_D^{25}$: +83.57 (c 0.9, CH₂Cl₂).

1.8.10c (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*S*,6'*R*) 1-(Benzyl)-3-phenoxy-4-[3',7',7'-trimethyl bicyclo(4.1.0)-hept-3'-en- 4'-yl]-azetidin-2-one 1.15c & 1.16c.

The imine **1.13b** (1.0 g, 4 mmol) on treatment with phenoxyacetyl chloride (0.850 g, 5 mmol) at -23°C in the presence of triethylamine (1.5 g, 15 mmol), provided the β-lactam **1.15c** & **1.16c** (0.5 g, 32%) as the diastereomeric mixture. The two diastereomers could not be separated by column chromatography.

¹H NMR : 0.90 & 1.05 (s, total 3H, CH₃); 1.0 - 1.25 (m, 2H, CH₂); 1.15 & 1.20 (s, total 3H, CH₃); 1.45 - 1.55 (m, 2H, CH₂); 1.6 & 1.7 (s, total 3H, CH₃); 2.3 - 3.0 (m, 2H, CH); 3.93 & 4.07 (d, *J* = 14 Hz, total 1H, CH₂); 4.67 & 4.74 (d, *J* = 5 Hz, total 1H, C4H); 4.95 & 5.03 (d, *J* = 14 Hz, total 1H, CH₂); 4.37 & 4.41 (d, *J* = 5 Hz, total 1H, C3H); 6.8 - 7.1 (m, 3H, Ar); 7.2 - 7.6 (m, 7H, Ar).

¹³C NMR : 10.5, 10.6, 14.7, 14.8, 22.2, 22.6, 23.7, 24.9, 25.8, 28.3, 28.4, 33.2, 46.3, 58.3, 59.1, 82.3, 82.4, 115.5, 115.8, 122.6, 122.8, 128.4, 128.6, 128.7, 128.9, 129.1, 129.2, 129.6, 134.1, 134.2, 134.9, 146.8, 157.1, 157.3, 165.7, 195.3, 195.6

IR : 3040, 1770, 1230.

$[\alpha]_D^{25}$: +105.7 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₆H₂₉O₂N

Calculated : C, 80.59; H, 7.54; N, 3.61.

Found : C, 80.74; H, 7.43; N, 3.78

1.8.10d (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*S*,6'*R*) 1-(Benzyl)-3-benzyloxy-4-[3',7',7'-trimethyl bicyclo (4.1.0)-hept-3'-en- 4'-yl]-azetidin-2-one 1.15d & 1.16d.

The imine **1.13b** (1.7 g, 7 mmol) on treatment with benzyloxyacetyl chloride (1.84 g, 10 mmol) at -23°C in the presence of triethylamine (3.0 g, 30 mmol), provided the β-lactam **1.15d** &

1.16d (1.45 g, 53%) as the diastereomeric mixture. The two diastereomers could not be separated by column chromatography.

^1H NMR : 0.9 & 1.05 (s, total 3H, CH_3); 1.1 & 1.2 (s, total 3H, CH_3); 1.40 - 1.55 (m, 2H, CH_2); 1.60 & 1.65 (s, total 3H, CH_3); 2.3 - 2.6 (m, 2H, CH_2); 2.75 (m, 1H, CH); 3.0 - 3.25 (m, 1H, CH); 3.86 & 3.98 (d, $J = 15$ Hz, total 1H, CH_2); 4.40 - 5.05 (m, total 5H, C_3H , C_4H & CH_2); 7.1 - 7.4 (m, 10H, Ar).

^{13}C NMR : 10.2, 10.3, 14.6, 22.9, 23.0, 24.0, 24.1, 25.0, 26.0, 28.1, 28.3, 33.0, 45.9, 58.4, 59.0, 73.3, 83.1, 83.6, 127.9, 128.1, 128.3, 128.3, 128.5, 128.7, 128.8, 129.2, 129.2, 136.3, 148.1, 148.2, 167.0, 167.5, 195.0, 195.5.

IR : 3010, 1770, 1730.

$[\alpha]_{\text{D}}^{25}$: +82.88 (c 1, CH_2Cl_2).

Analysis M.F. $\text{C}_{27}\text{H}_{31}\text{O}_2\text{N}$

Calculated : C, 80.76; H, 7.78; N, 3.49.

Found : C, 80.56; H, 7.53; N, 3.65.

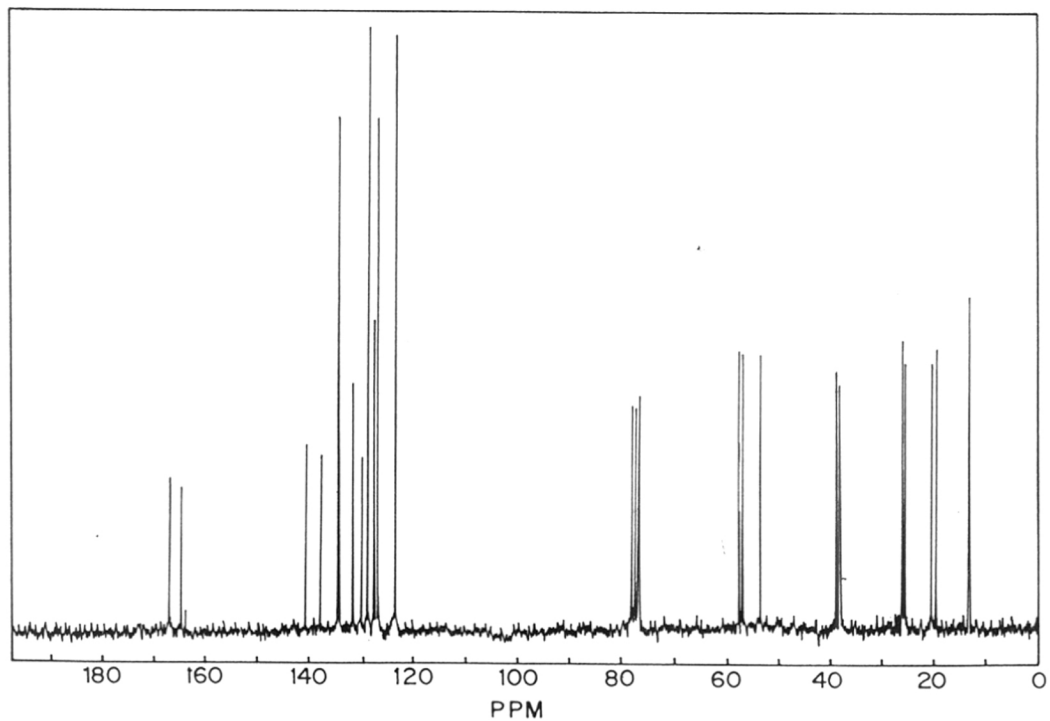
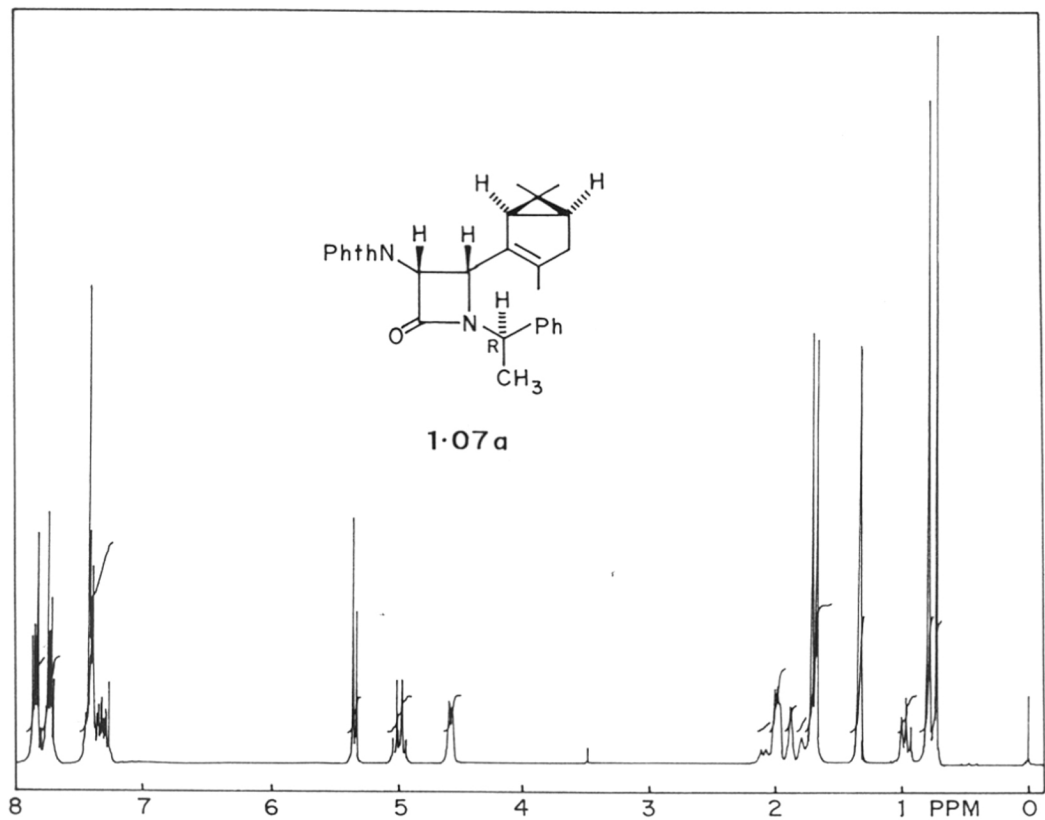
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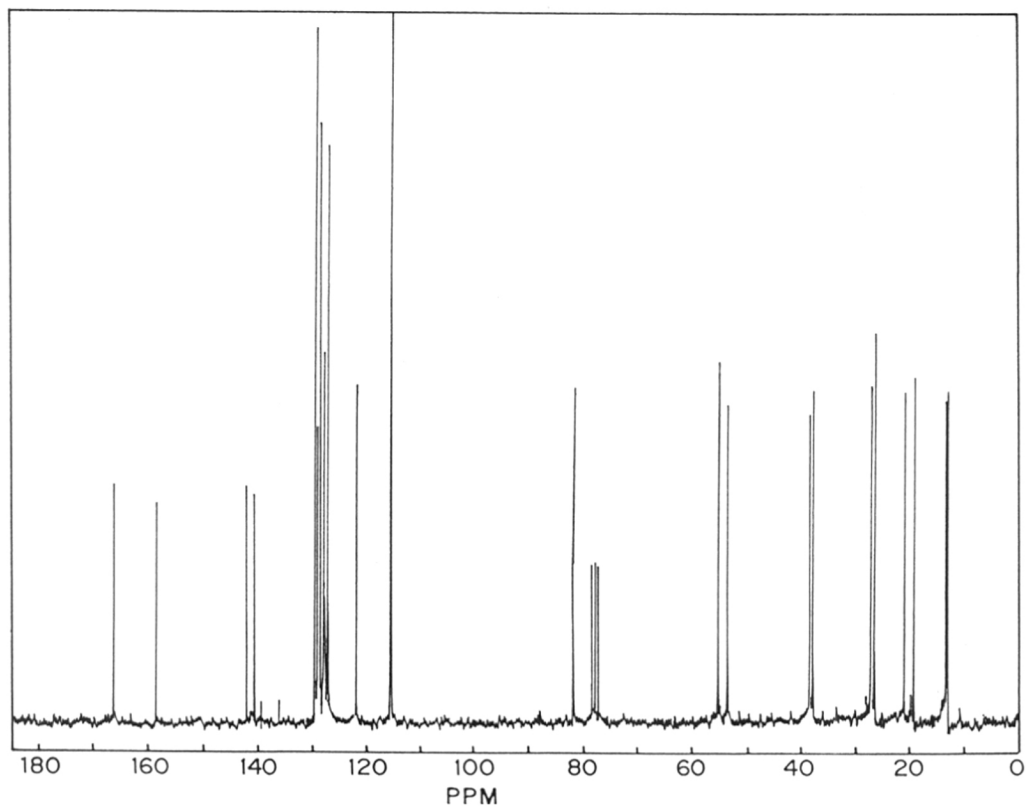
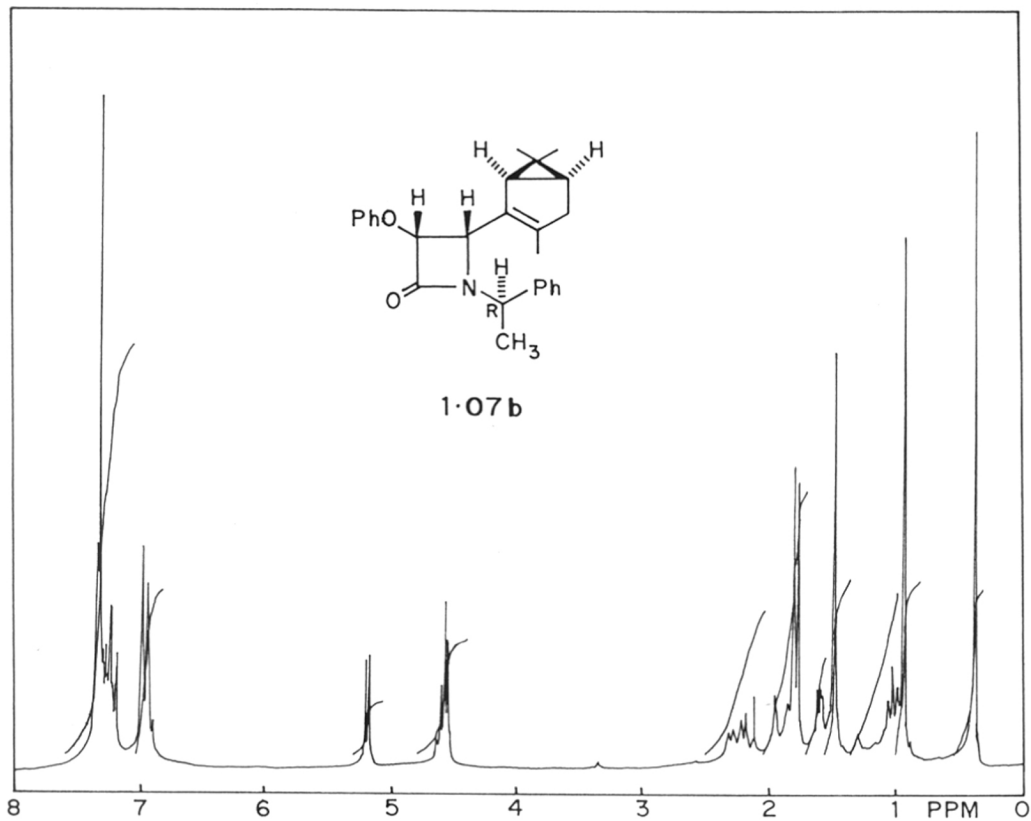
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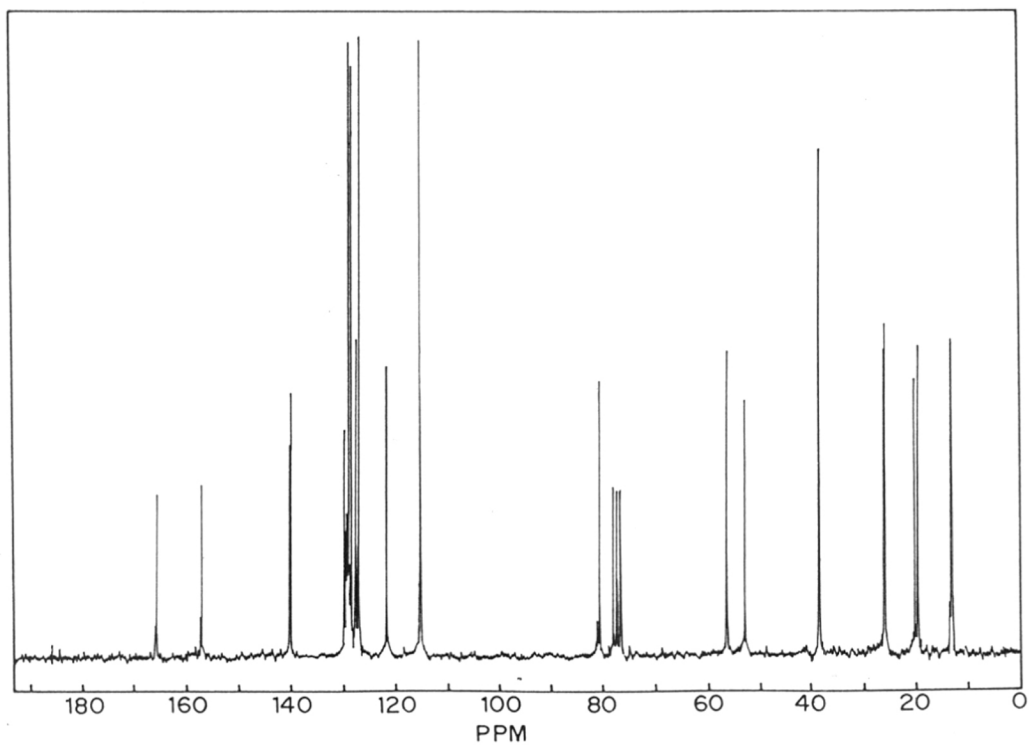
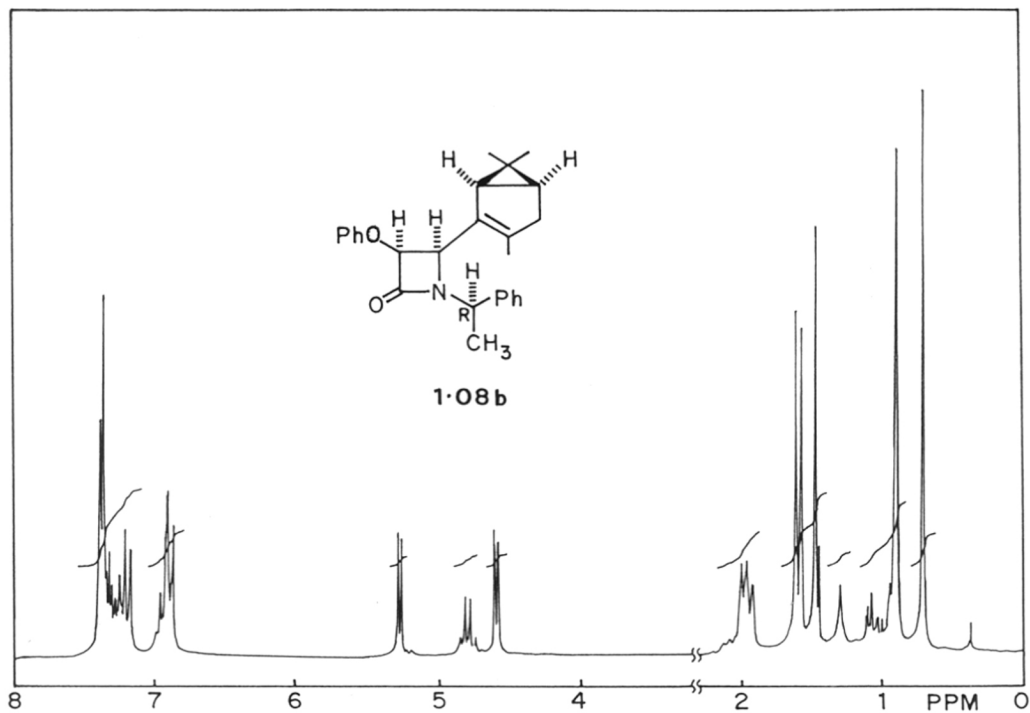
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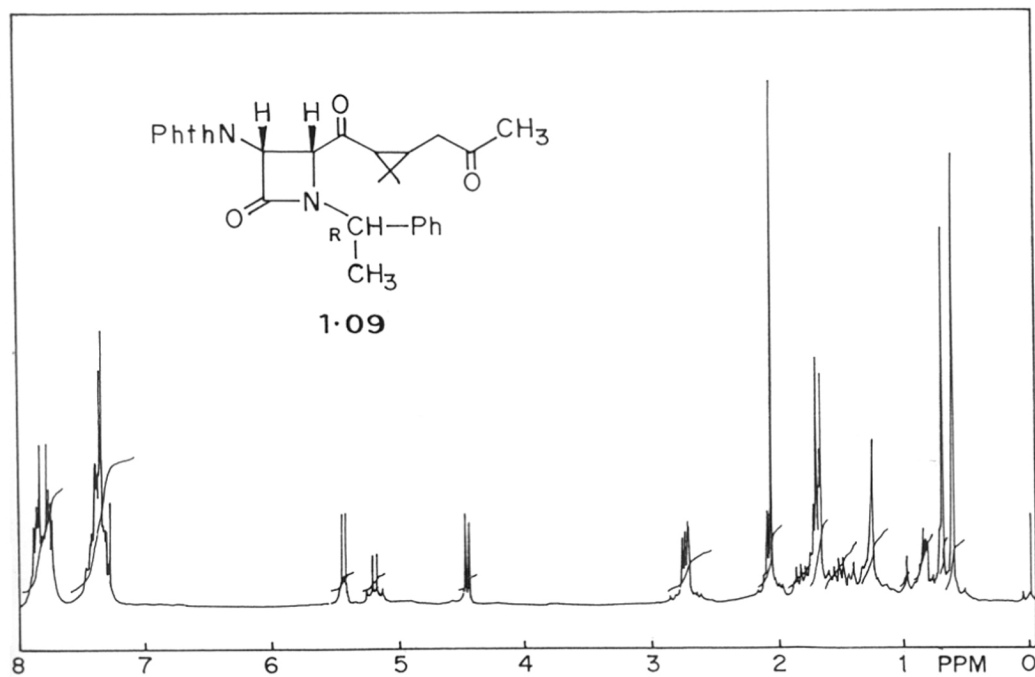
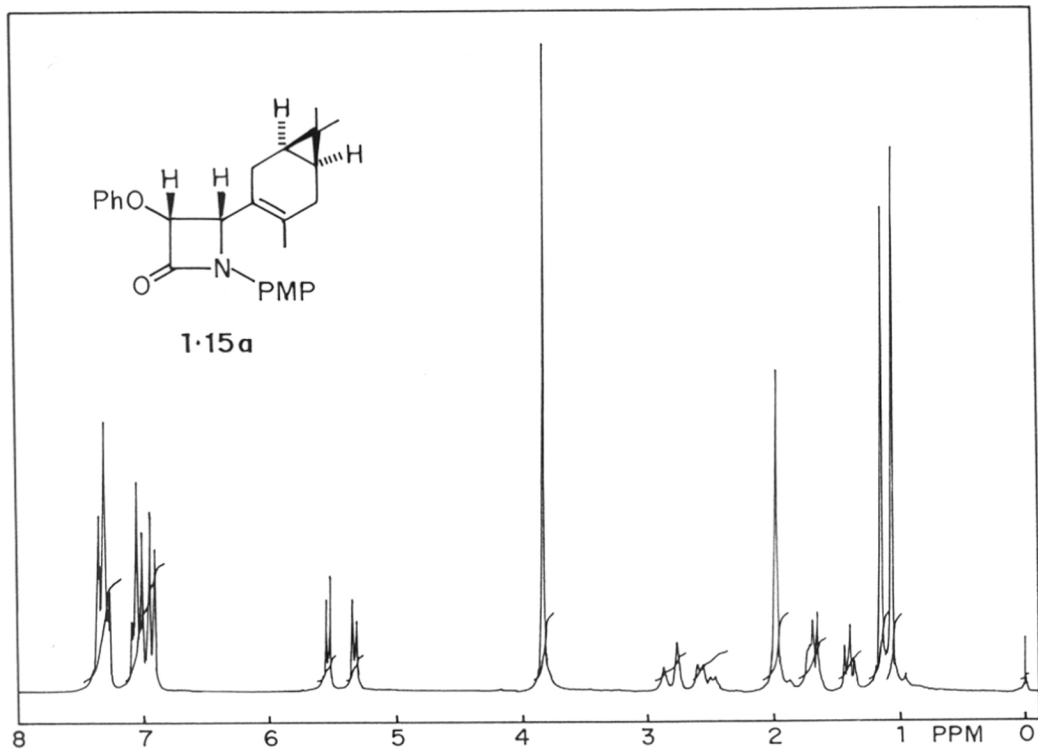
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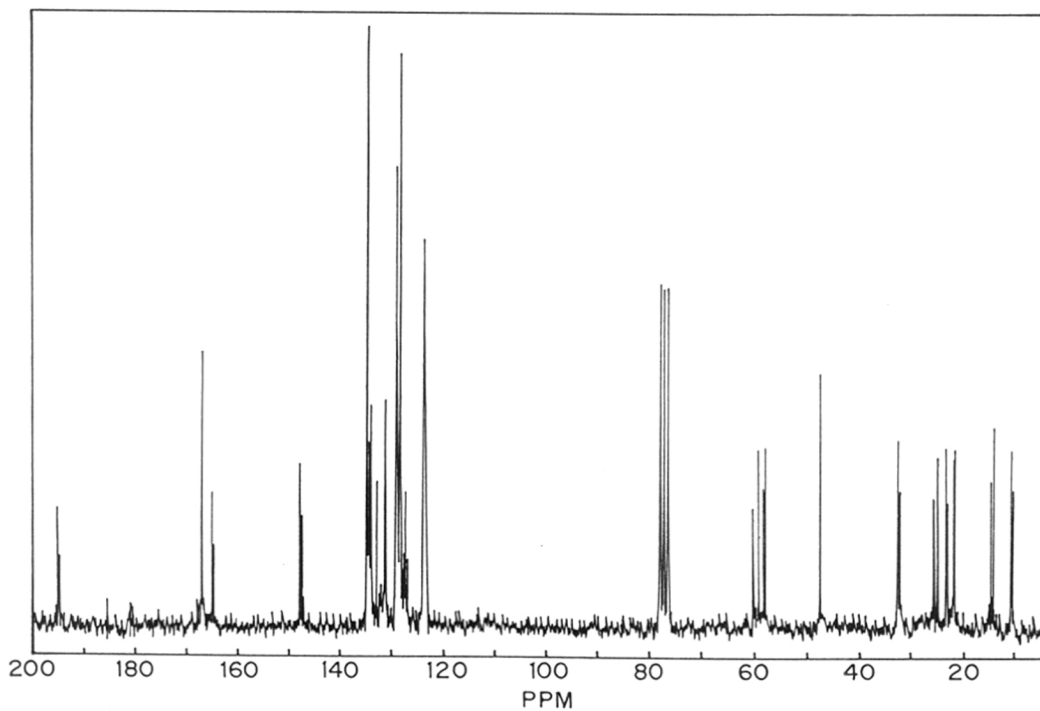
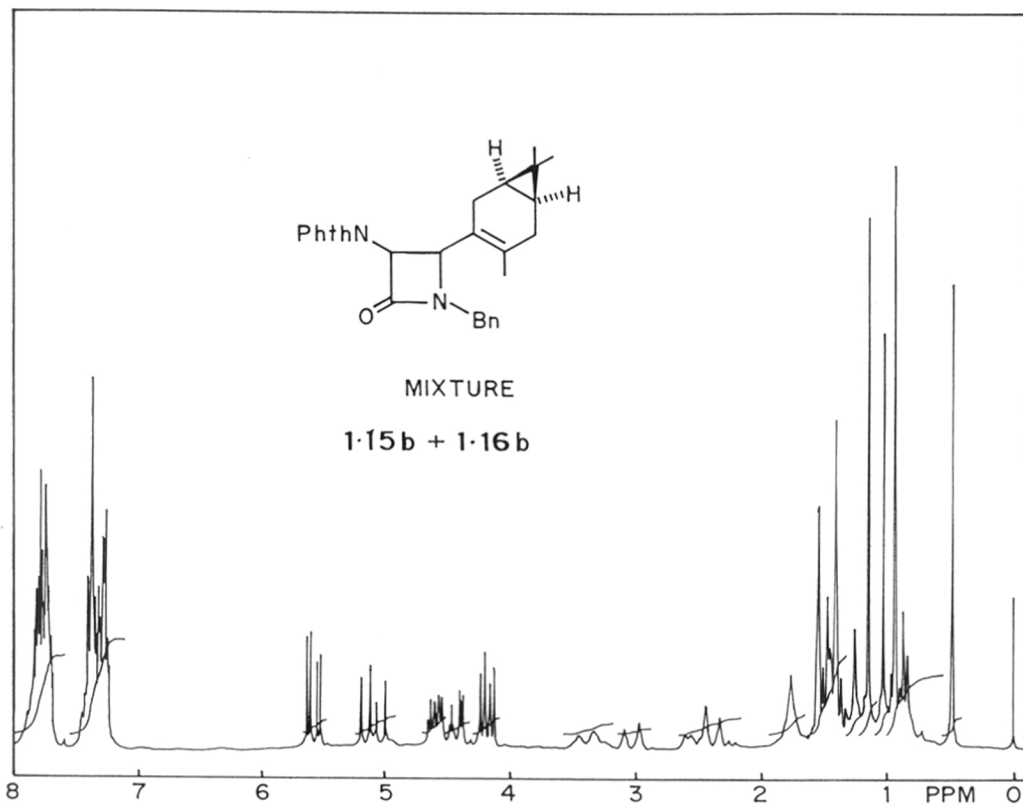
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44. HPLC : Perkin-Elmer 410-pump. H-P 1050 MWD at 254 nm connected to H-P 3396 Ser-II integrater. Col. MN-C-18, 8 nm, 4 mm x 100 mm length. Solvent system (v/v) : MeCN : H₂O (60 : 40), flow rate 2 mL/min.

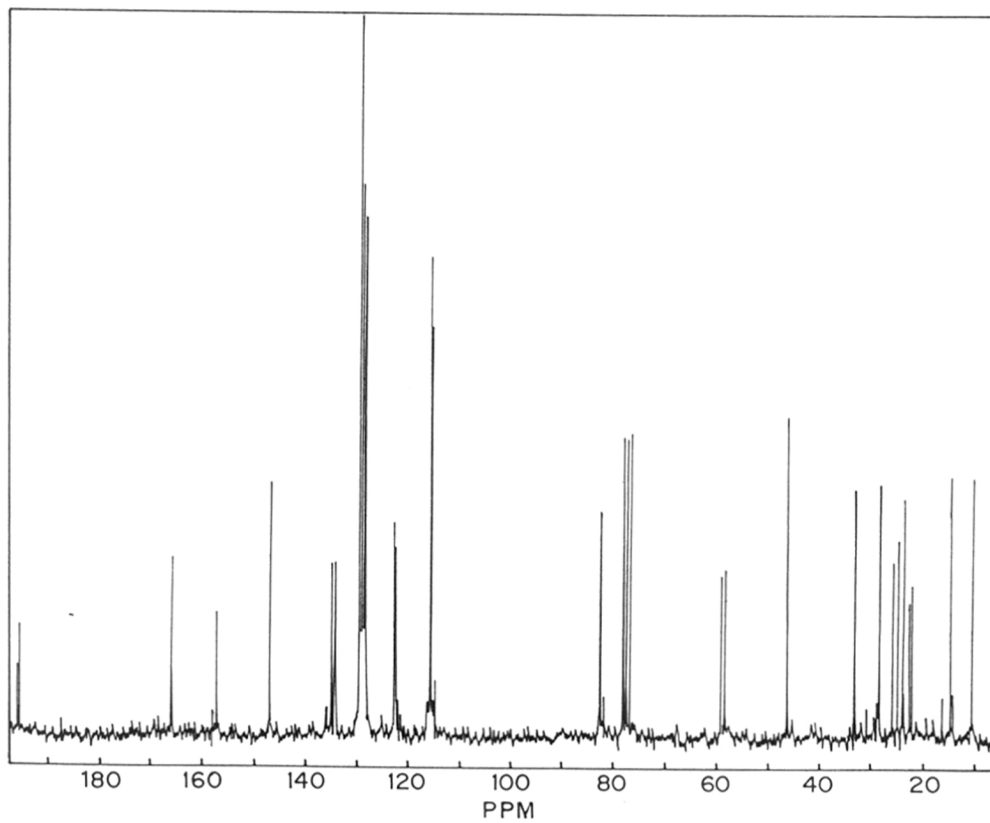
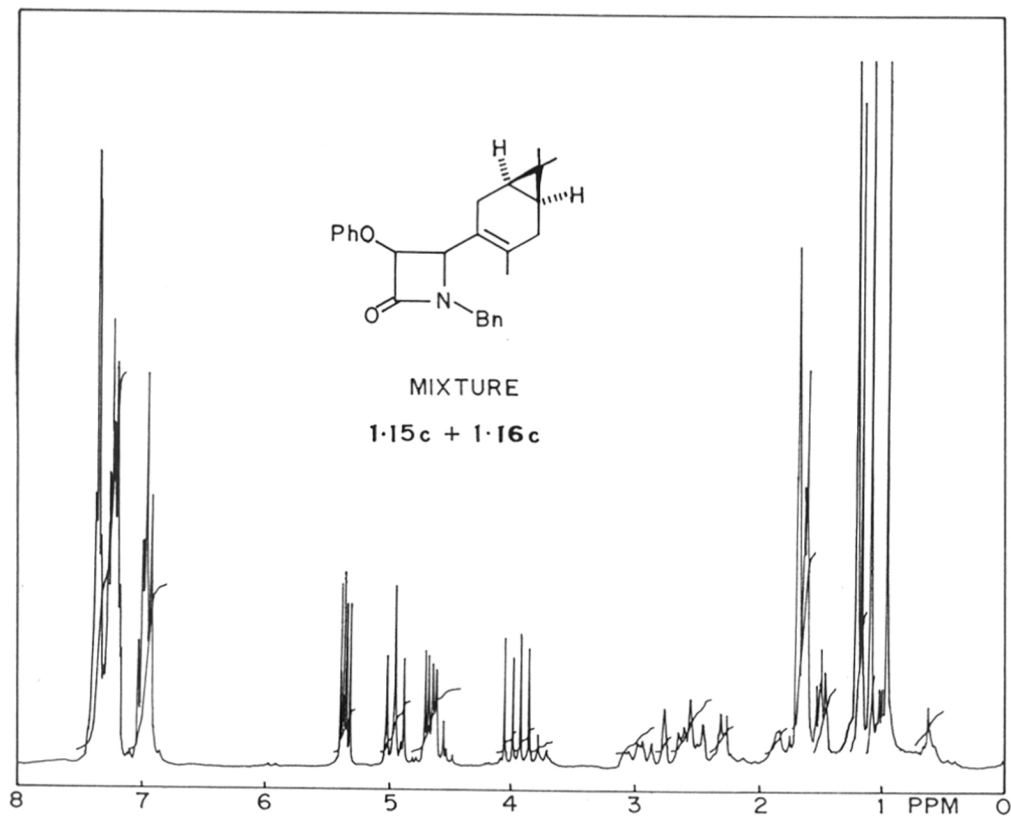












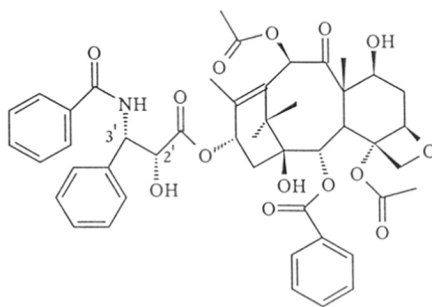
CHAPTER II

SYNTHESIS OF TAXOL SIDE CHAIN

Part of this work has been published in
Tetrahedron, 1996, 52, 5585

2.1 INTRODUCTION

Taxol, a complex diterpene, isolated from the bark of *Taxus brevifolia*¹, received an extraordinary attention from the biologists and chemists, due to its unique mechanism of action, high cytotoxicity and strong antitumor activity against different cancers. Taxol is currently in phase III clinical trial for advanced ovarian cancer, phase II for breast cancer and phase I for lung cancer and colon cancer.² Taxotere, a *N*-*t*-butoxycarbonyl derivative of taxol obtained by replacing the *N*-benzoyl group, has shown more cytotoxicity than taxol.³ The taxotere is currently undergoing clinical trials in the United States and Europe.



Taxol

The study of taxol showed that the C-13 side chain and taxane ring are required for cytotoxicity.⁴ It has been observed that the 2'*R* and 3'*S* stereochemistry of the side chain is essential for the cytotoxicity.⁵ A study of the Structure Activity Relationship (SAR) of analogues of taxol has shown that the phenylisoserine unit with a hydroxy group at C2' is essential as it participates in the intermolecular hydrogen bonding at the receptor site. However, the replacement of hydroxyl group at the 2' position by a halogen resulted in loss of cytotoxicity.⁶ The Structure Activity Relationship (SAR) studies based on X-ray structure determination have shown that the 2'-hydroxyl group may play two important roles in rendering cytotoxicity to the taxol molecule.⁷

- The 2' hydroxyl group may stabilize the amino acid side chain conformation to promote a proper binding of the molecule with receptor *via* intramolecular hydrogen bonding between the ester carbonyl, 2'-hydroxyl and 3'-NH groups.

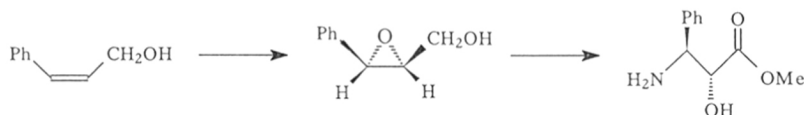
ii) There is a possibility of direct participation of 2'-hydroxyl group in the intermolecular hydrogen bonding with the receptor site.

The supply of taxol depends on its extraction from the bark of *Taxus brevifolia*,¹ which is found only in the northwest of United States. A large scale sacrifice of these trees is required to get taxol in sufficient quantities, which will not only affect the ecological system but also the future supply of taxol. Therefore, efforts have been made to search for semi-synthetic routes to taxol starting from other plant-derived products isolable in relatively larger quantities. For instance, 10-deacetylbaccatin III (10-DBA) is available from the needles of *Taxus baccata*⁸ (a renewable sources) in sufficient quantities. 10-Deacetylbaccatin III can be linked with (2*R*, 3*S*)-*N*-benzoyl-3-phenylisoserin or its equivalent, a suitably protected β -lactam, to produce taxol.⁹

An efficient synthesis of C-13 side chain and availability of Baccatin III will solve the problem of large scale availability of taxol to some extent. Following is the brief review for the synthesis of taxol side-chain.

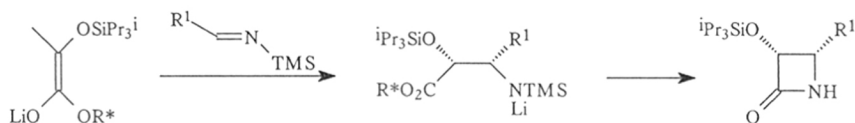
The first synthesis of taxol side-chain was achieved in eight steps by Denis *et al*¹⁰ via asymmetric epoxidation of cinnamyl alcohol and the regioselective epoxide cleavage, which provided the methyl phenylisoserin in 95% enantiomeric excess, in 23% yield (Scheme 2.01).

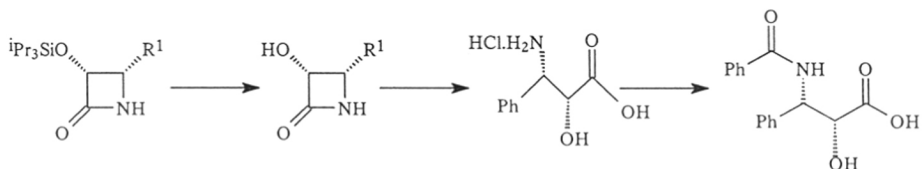
Scheme 2.01



Ojima *et al* have developed an excellent route for the synthesis of 3-hydroxy-4-phenyl- β -lactam, a key intermediate for the taxol side-chain (Scheme 2.02). They have used chiral ester enolate - imine cycloaddition method for the synthesis of β -lactams in very high enantiomeric purity. The effectiveness of this method has been shown by recovering and recycling the chiral auxiliary, (-)-*trans*-2-phenylcyclohexanol.¹¹

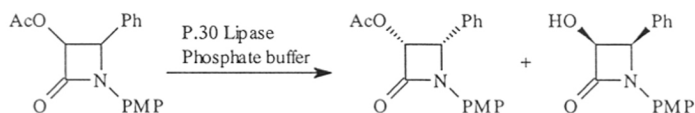
Scheme 2.02





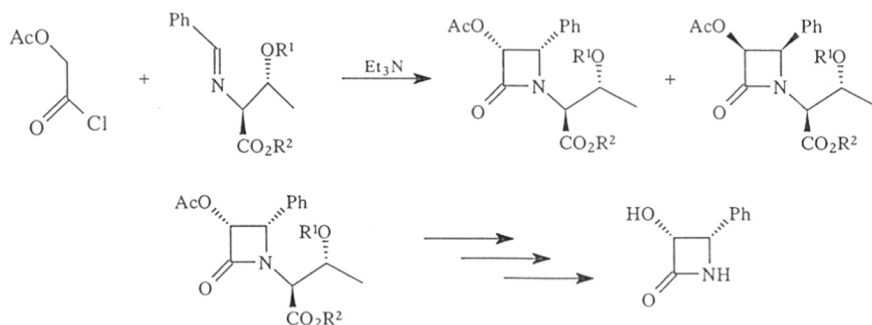
An enzymatic route has also been reported for the asymmetric synthesis of β -lactams (Scheme 2.03). The hydrolysis and transesterification of the racemic ester and alcohols catalysed by bacterial lipase have been reported to give enantiomerically pure 3-hydroxy-4-phenyl- β -lactam.¹²

Scheme 2.03



3-Acetoxy-4-phenyl- β -lactam has been obtained in good enantiomeric excess by cycloaddition of imine derived from silylated (L)-threonine ester with benzyloxyacetyl chloride in the presence of triethylamine (Scheme 2.04). This β -lactam was transformed into (3*R*, 4*S*)-3-hydroxy-4-phenyl- β -lactam in three steps.¹³

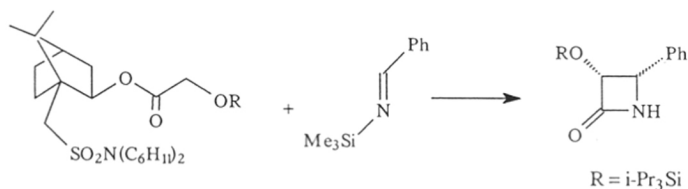
Scheme 2.04



The enolate-imine cycloaddition reaction of lithium enolate derived from the (-)-10-dicyclohexylsulfamoyl-D-isoborneol with *N*-(trimethylsilyl)benzaldimine has been reported to give *O*-trimethylsilyl 3-hydroxy-4-phenyl- β -lactam in high enantiomeric excess (Scheme 2.05).

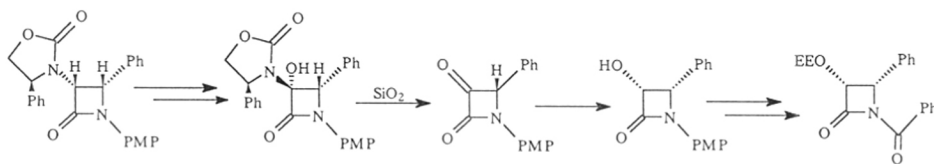
The phenylisoserine derived from 3-hydroxy-4-phenyl- β -lactam has been successfully coupled with 7-(triethylsilyl)baccatin III to give taxol. Recently Georg et al have reported that the (3*R*, 4*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-4-heteroaryl-2-azetidinones prepared via ester - enolate method can be converted to heteroaromatic taxol side chain.¹⁴

Scheme 2.05



Holton et al¹⁵ have prepared 3-keto-4-phenyl- β -lactam from oxazolidone derived ketene *via* ketene - imine cycloaddition reaction in four steps (Scheme 2.06). The 3-keto- β -lactam was reduced with sodium borohydride to get *cis*-3-hydroxy-4-phenyl- β -lactam, which is synthetically equivalent to the taxol side-chain.

Scheme 2.06



2.2 PRESENT WORK

3-Hydroxy-4-phenyl- β -lactam is synthetically equivalent to the phenyl isoserine unit of the taxol side-chain. 3-Hydroxy- β -lactams can also serve as synthons for various naturally occurring alkaloids and amino acids. Therefore, considerable interest has been developed to devise methodologies for the asymmetric synthesis of these β -lactams using sterically demanding chiral starting materials. In this line, we therefore decided to explore the use of (+)-3-carene as a chiral ketene precursor hoping that the steric environment provided by the three-six fused ring system of 3-carene will help in diastereoselective β -lactam ring formation. The chiral ketene precursor prepared from readily available (+)-3-carene, was used for diastereoselective formation of β -lactams. The major diastereomer was separated by crystallization and converted into 3-hydroxy 4-phenyl- β -lactam by Baeyer-Villiger oxidation.

2.3 RESULTS AND DISCUSSION

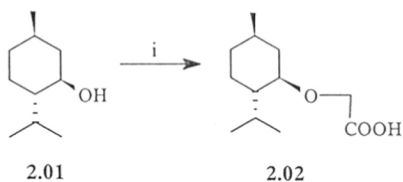
2.3a L-(-)-Menthyl derived ketene precursor.

The optically pure menthyloxyacetic acid **2.02** was selected as a model chiral ketene precursor for the diastereoselective synthesis of β -lactams.

Preparation of menthyloxyacetic acid 2.02.

The alkylation of secondary alcoholic group of L-(-)-menthol **2.01** with chloroacetic acid using sodium metal in dry toluene under reflux condition gave menthyloxyacetic acid **2.02** in good yield¹⁶ (Scheme 2.07).

Scheme 2.07



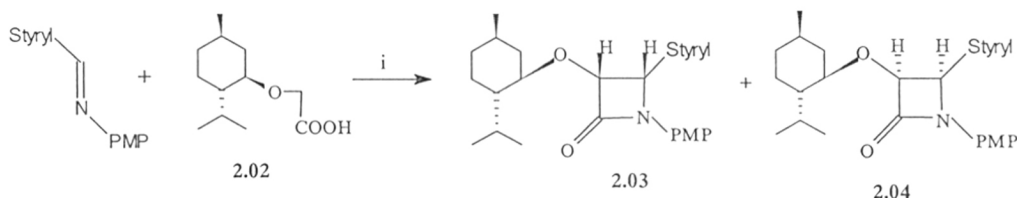
Reagents and conditions : i) Na/ClCH₂COOH/ dry toluene.

The IR spectrum of **2.02** showed a broad band at 3600-2800 for OH stretching and 1730 for the acid carbonyl stretching. The ^1H NMR spectrum of **2.02** showed two doublets at 0.53 and 0.65, each for three protons of *gem* dimethyl group with 8 Hz coupling constant. The angular methyl group appeared as doublet at 0.70. Several multiplets appeared in between 0.75 and 2.93 for the methine and methylene protons. Due to diastereotropic nature, the methylene protons adjacent to carboxylic group appeared as two doublets at 3.75 and 3.90 with 16 Hz coupling constant. A broad singlet appeared at 7.0 was interpreted for carboxylic proton.

*Preparation of β -lactams **2.03** & **2.04**.*

The acid **2.02** on annulation reaction with the imine using phenoxy dichlorophosphate at 0°C gave a diastereomeric mixture of β -lactams **2.03** & **2.04** in good yield (Scheme 2.08). However, the diastereoselectivity obtained in this reaction was very poor as confirmed by ^1H NMR spectral data of the crude reaction mixture, which showed the presence of two diastereomers **2.03** & **2.04** in almost equal proportions. Moreover, these diastereomers **2.03** & **2.04** could not be separated either by column chromatography or by crystallization.

Scheme 2.08



Reagents and Conditions : i) $\text{Et}_3\text{N}/\text{PhO}-\text{P}(\text{O})-\text{Cl}_2/\text{dry } \text{CH}_2\text{Cl}_2$, 0°C to r. t.

The structures of **2.03** & **2.04** were confirmed from IR and ^1H NMR spectral and analytical data of the mixture. The ^1H NMR spectrum of **2.03** & **2.04** showed two sets of signals, implying the presence of two diastereomers. The *gem* dimethyl groups of the chiral auxiliary appeared as two sets of doublets at 0.55 & 0.85 and 0.75 & 0.87 with *J* value of 7 Hz. each set integrating for a total of three protons. The angular methyl group appeared as doublets at 0.93 & 0.98 for two diastereomers. The ratio of these diastereomers was found to be 1:1 from the relative peak integration. The methylene and methine protons of the chiral auxiliary appeared as multiplets

in between 1.05 and 2.40, integrating for a total of nine protons. The methine proton adjacent to the oxygen atom appeared as a multiplet in between 3.22 and 3.50, integrating for a total of one proton. The methoxy proton appeared as a singlet at 3.75 integrating for three protons. The C4 proton of the diastereomeric mixture appeared as a multiplet at 4.78, integrating for total one proton. The C3 proton of the β -lactam ring appeared as doublets at 4.93 and 4.97 for two isomers with J value of 5 Hz. One of the styryl protons appeared as two merged doublet of doublet at 6.35 ($J = 7$ & 14 Hz), while the other styryl proton appeared as doublets at 6.78. Two of the aromatic protons appeared as doublets at 6.83. Several multiplets appearing in between 7.22 and 7.50 accounted for total seven protons of the aromatic groups. The IR spectrum showed a band at 1740 for the β -lactam carbonyl stretching. This compound gave satisfactory microanalysis.

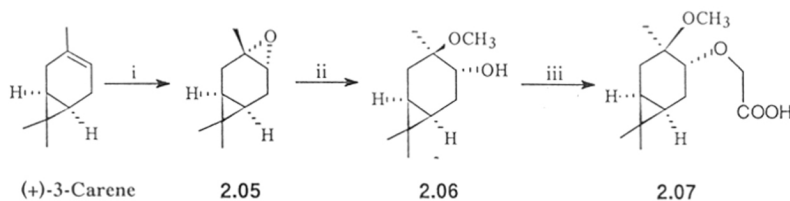
2.3b (+)-3-Carene derived ketene precursor.

In order to improve the diastereoselectivity, a sterically demanding bicyclic acid **2.07**, derived from (+)-3-carene¹⁷ (fused cyclopropane ring with gem dimethyl group) was selected as a ketene precursor for the synthesis of β -lactams. It was thought that the acid **2.07** might provide the necessary steric requirement in facial discrimination of ketene. The (+)-3-carene was converted into carene oxide **2.05** by known procedure.¹⁸

Preparation of acid 2.07.

The (+)-3-carene oxide was opened with methanolic PTSA to afford methoxy alcohol **2.06** in excellent yield. The alcohol **2.06** on alkylation with chloroacetic acid in presence of NaH in dry toluene gave acid **2.07** (Scheme 2.09) in 62% yield, which was purified by distillation, b.p. 180°C/10mm.

Scheme 2.09



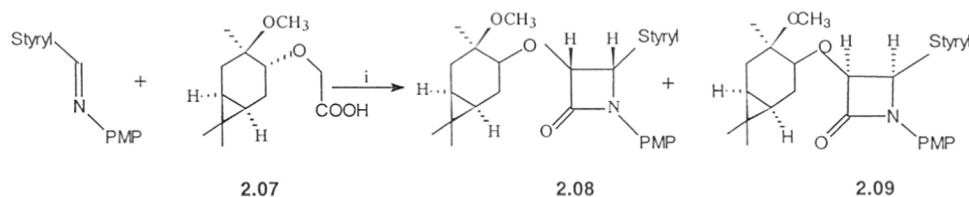
Reagents and conditions: i) $\text{ClCO}_2\text{Et}/\text{H}_2\text{O}_2/\text{Na}_3\text{PO}_4, \text{CH}_2\text{Cl}_2$ ii) $\text{CH}_3\text{OH}/\text{PTSA}$, 2 h. iii) $\text{Na}/\text{ClCH}_2\text{CO}_2\text{H}$, Toluene.

The ^1H NMR spectrum of **2.07** showed two singlets at 0.95 and 1.05 for the *gem* dimethyl group of the carene moiety. The angular methyl and methoxy groups were observed at 1.25 and 3.38 respectively. The methine and methylene protons of the chiral auxiliary appeared as multiplets in between 1.2 and 2.4. The methylene protons attached to the carboxylic group appeared as doublet at 3.90 and 4.35 ($J = 17.6$ Hz) due to their diastereotropic nature. The carboxylic acid proton appeared as a broad singlet at 9.3.

*Preparation of β -lactams **2.08** & **2.09**.*

The acid **2.07** on annulation reaction with imine derived from *trans*-cinnamaldehyde and *p*-anisidine in the presence of triethylamine at 0°C afforded a β -lactam (Scheme 2.10) in 55% yield. The analysis of the crude product by ^1H NMR and HPLC showed the presence of two diastereomers **2.08** & **2.09** in the ratio of 60 : 40. The major diastereomer **2.08** was separated by crystallization (pet. ether/acetone).

Scheme 2.10



Reagents and conditions: i) $\text{Et}_3\text{N}/\text{PhO}-\text{P}(\text{O})-\text{Cl}_2/\text{dry } \text{CH}_2\text{Cl}_2$, 0°C to r. t.

The ^1H NMR spectrum of the β -lactam **2.08** showed two singlets at 0.71 and 0.87 of three protons each, corresponding to a *gem* dimethyl group. The angular methyl group as a singlet appeared at 1.27. Several multiplets appeared in between 1.02 and 2.15 for seven protons of the chiral auxiliary. The methoxy proton of the chiral moiety and that of the *p*-anisyl group appeared at 3.27 and 3.75 respectively. A doublet of doublet was observed at 4.70 corresponding to the C4 proton of the β -lactam ($J = 4.8$ & 9.7 Hz). The C3 proton of the β -lactam appeared as a doublet at 5.42 ($J = 4.8$ Hz). The stereochemistry of the β -lactam was assigned as *cis* from the coupling constant value of 4.8 Hz of C3 and C4 protons. One of the styryl protons appeared as a doublet of

doublet at 6.37 with J value of 8.5 & 14.4 Hz. A multiplet appeared at 6.85 accounting for three protons, two from aromatic and one from styryl moiety. The multiplets appearing in between 7.15 and 7.55 were assigned to seven protons of the aromatic ring. The IR spectrum of the compound showed a strong band at 1740 corresponding to the β -lactam carbonyl group.

The ^{13}C NMR spectrum of **2.08** showed a peak at 164.0 corresponding to the β -lactam carbonyl. The aromatic quaternary carbon bearing the methoxy group appeared at 156.1. The other quaternary aromatic carbon attached to the nitrogen atom of the β -lactam ring resonated at 135.9. The styryl olefinic carbon attached to the phenyl group appeared at 135.5. The quaternary carbon of the aromatic carbon was observed at 131.5. The other styryl carbon and aromatic carbons appeared at 128.7, 128.2, 126.5, 125.1, 118.5 and 114.2. The C4 and C3 carbons of the β -lactam ring were observed at 81.9 and 84.2. The quaternary carbon of the chiral auxiliary-bearing methyl and methoxy groups appeared at 78.2. The methine carbon atom of the carene moiety which was attached to an oxygen atom appeared at 61.5. The methoxy carbon of the *p*-anisyl resonated at 55.4. The methoxy group of the chiral auxiliary was observed at 48.9. The methylene carbons of the chiral moiety appeared at 29.7 and 26.2. The two methine carbons of the cyclopropyl group appeared at 28.2 and 20.5. The methyl carbon of the chiral auxiliary was observed at 19.1. The quaternary carbon of the cyclopropyl group appeared at 17.6. The *gem* dimethyl group was observed at 15.5 and 14.8. This compound gave satisfactory microanalysis.

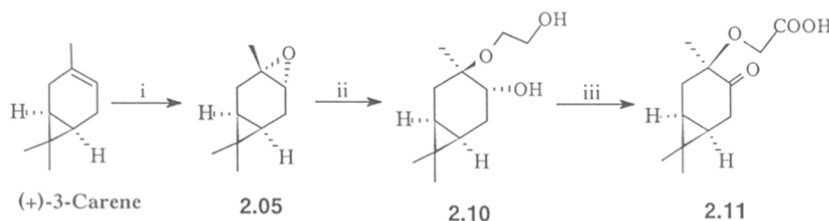
The use of acid **2.07**, derived from secondary alcohol **2.06** as chiral ketene precursor, gave only moderate diastereoselectivity (60 : 40) in β -lactam ring formation. We, therefore, thought that the ketene derived from tertiary alcohol might provide the required steric environment for high diastereoselective cycloaddition. This was achieved by synthesizing acid **2.11** from (+)-3-carene, which was subsequently converted to homochiral 3-hydroxy-4-phenyl- β -lactam *via* ketene-imine cycloaddition reaction.

Preparation of acid 2.11.

The optically pure (+)-3-carene was converted into carene oxide **2.05** using ethyl chloroacetate and hydrogen peroxide in the presence of triethylamine in excellent yield by known

procedure. This epoxide **2.05** on treatment with ethylene glycol in the presence of PTSA gave diol **2.10** in quantitative yield (Scheme 2.11). The diol **2.10** on oxidation with Jones reagent at 0°C for about 4 h afforded the keto acid **2.11** in 77% yield. The acid **2.11** was purified by crystallization from EtOAc/pet. ether.

Scheme 2.11



Reagents and conditions : i) $\text{ClCOOEt}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}_2$, 10 - 20°C, 24 h. ii) $\text{OHCH}_2\text{CH}_2\text{OH}/\text{PTSA}$, r. t. 2 h. iii) Jones' reagent /0°C, 4 h.

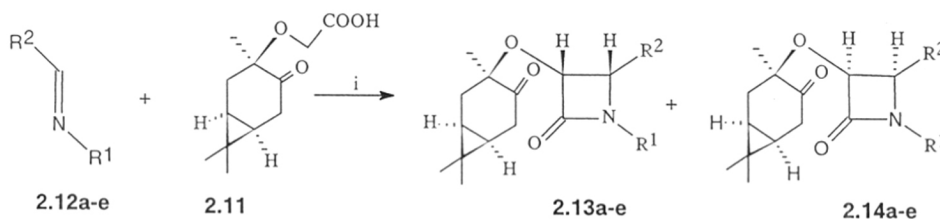
The structure of **2.11** was deduced from ^1H NMR and IR spectral analysis. The ^1H NMR spectrum of **2.11** showed two singlets at 0.91 and 1.05 for *gem* dimethyl groups, integrating for three protons each. Multiplets appeared at 1.00 and 1.15 accounting for two protons of the chiral auxiliary. The angular methyl protons of the chiral moiety appeared as a singlet at 1.6. Three doublet of doublets and a doublet was observed at 1.85, 2.25, 2.75, 2.50 respectively for methylene and methine protons. Due to diastereotropic nature, the methylene protons attached to the carboxylic group appeared as a doublet at 4.03 & 4.12 with coupling constant of 10 Hz. A broad singlet appearing at 7.7 was assigned to the carboxylic proton. The IR spectrum showed a broad band at 3200 - 3500 for the hydroxyl group of the carboxylic acid while the carbonyl stretching band was observed at 1720. This compound gave satisfactory microanalysis.

Preparation of β -lactams 2.13a-e & 2.14a-e.

The acid **2.11** on reaction with imines **2.12a-e** using phenyl dichlorophosphate as an acid activator in the presence of triethylamine at 0°C underwent cycloaddition reaction to give β -lactams **2.13a-e** & **2.14a-e** in good yields (Scheme 2.12). The diastereomeric ratio of the β -lactams were determined by HPLC and ^1H NMR analysis of the crude reaction mixture. In all the

cases, only *cis* β -lactams were obtained in moderate diastereoselectivity. Several attempts made to separate the diastereomeric mixture by column chromatography were unsuccessful. However, in one case, the major diastereomer **2.13a** was isolated in pure form from the mixture by crystallization (benzene/pet. ether).

Scheme 2.12



Reagents and conditions : i) Et₃N/ CH₂Cl₂/ PhOP(O)Cl₂, 0 °C , 15 h.

Table 1. Synthesis of β -lactams **2.13a-e** & **2.14a-e** via cycloaddition reaction of imines **2.12a-e** with ketens derived from acid **2.11**.

β -Lactams 2.13 & 2.14	R ¹	R ²	Ratio of 2.13 & 2.14	Yield (%)
a	PMP	Ph	70 : 30	74
b	PMP	Styryl	53 : 47	69
c	PMP	PMP	56 : 44	79
d	Bn	Ph	61 : 39	47
e	Bn	Styryl	54 : 46	66

The spectral data of a mixture of compounds **2.13a** & **2.14a** was chosen for discussion and characterization as a representative of this series. The IR spectrum of the mixture showed the presence of β -lactam carbonyl and keto carbonyl stretching at 1740 and 1730 respectively. The ¹H NMR spectrum of the mixture showed two sets of signals showing the presence of two diastereomers in the mixture. One of the two *gem* dimethyl groups appeared as two singlets at 0.7

and 0.9 for the major and minor isomers respectively, integrating for a total of three protons. The diastereomeric ratio was found to be 7 : 3 based on their relative abundance. The other *gem* dimethyl group appeared as two singlets at 1.00 and 1.05 integrating for a total of three protons. The methylene and methine protons of the chiral auxiliary appeared as several multiplets in between 0.75 and 2.65. The angular methyl group of the chiral auxiliary appeared as two singlets at 1.2 and 1.5 integrating for total three protons. The methoxy of the aromatic group appeared as a singlet at 3.75 integrating for a total of three protons. The C4 proton of the minor isomer was observed as a doublet at 5.05. The C3 proton of the minor isomer and C4 proton of the major isomer appeared as two merged doublet at 5.2. The C3 proton of the major isomer appeared as a doublet at 5.3. The *cis* stereochemistry at C3 and C4 centers of the major and minor isomer was established based on the coupling constant value ($J = 5$ Hz) of these protons. The two aromatic protons of the *p*-anisyl group appeared as a merged doublet at 6.8, while other aromatic protons appeared as multiplets in between 7.3 and 7.5, integrating for a total of seven protons.

The ^{13}C NMR spectrum of a mixture of **2.13a** & **2.14a** showed the presence of β -lactam carbonyl at 212.5 and 212.3 for the major and minor isomer respectively. The peak intensity ratio was found to be 7 : 3. The two keto carbonyls of the chiral auxiliary resonated at 165.3 and 165.2. The aromatic carbon bearing the methoxy group of the *p*-anisyl moiety appeared at 156.1 and the aromatic carbon attached to the nitrogen of the β -lactam moiety appeared at 134.3. The quaternary carbon of the phenyl group appeared at 130.9. The other aromatic carbons resonated at 128.7, 128.4, 127.9, 118.7 and 114.2. The C3 carbon atom of the β -lactam resonated at 79.2 and 78.9, whereas the C4 carbon atom of the β -lactam resonated at 63.0 and 63.2 for the major and minor respectively. The calculation of the peak intensity measurement showed a 7 : 3 ratio of the diastereomeric mixture. The methoxy carbon of the *p*-anisyl group appeared at 55.3. The methylene carbon of the chiral auxiliary appeared as two sets of signals at 32.9 & 33.5 and 35.6 & 36.0. The quaternary carbon of the cyclopropyl ring appeared at 18.3 and 22.7. One of the *gem* dimethyl groups was observed at 14.2 and 14.9. The other *gem* dimethyl group appeared at 19.6 and 19.7. The other methyl carbon of the chiral auxiliary appeared at 21.0 and 21.7 for the major

and minor isomers respectively. The methine carbon of the cyclopropyl ring resonated at 27.6 and 20.8. The diastereomeric mixture provided satisfactory microanalysis. The diastereomeric ratio was further confirmed by HPLC analysis.

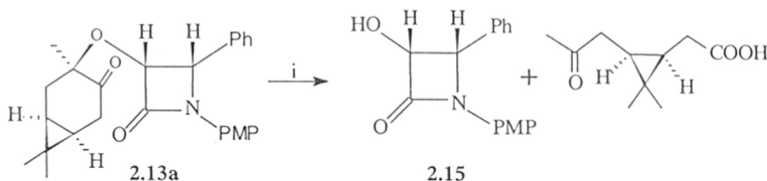
The pure major diastereomer **2.13a** obtained by crystallization from benzene/pet. ether was characterized by spectral analytical data. The ^1H NMR spectrum of the compound **2.13a** showed two singlets at 0.7 and 1.0 for the *gem* dimethyl protons. The methine and methylene protons appeared as multiplets in between 0.7 and 2.4 integrating for six protons. The angular methyl and the methoxy of the *p*-anisyl group appeared as singlets at 1.50 and 3.75 respectively. The C4 and C3 protons of the β -lactam ring appeared as doublets at 5.2 and 5.3 with the coupling constant value of 5 Hz indicating *cis* stereochemistry for these protons. The two aromatic protons of the *p*-anisyl group appeared as a doublet at 6.75 ($J = 10$ Hz) and the other seven aromatic protons appeared as multiplets at 7.3 - 7.4. The IR spectrum showed a band at 1740 and 1730 for the β -lactam carbonyl and keto carbonyl respectively. This compound gave satisfactory microanalysis.

The absolute configuration of **2.13a** was also confirmed by converting it to the known 3-hydroxy-4-phenyl- β -lactam and comparing its optical rotation with the reported value.

Preparation of 3-hydroxy-4-phenyl- β -lactam **2.14**.

To a solution of β -lactam **2.13a** in methylene chloride, *m*-CPBA was added and the reaction mixture was stirred for two days at room temperature. The crude reaction mixture was purified by column chromatography to provide 3-hydroxy-4-phenyl- β -lactam along with the chiral auxiliary (Scheme 2.13).

Scheme 2.13



Reagents and conditions : i) *m*-CPBA/ CH_2Cl_2 , r.t. 48 h.

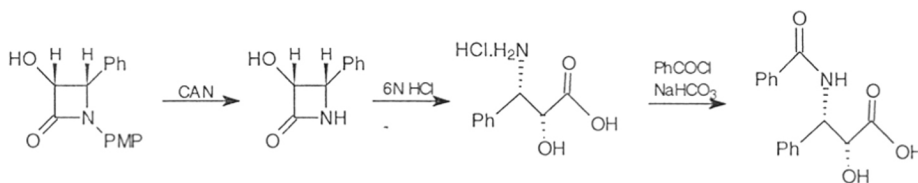
The IR spectrum of **2.15** showed β -lactam carbonyl stretching at 1740 and a broad band at 3200 - 3500 for the hydroxy group. The ^1H NMR spectrum of the compound **2.15** showed a broad singlet appearing in between 2.0 and 2.3 was assigned to hydroxyl proton. A sharp singlet observed at 3.8 was interpreted to the methoxy protons. All other characteristic peaks of the chiral auxiliary, which normally appeared below 2.2 δ were absent showing the cleavage of the chiral auxiliary. The C4 and C3 protons of the β -lactam ring appeared as doublets at 5.2 and 5.3 respectively. The 5 Hz coupling constant for these protons confirmed the *cis* geometry of β -lactam protons. A doublet appeared at 6.85 ($J = 10$ Hz) corresponding to two aromatic protons. The rest of the aromatic protons appeared in between 7.22 and 7.55 as a multiplet integrating for seven protons.

The absolute configuration of **2.15** was established as 3*R* and 4*S* by measuring the optical rotation $\{[\alpha]_D^{25} : +176$ (c 1, CHCl_3) $\}$ and comparing with the reported value for its antipode. {Lit.¹⁹ $[\alpha]_D^{25} : -179$ (c 1, CHCl_3)}. The enantiomeric purity of **2.15** was further confirmed by the ^1H NMR spectral analysis using chiral shift reagent.

The ^{13}C NMR spectrum of **2.15** showed the presence of β -lactam carbonyl at 166.1. The aromatic carbon of the *p*-anisyl group bearing methoxy appeared at 156.1 and the other aromatic carbon attached to the nitrogen atom of the β -lactam ring resonated at 134.0. The quaternary carbon of the phenyl group appeared at 131.1. The rest of the aromatic carbons appeared at 128.6, 128.4, 127.1, 118.4 and 114.0. The methoxy carbon of the *p*-anisyl group appeared at 55.0. The two β -lactam carbons C3 and C4 resonated at 76.1 and 61.9 respectively. This compound gave satisfactory microanalysis.

This 3-hydroxy-4-phenyl- β -lactam, which is a synthetic equivalent of the phenylisoserine unit (Scheme 2.14) has already been coupled with 10-deacetylbaccatin III to provide the taxol molecule.

Scheme 2.14



2.4 SUMMARY

The chiral ketene precursor derived from L-(-)-menthol gave a 1:1 mixture of *cis* β -lactams in very good yield. The diastereoselectivity in β -lactam ring formation was enhanced by using more sterically demanding chiral ketene precursors **2.07** and **2.11** derived from (+)-3-carene by ketene-imine cycloaddition reaction. All the β -lactams prepared were inseparable by column chromatography. However, the major diastereomers **2.08** & **2.13a** were separated by crystallization. The Baeyer-Villiger oxidation of **2.13a** afforded 3-hydroxy-4-phenyl β -lactam, a synthetic equivalent of phenyl isoserine unit of taxol side chain, in good yield.

2.5 EXPERIMENTAL

2.5.1 Preparation of acid 2.02.

To a solution of l-(-)-menthol **2.01** (10 g, 65 mmol) in dry toluene (60 mL), clean sodium pieces (2 g) were added and gently refluxed for 15 h. The reaction mixture was stirred at such a rate that the sodium was broken into fine globules. The reaction mixture was cooled to room temperature and the unreacted sodium was removed by filtration through glass wool. The filtrate was heated to 85 - 90°C and a solution of chloroacetic acid (2.4 g, 25 mmol) in dry toluene (50 mL) was added with stirring in such a way that the refluxing should not be vigorous. A heavy precipitate of sodium chloroacetate forms immediately. After the addition of chloroacetic acid, the reaction mixture was refluxed for 48 h. The reaction mixture was cooled and diluted with toluene (200 mL). It was then extracted with water (3 x 250 mL). The aqueous layer was acidified with 20% HCl. The crude menthyloxyacetic acid which separates as brown oil on the top, was extracted with benzene (2 x 30 mL). The removal of benzene by distillation under reduced pressure afforded crude product, which was purified by fractional distillation and the fraction boiling at 100 - 115°C/8-10 mm gave 9.0 g (65%) of required acid **2.02**.

¹H NMR : 0.53 (d, *J* = 8 Hz, 3H, CH₃); 0.65 (d, *J* = 8 Hz, 3H, CH₃); 0.7 (d, *J* = 6 Hz, 3H, CH₃); 0.75- 0.90 (m, 3H); 0.95 - 1.20 (m, 2H, CH₂); 1.27 - 1.50 (m, 2H, CH₂); 1.70 - 1.90 (m, 1H, CH); 1.93 - 2.2 (m, 1H, CH); 2.93 (m, 1H, CH); 3.75 & 3.90 (d, *J* = 16 Hz, 1H, CH₂); 7.0 (bs, 1H, OH).

IR : 3600-2800, 1730.

2.5.2 Preparation of β-lactam 2.03 & 2.04.

To a mixture of l-(-)-menthyloxyacid **2.02** (0.257 g, 1.2 mmol), imine (0.284 g, 1.2 mmol) and triethylamine (0.660 g, 6.6 mmol) in CH₂Cl₂ (15 mL), a solution of phenyl dichlorophosphate (0.252 g, 1.2 mmol) in CH₂Cl₂ (10 mL) was added with stirring at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. It was diluted with CH₂Cl₂ (20 mL) and washed successively with water (2 x 20 mL), satd. NaHCO₃ (2 x 20 mL), brine (20 mL), dried

(anhyd. Na_2SO_4). It was filtered and filtrate on concentration under reduced pressure provided the β -lactam **2.03** & **2.04** as the diastereomeric mixture (0.415 g, 79%). This diastereomeric mixture could not be separated either by column chromatography or crystallization. The spectral and analytical data for the diastereomeric mixture is as follows :

M.P. : 148 - 150°C.

^1H NMR : 0.55 & 0.85 (d, $J = 7$ Hz, total 3H, CH_3); 0.75 & 0.87 (d, $J = 7$ Hz, total 3H, CH_3); 0.93 & 0.98 (d, $J = 7$ Hz, total 3H, CH_3); 1.05 - 1.70 (m, total 6H, CH_2); 1.97 - 2.40 (m, total 3H, CH); 3.22 & 3.50 (m, total 1H, CH); 3.75 (s, total 3H, OCH_3); 4.78 (m, total 1H, C4H of major & minor isomers); 4.93 & 4.97 (two d, $J = 5$ Hz, total 1H, C3H of major & minor isomers); 6.35 (two merged dd, $J = 7$ & 14 Hz, total 1H, styryl H); 6.78 (d, $J = 15$ Hz, 1H); 6.83 (d, $J = 10$ Hz, 2H, Ar); 7.22 - 7.50 (m, 7H, Ar).

IR : 1740.

Analysis : M. F. $\text{C}_{28}\text{H}_{35}\text{O}_3\text{N}$

Calculated : C, 77.55; H, 8.14; N, 3.23.

Found : C, 77.18; H, 8.33; N, 3.34.

2.5.3 Preparation of alcohol **2.06**.

To a solution of (+)-3-carene oxide **2.05** (1.0 g, 6.5 mmol) in methanol (25 mL), a catalytic quantity of PTSA (30 mg) was added at 0°C and stirred for 2 h. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4 . It was filtered and filtrate was concentrated to give the crude product **2.06**, which on purification by column chromatography (silica gel, 60 - 120, 5% EtOAc in pet. ether) gave 1.1 g (90%) of pure alcohol **2.06**.

2.5.4 Preparation of Acid **2.07**.

To a solution of **2.06** (1.84 g, 10 mmol) in dry toluene (25 mL), clean sodium pieces (0.500 g) were added and gently refluxed for 15 h. The solution was cooled and the excess of

sodium was removed by filtration through glass wool. The filtrate was heated to 85 - 90°C with stirring and a solution of chloroacetic acid (0.470 g, 5 mmol) in dry toluene (30 mL) was added in such a way that the refluxing should not be vigorous. A heavy precipitate of sodium chloro acetate was formed immediately. The reaction mixture was refluxed under stirring for an additional 48 h. The reaction mixture was diluted with toluene (30 mL) and extracted with water (3 x 25 mL) and the aqueous layer was acidified with 20% HCl. The crude product which collects as brown oil on the top, was extracted with benzene. It was dried over Na₂SO₄ and the solvent was removed under reduced pressure to give crude product as an oil, which was purified by fractional distillation under reduced pressure to afford 1.5 g (62%) of the acid **2.07**.

¹H NMR : 0.95 (s, 3H, CH₃); 1.05 (s, 3H, CH₃); 1.25 (s, 3H, CH₃); 3.38 (s, 3H, OCH₃); 1.2 - 2.4 (m, 7H, CH₂ & CH); 3.90 (d, *J* = 17.6 Hz, 1H); 4.35 (d, *J* = 17.6 Hz, 1H); 9.3 (bs, 1H).

2.5.5 Preparation of β-lactam **2.08** & **2.09**.

To a mixture of acid **2.07** (0.241 g, 1 mmol), phenyl dichlorophosphate (0.210 g, 1 mmol) and CH₂Cl₂ (15 mL), a solution of imine (0.237 g, 1 mmol) and triethylamine (0.3 g, 3 mmol) in CH₂Cl₂ (10 mL) was added at 0°C with stirring. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. It was diluted with CH₂Cl₂ (20 mL) and washed successively with water (2 x 20 mL), satd. NaHCO₃ (2 x 20 mL), brine (20 mL), dried (anhyd. Na₂SO₄). It was filtered and filtrate on concentration under reduced pressure provided the β-lactams **2.08** & **2.09** as the diastereomeric mixture (0.255 g, 55%). The major diastereomer **2.08** was separated by crystallization from pet.ether/acetone, which showed following spectral and analytical data.

M.P. : 232 - 234°C.

¹H NMR : 0.71 (s, 3H, CH₃); 0.87 (s, 3H, CH₃); 1.02 (m, 1H, CH); 1.27 (s, 3H, CH₃); 1.55 - 2.00 (m, 5H, 2CH₂, & CH); 2.0 - 2.15 (m, 1H, CH); 3.27 (s, 3H, OCH₃); 3.75 (s, 3H, OCH₃); 4.70 (dd, *J* = 4.8 & 9.7 Hz, 1H, C4H); 5.42 (d, *J* = 4.8 Hz, 1H, C3H); 6.37 (dd, *J* = 8.5 & 14.4 Hz, 1H, styryl CH); 6.85 (m, 3H, styryl & Ar); 7.15 - 7.55

(m, 7H, Ar).

^{13}C NMR : 14.8, 15.5, 17.6, 19.1, 20.5, 26.2, 28.2, 29.7, 48.9, 55.4, 61.5, 78.2, 81.9, 84.2, 114.2, 118.5, 125.1, 126.5, 128.2, 128.6, 131.5, 135.5, 135.9, 156.1, 164.0.

IR : 2960, 1740.

$[\alpha]_{\text{D}}^{23}$: -3.3(c 1.2, CH_2Cl_2).

Analysis : M. F. $\text{C}_{29}\text{H}_{35}\text{O}_4\text{N}$

Calculated : C, 75.46; H, 7.64; N, 3.03.

Found : C, 75.72; H, 7.51; N, 3.14.

2.5.6 Preparation of diol 2.10.

To a solution of carene oxide **2.05** (0.760 g, 5 mmol) in ethylene glycol (5 mL), PTSA (0.020 g) was added at 0°C and the reaction mixture was stirred at this temperature for 4 h. After completion of the reaction (by TLC), the reaction mixture was diluted with water (40 mL) and it was extracted with EtOAc (3 x 20 mL). The combined organic extracts was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to give crude product. It was subsequently column chromatographed (silica gel, 60 - 120 mesh, pet. ether/EtOAc mixture) to give 1.0 g (93%) of diol **2.10** as an oil.

^1H NMR : 0.9 (s, 3H, CH_3); 0.95 (s, 3H, CH_3); 1.0 (m, 2H, CH_2); 1.2 (s, 3H, CH_3); 1.4 - 2.3 (90 MHz) (m, 5H, CH_2 & CH); 3.1 (bs, 2H, OH); 3.25 - 3.75 (m, 4H, CH_2).

IR : 3200 - 3500, 2840, 1200.

2.5.7 Preparation of keto-acid 2.11.

To a solution of diol **2.10** (0.535 g, 2.5 mmol) in acetone (10 mL), Jones reagent was added drop by drop at 0°C until the colour of the reagent persist. The reaction mixture was stirred further for 4 h at room temperature. The green precipitate formed was filtered-off and the excess of the reagent was destroyed by adding isopropyl alcohol at 0°C to avoid the exothermic reaction. The solution was then concentrated under vacuum and extracted with EtOAc (3 x 15 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 . It was then filtered and filtrate

on removal of solvent under reduced pressure gave crude product, which was crystallized from EtOAc/pet. ether to give 0.440 g (77%) of keto-acid **2.11** as colourless crystals.

M. P. : 104 - 106°C.

¹H NMR : 0.91 (s, 3H, CH₃); 1.0 (m, 1H, CH₂); 1.05 (s, 3H, CH₃); 1.15 (m, 1H, CH₂); 1.6 (s, 3H, CH₃); 1.85 (dd, *J* = 10 & 15 Hz, 1H, CH₂); 2.25 (dd, *J* = 10 & 15 Hz, 1H, CH₂); 2.50 (d, *J* = 18 Hz, 1H, CH); 2.75 (dd, *J* = 9 & 18 Hz, 1H, CH); 4.03 (d, *J* = 10 Hz, 1H, CH₂); 4.12 (d, *J* = 10 Hz, 1H, CH₂); 7.7 (bs, 1H, COOH).

IR : 3200 - 3500 (br), 1720.

[α]_D²⁵ : +20.7 (c 1, CH₂Cl₂).

Analysis : M. F. C₁₂H₁₈O₄

Calculated : C, 63.68; H, 8.12.

Found : C, 63.57; H, 8.08.

2.5.8 General procedure for the preparation of β-lactams **2.13a-e** & **2.14a-e**.

To a stirred mixture of the acid **2.11** (0.229 g, 1.0 mmol), imine **2.12a-e** (1.1 mmol), triethylamine (3 mmol) and dry CH₂Cl₂ (15 mL), a solution of phenyl dichlorophosphate (0.210 g, 1.0 mmol) in dry CH₂Cl₂ (20 mL) was added drop by drop at 0°C. The reaction mixture was allowed to warm-up to room temperature and stirred further for 15 h. It was then successively washed with water (30 mL), satd. sodium bicarbonate solution (20 mL), brine (30 mL) and dried over Na₂SO₄. It was then filtered and filtrate on removal of solvent under vacuum gave crude product, which was column chromatographed (silica gel, 60 - 120, Pet. ether/acetone) to yield diastereomeric mixture of β-lactams **2.13a-e** & **2.14a-e**. The diastereomeric ratio was determined by ¹H NMR spectral data and HPLC analysis.

2.5.8a Preparation of (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*R*,6'*S*) 1-(*p*-anisyl)-4-phenyl-3-[3',7',7'-trimethylbicyclo (4.1.0)-hept-4'-oxo-3'-yl oxy]-azetidin-2-one **2.13a** & **2.14a**.

The treatment of phenyl dichlorophosphate (0.210 g, 1 mmol) with a mixture acid **2.11** (0.230 g, 1 mmol), imine **2.12a** (0.232 g, 1.1 mmol) and triethylamine (0.3 g, 3 mmol) at 0°C,

provided 0.310 g (74%) of a diastereomeric mixture of β -lactams **2.13a** & **2.14a**. The spectral and analytical data for the diastereomeric mixture is as follows :

M. P. : 192 - 194°C.

^1H NMR : 0.7 & 0.9 (s, total 3H, CH_3); 0.75 (m, 2H, CH); 1.0 & 1.05 (s, total 3H, CH_3); 1.10 (m, 1H, CH_2); 1.2 & 1.5 (s, total 3H, CH_3); 1.65 - 1.8 (m, 3H, CH_2 & CH); 2.0 (m, 3H, CH_2 & CH); 2.4 (dd, $J = 9$ & 18 Hz, 2H, CH_2); 2.65 (dd, $J = 9$ & 18 Hz, 1H, CH); 3.75 (s, total 3H, OCH_3); 5.05 (d, $J = 5$ Hz, C4H of minor isomer); 5.2 (two merged doublets, $J = 5$ Hz, C3H of minor & C4H of major isomers); 5.3 (d, $J = 5.0$ Hz, C3H of major isomer); 6.8 (d, $J = 10$ Hz, total 2H, Ar.); 7.3 - 7.5 (m, total 7H, Ar.).

^{13}C NMR : 14.2, 14.9, 18.3, 19.6, 19.7, 20.8, 21.0, 21.7, 22.7, 27.6, 32.9, 33.5, 35.6, 36.0, (300 MHz) 55.3, 63.0, 63.2, 78.9, 79.2, 114.2, 118.7, 127.9, 128.4, 128.7, 130.9, 134.3, 156.1, 165.2, 165.3, 212.3, 212.5.

IR : 2940, 1740, 1730.

$[\alpha]_D^{25}$: -23.20 (c 1, CH_2Cl_2).

Analysis : M. F. $\text{C}_{26}\text{H}_{29}\text{NO}_4$

Calculated : C, 74.5; H, 6.9; N, 3.4.

Found : C, 75.0; H, 7.2; N, 3.1.

(3*R*,4*S*,1'*S*,6'*R*) 1-(*p*-Anisyl)-4-(phenyl)-3-[3',7',7'-trimethylbicyclo(4.1.0)-hept-4'-oxo-3'-yloxy]-azetidin-2-one **2.13a**.

The pure major isomer **2.13a** was isolated from above diastereomeric mixture of **2.13a** & **2.14a** by crystallization from benzene/pet.ether in 57 % yield.

M. P. : 214°C.

^1H NMR : 0.70 (s, 3H, CH_3); 0.7 - 0.9 (m, 2H, CH); 1.0 (s, 3H, CH_3); 1.15 (dd, $J = 5$ & 15 Hz, 1H, CH_2); 1.5 (s, 3H, CH_3); 1.75 (dd, $J = 3$ & 15 Hz, 1H, CH_2); 2.0 (dd, $J = 6$ & 15 Hz, 1H, CH_2); 2.4 (dd, $J = 7.5$ & 15 Hz, 1H, CH_2); 3.75 (s, 3H, CH_3); 5.2 (d, $J = 5$ Hz, 1H, C4H); 5.3 (d, $J = 5$ Hz, 1H, C3H); 6.75 (d, 2H, $J = 10$ Hz, Ar);

7.3 - 7.4 (m, 7H, Ar).

IR : 1740, 1730.

MS (m/z) : 419 (M⁺)

$[\alpha]_D^{25}$: +44.6 (c 1, CHCl₃).

Analysis : C₂₆H₂₉NO₄

Calculated : C, 74.5, H, 6.9, N, 3.3.

Found : C, 74.1, H, 6.5, N, 3.0.

2.5.8b Preparation of (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*R*,6'*S*) 1-(*p*-Anisyl)-4-(styryl)-3-[3',7',7'-trimethylbicyclo (4.1.0)-hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.13b & 2.14b.

The phenyl dichlorophosphate (0.210 g, 1 mmol) when treated with a mixture solution of the (+)-3-carene derived acid **2.11** (0.230 g, 1 mmol), imine **2.12b** (0.260 g, 1.1 mmol) and triethylamine (0.3 g, 3 mmol) at 0°C, provided a diastereomeric mixture of β-lactams **2.13b** & **2.14b** (0.305 g, 69%). The spectral and analytical data for the diastereomeric mixture is as follows.

M. P. : 184 - 185°C.

¹H NMR : 0.8 & 0.9 (two s, total 3H, CH₃); 0.9 - 1.1 (m, 2H); 1.05 & 1.08 (two s, total 3H, CH₃); 1.50 & 1.65 (two s, total 3H, CH₃); 1.2 - 1.8 (m, 2H, CH₂); 2.0 (m, total 2H, CH₂); 2.3 (m, 3H); 2.50 & 2.75 (two merged dd, *J* = 9 & 17 Hz, total 1H, CH); 3.75 (s, total 3H, OCH₃); 4.85 (two merged dd, *J* = 5 & 7.5 Hz, total 1H, C4H of major and minor isomers); 4.95 & 5.15 (d, *J* = 5 Hz, total 1H, C3H of major and minor isomers); 6.3 (two merged dd, *J* = 7.5 & 14 Hz, 2H, styryl CH); 6.75 - 6.90 (m, 4H, styryl CH & Ar); 7.25 - 7.40 (m, total 7H, Ar).

¹³C NMR : 14.7, 15.2, 18.8, 19.2, 19.9, 21.5, 21.9, 23.1, 27.8, 32.9, 33.9, 35.0, 36.2, 55.5, 61.9, 62.0, 79.7, 80.1, 114.4, 118.8, 124.9, 126.8, 128.1, 128.7, 131.5, 135.6, 136.6, 156.3, 165.2, 219.0.

IR : 1740, 1730, 1520.

$[\alpha]_D^{25}$: -3.0 (c 1, CH₂Cl₂).

Analysis : M. F. C₂₈H₃₁NO₄

Calculated : C, 75.5; H, 6.9; N, 3.1.

Found : C, 75.9; H, 7.3; N, 2.9.

2.5.8c Preparation of (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*R*,6'*S*) 1-(*p*-anisyl)-4-(*p*-anisyl)-3-[3',7',7'-trimethylbicyclo (4.1.0)-hept-4'-oxo- 3'-yloxy]-azetidin-2-one 2.13c & 2.14c.

The phenyl dichlorophosphate (0.210 g, 1 mmol) was when treated with a mixture of acid 2.11 (0.230 g, 1 mmol), imine 2.12c (0.265 g, 1.1 mmol) and triethylamine (0.3 g, 3 mmol) at 0°C, provided 0.355 g (79%) of a diastereomeric mixture of β-lactams 2.13c & 2.14c. The spectral and analytical data for the diastereomeric mixture is as follows :

M. P. : 158 - 161°C.

¹H NMR : 0.65 & 0.9 (s, total 3H, CH₃); 0.8 - 0.9 (m, 2H,); 1.0 & 1.05 (s, total 3H, CH₃); 1.10 (m, 2H, CH₂); 1.2 & 1.5 (s, total 3H, CH₃); 1.7 - 2.2 (m, 5H, CH₂ & CH); 2.4 (m, 2H, CH₂ & CH); 2.65 (dd, *J* = 9 & 18 Hz, 1H, CH); 3.75 (s, total 3H, OCH₃), 3.78 & 3.79 (two s, total 3H, OCH₃); 5.0 (d, *J* = 5 Hz, C4H of major isomer); 5.15 (two merged d, *J* = 5 Hz, C4H & C3H of minor & major isomers); 5.25 (d, *J* = 5 Hz, C3H of minor isomer); 6.7 - 6.95 (m, total 4H, Ar.); 7.2 - 7.45 (m, total 4H, Ar.).

¹³C NMR : 14.4, 15.1, 18.5, 19.1, 19.8, 20.9, 21.2, 22.7, 27.7, 33.1, 35.8, 36.2, 55.3, 55.5, 62.9, 79.3, 79.9, 81.1, 113.5, 114.4, 118.9, 129.9, 130.2, 131.2, 156.2, 159.6, 167.6, 189.4, 212.5.

IR : 2940, 1740, 1730, 1520.

$[\alpha]_D^{25}$: -17.50 (c 0.6, CH₂Cl₂).

Analysis : M. F. C₂₇H₃₁NO₅

Calculated : C, 72.2; H, 6.9; N, 3.1.

Found : C, 71.9; H, 7.2; N, 3.0.

2.5.8d Preparation of (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*R*,6'*S*) 1-(Benzyl)-4-(phenyl)-3-[3',7',7'-trimethylbicyclo(4.1.0)hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.13d & 2.14d.

The phenyl dichlorophosphate (0.252 g, 1.2 mmol) was when treated with a mixture solution of the (+)-3-carene derived acid **2.11** (0.275 g, 1.2 mmol), imine **2.12d** (0.253 g, 1.3 mmol) and triethylamine (0.710 g, 7 mmol) at 0°C, provided a diastereomeric mixture of β -lactams **2.13d** & **2.14d** (0.230 g, 47%). The spectral and analytical data for the diastereomeric mixture is as follows :

M. P. : 172 - 174°C.

¹H NMR : 0.65 & 0.85 (two s, total 3H, CH₃); 0.7 - 0.9 (m, 2H); 0.95 & 1.0 (two s, total 3H, CH₃); 1.1 & 1.42 (two s, total 3H, CH₃); 1.15 (m, 2H); 1.6 (dd, *J* = 5 & 18 Hz, 1H, CH₂); 1.6 - 1.85 (m, 5H); 2.27 (m, 2H); 2.6 (dd, *J* = 8 & 18 Hz, CH); 3.79 & 3.8 (two d, *J* = 15 Hz, total 1H, CH₂); 4.84 & 4.85 (two d, *J* = 15 Hz, total 1H, CH₂); 4.55 (two merged d, *J* = 5 Hz, total 1H, C4H of major & minor isomers); 5.0 & 5.15 (d, *J* = 5 Hz, total 1H, C3H of minor & major isomers); 7.1 - 7.45 (m, total 10H, Ar.).

¹³C NMR : 14.2, 14.9, 18.3, 19.0, 19.6, 20.9, 21.7, 22.7, 27.6, 32.9, 33.5, 35.6, 36.1, 55.3, 63.1, 63.2, 79.2, 79.5, 81.1, 114.3, 118.7, 118.9, 127.8, 127.9, 128.4, 128.8, 130.9, 134.4, 156.1, 165.4, 212.4, 212.6.

IR : 1740, 1730, 1520.

[α]_D²⁵ : -22.9 (c 1, CH₂Cl₂).

Analysis : M. F. C₂₆H₂₉NO₃

Calculated : C, 77.4; H, 7.2; N, 3.4.

Found : C, 77.9; H, 7.3; N, 3.1.

2.5.8e Preparation of (3*R*,4*S*,1'*S*,6'*R*) and (3*S*,4*R*,1'*R*,6'*S*) 1-(Benzyl)-4-(styryl)-3-[3',7',7'-trimethylbicyclo(4.1.0)hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.13e & 2.14e.

The phenyl dichlorophosphate (0.252 g, 1.2 mmol) was when treated with a mixture of acid **2.11** (0.275 g, 1.2 mmol), imine **2.12e** (0.290 g, 1.3 mmol) and triethylamine (0.710 g, 7 mmol) at 0°C, provided a diastereomeric mixture of β -lactams **2.13e** & **2.14e** (0.440 g, 66%). The spectral and analytical data for the diastereomeric mixture is as follows :

M. P. : 82 - 84°C.

¹H NMR : 0.8 & 0.9 (s, total 3H, CH₃); 0.85 -1.10 (m, 2H, CH); 1.0 & 1.02 (s, total 3H, CH₃); 1.35 - 1.70 (m, 4H); 1.48 & 1.63 (s, total 3H, CH₃); 1.95 (dd, *J* = 5.5 & 15 Hz, 1H); 2.12 - 2.75 (m, 5H); 4.0 (d, *J* = 15 Hz, 1H, CH₂); 4.25 (two merged dd, *J* = 5 & 5.5 Hz, total 1H, C4H of major and minor isomers); 4.7 (d, *J* = 15 Hz, 1H, CH₂); 4.85 & 5.05 (d, *J* = 5 Hz, total 1H, C3H of major & minor isomers); 6.2 (two merged dd, *J* = 7 & 16 Hz, total 1H, styryl-CH); 6.53 & 6.56 (d, *J* = 15 Hz, total 1H, styryl-CH); 7.1 - 7.55 (m, total 10H, Ar.).

¹³C NMR : 14.7, 15.1, 18.8, 19.2, 19.9, 21.3, 22.0, 22.9, 27.8, 33.1, 33.6, 36.0, 36.2, 44.2, 61.3, 61.5, 79.9, 80.1, 80.4, 124.9, 126.7, 127.7, 128.0, 128.2, 128.6, 128.7, 128.8, 129.0, 135.7, 135.8, 136.6, 167.9, 212.7.

IR : 2920, 1750, 1730.

[α]_D²⁵ : -15.7 (c 1, CH₂Cl₂)

Analysis : C₂₈H₃₁NO₃

Calculated : C, 78.3; H, 7.2; N, 3.2.

Found : C, 78.7; H, 7.4; N, 2.9.

2.5.9 Preparation of (3*R*, 4*S*)-3-hydroxy-4-phenyl- β -lactam 2.15.

To a solution of β -lactam **2.13a** (0.221 g, 0.5 mmol) in CH₂Cl₂ (10 mL), solid m-chloroperbenzoic acid (0.172 g, 1 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with CH₂Cl₂ (15 mL) and washed

successively with water (15 mL), satd. NaHCO_3 (2 x 15 mL), water (15 mL) and finally with brine (15 mL). The CH_2Cl_2 solution was dried over anhyd Na_2SO_4 and filtered. The filtrate on removal of solvent by distillation under reduced pressure gave the crude product, which on purification by crystallization afforded 0.096 g (72%) of pure (3*R*, 4*S*)-3-hydroxy-4-phenyl- β -lactam **2.15**.

M. P. : 198-201°C.

^1H NMR : 2.0-2.3 (broad s, 1H, OH); 3.8 (s, 3H, CH_3); 5.2 (d, $J = 5$ Hz, 1H, C4H); 5.3 (d, $J = 5$ Hz, 1H, C3H); 6.85 (d, $J = 10$ Hz, 2H, Ar); 7.22 - 7.55 (m, 7H, Ar).

^{13}C NMR : 55.0, 61.9, 76.1, 114.0, 118.4, 127.1, 128.4, 128.6, 131.0, 134.1, 156.1, 166.1.

IR : 3200 - 3500, 1740.

$[\alpha]_{\text{D}}^{25}$: +176 (c 1, CHCl_3) [Lit.³ for antipode $[\alpha]_{\text{D}}^{25}$: -179 (c 1, CHCl_3)].

Analysis : $\text{C}_{16}\text{H}_{15}\text{NO}_3$

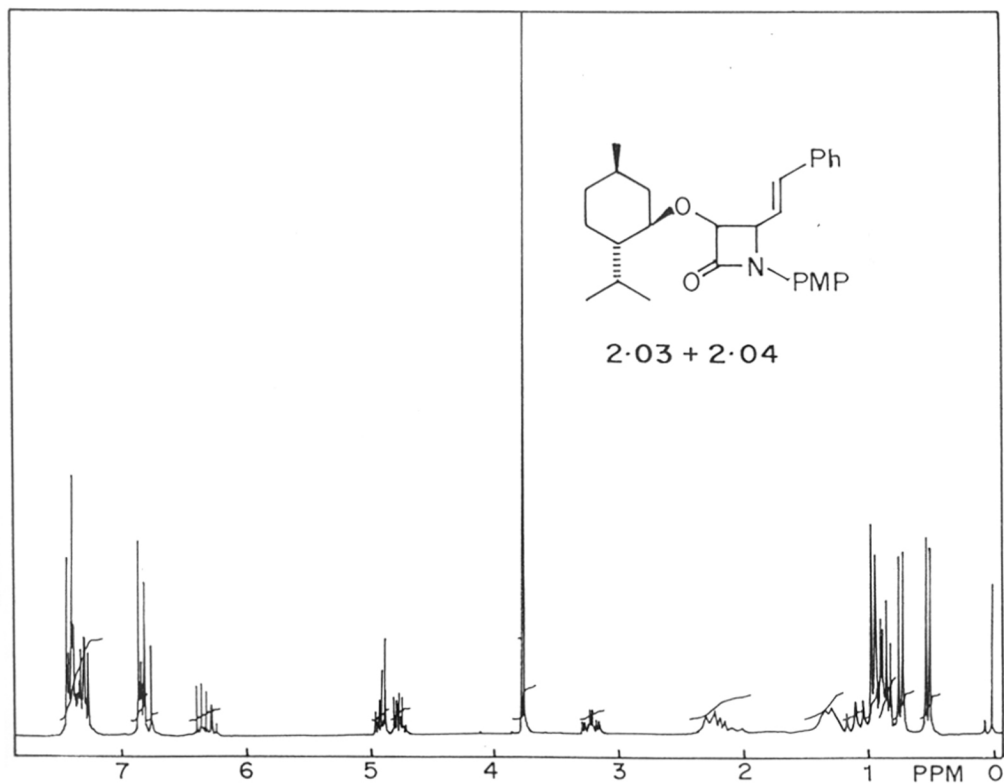
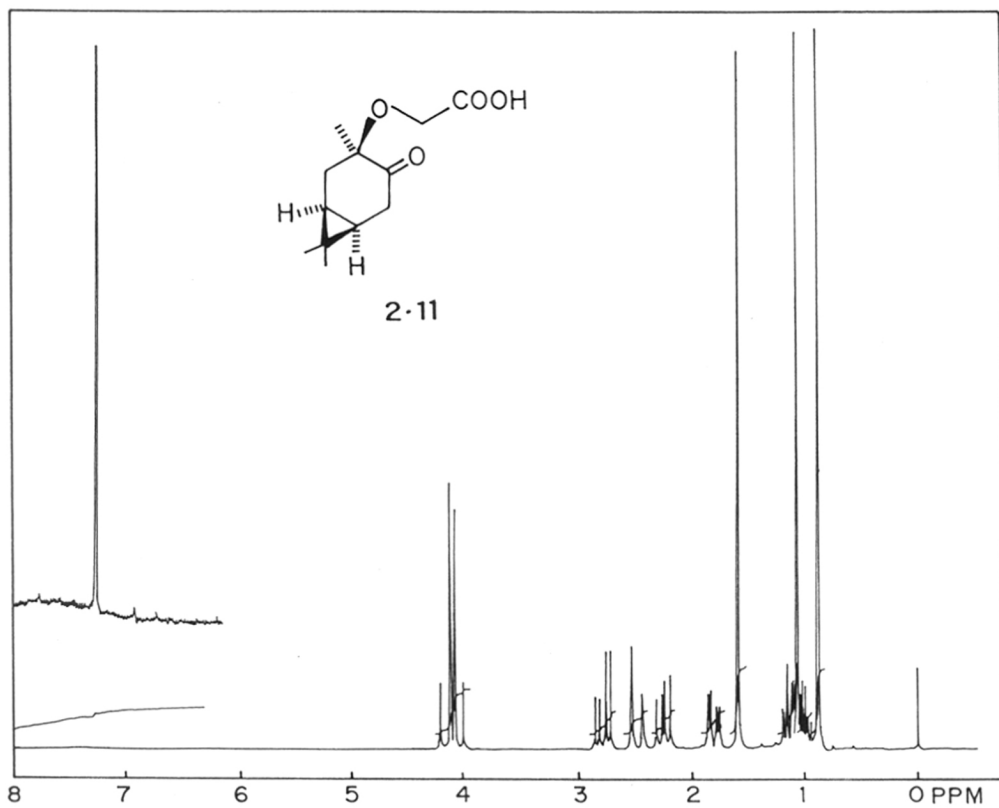
Calculated : C, 71.4; H, 5.6; N, 5.2.

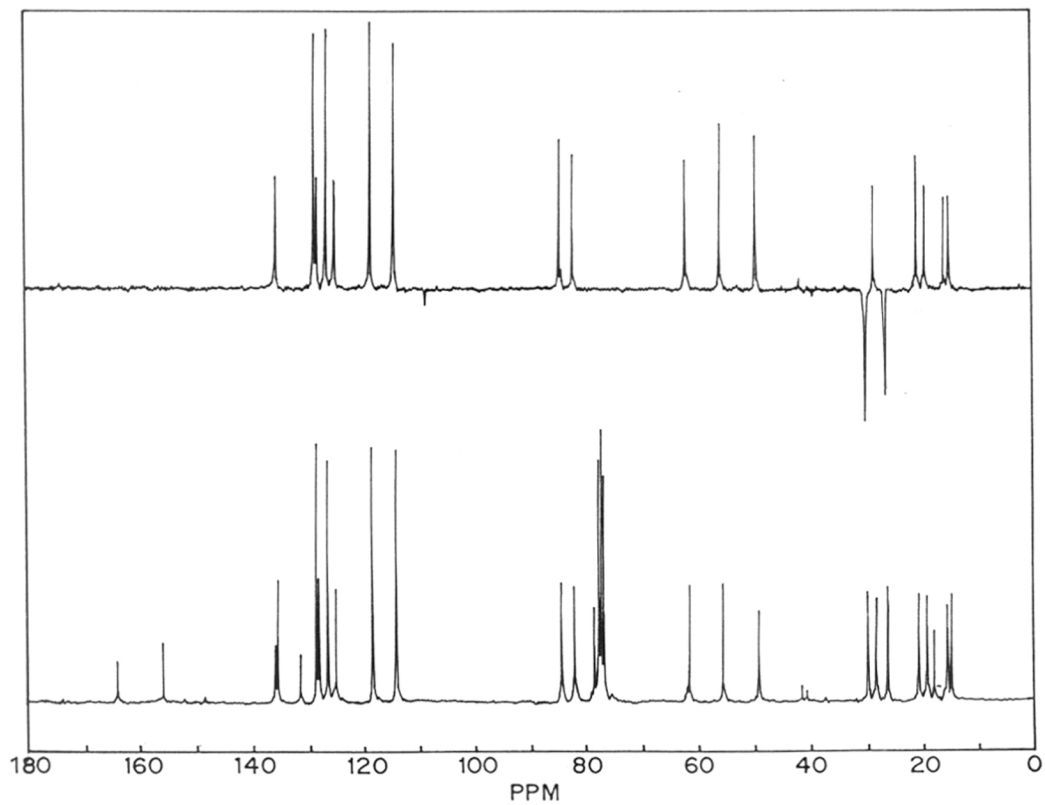
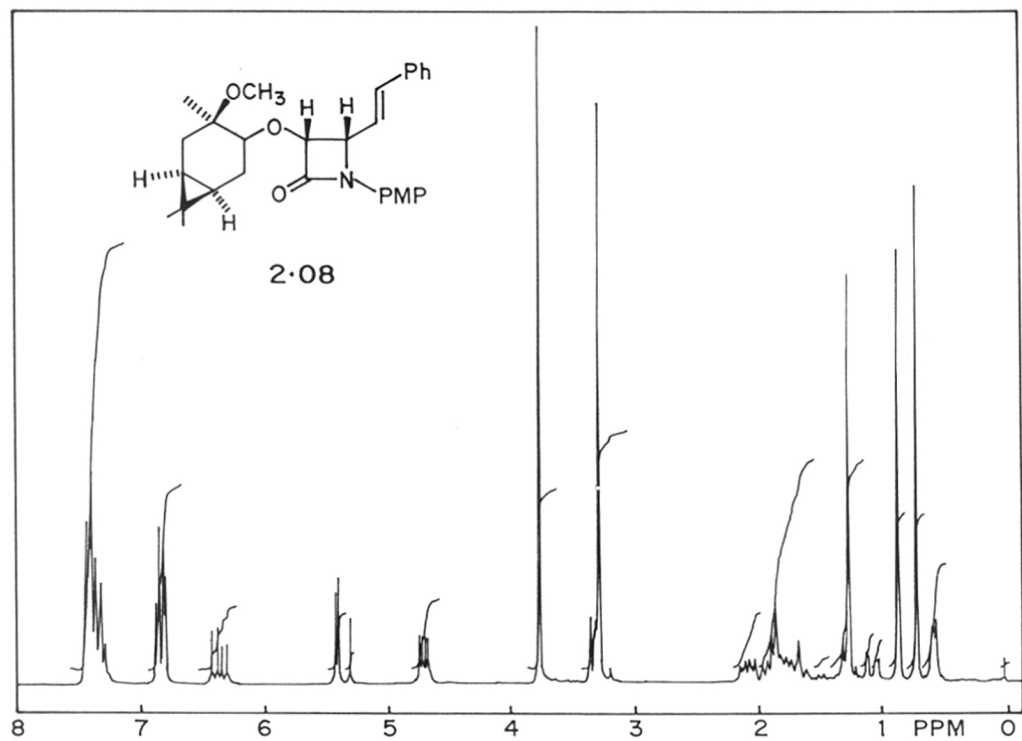
Found : C, 71.9; H, 5.9; N, 4.9.

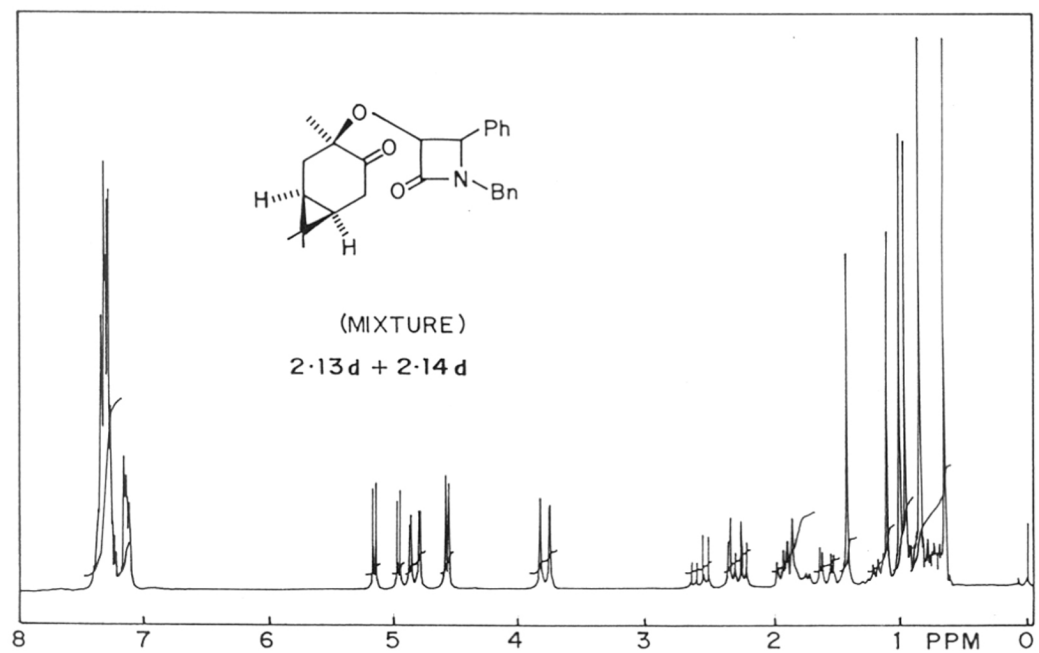
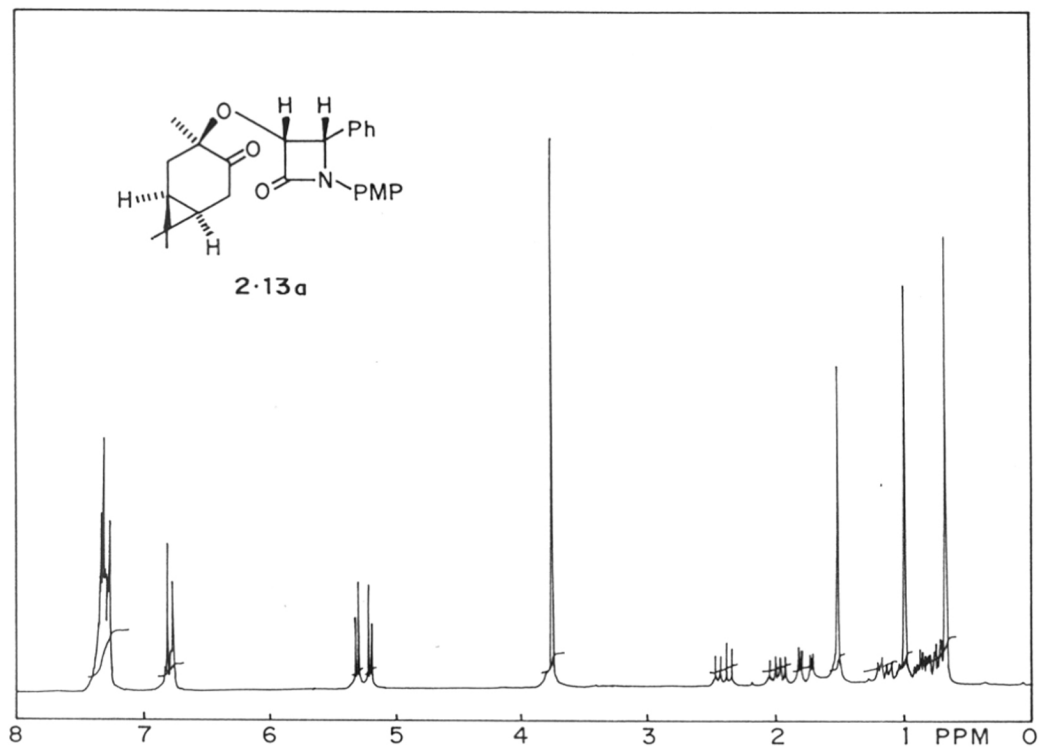
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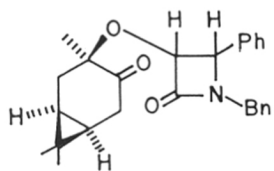
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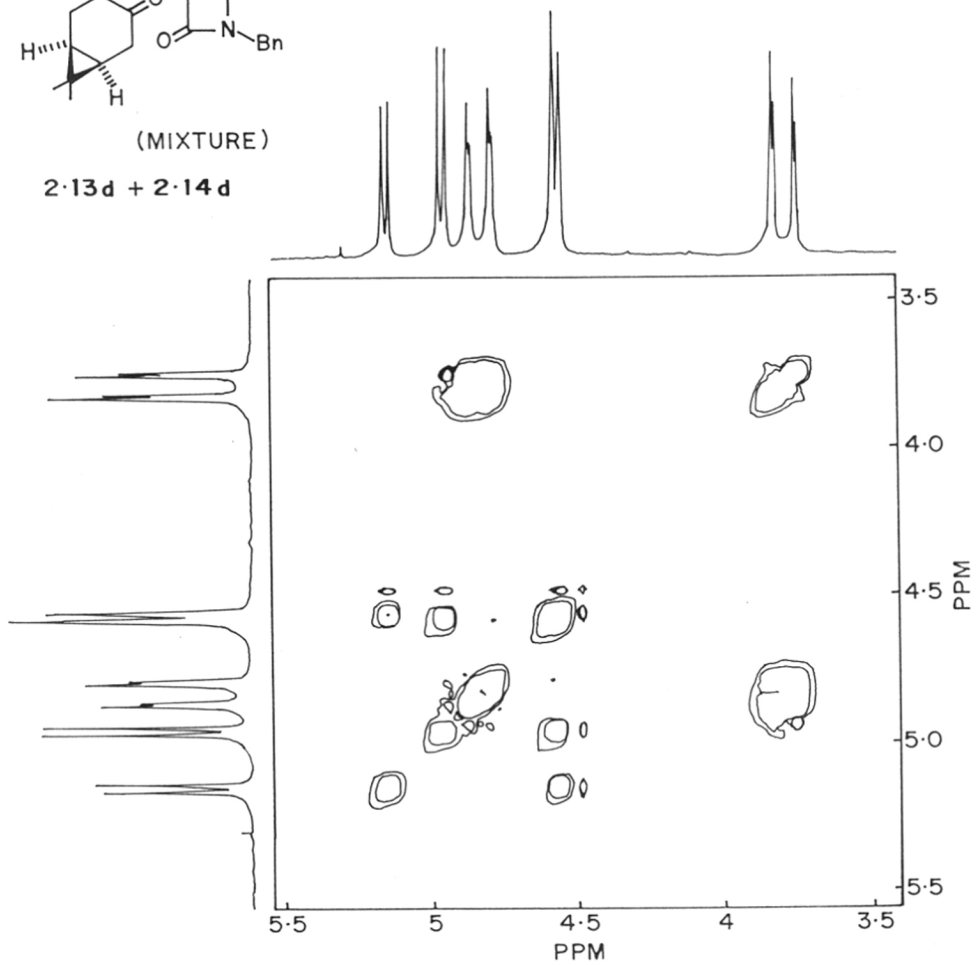


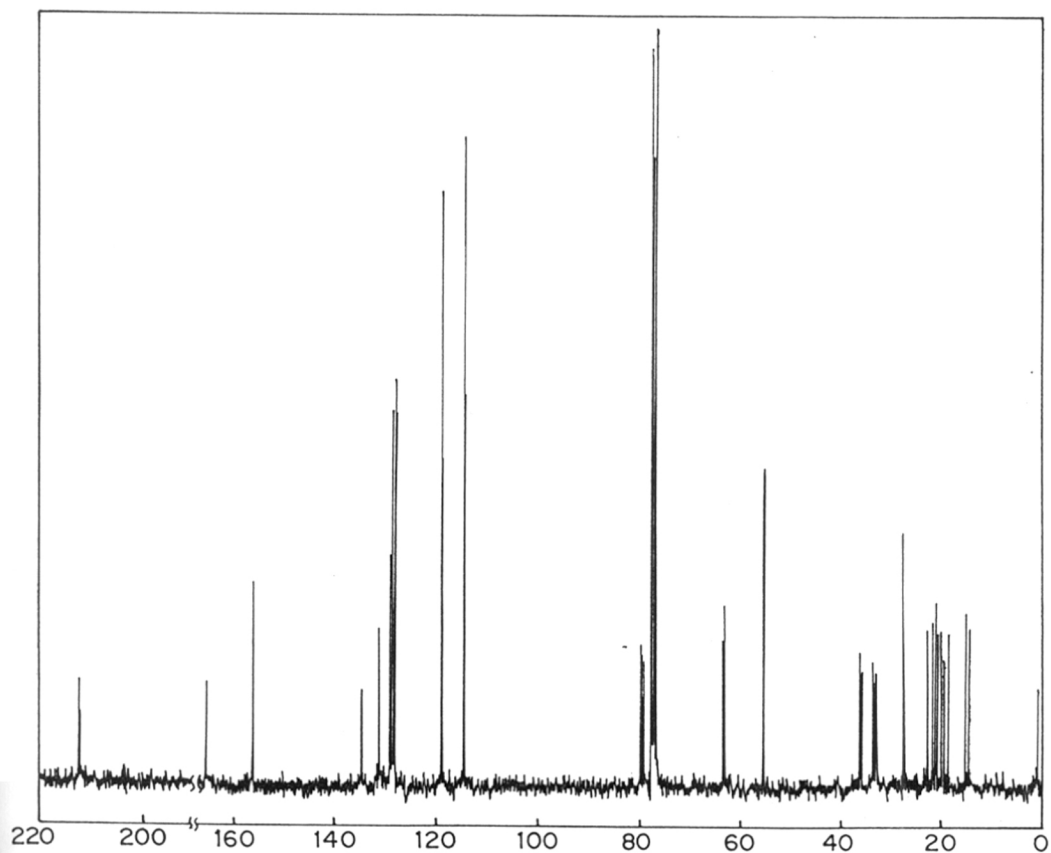
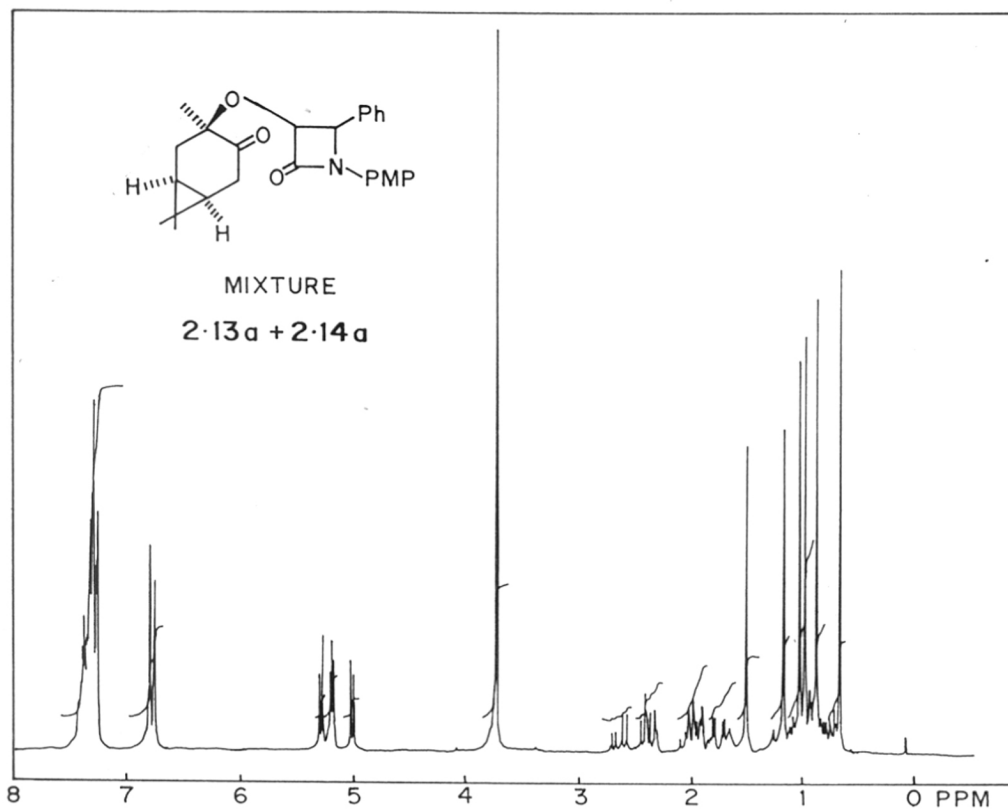


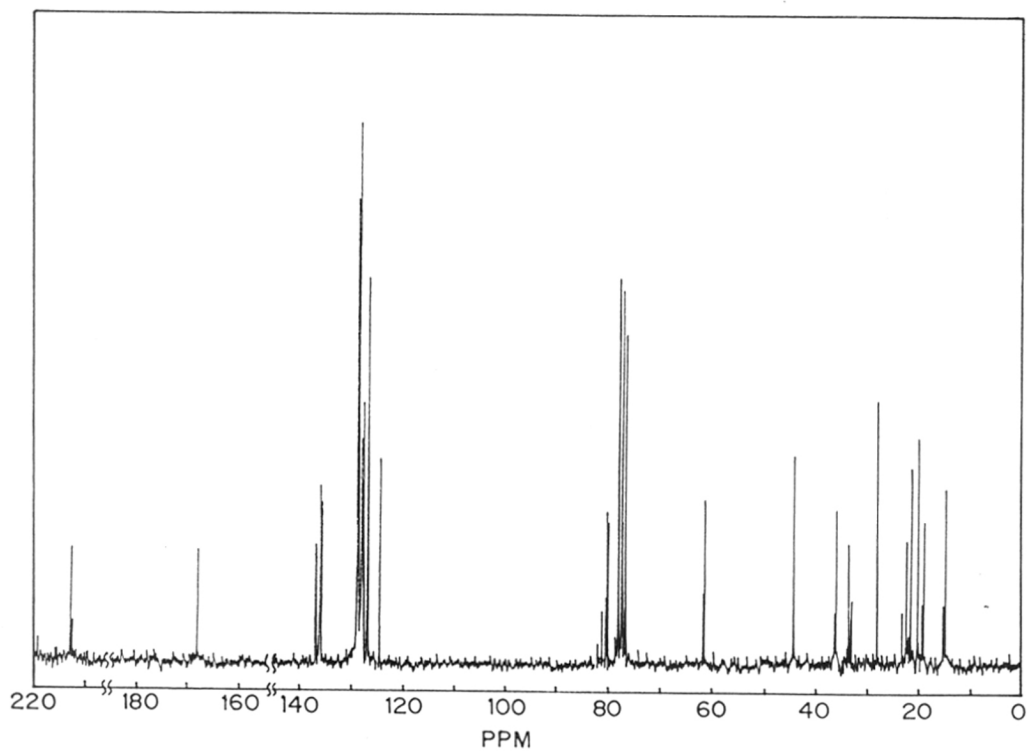
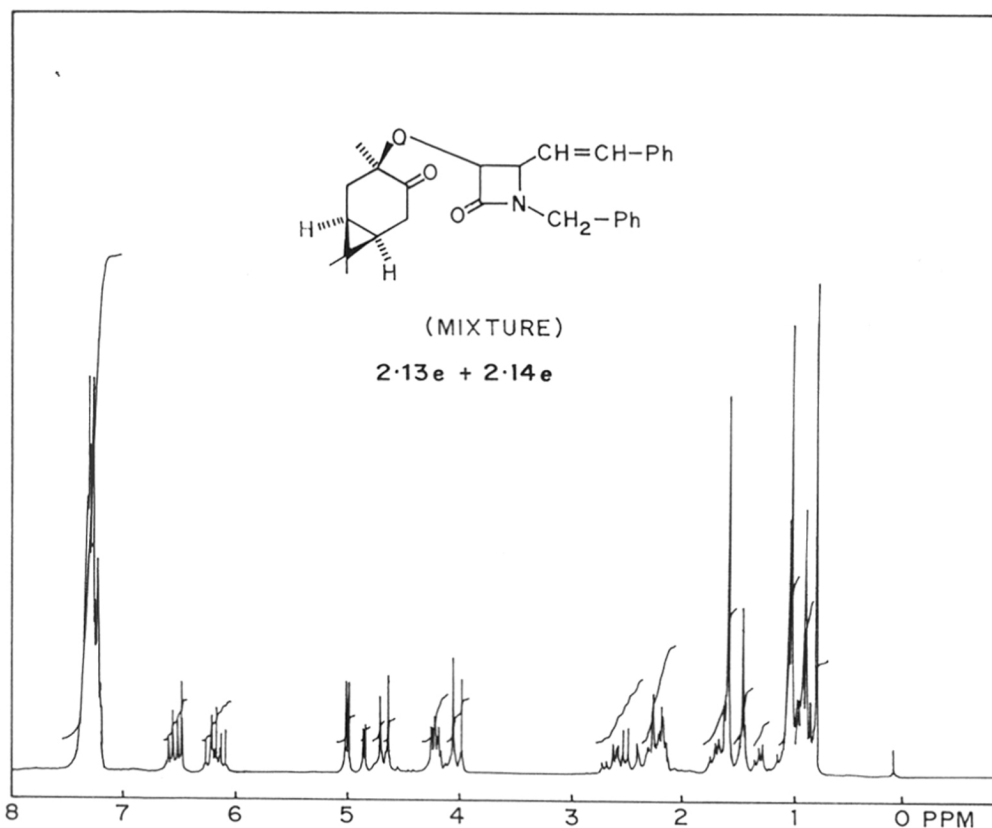


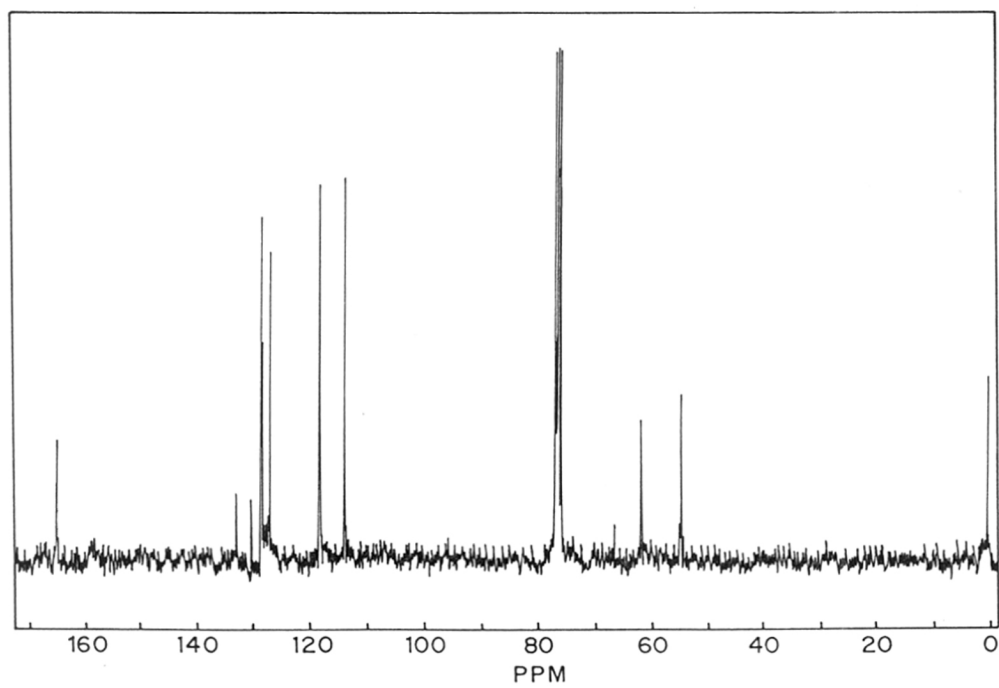
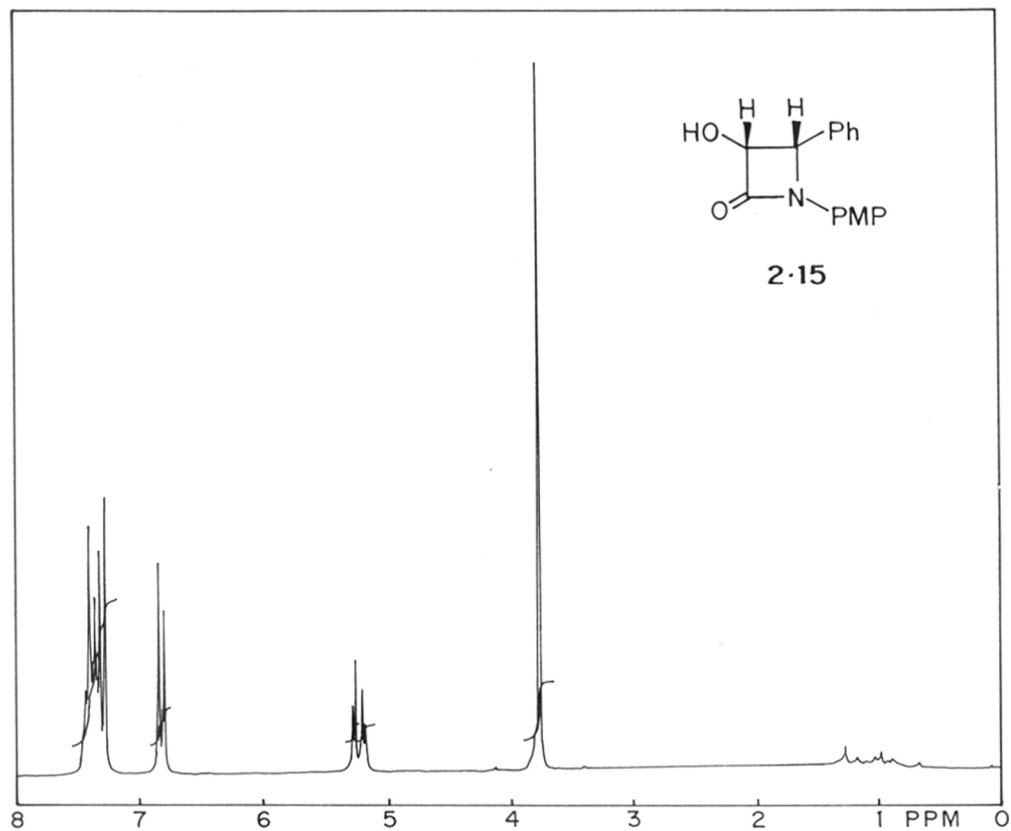
(MIXTURE)

2-13d + 2-14d









CHAPTER III

ENANTIOSPECIFIC SYNTHESIS OF β -LACTAMS USING OPPOLZER SULTAM

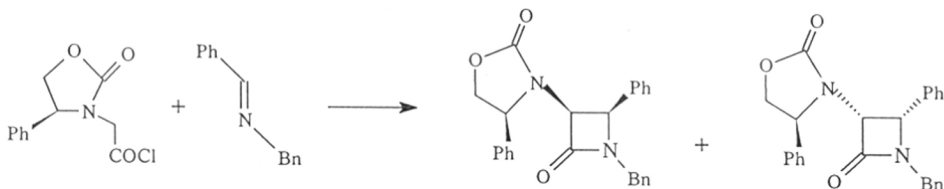
Part of this work has been published in
Tetrahedron, 1996, 52, 5579.

3.1 INTRODUCTION

The immense progress made in the asymmetric synthesis of β -lactams emphasizes that the β -lactams are not only important for the synthesis of antibiotics but also serve as synthons for synthesis of various natural products. Of the various methodologies reported for the synthesis of β -lactams, ketene-imine cycloaddition reaction (Staudinger reaction) is the widely used method due to the simplicity and predictability of its stereochemical outcome. The asymmetric induction in Staudinger reaction can be achieved by using either chiral ketene or chiral imine. The imines derived from aldehydes with α chiral center in ketene-imine cycloaddition reaction are reported to give very high diastereoselectivity in β -lactam ring formation (see Chapter 1 for literature reports). Various levels of diastereoselectivities in β -lactam ring formation have also been reported by using chiral ketene precursors. Following is a brief review of the asymmetric synthesis of β -lactams *via* the Staudinger reaction using chiral ketenes.

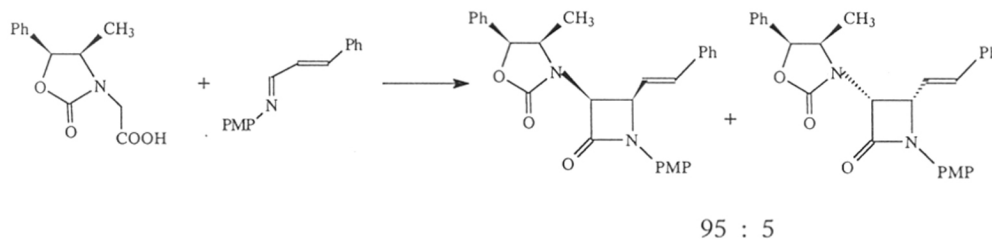
Evans and Sjogren designed a chiral oxazolidone derivative as a ketene component derived from (S)-phenylglycine for a cycloaddition reaction¹ and showed an excellent asymmetric induction in the *cis*- β -lactam ring formation (Scheme 3.01). In this reaction no trace of *trans* isomer was detected. The other enantiomer of the oxazolidone was employed by Boger and Mayer^{2a} for the preparation of the other diastereomer of the β -lactam. This β -lactam has been used as a synthon for the synthesis of the anti-tumor drug, deoxybouvardin. Holten et al have also used oxazolidone as the chiral ketene for the synthesis of β -lactam, which was then successfully converted into 3-hydroxy-4-phenyl- β -lactam.^{2b}

Scheme 3.01



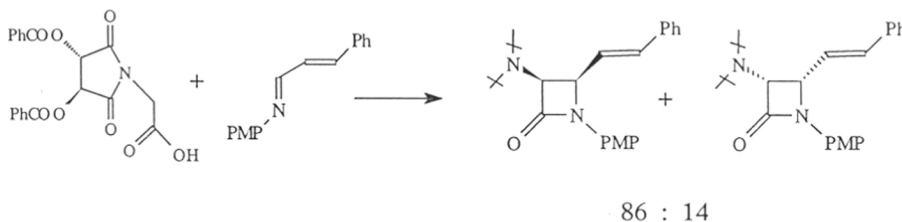
Cooper et al, have used norephedrine derived oxazolidone³ as the chiral ketene component in the cycloaddition reaction. In this case more than 95% of diastereoselectivity was reported in the β -lactam formation (Scheme 3.02).

Scheme 3.02



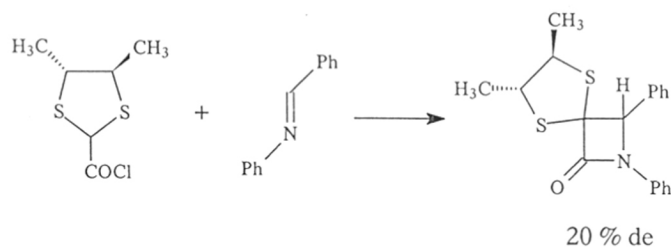
Cooper et al³ have used tartramide derived from S,S-tartaric acid as a chiral ketene precursor. However, very low level of diastereoselectivity was obtained, as the chirality directing group was away from the amide nitrogen (Scheme 3.03).

Scheme 3.03



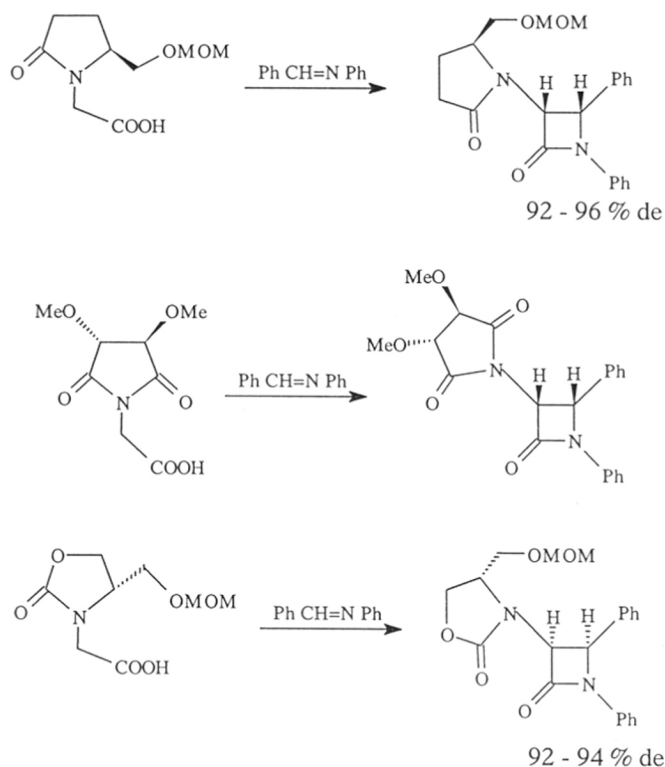
The use of chiral ketenes derived from 1,3-dithiolane-2-carboxylic acid in the cycloaddition reaction to form spiro β -lactam (Scheme 3.04) has been reported to give poor diastereoselectivity.⁴

Scheme 3.04



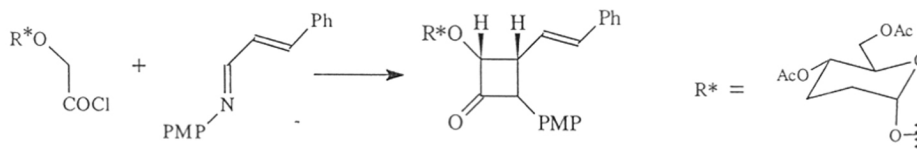
Ikota et al⁵ have used mixed anhydride of the substituted acetic acid derived from L-(+)-tartaric acid, (S)-glutamic acid and (S)-serine as the chiral ketene component in the β -lactam formation and they got very high level of diastereoselectivity (Scheme 3.05). The chiral auxiliaries were removed to afford the 3-amino-2-azetidinone derivatives.

Scheme 3.05



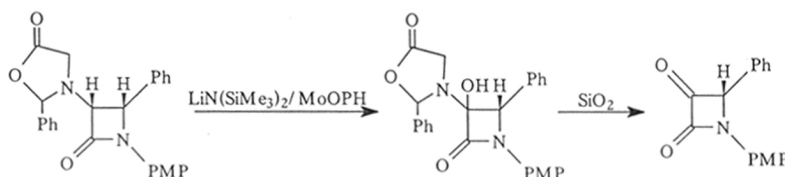
Borer and Balogh⁶ have achieved 70% enantiomeric excess in the β -lactam formation when a chiral ketene derived from a carbohydrate was used (Scheme 3.06). An excellent review on the use of carbohydrates in β -lactam synthesis has appeared recently.⁷

Scheme 3.06



Palomo et al¹¹ have used Evans oxazolidone as a chiral ketene for the synthesis of *cis* β -lactams *via* a cycloaddition reaction. Stereoselective hydroxylation of the C3 center with lithium hexamethyldisilane in the presence of $\text{MoO}_5 \cdot \text{HMPA}$ and subsequent deprotection of the chiral auxiliary afforded α -keto- β -lactam (Scheme 3.10).

Scheme 3.10



Ojima et al¹² have also used Evans oxazolidone as the chiral ketene in β -lactam formation and they reported a novel rearrangement of the oxazolidone derived β -lactam to a new class of heterocyclic compounds.

3.2 PRESENT WORK

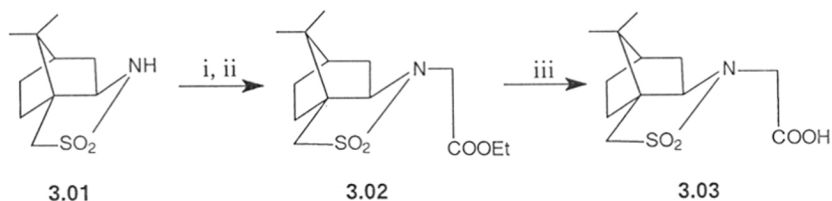
Oppolzer sultam has been extensively studied as the chiral auxiliary in various organic reactions as it provides a very high level of asymmetric induction.¹³ The rigid bicyclic structure of this chiral auxiliary provides the necessary chiral steric requirements for the asymmetric induction. A high level of diastereoselectivity in β -lactam formation has been reported by using camphor-derived amines *via* enolate-imine cycloaddition reactions.¹⁴ However, Oppolzer sultam-derived chiral auxiliary has not been used so far for the asymmetric synthesis of β -lactams. This chapter deals with the use of Oppolzer sultam-derived acid as a chiral ketene precursor for diastereospecific synthesis of β -lactams *via* Staudinger reaction.

3.3 RESULTS AND DISCUSSION

Preparation of Acid 3.03.

The Oppolzer sultam **3.01** was prepared from camphor-10-sulphonic acid by the known procedure.¹⁵ The sultam **3.01** on N-alkylation with ethyl bromoacetate in the presence of sodium hydride base and tetrabutylammonium bromide as phase transfer catalyst, gave the ester **3.02** in 90% yield. The hydrolysis of the N-alkylated sultam ester **3.02** using methanolic potassium hydroxide afforded N-alkylated sultam acid **3.03** in good yield (Scheme 3.11).

Scheme 3.11



Reagents and conditions : i) NaH/dry THF, reflux, 1h. ii) NBu₄I/BrCH₂COOEt, r.t., 3 h. iii) CH₃OH/KOH, r.t., 16 h.

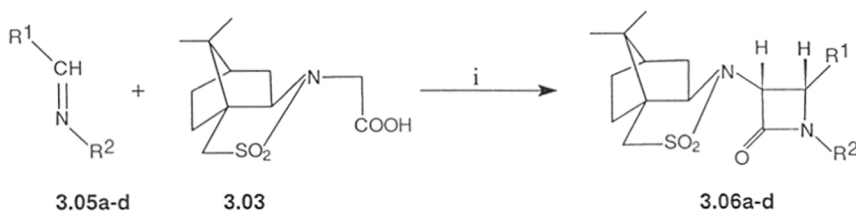
The ¹H NMR spectrum of **3.03** showed two singlets at 0.95 and 1.10 for the *gem* dimethyl groups. The methylene protons of the chiral auxiliary appeared as multiplets in between 1.20 and 2.25. The methylene protons adjacent to the sulfonyl group appeared as a singlet at 3.12. The

methine proton adjacent to the nitrogen atom of the chiral auxiliary appeared as a multiplet at 3.3. The methylene protons adjacent to the carboxylic group appeared as doublets at 3.45 and 3.85 ($J = 16$ Hz). The carboxylic proton appeared as a broad singlet at 7.6. This compound gave satisfactory microanalysis.

Preparation of β -lactams **3.06a-d**.

The imines **3.05** on reaction with acid **3.03** in presence of phenyl dichlorophosphate, an acid activator and triethylamine at -23°C underwent a cycloaddition reaction and gave stereospecifically *cis*- β -lactams **3.06a-d** as single diastereomers in good yields (Scheme 3.12). The HPLC and ^1H NMR analysis of the crude reaction mixture showed the presence of only *cis* diastereomer and not even a trace of other isomers could be detected.

Scheme 3.12

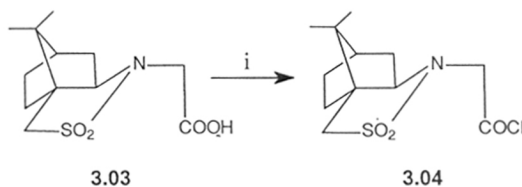


Reagents and conditions : i) $\text{PhOP(O)Cl}_2/\text{Et}_3\text{N}/\text{dry CH}_2\text{Cl}_2$, -23°C to r.t., 15 h.

Preparation of acid chloride **3.04**.

In an alternative method the acid chloride **3.04**, derived from N-alkylated sultam acid **3.03** was used as a ketene precursor for the preparation of β -lactams. The N-alkylated sultam acid **3.03** on heating with thionyl chloride at reflux for 5 h gave acid chloride **3.04** in very good yield (Scheme 3.13).

Scheme 3.13

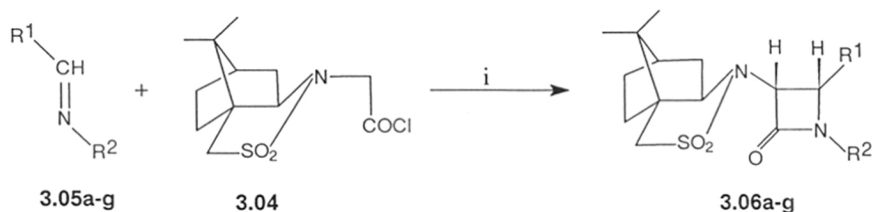


Reagents and conditions : i) SOCl_2 , reflux, 5 h.

Preparation of β -lactams 3.06a-g.

The acid chloride 3.04 on cycloaddition reaction with various imines 3.05a-g in the presence of triethylamine at -23°C in dry methylene chloride gave *cis*- β -lactams 3.06a-g as a single diastereomer in excellent yields (Scheme 3.14). The HPLC and ^1H NMR analysis of the crude reaction mixture showed the presence of only one *cis* diastereomer.

Scheme 3.14



Reagents and conditions : i) Et_3N /dry CH_2Cl_2 , -23°C to r.t., 15 h.

Table 1. Synthesis of β -lactams 3.06a-g via cycloaddition reaction of imines 3.05a-g with ketenes derived from acid 3.03 and acid chloride 3.04.

Compound. No.	R^1	R^2	Yield (%)		M. p. $^{\circ}\text{C}$	$[\alpha]_D^{25}$
			Method A	Method B		
3.06a	Styryl	PMP	70	82	208 - 210	+60.89
3.06b	Ph	PMP	88	61	242 - 243	+39.20
3.06c	PMP	PMP	91	83	215 - 216	+60.63
3.06d	Ph	Bn	60	47	221 - 222	+62.00
3.06e	Styryl	Bn	82	-	174 - 175	+55.20
3.06f	Styryl	(S)-PhEt	82	-	213 - 215	+22.10
3.06g	Styryl	(R)-PhEt	75	-	199 - 201	+68.90

The β -lactams obtained were purified by column chromatography (silica gel, 60 - 120, acetone/pet. ether) followed by crystallization from acetone/pet. ether. It has been reported that the

amino substituent at C3 can be cleaved by halogenation or hydroxylation at the C3 position of β -lactam ring followed by hydrolysis to give α -keto β -lactams with the recovery of chiral auxiliary. This methodology has failed to remove the chiral auxiliary at the 3-position of sultam substituted β -lactams **3.06**. We tried various halogenating agents like bromine, iodine, NCS, NBS and sulfonyl chloride in the presence of various bases like LiHMDS, LDA, etc. In all the cases the halogenation took place at the methylene group adjacent to the sulfonyl group of the sultam moiety. Other attempts to cleave the chiral auxiliary by reductive cleavage with Na/liq.NH₃, Na/naphthalene or Raney Ni and oxidative hydrolysis using LTA were also unsuccessful.

All the β -lactams prepared were characterized by using spectral and analytical data. The compound **3.06d** was selected as a representative of this series for the discussion of structural elucidation. The IR spectrum of this compound **3.06d** showed a band at 1760 corresponding to β -lactam carbonyl function. The ¹H NMR spectrum of **3.06d** showed the presence of *gem* dimethyl group of the sultam moiety at δ 0.20 and 0.75, integrating for three protons each. The multiplets at 1.3 and 1.7 integrating for two and five protons respectively were due to the protons of the chiral auxiliary. The methylene protons attached to the sulfonyl group of the sultam moiety appeared as doublets at 2.95 and 3.05 ($J = 14$ Hz). The methine proton of the chiral auxiliary bearing nitrogen atom was observed as a triplet at 3.55 ($J = 7$ Hz). Due to diastereotropic nature, the methylene protons of the benzyl group appeared as doublets at 4.05 and 5.00 ($J = 16$ Hz). The β -lactam protons were found to be of *cis* geometry from the coupling constant value ($J = 5.4$ Hz) and the protons at C4 and C3 appeared as doublets at 4.7 and 5.05 integrating for one proton each. The aromatic protons appeared in between 7.10 and 7.45 as complex multiplets, integrating for ten protons.

All other β -lactams **3.06a-g** showed two characteristic doublets in the range of δ 4.2 and 5.3 for corresponding protons at C4 and C3 of β -lactam ring with 4.8 - 5.7 Hz coupling constant, indicating the *cis* stereogeometry of these protons.

The ¹³C NMR spectrum of β -lactam **3.06d** showed *gem* dimethyl carbons at 19.2 and 20.5. The four methylene carbons of the chiral auxiliary appeared at 26.7, 32.6, 37.6 and 45.5. The

methylene carbon of the benzylic group appeared at 48.5. The two β -lactam carbons observed at 62.6 and 65.8. The two quaternary carbons of the sultam moiety were appeared at 47.4 and 50.0. The two methine carbon atoms of the sultam moiety were appeared at 45.0 and 59.6. The aromatic

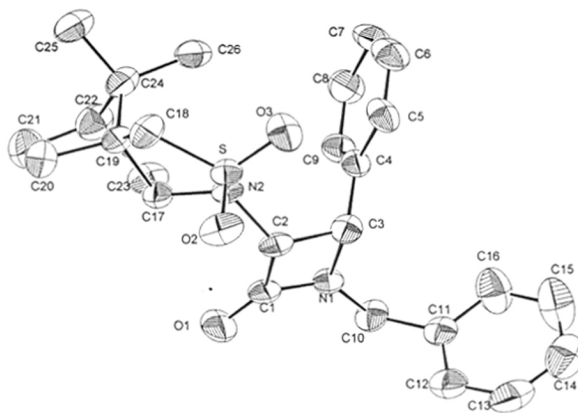
Table 2 : ^1H NMR data for β -lactam protons **3.06a-g**.

Compd. No.	β -lactam protons	
	C4	C3
3.06a	4.85 (dd, $J = 5$ & 7 Hz)	5.05 (d, $J = 5$ Hz)
3.06b	5.3 (two merged doublets)	
3.06c	5.20 (d, $J = 5$ Hz)	5.25 (d, $J = 5$ Hz)
3.06d	4.70 (d, $J = 5.4$ Hz)	5.05 (d, $J = 5.4$ Hz)
3.06e	4.25 (t, $J = 5$ Hz)	4.90 (d, $J = 5$ Hz)
3.06f	4.2 (dd, $J = 4.8$ & 7 Hz)	4.75 (d, $J = 4.8$ Hz)
3.06g	4.3 (dd, $J = 4.8$ & 7 Hz)	4.85 (d, $J = 4.8$ Hz)

carbons were observed in the usual region of 127.7, 128.1, 128.2, 128.5, 129.0. The two quaternary carbons of the aromatic group appeared at 134.5 and 134.8 and the β -lactam carbonyl resonated at 164.1. The IR spectrum of β -lactam **3.06d** showed a strong band at 1760 corresponding to the β -lactam carbonyl stretching. All the compounds gave satisfactory microanalysis.

X - ray structure determination.

In order to ascertain the relative configuration of the molecule, the X-ray crystal analysis was undertaken. The β -lactam **3.06d** was selected as a representative of this series. It was crystallized from acetone/pet. ether to get suitable crystals for single crystal X-ray analysis. The absolute configuration of the β -lactam **3.06d** was assigned as 3*R* and 4*S*, based on the known absolute configuration of 2*R*, 3*S*, 6*R* of the sultam moiety.



pluto diagram of 3.06d

X-ray determination of 3.06d : Data were measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer with Mo-K α ($\lambda = 0.7107 \text{ \AA}$) radiation at 293 K. Crystal belongs to orthorhombic, space group $P2_12_12_1$ with $a = 8.552(2)$, $b = 15.515(4)$, $c = 17.680(4)$ $\text{\AA}$; $V = 2345.9(10) \text{ \AA}^3$, $Z = 4$, $d_{\text{calc}} = 1.276 \text{ Mg m}^{-3}$, $\mu = 0.16 \text{ mm}^{-1}$, data collection of 1978 unique reflections ($2\theta_{\text{max}} = 47^\circ$), 1602 observed [$I > 3.0 \sigma(I)$]. The structure was solved by direct methods using MULTAN-80 Least squares refinement of scale factor, positional and anisotropic thermal parameters for non hydrogen atoms (289 parameters) converged to $R = 0.041$ and $R_w = 0.048$. Hydrogen atoms geometrically fixed and confirmed by difference fourier were held fixed during refinement. Structure solution and refinement were carried out using NRCVAX programs.

3.4 SUMMARY

The Oppolzer sultam derived acid 3.03 and the acid chloride 3.04 were used as ketene precursor for the β -lactam formation *via* ketene-imine cycloaddition method (Staudinger reaction). Both the methods provided diastereospecifically *cis*- β -lactams. The configuration at the chiral centers C3 and C4 were assigned as 3*R* and 4*S* from single crystal X-ray structure analysis. Attempts to cleave the chiral auxiliary at C3 position of β -lactam were unsuccessful.

3.5 EXPERIMENTAL

3.5.1 Preparation of N-alkylated (2R, 3S, 6R)-2,10-camphorsultam 3.02.

To a solution of d-2,10-camphorsultam (Oppolzer sultam) **3.01** (0.537, 2.5 mmol) in dry THF (20 mL), a suspension to NaH (0.065, 2.8 mmol) in THF (5 mL) was added with stirring at 0°C and it was then refluxed for 1.5 h. The reaction mixture was cooled to 0°C and tetrabutylammonium iodide (0.018 g, 0.05 mmol) and ethyl bromoacetate (0.467 g, 2.8 mmol) were added successively and refluxed for 4 h. The reaction mixture was then cooled to room temperature, quenched with water (5 mL) and extracted with ether (2 x 25 mL). The ether extract was dried (Na₂SO₄) and concentrated to give crude product, which was column chromatographed (silica gel, pet. ether/acetone) to give 0.680 g (90.5%) of pure N-alkylated ester **3.02** as a white solid.

M.P. : 75 - 77°C.

¹H NMR : 0.9 (s, 3H, CH₃); 1.2 (s, 3H, CH₃); 1.25 (t, *J* = 7 Hz, 3H, CH₃); 1.3-2.2 (m, 7H (90 MHz) CH₂ & CH); 3.15 (s, 2H, CH₂); 3.3 (t, *J* = 7 Hz, 1H); 3.35 (d, *J* = 16 Hz, 1H, CH₂); 3.85 (d, *J* = 16 Hz, 1H, CH₂); 4.1 (q, *J* = 7 Hz, 2H, CH₂).

[α]_D²⁵ : -35.4 (c 1, CH₂Cl₂).

3.5.2 Preparation of acid 3.03.

To a solution of N-alkylated sultam **3.02** (0.600 g, 3 mmol) in methanol (20 mL), KOH (2.0 g) was added slowly and stirred overnight. The methanol was then removed under reduced pressure, water (15 mL) was added to the residue and acidified with 20% dil. HCl. The acidic solution was extracted with ethyl acetate (2 x 30 mL), washed with brine (10 mL) and dried (Na₂SO₄). It was then filtered and filtrate on removal of solvent gave 0.375 g (68.9%) of acid **3.03** as a white crystalline solid.

M.P : 205 - 207°C.

IR : 3200 - 3500 (br), 2900, 1730, 1440.

¹H NMR : 0.95 (s, 3H, CH₃); 1.10 (s, 3H, CH₃); 1.20 - 2.25 (m, 7H, CH₂ & CH); 3.12 (s, 2H, (90 MHz) CH₂); 3.3 (m, 1H, CH); 3.45 (d, *J* = 16 Hz, 1H, CH₂); 3.85 (d, *J* = 16 Hz, 1H,

CH₂); 7.6 (bs, 1H, COOH).

$[\alpha]_D^{25}$: -40.6 (c, 1, CH₂Cl₂);

Analysis : M.F. C₁₂H₁₉NO₄S

Calculated : C, 52.73; H, 7.01; N, 5.12; S, 11.73.

Found : C, 52.39; H, 6.84; N, 5.43; S, 11.39.

3.5.3 Preparation of acid chloride 3.04.

A mixture of acid **3.03** (0.410 g, 1.5 mmol) and thionyl chloride (0.212 g, 1.8 mmol) was refluxed until the evolution of HCl ceases (about 4 h). The excess of thionyl chloride was removed under vacuum at 50°C to afford the acid chloride **3.04** as solid in quantitative yield.

M.P. : 85 - 87°C.

IR : 3020, 2960, 1800, 1410.

$[\alpha]_D^{25}$: -25.8 (c, 1, CH₂Cl₂).

3.5.4 General procedure for the preparation of β -lactams **3.06a-g**.

Method A

A solution of acid chloride **3.04** (0.291 g, 1 mmol) in dry CH₂Cl₂ (15 mL), was added to a stirred solution of imines **3.05a-g** (1.2 mmol) in dry CH₂Cl₂ (10 mL) in presence of excess of triethylamine (6.0 mmol) at -23°C. The resulting solution was allowed to warm up to room temperature and stirred further for 15 h. The reaction mixture was then successively washed with water (30 mL), satd. bicarbonate solution (30 mL) and brine (30 mL) and dried (Na₂SO₄). It was filtered and filtrate on concentration gave the crude product, which was column chromatographed (silica gel, 60-120, pet. ether/acetone) to furnish pure β -lactams **3.06a-g** in 60-91% yield. All compounds were crystallized from pet. ether/acetone.

Method B

To a stirred mixture of acid **3.03** (0.400 g, 1.5 mmol), imines **3.05a-d** (1.8 mmol), triethylamine (6.0 mmol) in dry CH₂Cl₂ (15 mL), a solution of phenyl dichlorophosphate (0.378 g, 1.8 mmol) in dry CH₂Cl₂ (20 mL) was added at -23°C. The reaction mixture was then allowed

to warm-up to room temperature and stirred further for 15 h. The usual work-up as described in Method A gave pure β -lactams **3.06a-d** in 47-83% yield.

3.5.4a (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*)-N-[1'-(*p*-Anisyl)-4'-styrylazetidin-2'-one-3'-yl]-2,10-camphorsultam 3.06a.

Method A

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05a** (0.285 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided pure β -lactam **3.06a** (0.345 g, 70%) as a crystalline solid.

Method B

The phenyl dichlorophosphate (0.380 g, 1.8 mmol) when treated with a mixture solution of the sultam derived acid **3.03** (0.410 g, 1.5 mmol), imine **3.05a** (0.430 g, 1.8 mmol) and triethylamine (0.6 g, 6.0 mmol) at -23°C, provided the β -lactam **3.06a** (0.610 g, 82%) as a crystalline solid.

M.P. : 208 - 210°C.

¹H NMR : 0.85 (s, 3H, CH₃); 0.95 (s, 3H, CH₃); 1.35 - 1.55 (m, 2H, CH₂); (m, 5H, CH₂ & CH); 3.10 (d, *J* = 14 Hz, 1H, CH₂); 3.20 (d, *J* = 14 Hz, 1H, CH₂); 3.7 (dd, *J* = 5 & 8 Hz, 1H, CH); 3.8 (s, 3H, OCH₃); 4.85 (dd, 1H, *J* = 5 & 7 Hz, C4H); 5.05 (d, 1H, *J* = 5 Hz, C3H); 6.35 (dd, 1H, *J* = 7 & 17 Hz, styryl CH); 6.6 (d, 1H, *J* = 17 Hz, styryl CH); 6.8 (d, 2H, *J* = 10 Hz, Ar); 7.25 - 7.50 (m, 7H, Ar).

¹³C NMR : 20.0, 20.4, 26.4, 32.7, 38.3, 45.0, 47.6, 49.0, 50.4, 55.5, 58.5, 60.8, 66.2, 114.4, 118.5, 124.0, 126.7, 128.1, 128.5, 131.2, 133.9, 136.0, 56.5, 160.0.

IR : 1750.

[α]_D²⁵ : +60.89 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₈H₃₂N₂O₄S

Calculated : C, 68.27; H, 6.55; N, 5.69; S, 6.51.

Found : C, 68.63; H, 6.65; N, 5.69; S, 5.90.

3.5.4b (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*)-N-[1'-(*p*-Anisyl)-4'-phenylazetidin-2'-one-3'-yl]-2,10-camphorsultam 3.06b.

Method A

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05b** (0.25 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided the β-lactam **3.06b** (0.410 g, 88%) as a pure solid.

Method B

Phenyl dichlorophosphate (0.400 g, 1.9 mmol) when treated with a mixture solution of the sultam derived acid **3.03** (0.410 g, 1.5 mmol), imine **3.05b** (0.400 g, 1.9 mmol) and triethylamine (0.6 g, 6.0 mmol) at -23°C, provided the β-lactam **3.06b** (0.430 g, 61%) as a pure solid.

M.P. : 242 - 243°C.

¹H NMR : 0.1 (s, 3H, CH₃); 0.75 (s, 3H, CH₃); 1.25 - 1.45 (m, 2H, CH₂); 1.75 (m, 5H, CH₂ & CH); 2.95 (d, 1H, *J* = 14 Hz, CH₂); 3.05 (d, 1H, *J* = 14 Hz, CH₂); 3.7 (t, *J* = 7.5 Hz, 1H, CH); 3.8 (s, 3H, CH₃); 5.3 (two merged doublets, 2H, C3H & C4H); 6.85 (d, 2H, *J* = 10 Hz, Ar); 7.25 - 7.45 (m, 7H, Ar).

¹³C NMR : 19.1, 20.7, 26.8, 32.6, 37.6, 45.0, 47.4, 48.5, 50.0, 55.5, 60.2, 61.4, 65.6, 114.5, 118.7, 127.8, 128.3, 128.7, 130.9, 133.8, 156.6, 160.6.

IR : 1750.

[α]_D²⁵ : +39.20 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₆H₃₀N₂O₄S

Calculated : C, 66.93; H, 6.48; N, 6.00; S, 6.87.

Found : C, 66.69; H, 6.23; N, 5.89; S, 6.70.

3.5.4c (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*)-N-[1'-(*p*-Anisyl)-4'-*p*-anisylazetidin-2'-one-3'-yl]-2,10-camphorsultam 3.06c.

Method A

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05c** (0.29 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided the β-lactam **3.06c** (0.450 g, 91%) as a pure crystalline solid.

Method B :

The phenyl dichlorophosphate (0.400g, 1.9 mmol) when treated with a mixture solution of the sultam derived acid **3.03** (0.410 g, 1.5 mmol), imine **3.05c** (0.460 g, 1.9 mmol) and triethylamine (0.6 g, 6.0 mmol) at -23°C, provided the β -lactam **3.06c** (0.620 g, 83%) as a pure crystalline solid.

M.P. : 215 - 216°C.

^1H NMR : 0.2 (s, 3H, CH_3); 0.75 (s, 3H, CH_3); 1.25 - 1.50 (m, 2H, CH_2); 1.65 - 1.80 (m, 5H, CH_2 & CH); 2.95 (d, $J = 14$ Hz, 1H, CH_2); 3.05 (d, $J = 14$ Hz, 1H, CH_2); 3.65 (t, $J = 7.5$ Hz, 1H, CH); 3.8 (s, 6H, CH_3); 5.20 (d, $J = 5$ Hz, 1H, C4H); 5.25 (d, $J = 5$ Hz, 1H, C3H); 6.85 (d, $J = 5$ Hz, 2H, Ar); 6.90 (d, $J = 5$ Hz, 2H, Ar); 7.22 (d, $J = 10$ Hz, 2H, Ar); 7.32 (d, $J = 10$ Hz, 2H, Ar).

^{13}C NMR : 19.0, 20.0, 26.7, 32.5, 37.5, 45.0, 47.3, 48.4, 49.9, 55.3, 55.4, 59.7, 61.2, 65.5, 114.1, 114.4, 118.6, 125.6, 128.9, 130.9, 156.7, 160.6.

IR : 1750.

$[\alpha]_D^{25}$: +60.63 (c 1, CH_2Cl_2).

Analysis : M.F. $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$

Calculated : C, 65.30; H, 6.49; N, 5.64; S, 6.46.

Found : C, 65.61; H, 6.89; N, 5.33; S, 6.70.

3.5.4d (**2R**, **3S**, **6R**, **3'R**, **4'S**)-N-[1'-(Benzyl)-4'-phenylazetidin-2'-one-3'-yl]-2,10-camphorsultam **3.06d**.

Method A

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05d** (0.235 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided the β -lactam **3.06d** (0.270 g, 60%) as a pure crystalline solid.

Method B

Phenyl dichlorophosphate (0.380 g, 1.8 mmol) when treated with a mixture of the sultam derived acid **3.03** (0.410 g, 1.5 mmol), imine **3.05d** (0.350 g, 1.8 mmol) and triethylamine (0.6 g, 6.0 mmol) at -23°C, provided the β -lactam **3.06d** (0.320 g, 47%) as a pure crystalline solid.

M.P. : 221 - 222°C.

^1H NMR : 0.20 (s, 3H, CH₃); 0.75 (s, 3H, CH₃); 1.30 (m, 2H, CH₂); 1.7 (m, 5H, CH₂ & CH); 2.95 (d, J = 14 Hz, 1H, CH₂); 3.05 (d, J = 14 Hz, 1H, CH₂); 3.55 (t, J = 7 Hz, 1H, CH); 4.05 (d, J = 16 Hz, 1H, CH₂); 4.7 (d, J = 5.4 Hz, 1H, C4H); 5.0 (d, J = 16 Hz, 1H, CH₂); 5.05 (d, J = 5.4 Hz, 1H, C3H); 7.10 - 7.45 (m, 10H, Ar).

^{13}C NMR : 19.2, 20.5, 26.7, 32.6, 37.6, 45.0, 45.5, 47.4, 48.5, 50.0, 59.6, 62.6, 65.8, 127.7, 128.1, 128.2, 128.5, 129.0, 134.5, 134.8, 164.1.

IR : 1760.

$[\alpha]_D^{25}$: +62.00 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₆H₃₀N₂O₃S

Calculated : C, 69.31; H, 6.71; N, 6.22; S, 7.12.

Found : C, 68.97; H, 6.46; N, 6.12; S, 7.25.

3.5.4e (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*)-N-[1'-Benzyl-4'-(2''-styryl)azetidin-2'-one-3'-yl]-2,10-camphorsultam **3.06e**.

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05e** (0.265 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided the β -lactam **3.06e** (0.390 g, 82%) as a pure crystalline solid.

M.P. : 174 - 175°C.

^1H NMR : 0.85 (s, 3H, CH₃); 1.1 (s, 3H, CH₃); 1.3 - 1.6 (m, 2H, CH₂); 1.8 - 1.9 (m, 5H, CH₂ & CH); 3.10 (d, J = 15 Hz, 1H, CH₂); 3.17 (d, J = 15 Hz, 1H, CH₂); 3.6 (dd, J = 5 & 8 Hz, 1H, CH); 4.20 (d, J = 14 Hz, 1H, CH₂); 4.25 (t, J = 5 Hz, 1H, C4H); 4.75 (d, J = 14 Hz, 1H, CH₂); 4.9 (d, J = 5 Hz, 1H, C3H); 6.15 (dd, J = 5 & 15 Hz, 1H, styryl CH); 6.5 (d, J = 15 Hz, 1H, styryl CH); 7.15 - 7.50 (m, 10H, Ar).

^{13}C NMR : 20.1, 20.58, 26.8, 32.8, 38.4, 45.1, 45.7, 47.8, 49.1, 50.3, 58.3, 61.9, 66.5, 124.6, 126.7, 128.1, 128.2, 128.6, 128.7, 129.0, 134.1, 135.2, 136.3, 163.0.

IR : 1750.

$[\alpha]_D^{25}$: +55.20 (c 1, CH_2Cl_2).

Analysis : M.F. $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_3\text{S}$

Calculated : C, 70.56; H, 6.77; N, 5.88; S, 6.73.

Found : C, 70.51; H, 6.71; N, 5.79; S, 6.20.

3.5.4f (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*, 1''*S*)-N-[1'-(1''-phenyl)ethyl-4'-(2'''-styryl)azetidin-2'-one-3'-yl]-2,10-camphorsultam 3.06f.

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05g** (0.28 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C , provided the β -lactam **3.06f** (0.405 g, 82%) as a pure crystalline solid.

M.P. : $213 - 215^\circ\text{C}$.

^1H NMR : 0.9 (s, 3H, CH_3); 1.1 (s, 3H, CH_3); 1.25 - 1.55 (m, 2H, CH_2); 1.65 (d, $J = 7$ Hz, 3H, CH_3); 1.85 - 2.05 (m, 5H, CH_2 & CH); 3.07 (d, $J = 15$ Hz, 1H, CH_2); 3.17 (d, $J = 15$ Hz, 1H, CH_2); 3.65 (dd, $J = 5$ & 7.5 Hz, 1H, CH); 4.2 (dd, $J = 4.8$ & 7 Hz, 1H, C4H); 4.75 (d, $J = 4.8$ Hz, 1H, C3H); 4.95 (q, $J = 7$ Hz, 1H, CH); 6.10 (dd, $J = 7$ & 15 Hz, 1H, styryl CH); 6.45 (d, $J = 15$ Hz, 1H, styryl CH); 7.25 - 7.45 (m, 10H, Ar).

^{13}C NMR : 19.5, 20.1, 20.6, 26.8, 32.8, 38.4, 45.2, 47.8, 49.0, 50.4, 53.2, 58.9, 61.1, 66.4, 125.8, 126.7, 127.3, 128.1, 128.6, 128.9, 134.6, 136.4, 139.9, 163.1.

IR : 1750.

$[\alpha]_D^{25}$: +22.10 (c 1, CH_2Cl_2).

Analysis : M.F. $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_3\text{S}$

Calculated : C, 70.99; H, 6.98; N, 5.71; S, 6.53.

Found : C, 70.64; H, 6.71; N, 5.57; S, 6.29.

3.5.4g (2*R*, 3*S*, 6*R*, 3'*R*, 4'*S*, 1''*R*)-N-[1'-(1''-phenyl)ethyl-4'-(2'''-styryl)azetidin-2'-one-3'-yl]-2,10-camphorsultam 3.06g.

The sultam derived acid chloride **3.04** (0.29 g, 1 mmol) on treatment with imine **3.05g** (0.28 g, 1.2 mmol) in the presence of triethylamine (0.6 g, 6 mmol) at -23°C, provided the β -lactam **3.06g** (0.367 g, 75%) as a pure crystalline solid.

M.P. : 199 - 201°C.

¹H NMR : 0.85 (s, 3H, CH₃); 1.0 (s, 3H, CH₃); 1.2 - 1.6 (m, 2H, CH₂); 1.8 (d, 3H, *J* = 7 Hz, CH₃); 1.8 - 2.0 (m, 5H, CH₂ & CH); 3.10 (d, *J* = 15 Hz, 1H, CH₂); 3.17 (d, *J* = 15 Hz, 1H, CH₂); 3.65 (t, *J* = 5 Hz, 1H, CH); 4.30 (dd, *J* = 4.8 & 7 Hz, 1H, C4H); 4.7 (q, *J* = 7 Hz, 1H, CH); 4.85 (d, *J* = 4.8 Hz, 1H, C3H); 6.0 (dd, *J* = 7 & 15 Hz, 1H, styryl CH); 6.35 (d, *J* = 15 Hz, 1H, styryl CH); 7.15 - 7.50 (m, 10H, Ar).

¹³C NMR : 18.8, 20.1, 20.5, 26.8, 32.8, 38.4, 45.1, 47.7, 49.0, 50.4, 53.8, 58.1, 61.0, 66.4, 124.9, 126.7, 127.0, 127.9, 128.5, 128.9, 134.3, 136.3, 141.0, 163.1.

IR : 1750.

$[\alpha]_D^{25}$: +68.90 (c 1, CH₂Cl₂).

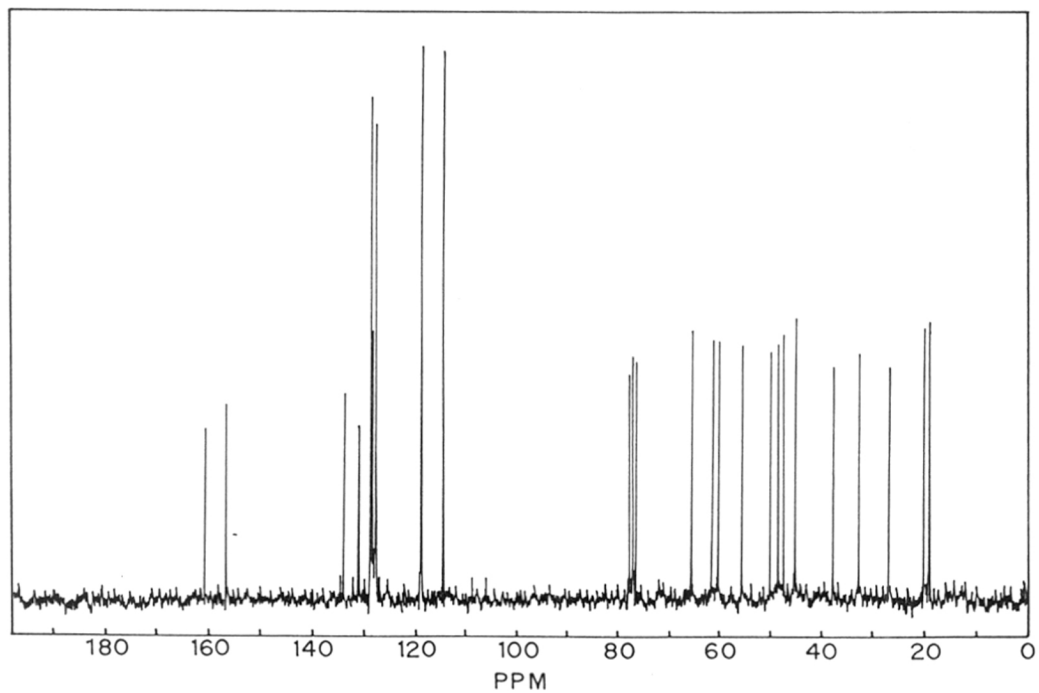
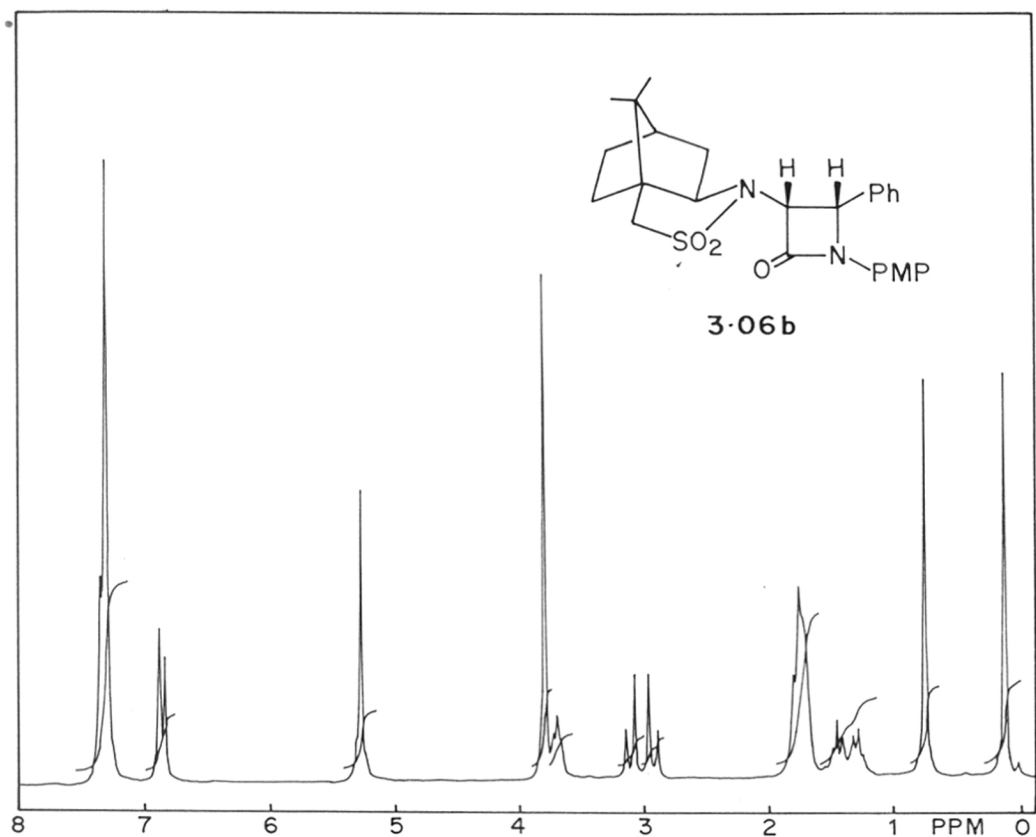
Analysis : M.F. C₂₉H₃₄N₂O₃S

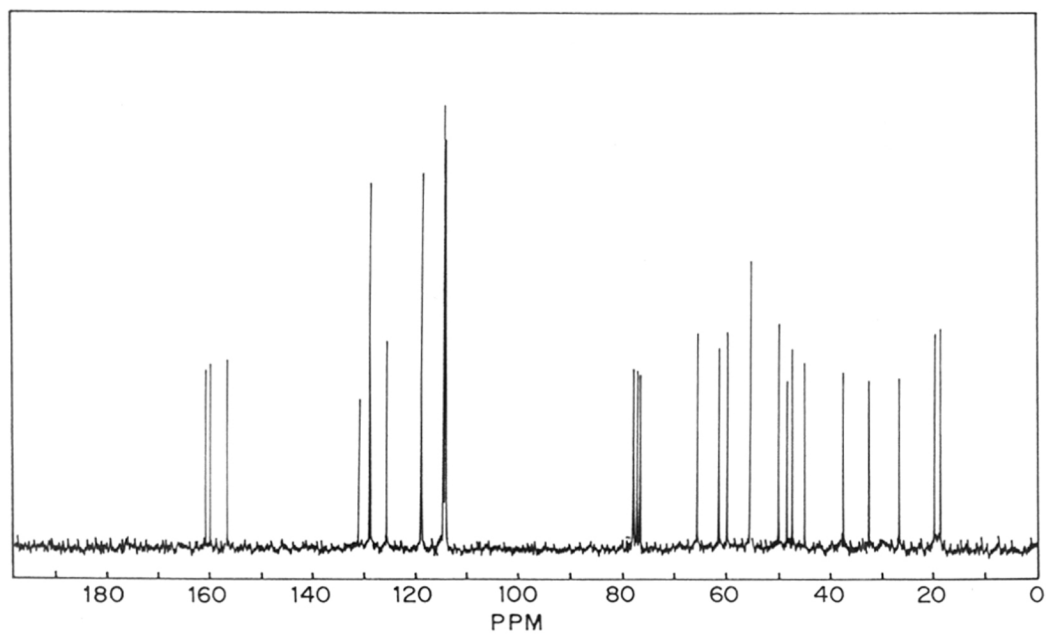
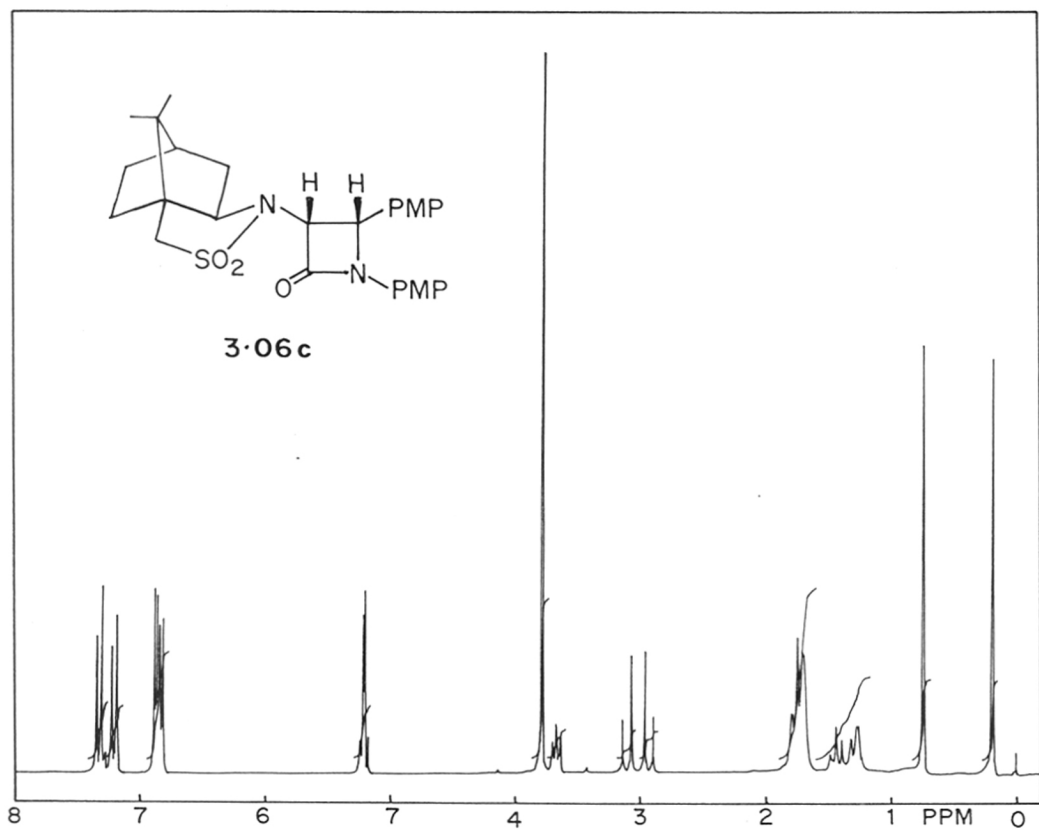
Calculated : C, 70.99; H, 6.98; N, 5.71; S, 6.53.

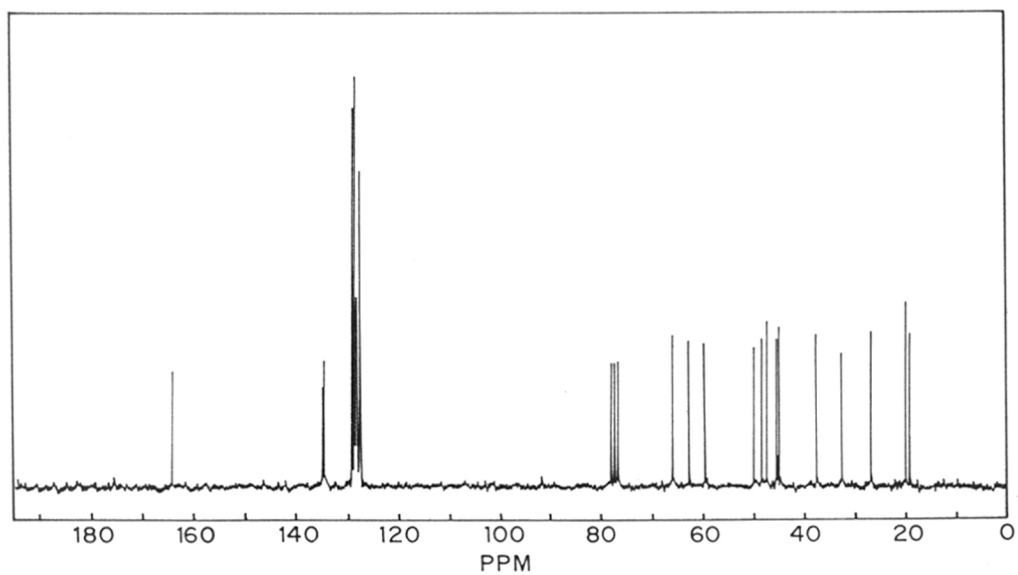
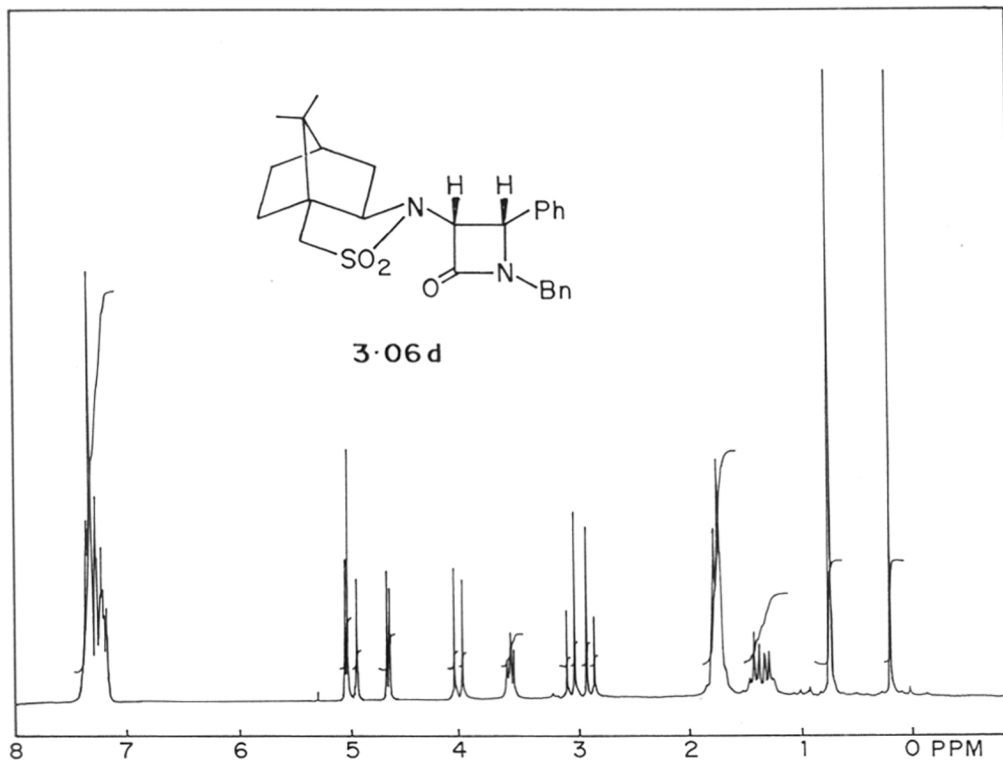
Found : C, 70.80; H, 6.50; N, 5.70; S, 6.80.

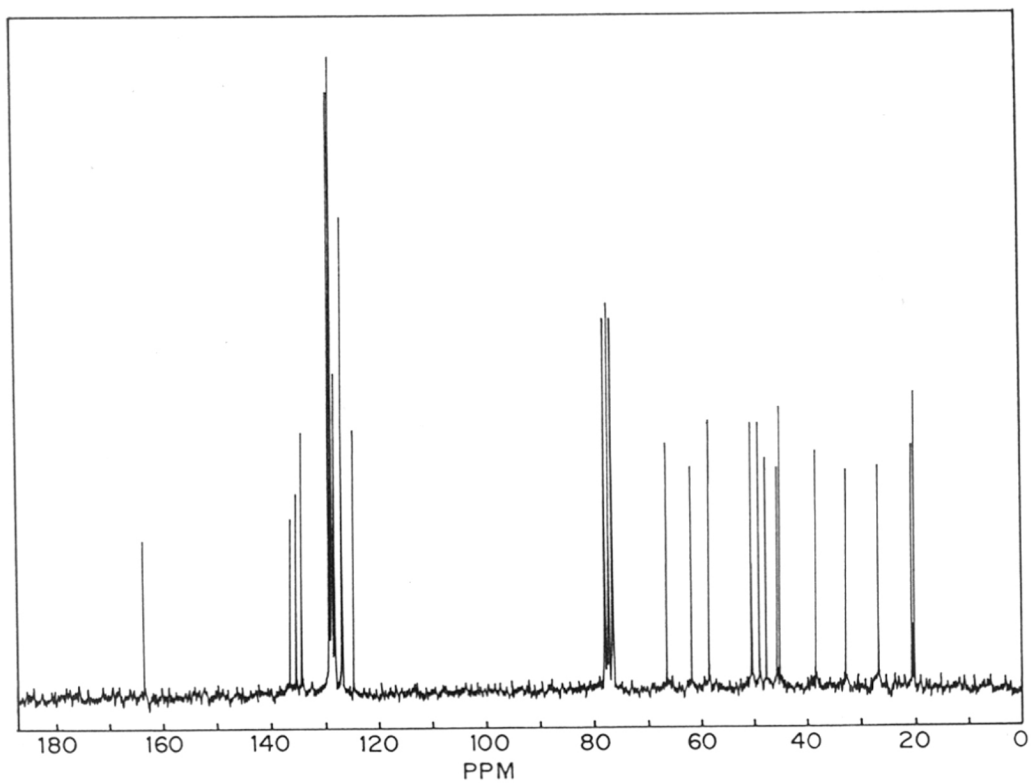
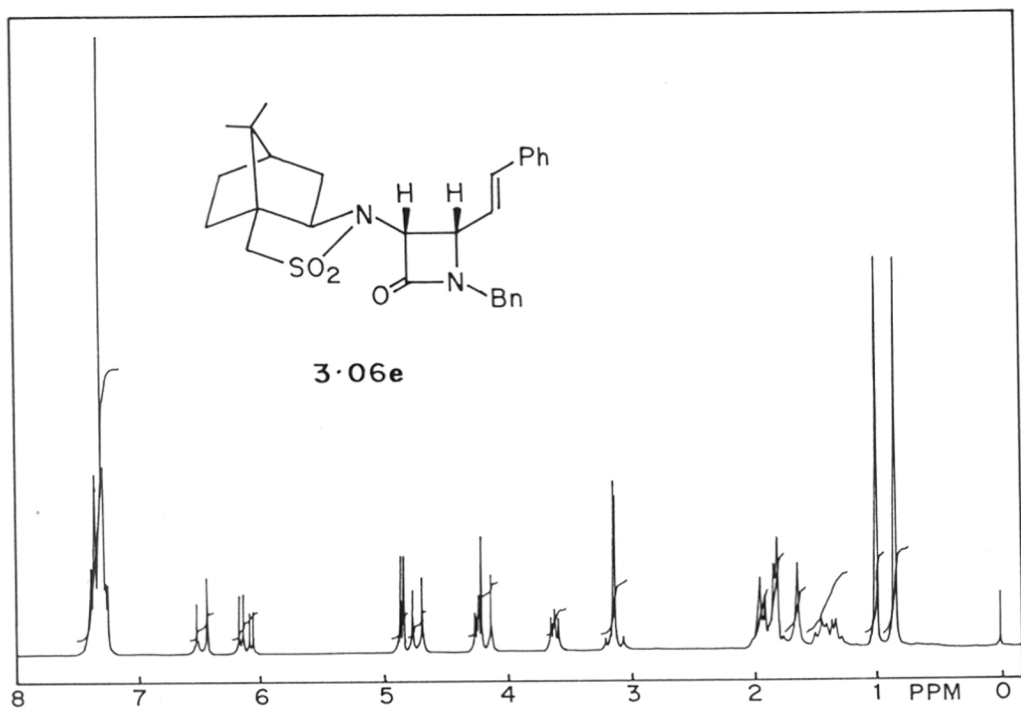
3.6 REFERENCES

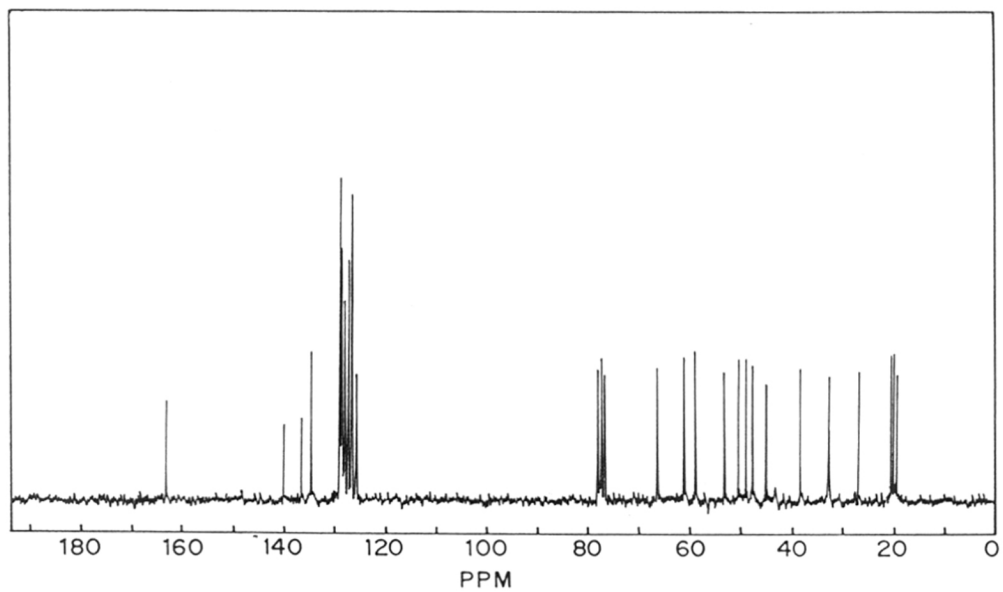
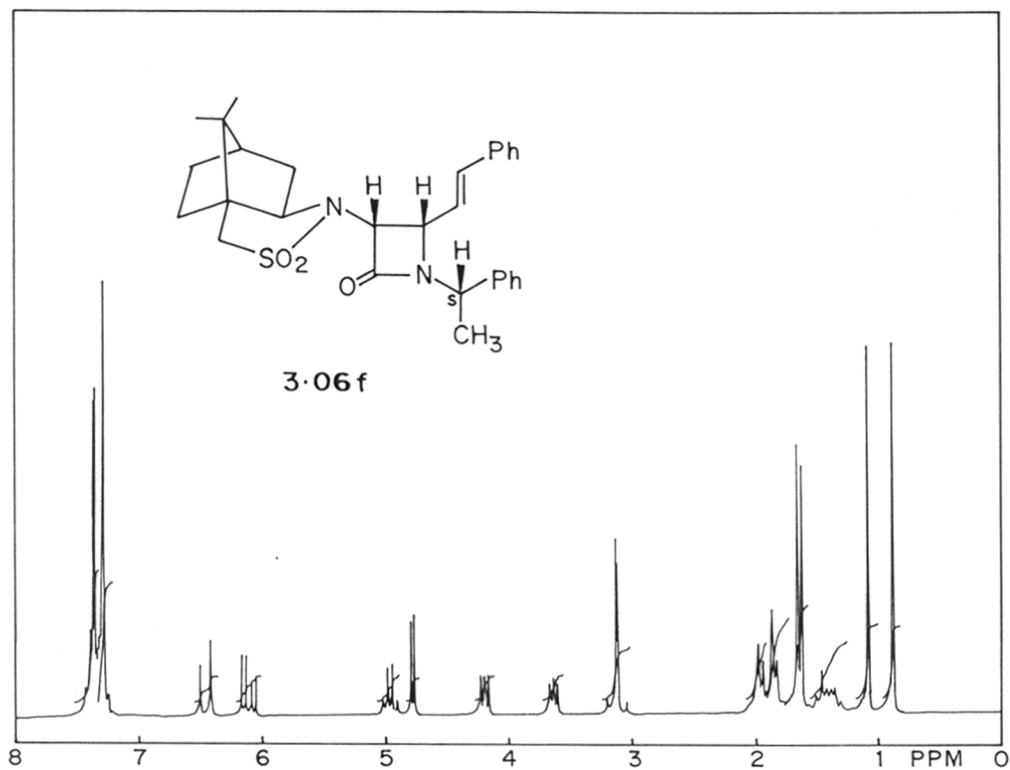
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CHAPTER IV

PREPARATION OF α -HYDROXY ESTERS

via β -LACTAMS

Part of this work has been published in
Tetrahedron Asymmetry. (in press)

4.1 INTRODUCTION

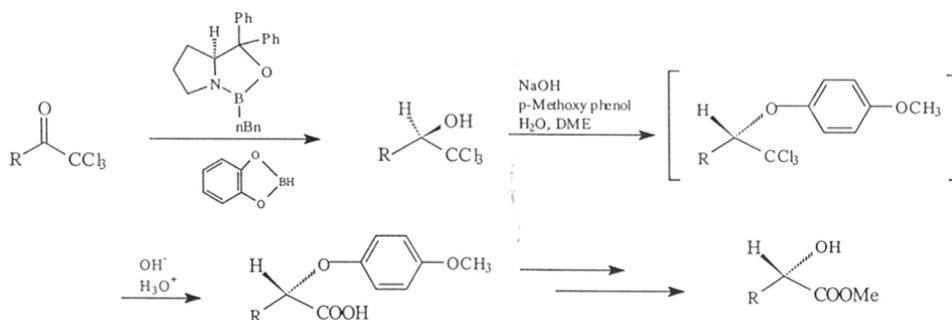
Homochiral α -hydroxy acid derivatives are versatile building blocks for the synthesis of natural products and biologically active compounds.¹ Considerable efforts have been directed toward the development of synthetically viable methods to obtain α -hydroxy acid derivatives using chiral starting materials or chiral reagents. The most commonly used chiral auxiliaries were selected either from amino acids and sugars. The reduction of α -keto esters or α -keto amides is the widely explored method for the synthesis of α -hydroxy acids/esters using various metal hydrides as the reducing agent. There are few reports wherein α -keto esters were reduced to their corresponding α -hydroxy esters with organometallic reagent and microbial organism.^{9a} Following methodologies have also been used for the synthesis of chiral α -hydroxy esters.

- i. Alkylation of the prochiral carbon center of the hydroxy acid/ester derivatives.
- ii. Hydroxylation of the prochiral carbon center of the acid/ester derivatives.
- iii. Acetoxylation of the prochiral carbon of the acid/ester derivatives and subsequent deprotection of the acetyl group to get α -hydroxy acids/esters.

The camphor derivatives, that are excellent chiral auxiliaries, were widely explored in the field of synthetic organic chemistry for asymmetric induction. However, there are very few syntheses reported for α -hydroxy acids using camphor derivatives as chiral auxiliary.

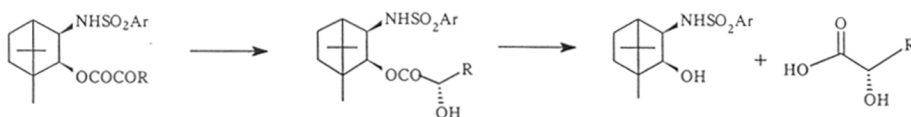
The enantioselective reduction of trichloromethyl ketone to trichloromethyl carbinol has been effected by catecholborane in the presence of a chiral catalyst, oxazoborolidine (Scheme 4.01). This carbinol has been converted into an α -hydroxy ester in two steps.²

Scheme 4.01



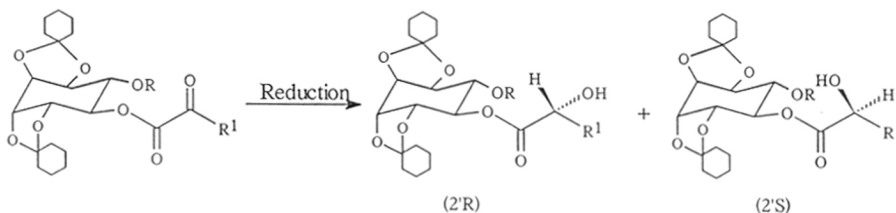
The α -(arylsulfonamido)borneol was used as the chiral auxiliary for the reduction of α -keto esters to α -hydroxy esters (Scheme 4.02). The chiral auxiliary was removed by the saponification using LiOH in THF.³

Scheme 4.02



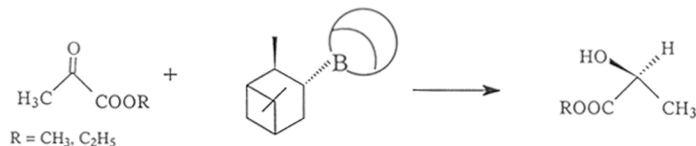
Akiyama et al. carried-out the reduction of α -keto esters derived from inositol. Various metal hydrides such as NaBH_4 , $i\text{-Bu}_2\text{AlH}$, LiBH_4 and LiEt_3BH were screened for the reduction and in all the cases low diastereoselectivity has been reported (Scheme 4.03). However, high diastereoselective reduction of α -keto esters to α -hydroxy esters has been achieved by using potassium tri-*s*-butylborohydride (K-Selectride) and lithium tri-*s*-butylborohydride (L-Selectride) in the presence of 18-crown-6 as an additive.⁴

Scheme 4.03



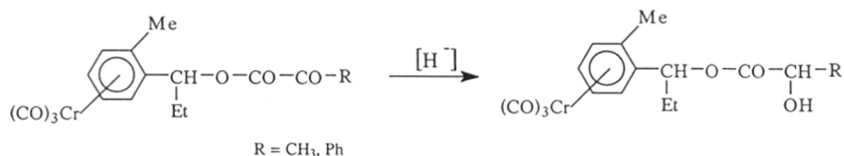
A high enantiomeric excess was reported (Scheme 4.04) in the reduction of α -keto esters to α -hydroxy esters using chiral trialkylborane B-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Alphine -Borane, Midland's reagent).⁵

Scheme 4.04



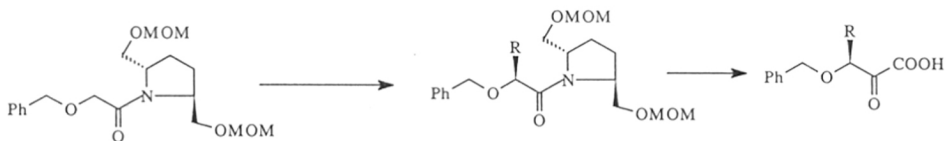
The α -hydroxy esters were also prepared by reducing the chromium complexed carbinol of the α -keto esters.⁶ A low asymmetric induction was reported by this method (Scheme 4.05).

Scheme 4.05



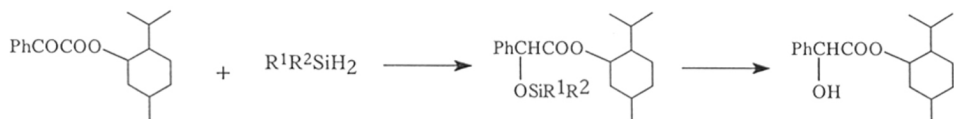
The α -hydroxy esters were also prepared by the alkylation of the prochiral carbon center (Scheme 4.06). The alkylation of lithiated N-(benzyloxyacetyl)-*trans*-2,5-bis-(methoxymethyl)pyrrolidine and subsequent hydrolysis of the alkylated product gave α -hydroxy esters of high enantiomeric purity.⁷

Scheme 4.06



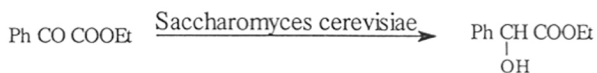
Ojima et al reported a high enantiomeric excess in the reduction of α -keto menthyl esters⁸ to α -hydroxy menthyl esters *via* hydrosilylation catalysed by rhodium complexes (Scheme 4.07).

Scheme 4.07



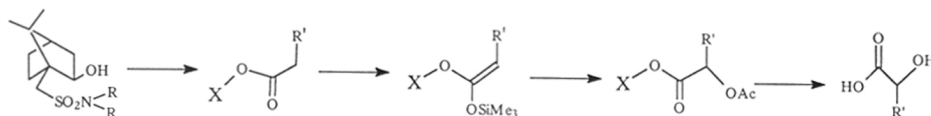
Ridley et al. reported the preparation of α -hydroxy esters (Scheme 4.08) by enzymatic reduction of α -keto esters using the fermenting yeast namely *Saccharomyces cerevisiae*.⁹

Scheme 4.08



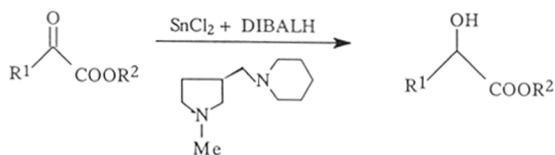
Oppolzer et al have reported a new methodology for the synthesis of α -hydroxy esters *via* stereoselective α -acetoxylation.¹⁰ The camphor-10-sulfonamide shielded O-silylated enol esters were subjected to α -acetoxylation. These acetylated compounds on deprotection of chiral auxiliary and acetyl group yielded α -hydroxy acids (Scheme 4.09).

Scheme 4.09



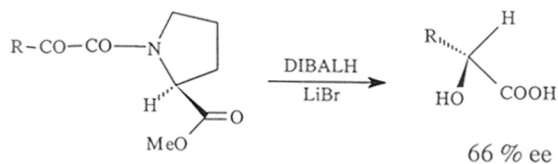
Mukaiyama¹¹ has reported the reduction of α -keto esters to α -hydroxy esters using DIBALH in presence of a reagent generated from chiral diamine derived from (S)-proline by the treatment of tin (II) chloride (Scheme 4.10).

Scheme 4.10



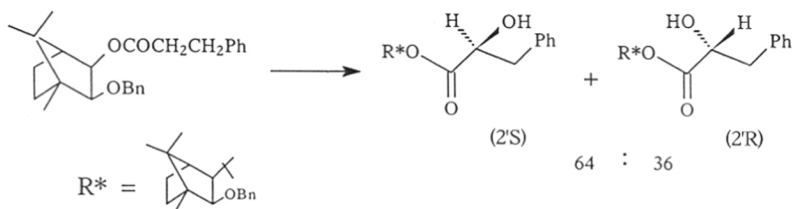
Soai et al have reported moderate enantioselectivity in the preparation of α -hydroxy acids (Scheme 4.11) by the reduction of α -keto amides derived from (S)-proline methyl ester using DIBALH in presence of various metal salts.¹²

Scheme 4.11



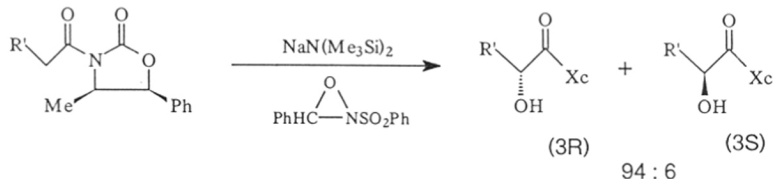
An oxidative α -hydroxylation of camphor derived 3-phenylpropionate ester has been reported by Gamboni et al.¹³ using $\text{MoO}_5 \cdot \text{Py} \cdot \text{HMPT}$ (MoOPH) with poor diastereoselectivity (Scheme 4.12).

Scheme 4.12



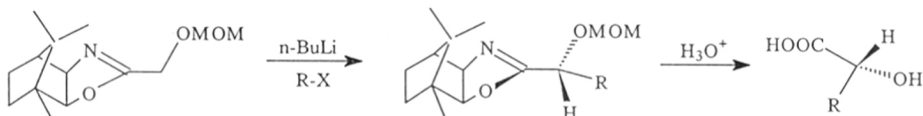
A very high diastereoselectivity in hydroxylation of chiral imide enolates derived from oxazolidines has been reported (Scheme 4.13) by Evans et al using oxaziridine as the oxidant.¹⁴

Scheme 4.13



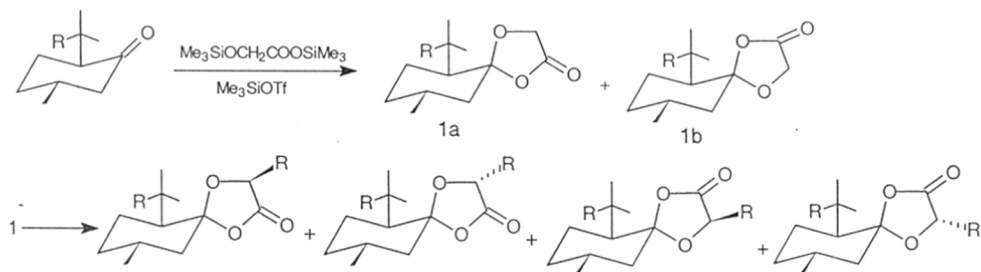
Kelly et al have reported preparation of α -hydroxy esters *via* alkylation of the anion derived from chiral oxazoline, with a variety of alkylating agents (Scheme 4.14). Hydrolysis of the alkylated oxazoline gave α -hydroxy acids in good yield and in good enantiomeric excess.¹⁵

Scheme 4.14



Pearson et al have achieved the synthesis of α -hydroxy esters *via* stereoselective alkylation of the camphor derived lactones¹⁶ (Scheme 4.15).

Scheme 4.15



4.2 PRESENT WORK

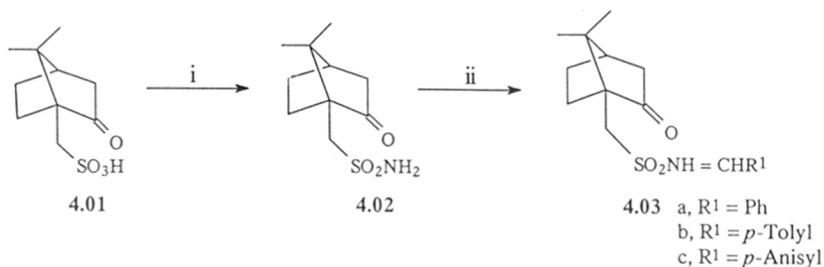
The α -hydroxy acids/esters are important synthons for various natural products. The reduction of α -keto acids or α -keto esters and alkylation or hydroxylation of the prochiral center are the most commonly used methods for the synthesis of α -hydroxy acids. However, little attention has been given for the utilization of β -lactams as synthons for the synthesis of α -hydroxy acids or esters. Camphor has been widely used as the chiral auxiliary in many organic reactions as it offers very high diastereoselectivity. We, therefore, thought that a practical asymmetric synthesis for α -hydroxy acids or esters could be achieved from suitably substituted β -lactams using camphor as a chiral auxiliary. This chapter deals with utilization of camphor-10-sulfonamide as a chiral starting material for the diastereoselective synthesis of β -lactams and their conversion to homochiral α -hydroxy esters and acids.

4.3 RESULTS AND DISCUSSION

Preparation of imines 4.03a-c.

The optically pure camphor-10-sulfonic acid **4.01** was converted into camphor-10-sulfonamide **4.02** by using reported procedure.¹⁷ The condensation of camphor-10-sulfonamide **4.02** with various ethyl acetals of aromatic aldehyde at 150°C, offered the imines **4.03a-c** in quantitative yields (Scheme 4.16).

Scheme 4.16



Reagents and Conditions: i) SOCl₂/NH₃ ii) R¹CH(OEt)₂, 140°C.

The formation of the imine was indicated by the evolution of ethanol during the reaction and ethanol was continuously removed using a distillation condenser. The internal cyclisation of

amide with keto group was observed when the reaction temperature goes above 150°C or the reaction was carried out over a longer period of time at 150°C. The imines **4.03a-c** were purified by crystallization from diethyl ether.

The structure of the imine **4.03a** was supported by its spectral data. The IR spectrum of the imine **4.03a** showed a sharp band at 1610 indicating the presence of C=N group. The ^1H NMR spectrum showed two sharp peaks at 0.9 and 1.2 for the *gem* dimethyl protons. Several multiplets appeared in the region of 1.4 to 2.7 integrating for seven protons of the camphor moiety. Due to the diastereotropic nature, the methylene protons adjacent to the sulfonyl group of the chiral auxiliary appeared as doublets at 3.1 and 3.7 with the coupling constant value of 15.6 Hz. A multiplet observed at 7.5 to 7.7 integrated for three protons of the aromatic group and the other two aromatic protons appeared as a doublet at 8.0 with *J* value of 10.4 Hz. The imine proton was observed as a singlet at 9.1.

The ^{13}C NMR spectrum of **4.03a** showed a sharp peak at 213.6 accounting for the keto carbonyl of the chiral auxiliary. The olefinic carbon resonated at 171.2. The quaternary aromatic carbon was observed at 131.9, while the rest of the aromatic carbons appeared at 134.7, 130.9 and 128.9. The quaternary carbon, adjacent to the keto carbonyl of the chiral auxiliary was seen at 58.1, while the other quaternary carbon of the chiral auxiliary appeared at 47.6. The methylene carbon adjacent to the sulfonyl group resonated at 49.2, whereas the other three methylene carbons were seen at 42.1, 26.6 and 24.7. The methine carbon of the chiral auxiliary appeared at 42.3. The *gem* dimethyl carbons appeared at 19.5 and 19.3.

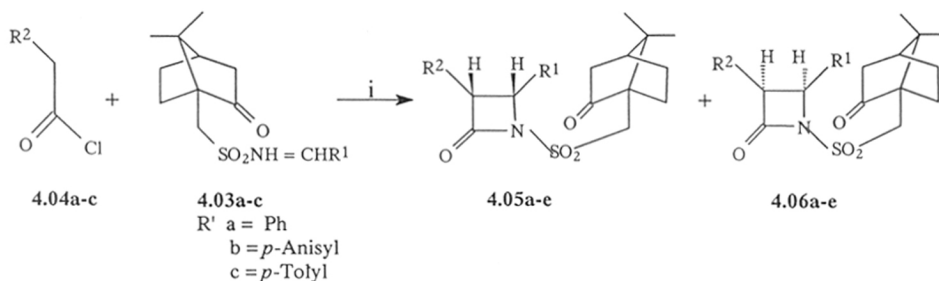
Similarly other imines **4.03b,c** showed spectral data characteristic to their assigned structures. All these imines **4.03a-c** also gave satisfactory microanalysis (see experimental).

Preparation of β -lactams 4.05 & 4.06.

These imines **4.03b,c** on treatment with different acid chlorides **4.04** in the presence of triethylamine at -23°C underwent cycloaddition reaction to give a diastereomeric mixture of β -lactams **4.05** & **4.06** after column chromatography (acetone/pet.ether solvent system in silica gel 60 - 120 mesh) in good yield (Scheme 4.17). The diastereomeric ratio of the β -lactams was

determined from HPLC and ^1H NMR spectral data of the mixture. In this reaction a moderate diastereoselectivity for the β -lactam formation was observed. The attempts to separate these diastereomers by column chromatography were unsuccessful. In all cases, a pure major diastereomer **4.5a-e** was obtained by crystallization from acetone/pet. ether. However, the minor diastereomer **4.06** could not be isolated in pure form even after repeated crystallization.

Scheme 4.17



Reagents and Conditions : i) Et_3N /dry. CH_2Cl_2 , -23°C to r.t.

Table 1 : Synthesis of β -lactams **4.05a-e** & **4.06a-e** via cycloaddition reaction of imines **4.03a-c** with acid chlorides **4.04a-c**.

Compound No.	R^1	R^2	Diastereoselectivity	Yield of 4.05 + 4.06 (%)
4.05a	Ph	PhO-	73 : 27	72
4.05b	Ph	BnO-	58 : 42	77
4.05c	Ph	AcO-	70 : 30	64
4.05d	<i>p</i> -Anisyl	PhO-	55 : 45	43
4.05e	<i>p</i> -Tolyl	PhO-	64 : 36	69

The ^1H NMR and ^{13}C NMR spectra of the major diastereomer **4.05b** was selected as a representative of this series for the discussion and characterization of the product.

The IR spectrum showed strong bands at 1800 and 1740 corresponding to the β -lactam carbonyl and the keto carbonyl of the chiral auxiliary respectively. The ^1H NMR spectrum showed

two sharp singlets at 0.81 and 1.05 for the *gem* dimethyl group, each peak integrating for three protons. Several multiplets appeared in between 1.45 and 2.35 integrating for seven protons of the chiral auxiliary. Due to the diastereotropic nature, the methylene protons adjacent to the sulfonyl group appeared as doublet at 3.05 and 3.45 with the coupling constant value of 15 Hz. The methylene protons of the benzylic group were observed as a doublet at 4.25 and 4.40 ($J = 10$ Hz). The protons at C4 and C3 of the β -lactam ring appeared as doublets at 5.20 and 5.51 respectively with 5 Hz coupling constant. The geometry at these chiral centers was assigned as *cis* from the coupling constant value ($J = 5$ Hz). Several multiplets in the range of 6.90 to 7.50 appeared for ten aromatic protons.

All other β -lactams **4.05a-e** showed two characteristic doublets in the range of δ 5.2 to 6.2 for corresponding protons at C4 and C3 of β -lactam ring with 5.0 - 5.3 Hz coupling constant indicating the *cis* stereochemistry of these protons (Table 2).

Table 2 : ^1H NMR data for β -lactam protons of major diastereomer **4.05a-e**.

Compd. No.	β -lactam protons		
	C4	C3	Coupling constant
4.05a	5.60 (d)	5.75 (d)	$J = 5$ Hz
4.05b	5.20 (d)	5.51 (d)	$J = 5$ Hz
4.05c	5.5 (d)	6.2 (d)	$J = 5$ Hz
4.05d	5.6 (d)	5.7 (d)	$J = 5.3$ Hz
4.05e	5.60 (d)	5.70 (d)	$J = 5$ Hz

The ^{13}C NMR spectrum of the compound **4.05b** showed a peak at 215.0 for the β -lactam carbonyl. The keto carbonyl of the camphor moiety was observed at 164.3. The quaternary carbons of two phenyl groups appeared at 135.9 and 132.8. The other aromatic carbon peaks appeared at 129.1, 128.7, 128.5, 128.4, 128.1. The C3 carbon of the β -lactam ring resonated at 83.6, while the C4 carbon atom resonated at 64.4. The methylene carbon of the benzylic group

appeared at 73.0. The quaternary carbon adjacent to the carbonyl group of the camphor moiety was seen at 58.6. The methylene carbon adjacent to the sulfonyl group of the camphor moiety appeared at 51.8. The quaternary carbon atom attached to the *gem* dimethyl group appeared at 48.7. The methine carbon and methylene carbon of the camphor moiety observed at 42.7 and 42.5. The two methylene carbons and the two *gem* dimethyl carbons of the camphor moiety appeared at 27.1, 24.8 and 19.66, 19.60 respectively.

All other β -lactams **4.05a-e** were also similarly characterized from their spectral analysis. All these compounds gave satisfactory C, H, N analysis (see experimental).

X-Ray crystal structure determination.

In order to establish the absolute configuration at the chiral centers of the molecule, X-ray structure analysis of β -lactam **4.05b** was carried out. Since absolute configuration of the chiral precursor is known, the absolute configuration of the molecule can be deduced from the relative stereochemistry of the chiral center. The configuration of the β -lactam was assigned as 3*R* and 4*S* on the basis of the known absolute configuration 1'*S* of the camphor-10-sulfonyl moiety (Fig. 1).

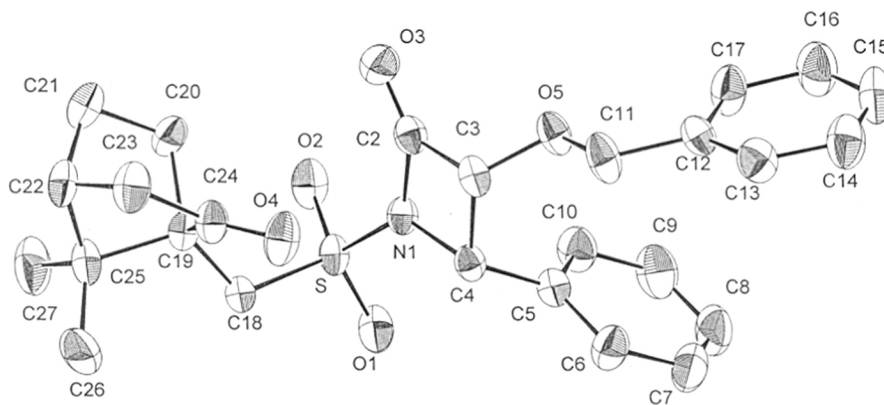


Fig. 1 ORTEP diagram of β -lactam **4.05b**

Data was measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer using graphite monochromator Mo-K α ($\lambda = 0.7107^\circ\text{\AA}$) radiation. Crystal belongs to triclinic space group P1 with $a = 6.751(1)$, $b = 9.270(2)$, $c = 9.926(2)^\circ\text{\AA}$; $\alpha = 86.97(1)$, $\beta =$

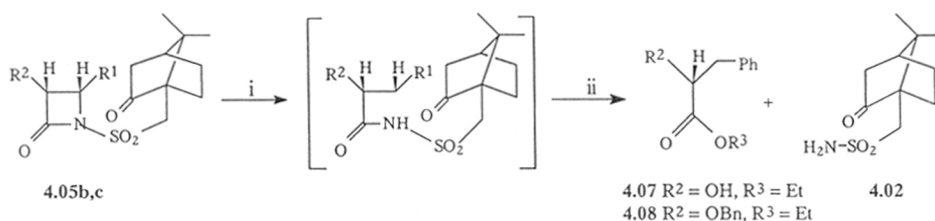
82.04(2), $\gamma = 89.01(1)^\circ$; $V = 614.3(2)^\circ\text{\AA}$; $Z = 1$, $d_{\text{calc}} = 1.264 \text{ Mg m}^{-3}$, $\mu = 0.168 \text{ mm}^{-1}$, out of 1989 reflections measured, 1955 were treated observed with $[I \geq 2.0 \sigma(I)]$. The structure was solved by the direct methods using MULTAN - 80 (NRCVAX - program). Least square refinement of scale factor positional and anisotropic thermal parameters for non-hydrogen atoms converged to $R = 0.0440$, $R_w = 0.130$. Hydrogen atoms were geometrically fixed during the refinement and confirmed by a different Fourier transform. Refinements were carried out by using SHELXL - 93 program.

Preparation of esters 4.07 & 4.08.

The major diastereomers **4.05b,c** separated by crystallisation from acetone/pet. ether, were converted to α -hydroxy esters in a one pot reaction.

The cleavage of N1 - C4 bond of compounds **4.05b,c** was effected by hydrogenation at 1 atm. pressure using 10 % Pd/C in ethanol under refluxing conditions. The reaction was completed in 12 h (TLC). The Pd/C was filtered off and to the filtrate, ethanolic hydrochloride solution was added and refluxed for 8 h (Scheme 4.18). The crude reaction product was obtained by usual work up. The column chromatography (pet.ether/acetone on 60 - 120 silica gel) of the crude reaction product gave α -hydroxy esters **4.07** & **4.08** in good yield along with the chiral auxiliary, camphor-10-sulfonamide.

Scheme 4.18



Reagents and Conditions : i) $\text{H}_2/\text{Pd-C}$, /EtOH, reflux, 12 h. ii) HCl/EtOH , reflux, 8 h.

The presence of the hydroxyl group of the α -hydroxy ester **4.07** was inferred from the broadening of the peak from 3100 to 2800 from the IR spectra. The presence of the ester carbonyl was also evident by the sharp peak at 1730 in the IR spectrum. The ^1H NMR spectrum of **4.07** showed a triplet at 1.3 ($J = 7 \text{ Hz}$) for the methyl proton of the ester group. A broad singlet appeared at 2.75 for the hydroxyl proton. Two doublet of doublets appeared at 3.01 and 3.15 for

the methylene protons of the benzylic group, integrating for one proton each. A quartet was observed at 4.25 for the methylene proton of the ester group ($J = 7$ Hz). The methine proton at the chiral center appeared as a triplet at 4.45 ($J = 5.5$ Hz) for one proton. The aromatic protons of the phenyl ring appeared as a multiplet at 7.17 - 7.35, integrating for five protons.

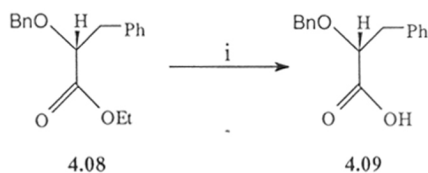
In ^{13}C NMR spectrum, the carbonyl carbon of the ester showed at 173.9. The quaternary carbon of the phenyl group appeared at 136.20. The rest of the aromatic carbons appeared at 129.3, 128.1, 126.6. The methine carbon of the chiral center appeared at 71.0. The methylene carbon of the ester and benzylic group appeared at 61.5 and 40.4. The methyl carbon of the ester group was seen at 13.9. This compound **4.07** gave satisfactory microanalysis and the optical purity was compared by checking the optical rotation with that of the reported lit. value.¹⁶

The IR spectrum of **4.08** showed a sharp peak at 1730 accounting for the ester group. The ^1H NMR spectrum showed a triplet at 1.3 corresponding to methyl protons of the ester group with the coupling constant value of 7.5 Hz. The methylene protons of the benzylic group appeared as a multiplet at 3.15. The methylene protons of the ester group and the methine proton appeared as a multiplet at 4.2 integrating for three protons. The methylene protons of the O-benzylic group, due to its diastereotropic nature, appeared as two separate doublets at 4.4 and 4.7 with the coupling constant value of 12.5 Hz. The aromatic protons appeared in the region of 7.10 - 7.45 as multiplets integrating for ten protons. This compound gave satisfactory microanalysis.

Preparation of acid 4.09.

To find out the optical purity of the ester **4.08**, it was converted into α -hydroxy acid by ester hydrolysis using methanolic KOH (scheme 4.19). The optical rotation of the α -hydroxy acid **4.09** was checked with the known lit. value.¹⁸

Scheme 4.19



Reagents and Conditions : i) KOH/MeOH, r.t., 8 h.

The IR spectrum of **4.09** showed the broadening of the peak from 3500 to 3000 for the O--H stretching of the carboxylic group. A peak at 1720 was corresponding to the ester carbonyl. The ^1H NMR spectrum showed a multiplet at 3.15 corresponding to the methylene protons of the benzylic group. The methine protons of the chiral center appeared as a multiplet at 4.2. The methylene protons of the O-benzylic group appeared as two separate doublets due to its diastereotropic nature at 4.4 and 4.7, with the coupling constant 12.9 Hz. The aromatic protons appeared as a multiplet in between 7.15 to 7.45, integrating for ten protons. A broad singlet appeared at 9.0 was accounted to the hydroxyl proton. This compound gave satisfactory microanalysis.

4.4 SUMMARY

The optically active camphor-10-sulfonamide was successfully used as the chiral amine component in the cycloaddition reaction. The β -lactams were prepared in good level of diastereoselectivity and in good yield. The stereochemistry at the chiral center C3 and C4 of the β -lactam **4.05b** was established as *3R* and *4S* by single crystal X-ray analysis. The β -lactams were converted into α -hydroxy acids/esters in two steps along the quantitative recovery of the chiral template, camphor-10-sulfonamide. All the attempts made to cleave the N-SO₂ bond of the chiral auxiliary to produce N-unsubstituted β -lactam failed.

4.5 EXPERIMENTAL

4.5.1 General Procedure for the Preparation of Imines 4.03a-c.

A mixture of camphor-10-sulfonamide **4.02** (10 mmol) and diethyl acetals of aromatic aldehydes (12 mmol) was heated at 140°C for 15 min. The ethanol formed during the reaction was continuously removed by using distillation condenser. After the completion of the reaction (ethanol formation ceases), the residue was crystallized from benzene/ pet. ether to give pure imines **4.03a-c** in 55 - 88% yields.

4.5.1a Preparation of (1'S)-N-camphor-10-sulfonyl benzaldimine **4.03a**.

The camphor-10-sulfonamide **4.02** (2.3 g, 10 mmol) was treated with diethyl acetal of benzaldehyde (2.2 g, 12 mmol) at 140°C, to provide crude product, which was purified by crystallization benzene/pet.ether to give 2.8 g (88%) of pure imine **4.03a**.

M. P. : 112 -114°C.

¹H NMR : 0.9 (s, 3H, CH₃); 1.2 (s, 3H, CH₃); 1.4 (m, 1H, CH); 1.8 - 2.1 (m, 4H, CH₂); 2.35-2.45 (m, 1H, CH₂); 2.55-2.70 (m, 1H, CH₂); 3.1 (d, *J* = 15.6 Hz, 1H, CH₂); 3.7 (d, *J* = 15.6 Hz, 1H, CH₂); 7.5 - 7.7 (m, 3H, Ar); 8.0 (two d, *J* = 10.4 Hz, 2H, Ar); 9.1 (s, 1H, CH).

¹³C NMR : 19.3, 19.5, 24.7, 26.6, 42.1, 42.3, 47.6, 49.2, 58.1, 128.9, 130.9, 131.9, 134.7, 171.2, 213.6.

IR : 1730, 1610.

[α]_D²⁵ : +20.6 (c 1, CH₂Cl₂).

Analysis : M.F. C₁₇H₂₁NO₃S

Calculated : C, 63.92; H, 6.63; N, 4.39; S, 10.02.

Found : C, 63.98; H, 6.72; N, 4.50; S, 10.35.

4.5.1b Preparation of (1'S)-N-Camphor-10'-sulfonyl *p*-tolualdimine 4.03b.

The camphor-10-sulfonamide **4.02** (2.3 g, 10 mmol) was treated with diethyl acetal of *p*-tolualdehyde (2.3 g, 12 mmol) at 140°C, to provide crude product, which was purified by crystallization benzene/pet.ether to give 2.4 g (72%) of pure imine **4.03b**.

M. P. : 79 - 80°C.

¹H NMR : 0.90 (s, 3H, CH₃); 1.15 (s, 3H, CH₃); 1.45 (m, 1H, CH); 1.7 - 2.2 (m, 4H, CH₂); 2.35 (m, 1H, CH₂); 2.5 (s, 3H, CH₃); 2.55-2.80 (m, 1H, CH₂); 3.15 (d, *J* = 15 Hz, 1H, CH₂); 3.75 (d, *J* = 15 Hz, 1H, CH₂); 7.35 (d, *J* = 8 Hz, 2H, Ar); 7.9 (d, *J* = 8 Hz, 2H, Ar); 9.0 (s, 1H, CH).

IR : 1730, 1600.

[α]_D²⁵ : +30.3 (c 1.3, CH₂Cl₂).

4.5.1c Preparation of (1'S)-N-Camphor-10'-sulfonyl *p*-anisaldimine 4.03c.

The camphor-10-sulfonamide **4.02** (2.3 g, 10 mmol) was treated with diethyl acetal of *p*-anisaldehyde (2.5g, 12 mmol) at 140°C, to provide the imines **4.03c** as an oil (2.1 g, 55 %).

¹H NMR : 0.85 (s, 3H, CH₃); 1.15 (s, 3H, CH₃); 1.4 (m, 1H, CH); 1.65 - 2.2 (m, 4H, CH₂); 2.3-2.7 (m, 2H, CH₂); 3.05 (d, *J* = 16 Hz, 1H, CH₂); 3.6 (d, *J* = 16 Hz, 1H, CH₂); 3.85 (s, 3H, OCH₃); 7.0 (d, *J* = 8 Hz, 2H, Ar); 7.9 (d, *J* = 8 Hz, 2H, Ar); 8.9 (s, 1H, CH).

IR : 1730, 1600.

[α]_D²⁵ : +24.9 (c 2.5, CH₂Cl₂).

4.5.2 General procedure for the preparation of β-lactams 4.05a-e & 4.06a-e.

A solution of the acid chloride **4.04a-c** (1.4 mmol) in dry CH₂Cl₂ (20 mL) was slowly added to a solution of imines **4.03a-c** (1.2 mmol) and triethylamine (6 mmol) in CH₂Cl₂ (15 mL) at -23°C. The reaction mixture was then allowed to warm-up to room temperature and stirred further for 15 h. It was then washed successively with water (2 x 15 mL), satd. NaHCO₃ (10 mL), brine (10 mL) and dried (Na₂SO₄). The organic solvent was removed by distillation and the

residue was passed through short silica gel column to get diastereomeric mixture of β -lactams **4.05a-e** & **4.06a-e** in 43-77% yields. The major diastereomers **4.05a-e** were isolated by crystallization from pet. ether/ acetone.

4.5.2a Preparation of (3*R*, 4*S*, 1'*S*)-1-(Camphor-10-sulfonyl)-3-phenoxy-4-phenyl-azetidin-2-one **4.05a**.

The imine **4.03a** (0.638 g, 2 mmol) on treatment with phenoxyacetyl chloride (0.408 g, 2.4 mmol) in the presence of triethylamine (0.7 g, 7 mmol), provided the β -lactams **4.05a** & **4.06a** (0.650 g, 72%) as a diastereomeric mixture. The pure major diastereomers **4.05a** was isolated in 62% yield by crystallization from pet. ether/actone.

M. P. : 128 - 131°C.

^1H NMR : 0.85 (s, 3H, CH_3); 1.05 (s, 3H, CH_3); 1.45-1.60 (m, 1H, CH); 1.85 - 2.2 (m, 4H, CH_2); 2.4 (m, 2H, CH_2); 3.05 (d, $J = 14.6$ Hz, 1H, CH_2); 3.55 (d, $J = 14.6$ Hz, 1H, CH_2); 5.6 (d, $J = 5$ Hz, 1H, C4H); 5.75 (d, $J = 5$ Hz, 1H, C3H); 6.7 (d, $J = 10$ Hz, 2H, Ar); 6.95 (t, $J = 10$ Hz, 1H, Ar); 7.1 - 7.65 (m, 7H, Ar).

^{13}C NMR : 19.5, 19.7, 26.1, 27.1, 42.8, 42.9, 48.9, 52.6, 59.3, 64.8, 81.6, 115.9, 122.7, 128.4, 128.5, 129.1, 129.5, 129.8, 132.6, 163.2, 215.4.

IR : 1800, 1740.

MS (m/z) : 453 (M+).

$[\alpha]_{\text{D}}^{25}$: +76.07 (c 1.6, CH_2Cl_2).

Analysis : M.F. $\text{C}_{25}\text{H}_{27}\text{NO}_5\text{S}$

Calculated : C, 66.20; H, 6.00; N, 3.09; S, 7.06.

Found : C, 65.96; H, 6.10; N, 3.24; S, 7.43.

4.5.2b Preparation of (3*R*, 4*S*, 1'*S*)-3-Benzoyloxy-1-(camphor-10-sulfonyl)-4-phenylazetidin-2-one **4.05b**.

The imine **4.03a** (0.382 g, 1.2 mmol) on treatment with benzyloxyacetyl chloride (0.257 g, 1.4 mmol) in the presence of triethylamine (0.4 g, 4 mmol), provided the β -lactams **4.05b** &

4.06b (0.435 g, 77%) as a diastereomeric mixture. The pure major diastereomer **4.05b** was isolated in 56% yield by crystallization from pet. ether/actone.

M. P. : 122 - 124 °C.

¹H NMR : 0.81 (s, 3H, CH₃); 1.05 (s, 3H, CH₃); 1.45 (m, 1H, CH); 1.8 - 2.2 (m, 4H, CH₂); 2.35 (m, 2H, CH₂); 3.05 (d, *J* = 15 Hz, 1H, CH₂); 3.45 (d, *J* = 15 Hz, 1H, CH₂); 4.25 (d, *J* = 10 Hz, 1H, CH₂); 4.40 (d, *J* = 10 Hz, 1H, CH₂); 5.20 (d, *J* = 5 Hz, 1H, C4H); 5.51 (d, *J* = 5 Hz, 1H, C3H); 6.90 - 7.50 (m, 10H, Ar).

¹³C NMR : 19.60, 19.66, 24.8, 27.1, 42.5, 42.7, 48.7, 51.8, 58.6, 64.4, 73.0, 83.6, 128.1, 128.4, 128.5, 128.7, 129.1, 132.8, 135.9, 164.3, 215.0.

IR : 1800, 1740.

[α]_D²⁵ : +119.3 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₆H₂₉NO₅S :

Calculated : C, 66.79; H, 6.25; N, 3.00; S, 6.86.

Found : C, 66.67; H, 6.34; N, 3.20; S, 7.12.

4.5.2c Preparation of (3*R*, 4*S*, 1'*S*)-3-Acetoxy-1-(camphor-10-sulfonyl)-4-phenylaze-tidin-2-one **4.05c**.

The imine **4.03a** (0.382 g, 1.2 mmol) on treatment with acetoxyacetyl chloride (0.190 g, 1.4 mmol) in the presence of triethylamine (0.4 g, 4 mmol), provided the β-lactams **4.05c** & **4.06c** (0.320 g, 64%) as a diastereomeric mixture. The pure major diastereomer **4.05c** was obtained in 42% yield by crystallization from pet. ether/actone.

M. P. : 144 - 146 °C.

¹H NMR : 0.9 (s, 3H, CH₃); 1.0 (s, 3H, CH₃); 1.45 (m, 1H, CH); 1.7 (s, 3H, COCH₃); 1.8 - 2.3 (m, 5H, CH₂); 2.45 (m, 1H, CH₂); 3.05 (d, *J* = 14.6 Hz, 1H, CH₂); 3.95 (d, *J* = 14.6 Hz, 1H, CH₂); 5.5 (d, *J* = 5 Hz, 1H, C4H); 6.2 (d, *J* = 5 Hz, 1H, C3H); 7.4 (m, 5H, Ar).

¹³C NMR : 19.5, 19.8, 26.2, 27.2, 42.7, 42.9, 49.1, 52.5, 59.3, 64.6, 128.1, 128.5, 129.1, 132.3, 162.6, 169.5, 216.0.

IR : 1800, 1740.

$[\alpha]_D^{25}$: -22.9 (c 1, CH₂Cl₂).

Analysis : M.F. C₂₁H₂₅NO₆S

Calculated : C, 60.12; H, 6.01; N, 3.34; S, 7.63.

Found : C, 60.25; H, 6.14; N, 3.64; S, 7.40.

4.5.2d Preparation of (3*R*, 4*S*, 1'*S*)-4-*p*-Anisyl-1-(camphor-10-sulfonyl)-3-phenoxy-azetidin-2-one 4.05d.

The imine 4.03c (0.420 g, 1.2 mmol) on treatment with phenoxyacetyl chloride (0.238 g, 1.4 mmol) in the presence of triethylamine (0.4 g, 4 mmol), provided the β-lactams 4.05d & 4.06d (0.250 g, 43%) as a diastereomeric mixture. The pure major diastereomer 4.05d was isolated in 27% yield by crystallization from pet. ether/actone.

M. P. : 138 -140°C.

¹H NMR : 0.9 (s, 3H, CH₃); 1.05 (s, 3H, CH₃); 1.40-1.65 (m, 1H, CH); 1.85 - 2.25 (m, 4H, CH₂); 2.3-2.5 (m, 2H, CH₂); 3.0 (d, *J* = 15 Hz, 1H, CH₂); 3.5 (d, *J* = 15 Hz, 1H, CH₂); 3.8 (s, 3H, OCH₃); 5.6 (d, *J* = 5.3 Hz, 1H, C4H); 5.7 (d, *J* = 5.3 Hz, 1H, C3H); 6.7 - 7.5 (m, 9H, Ar).

¹³C NMR : 19.7, 19.8, 24.9, 27.2, 42.7, 42.9, 48.9, 52.1, 55.4, 58.8, 64.5, 82.2, 114.0, 115.9, 122.8, 124.1, 129.6, 130.2, 160.4, 163.6, 215.4.

IR : 3020, 1800, 1740.

$[\alpha]_D^{25}$: +17.89 (c 0.6, CH₂Cl₂).

Analysis : M.F. C₂₆H₂₉NO₆S

Calculated : C, 64.57; H, 6.05; N, 2.90; S, 6.62.

Found : C, 64.71; H, 6.06; N, 3.10; S, 6.89.

4.5.2e Preparation of (3*R*, 4*S*, 1'*S*)-1-(Camphor-10-sulfonyl)-3-phenoxy-4-*p*-tolylaze-tidin-2-one 4.05e.

The imine 4.03b (0.400 g, 1.2 mmol) on treatment with phenoxyacetyl chloride (0.238 g, 1.4 mmol) in the presence of triethylamine (0.4 g, 4 mmol), provided the β-lactams 4.05e & 4.06e

(0.385 g, 69%) as a diastereomeric mixture. The pure major diastereomers **4.05e** was isolated by crystallization from pet. ether/actone.

M. P. : 186 - 188°C.

$^1\text{H NMR}$: 0.9 (s, 3H, CH_3); 1.05 (s, 3H, CH_3); 1.5 (m, 1H, CH); 1.75 - 2.2 (m, 5H, CH_2); 2.35 (s, 3H, CH_3); 2.8 (m, 1H, CH_2); 3.0 (d, $J = 14$ Hz, 1H, CH_2); 3.5 (d, $J = 14$ Hz, 1H, CH_2); 5.6 (d, $J = 5$ Hz, 1H, C4H); 5.7 (d, $J = 5$ Hz, 1H, C3H); 6.75 (d, $J = 8$ Hz, 2H, Ar); 6.95 (t, $J = 8$ Hz, 1H, Ar); 7.10 - 7.45 (m, 6H, Ar).

IR : 1800, 1740.

$[\alpha]_{\text{D}}^{25}$: +50.33 (c 0.18, CHCl_3).

Analysis : M. F. : $\text{C}_{26}\text{H}_{29}\text{NO}_5\text{S}$

Calculated : C, 66.79; H, 6.25; N, 3.00; S, 6.86.

Found : C, 66.94; H, 6.47; N, 2.96; S, 7.11.

4.5.3 Procedure for the preparation of α -hydroxy ester **4.07** & **4.08**.

The cleavage of the N1-C4 bond was carried out by refluxing an ethanolic solution of the β -lactams **4.05b** & **4.05c** (0.43 mmol) in presence of Pd/C (15 mg) for 12 h. The reaction mixture was filtered to remove Pd/C; the filtrate, on removal of ethanol, gave the crude amides, which were used for further reaction without purification. These crude amides were refluxed in ethanolic HCl solution for 8 h. The ethanol was removed by distillation and the residue was purified by column chromatography (silica gel, 60 - 120, pet.-ether/acetone) to give pure α -hydroxy esters **4.07** (70%) & **4.08** (65%) along with the recovered chiral auxiliary, camphor-10-sulfonamide **4.02**.

4.5.3a Preparation of (2*R*)-Ethyl 2-hydroxy-3-phenylpropionate **4.07**.

A solution of β -lactam **4.05c** (0.180 g, 0.43 mmol) in EtOH (20 mL) was refluxed with Pd/C (15 mg) for 12 h. The reaction mixture was filtered to remove Pd/C, the filtrate was concentrated to remove ethanol and the residue was refluxed with satd. ethanolic HCl (10 mL) for 8 h. The removal of ethanol from the reaction mixture by distillation afford the crude product,

which was purified by column chromatography to get 0.055 g (65%) of pure ethyl ester **4.07** as a viscous oil.

^1H NMR : 1.3 (t, $J = 7$ Hz, 3H, CH_3); 2.75 (bs, 1H, OH); 3.01 (dd, $J = 5.5$ & 14 Hz, 1H, CH_2); 3.15 (dd, $J = 5.5$ & 14 Hz, 1H, CH_2); 4.25 (q, $J = 7$ Hz, 2H, CH_2); 4.45 (t, $J = 5.5$ Hz, 1H, CH); 7.17 - 7.35 (m, 5H, Ar).

^{13}C NMR : 13.9, 40.4, 61.5, 71.0, 126.6, 128.1, 129.3, 136.2, 173.9.

IR : 3100-2800, 2980, 1730.

$[\alpha]^{25}_{\text{D}}$: +21.89 (c 0.57, C_6H_6).

Analysis : M. F. $\text{C}_{11}\text{H}_{14}\text{O}_3$

Calculated : C, 68.01; H, 7.27.

Found : C, 68.36; H, 7.30.

4.5.3b Preparation of (2*R*)-Ethyl 2-benzyloxy-3-phenylpropionate **4.08**.

A solution of β -lactam **4.05b** (0.450 g, 0.97 mmol) in EtOH (20 mL) was refluxed with Pd/C (20 mg) for 12 h. The reaction mixture was filtered to remove Pd/C, the filtrate was concentrated to remove ethanol. The residue was refluxed with satd. ethanolic HCl (15 mL) for 8 h. The ethanol was removed from the reaction mixture by distillation and residue was purified by column chromatography to afford 0.190 g (70%) of pure ester **4.08** as an oil.

^1H NMR : 1.3 (t, $J = 7.5$ Hz, 3H, CH_3); 3.15 (m, 2H, CH_2); 4.2 (m, 3H, CH_2 & CH); 4.4 (d, $J = 12.5$ Hz, 1H, CH_2); 4.7 (d, $J = 12.5$ Hz, 1H, CH_2); 7.1 - 7.45 (m, 10H, Ar).

^{13}C NMR : 14.1, 39.2, 60.8, 72.3, 79.2, 126.1, 127.7, 128.1, 128.3, 129.4, 136.9, 137.2, 172.8.

IR : 2990, 1730.

$[\alpha]^{25}_{\text{D}}$: +5.18 (c 1.2, CH_2Cl_2).

Analysis : M. F. $\text{C}_{18}\text{H}_{20}\text{O}_3$

Calculated : C, 76.02; H, 7.09.

Found : C, 76.17; H, 7.30.

4.5.4 Preparation of (2*R*)-2-Benzoyloxy-3-phenylpropionic acid **4.09**.

To a solution of ester **4.08** (0.190 g, 0.7 mmol) in methanol (10 mL), a solution of KOH (1.0 g) in methanol (10 mL) was added and it was stirred at room temperature for 8 h. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The aqueous layer was acidified with 20% aq. HCl and extracted with ethyl acetate (3 x 10 mL). The ethyl acetate extract was washed with brine (10 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to get crude product, which on purification by column chromatography afforded 0.160 g (93%) of pure acid **4.09** as an oil.

¹H NMR : 3.15 (m, 2H, CH₂); 4.2 (m, 1H, CH); 4.4 (d, *J* = 12.9 Hz, 1H, CH₂); 4.7 (d, *J* = 12.9 Hz, 1H, CH₂); 7.15 - 7.45 (m, 10H, Ar); 9.0 (bs, 1H, OH).

¹³C NMR : 38.8, 72.7, 78.5, 126.7, 127.7, 127.8, 128.3, 129.4, 136.5, 136.6, 176.1.

IR : 3500 - 3000, 1720.

MS (m/z) : 256 (M⁺)

[α]_D²⁵ : +79.10 (c 2.37, EtOH).

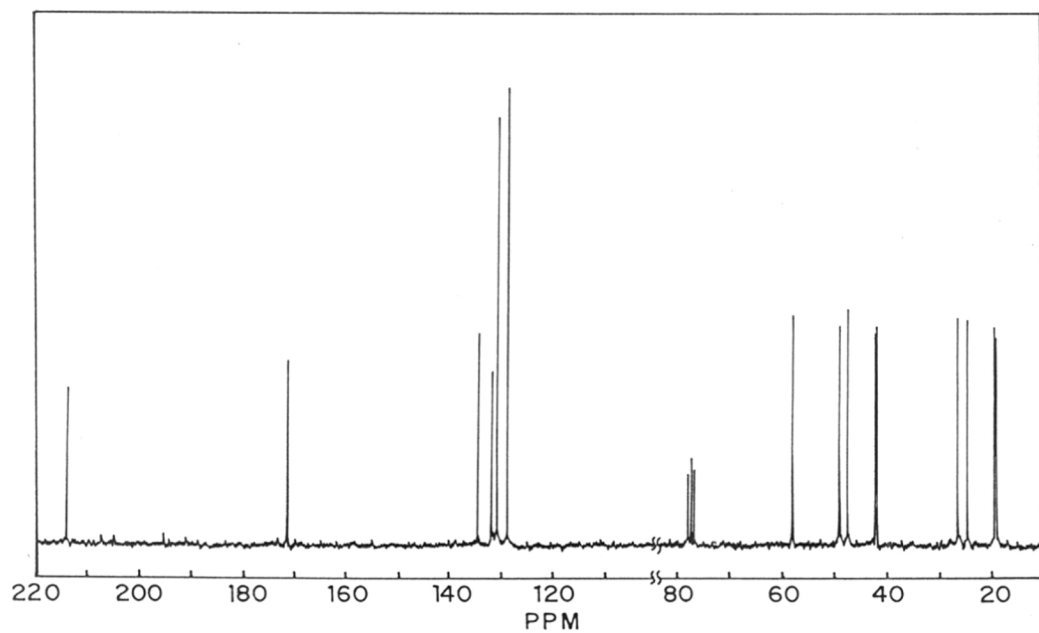
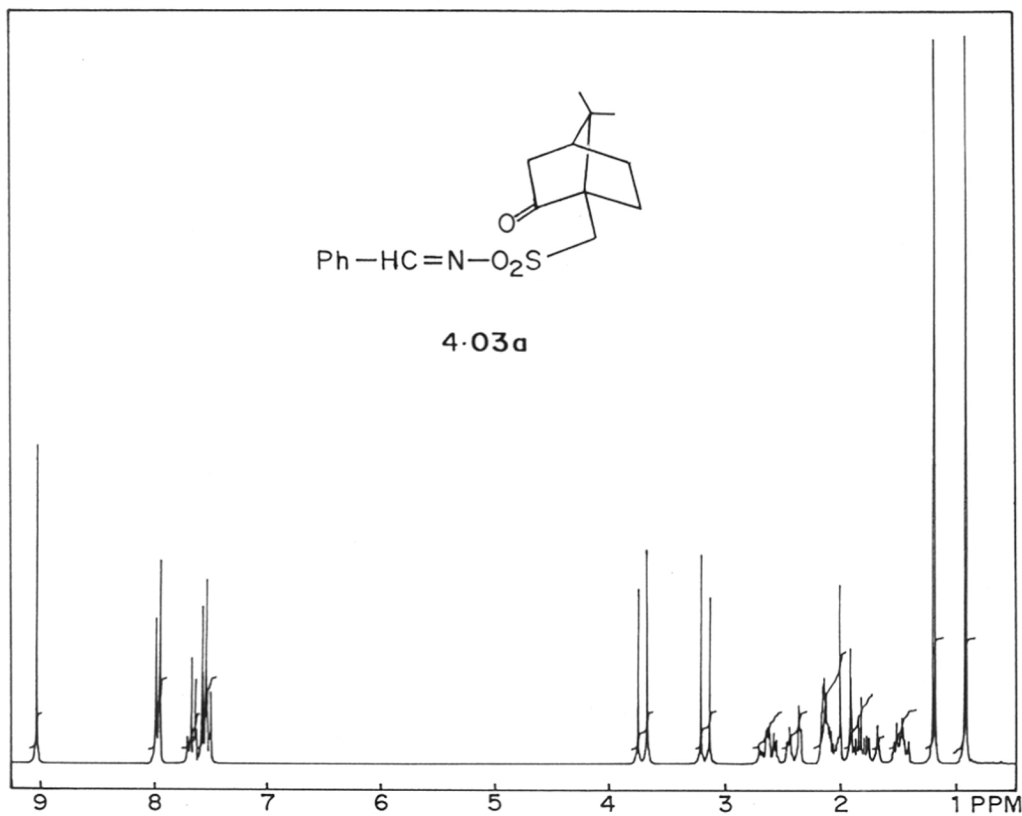
Analysis : M. F. C₁₆H₁₆O₃

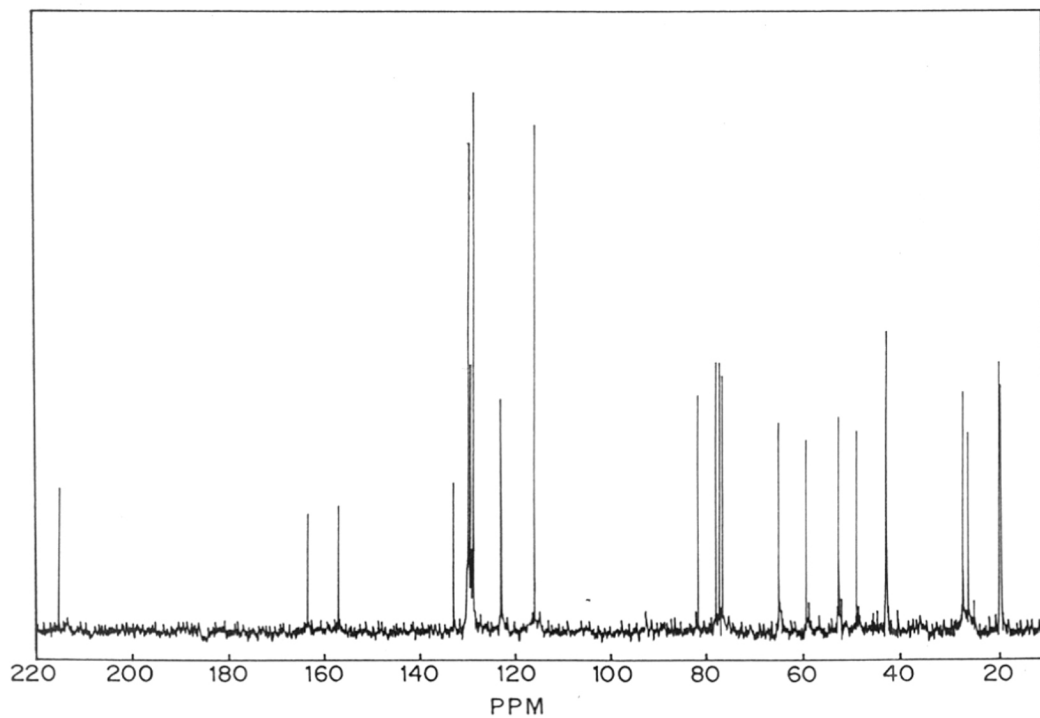
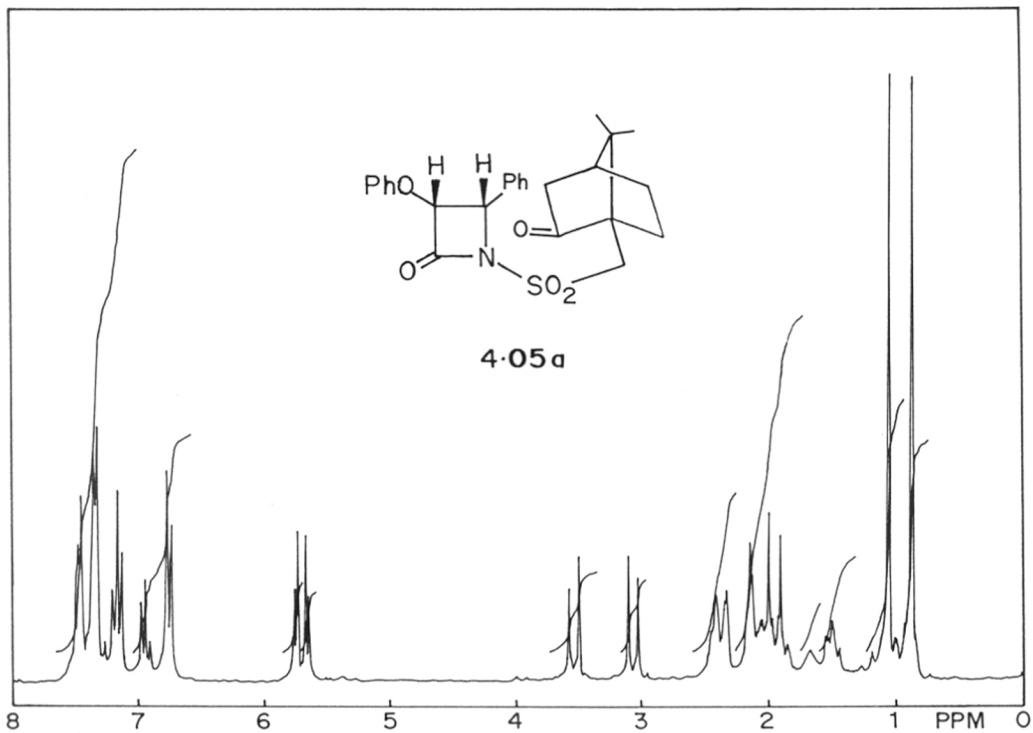
Calculated : C, 74.97; H, 6.30.

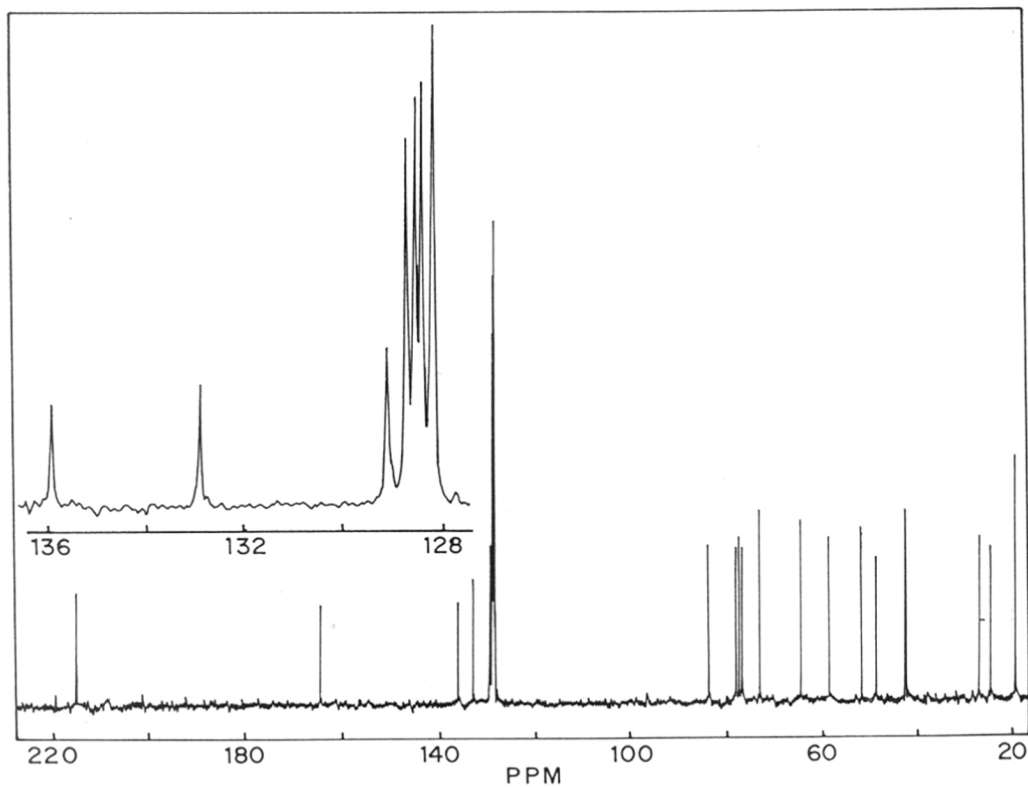
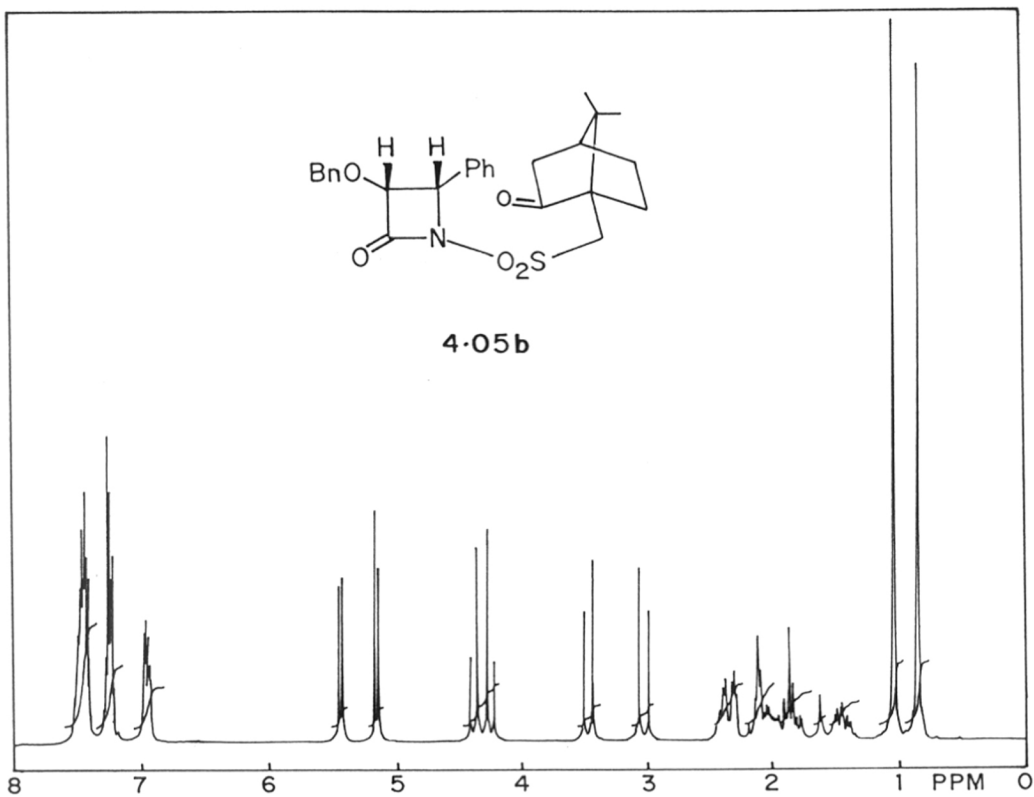
Found : C, 74.83; H, 6.52.

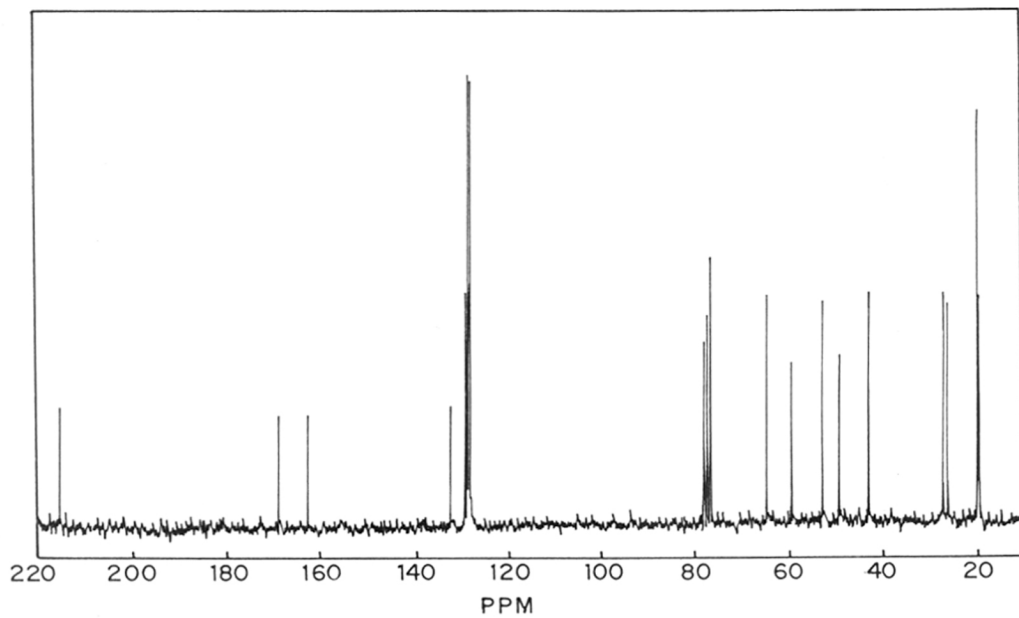
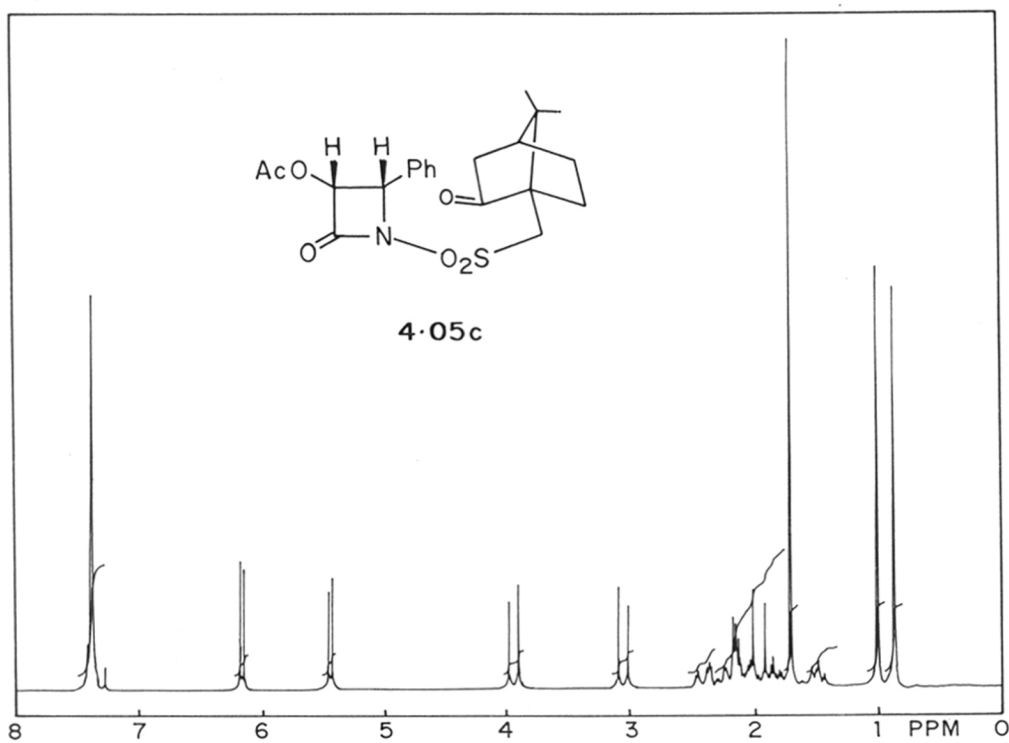
4.6 REFERENCES

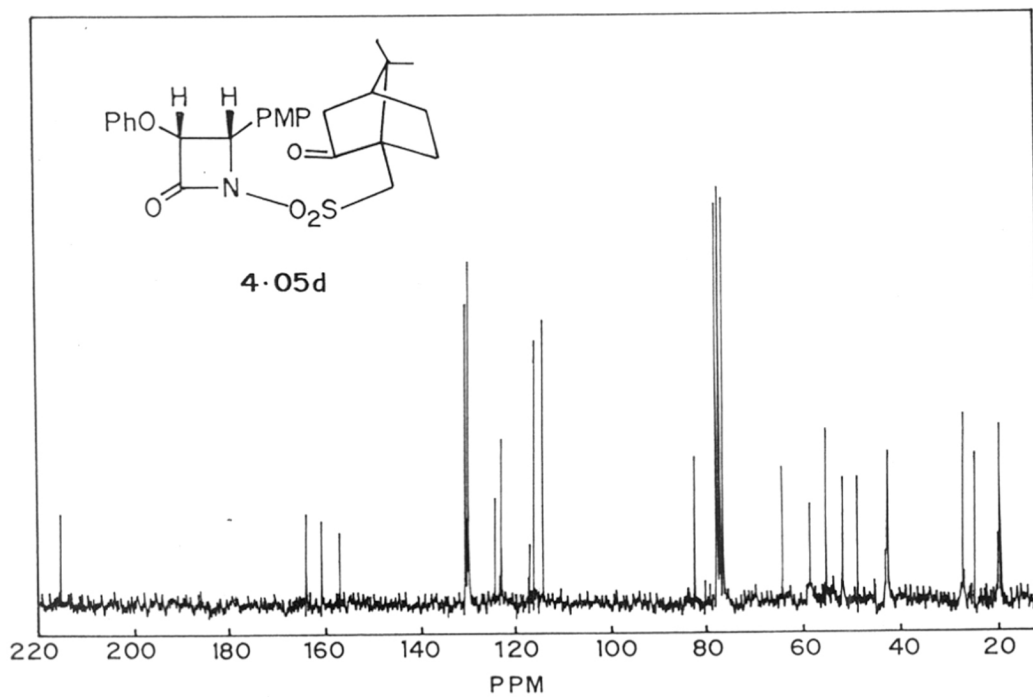
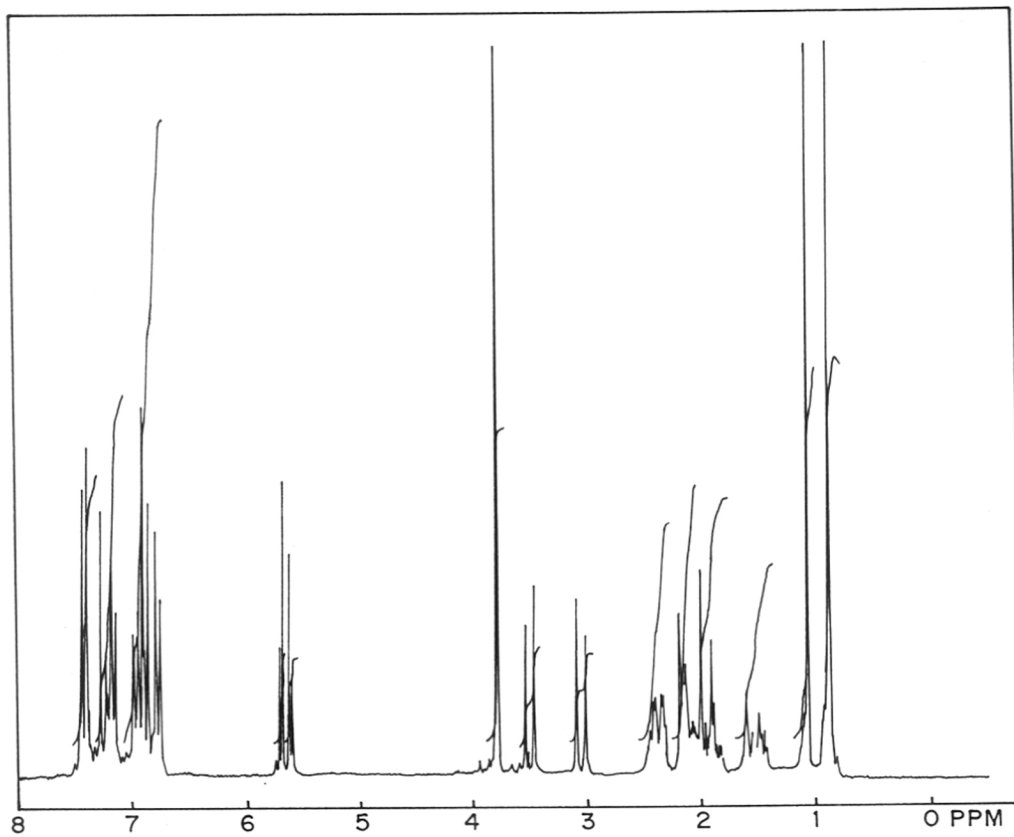
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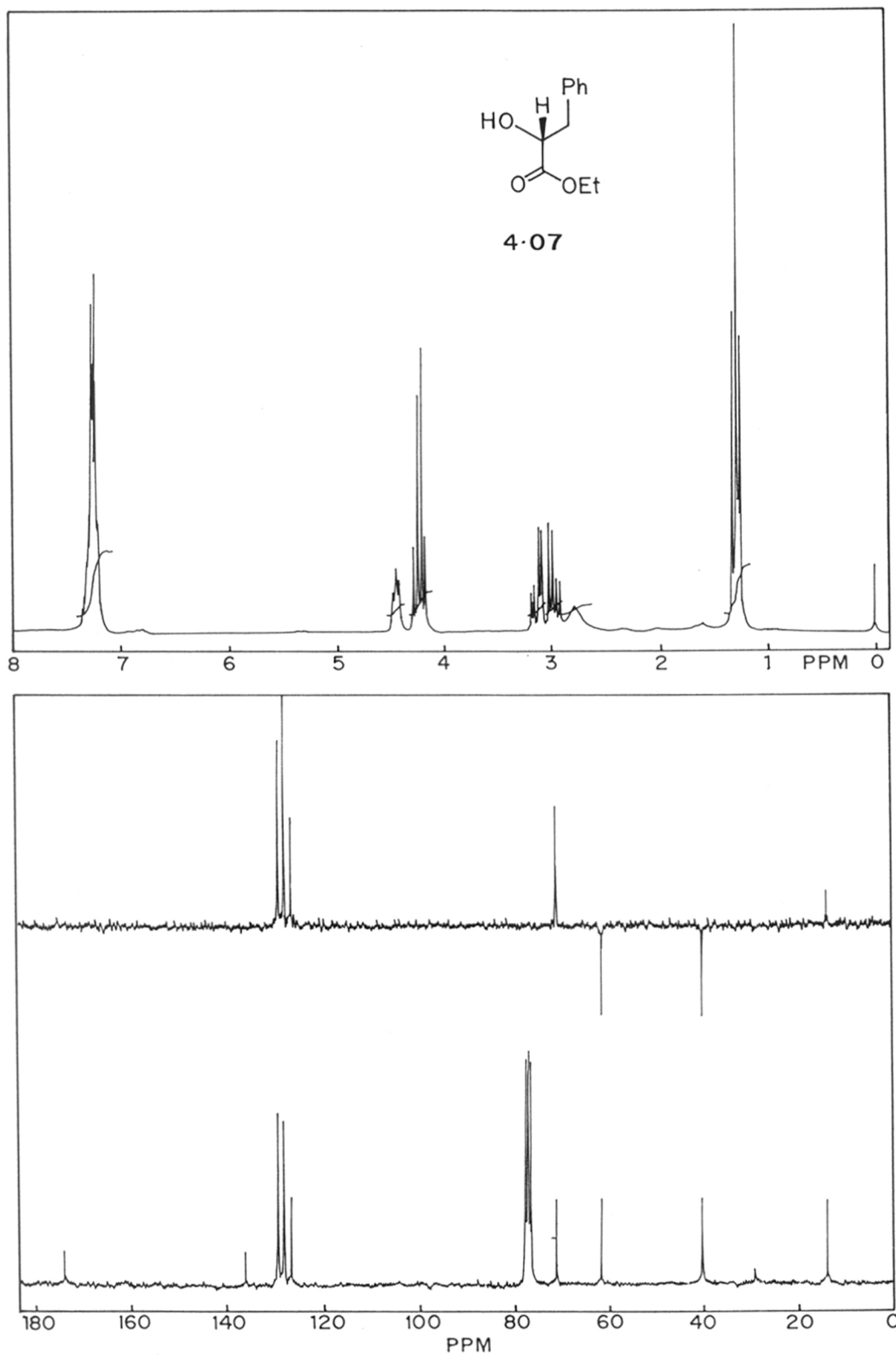


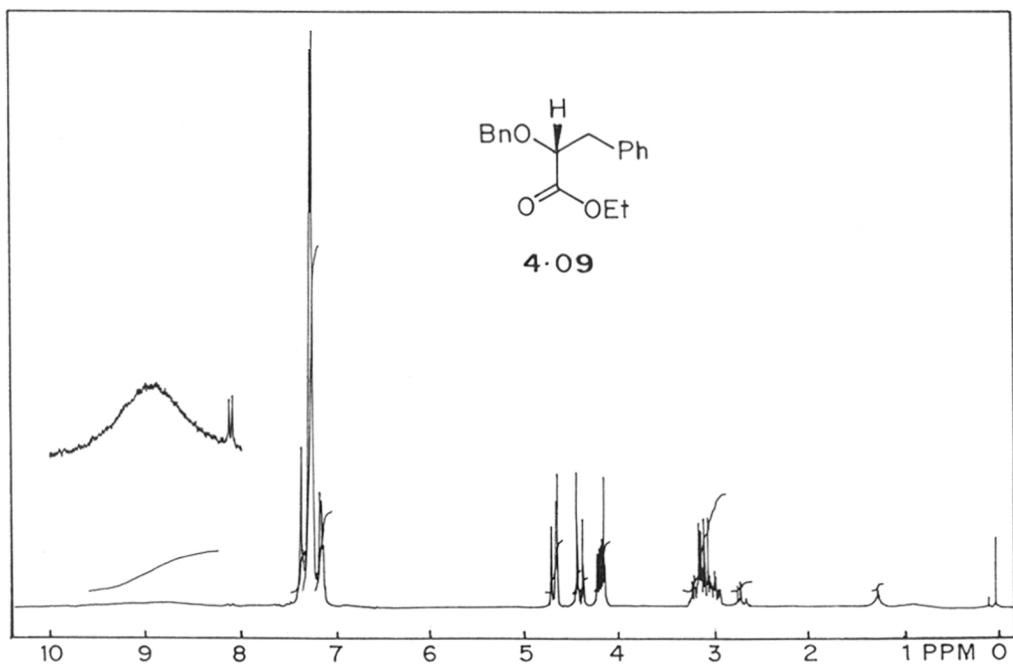
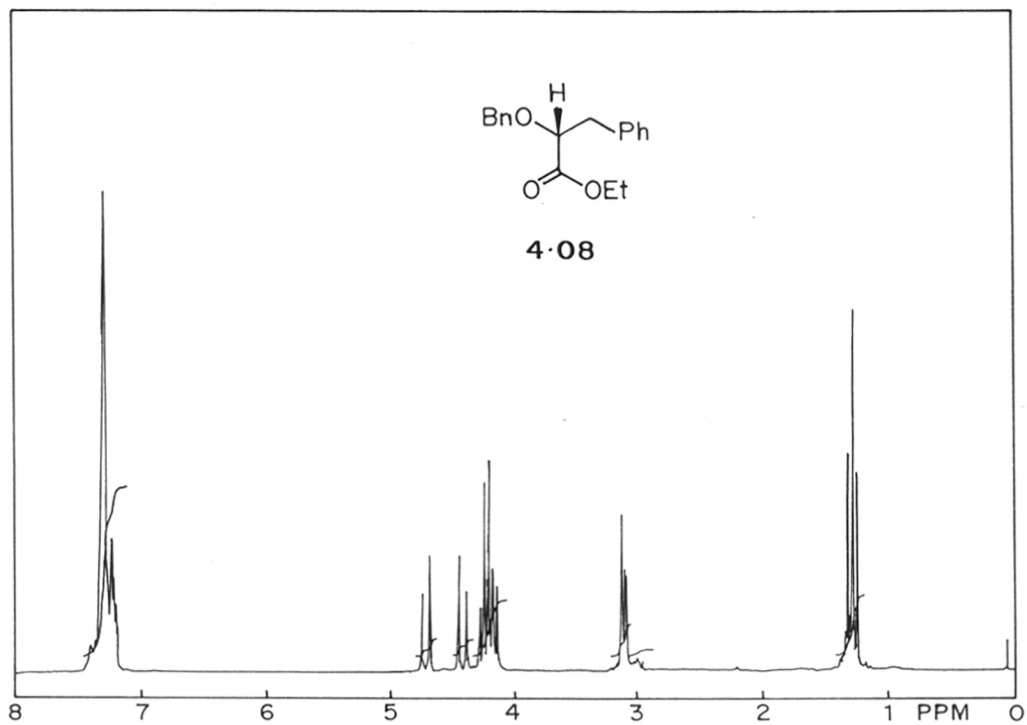












CHAPTER V

PREPARATION OF N-UNSUBSTITUTED β -LACTAMS

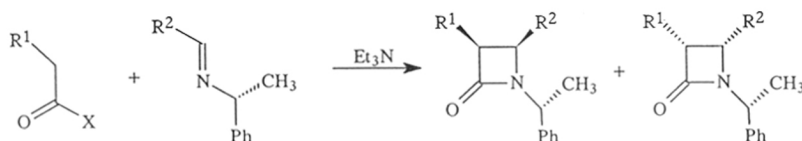
Part of this work has been published in Acta. Cryst. C (in press)
Tetrahedron (to be communicated)

5.1 INTRODUCTION

The β -lactams with easily deprotectable N-substituents are important building blocks for the synthesis of β -lactam antibiotics and β -amino acids.¹ The use of an easily deprotectable chiral auxiliary attached to the nitrogen of an imine provides the flexibility for the introduction of the various substituents at C3 and C4 positions of the β -lactam ring. A poor diastereoselectivity in ketene-imine cycloaddition has been reported by using an amine as a chiral auxiliary, except in very few cases.² The poor selectivity may be due to the presence of additional atoms, nitrogen being in between the chiral center and the newly formed carbon-carbon bond in the zwitterionic intermediate.³ Following is the brief review on the use of chiral amines in diastereoselective synthesis of β -lactam *via* ketene-imine cycloaddition.

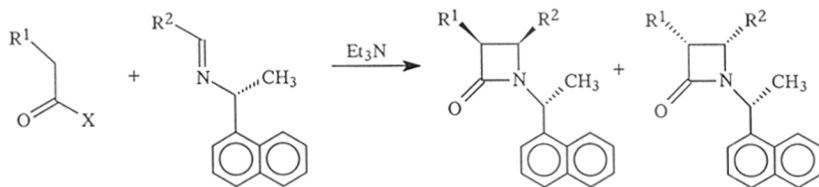
The readily available optically pure α -methylbenzylamine has been used as the chiral amine in the β -lactam formation (see Chapter 1). A maximum diastereomeric ratio of 90 : 10 was obtained in this reaction when phthalimidoacetyl chloride was used.⁴ This chiral auxiliary can be removed by reduction with Na/liq.NH₃ or treating it with potassium persulfate (Scheme 5.01).

Scheme 5.01



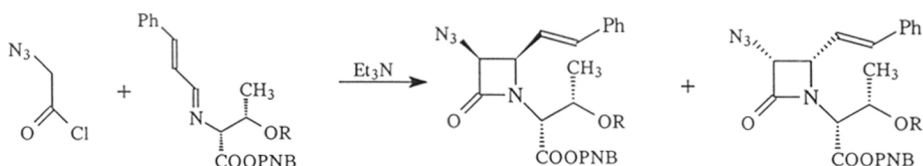
The use of optically pure (R)-(+)-1-(1'-Naphthyl)ethylamine as a chiral template in the β -lactam formation has been reported to give similar results.⁵ An extensive study of this reaction carried out by G. I. George et al³ has shown that the diastereomeric ratio of the *cis* : *trans* mixture was solvent dependent (Scheme 5.02).

Scheme 5.02



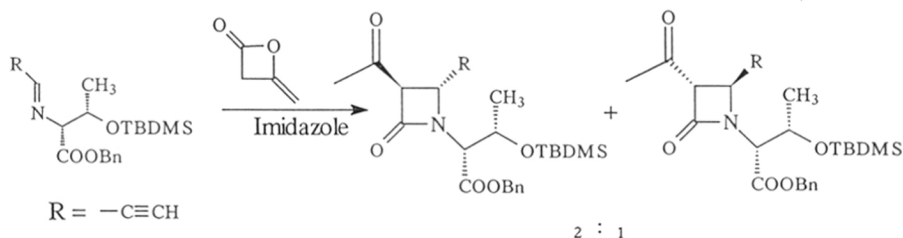
D-Threonine as a chiral amine component of imines has been used in the ketene-imine reaction (Scheme 5.03). The diastereoselectivity for this reaction was dependent on the size of the protective group R.⁶ A high level of diastereoselectivity (9:1) was obtained with R = TBDMS.

Scheme 5.03



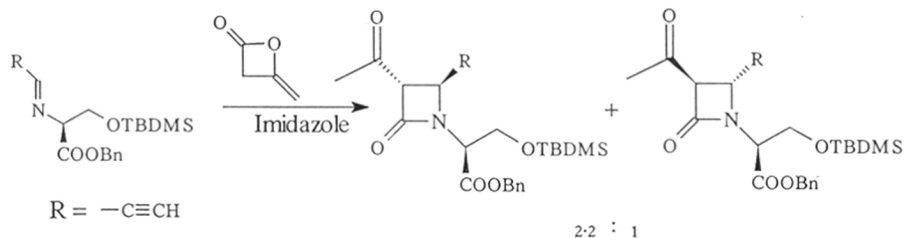
The imines derived from TBDMS protected D-threonine and propargyl aldehyde when reacted with a diketene gave only *trans* diastereomers in 2 : 1 ratio⁷ (Scheme 5.04).

Scheme 5.04



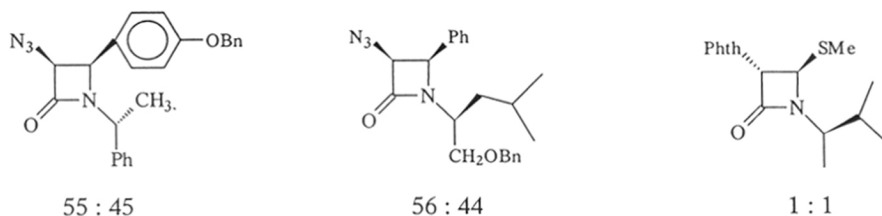
However, the propargylidene Schiff's base derived from L-serine on cycloaddition reaction with diketene provided a mixture of *cis* and *trans* β-lactams in the ratio of 1 : 2.2 (Scheme 5.05). Just and Liak have reported that the L-serine cinnamylidene Schiff's base gets racemised when azidoacetyl chloride and triethylamine were used in the β-lactam formation.⁸

Scheme 5.05



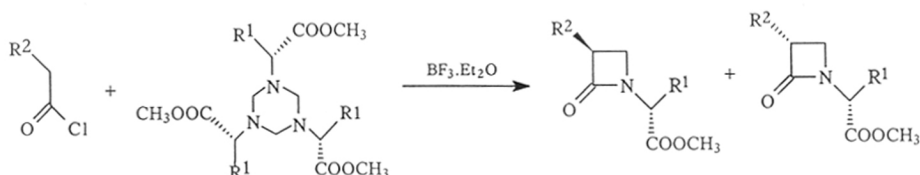
The formation of a mixture of *cis* diastereomers in the ratio of 55 : 45 has been reported by using imines derived from alanine and leucine *via* Staudinger reaction⁹ (Scheme 5.06).

Scheme 5.06



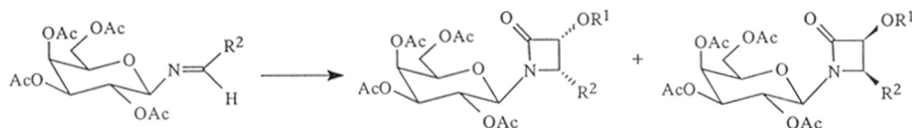
The reaction of phthalimidoacetyl chloride with chiral triazine, an imine equivalent, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ gave the β -lactams (Scheme 5.07) with high diastereoselectivity (10 : 1).¹⁰

Scheme 5.07



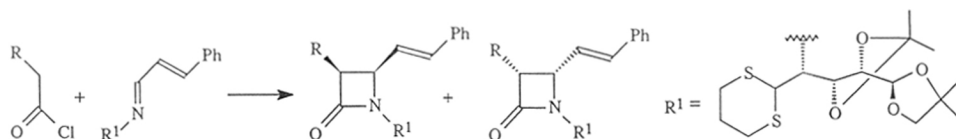
G. I. George et al have used 2,3,4,6-tetra-O-acetyl- β -D-galactose derived chiral imine in the cycloaddition reaction and reported a maximum diastereomeric ratio of 60 : 40 in *cis*- β -lactam formation¹¹ (Scheme 5.08).

Scheme 5.08



Barton et al have reported the preparation of β -lactams (Scheme 5.09) from phthalimidoacetic acid and methoxyacetic acid with the chiral Schiff's base derived from 3,4 : 5,6-di-O-isopropylidene-D-glucosamine propanedithioacetal and cinnamaldehyde.¹²

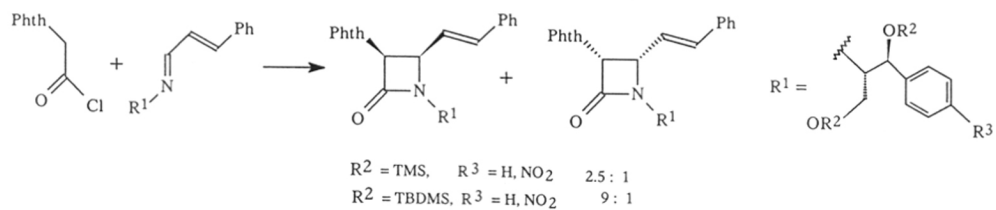
Scheme 5.09



Gunda et al have used the aldimines derived from (1*S*, 2*S*)-2-amino-1-phenyl-1,3-propanediols as the chiral amine for the β -lactam formation (Scheme 5.10). It was shown that the

size of the hydroxyl protective group plays considerable influence on the diastereoselectivity of the reaction.¹³

Scheme 5.10



5.2 PRESENT WORK

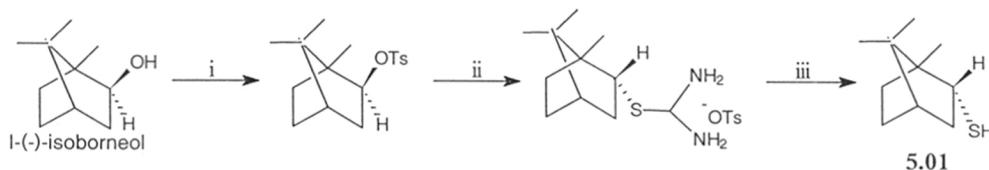
This chapter describes the synthesis of β -lactams with N1-phenylsulfinyl as a novel protective group. The removal of this group can be effected under mild conditions leading to N-unsubstituted β -lactams. This methodology was also extended for the asymmetric synthesis of β -lactams using sulfinylimines derived from 1-(-)-isoborneol.

5.3 RESULTS AND DISCUSSION

Preparation of thioborneol 5.01.

The thioborneol **5.01** was prepared from optically pure 1-(-)-isoborneol by a reported procedure¹⁴ (Scheme 5.11)

Scheme 5.11



Reagents and Conditions : i) TsCl/Py. 0°C to r. t. ii) Thiourea/*i*-PrOH, Reflux, 13 h. iii) 0.4 N NaOH/H₂O, 4 h.

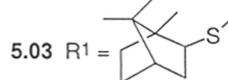
Preparation of imines 5.02 & 5.03.

The imine **5.02** was prepared in 96.5% yield by reacting thiophenol with liq. ammonia in presence of N-chlorosuccinimide followed by the reaction of benzaldehyde with the intermediate sulfinylamide as per the reported procedure.¹⁵ Following a similar procedure, imine **5.03** was also prepared in 37% yield from thiol **5.01** (Scheme 5.12).

Scheme 5.12



5.02 R¹ = Ph



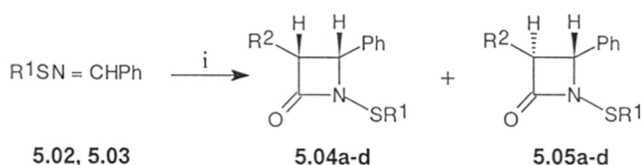
The IR spectrum of **5.02** showed a band at 1610 for C=N stretching. The ^1H NMR spectrum of **5.02** showed several multiplets between 7.15 and 7.95 for ten aromatic protons. A singlet appeared at 8.5 which was assigned to methine proton of the imine.

The ^1H NMR (90 MHz) spectrum of **5.03** showed three singlets at 0.8, 0.9 and 1.8, corresponding to *gem* dimethyl and angular methyl protons. The methylene and methine protons appeared in between 1.1 and 3.4. The aromatic protons appeared as multiplet in between 7.1 and 7.8. The methine protons of the imine appeared as a singlet at 9.8. The IR spectrum showed a band at 1600 for C=N stretching.

Preparation of β -lactams 5.04a-d & 5.05a-d.

A solution of the acid chloride in dry CH_2Cl_2 was slowly added to a solution of imines and triethylamine in CH_2Cl_2 at -23°C . The reaction mixture was then allowed to warm to room temperature and stirred further for 15 h. After the usual work-up followed the purification by column chromatography offering a mixture of *cis* and *trans* β -lactams **5.04a-d** & **5.05a-d** in 39 - 54% yields (Scheme 5.13, Table 1). The ratio of these isomers was determined from ^1H NMR spectral data. The mixture of *cis* and *trans* isomers was separated by column chromatography (silica gel, 60-120, pet. ether/actone) . The *cis* isomer **5.04c** could not be isolated in pure form.

Scheme 5.13

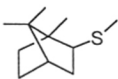


Reagents and Conditions : i) $\text{R}^2\text{CH}_2\text{COCl/Et}_3\text{N}$, -23°C .

The compound **5.05a** was chosen as a representative of *trans* β -lactam series for spectral discussion and characterization. The ^1H NMR spectrum of **5.05a** showed a doublet at 4.75 for the C4 proton of the β -lactam ring with a coupling constant value of 3 Hz. The C3 proton of the β -lactam ring appeared as a doublet at 5.2 with the *J* value of 3 Hz. This indicates that the C3 and C4 protons are *trans* to each other. A doublet was observed at 6.85 integrating for the two protons of the aromatic ring with a *J* value of 8 Hz. A triplet was observed at 7.0, integrating for one

proton. Multiplets appearing between 7.15 and 7.50 accounted for twelve aromatic protons. The IR spectrum showed a band at 1760 for the β -lactam carbonyl stretching.

Table 1. Synthesis of β -lactams **5.04a-d** & **5.05a-d** via cycloaddition reaction of imines **5.02** & **5.03** with acid chlorides.

Compound 5.04 + 5.05	R ¹	R ²	Temp. °C	Ratio of <i>trans</i> : <i>cis</i>	Yield of 5.04 + 5.05 (%)
a	Ph	PhO-	-23	66 : 34	54
b	Ph	BnO-	-23	72 : 28	53
c	Ph	AcO-	-23	55 : 45	42
d		PhO-	+28	60 : 40	39

The ^{13}C NMR spectrum of **5.05a** showed a peak at 169.0 which was assigned to the β -lactam carbonyl carbon. One of the quaternary carbons of the aromatic group attached to the oxygen atom resonated at 157.0. The other two quaternary carbon of the aromatic group appeared at 135.4 and 134.9. The rest of the aromatic carbons were observed at 129.8, 129.5, 129.3, 128.8, 127.5, 122.6, 115.7. The C3 and C4 carbons of the β -lactam ring appeared at 88.3 and 67.6 respectively. These spectral data are in good agreement with the assigned structure for this compound. This compound gave satisfactory micro analysis.

The compound **5.04b** was chosen as a representative of the *cis* β -lactam series for spectral discussion and characterization. The ^1H NMR spectrum of **5.04b** showed doublets at 4.27 and 4.31 for the benzylic protons with *J* value of 18 Hz. The C4 and C3 β -lactam protons appeared as doublets at 4.9 and 5.05. The stereochemistry of the C4 and C3 centers was established as *cis* from the coupling constant value (*J* = 4.8 Hz). The fifteen aromatic protons appeared as several multiplets between 6.90 and 7.45. This compound gave satisfactory microanalysis. The IR spectrum showed β -lactam carbonyl stretching at 1760.

The ^{13}C NMR spectrum of **5.04b** showed a peak at 170.3. The three aromatic quaternary carbons appeared at 136.2, 135.8 and 133.2. The rest of the aromatic carbons appeared at 129.9, 129.3, 129.0, 128.9, 128.7, 128.4, 128.2, 128.1. The C3 and C4 β -lactam carbons resonated at 84.6 and 66.7. The methylene carbon of the benzyloxy group was observed at 72.4. This compound gave satisfactory microanalysis.

Table 2 : ^1H NMR data for β -lactam protons **5.04a,b,d** & **5.05a-c**.

Compound. No.	Chemical shift for C4 & C3 protons of the β -lactam ring		
	C4-H	C3-H	<i>J</i> , Hz
5.04a	5.05 (d)	5.6 (d)	5.4
5.04b	4.90 (d)	5.05 (d)	4.8
5.04d	5.0 (d)	5.5 (d)	4.8
5.05a	4.75 (d)	5.20 (d)	3
5.05b	4.65 (d)	4.68 (d)	3.2
5.05c	4.7 (d)	5.5 (d)	2.7

The ^1H NMR spectrum of **5.04d** showed two singlets at 0.75 and 0.8 corresponding to the *gem* dimethyl protons. The angular methyl group of the chiral moiety appeared as a singlet at 1.1. The methylene protons and the methine protons were observed as multiplets in between 1.55 - 1.65, integrating for seven protons. The methine proton adjacent to the sulfur group appeared as a triplet at 2.95 with the coupling constant value of 7 Hz. The C4 proton and the C3 proton of the β -lactam ring appeared as doublets at 5.0 and 5.5 respectively with the coupling constant value of 4.8 Hz, which implies that the protons are *cis* to each other. The *o*-aromatic protons appeared as a doublet at 6.75 with the coupling constant value of 9 Hz, integrating for two protons. The rest of the eight aromatic protons appeared as multiplets between 6.85 and 7.4. This compound gave satisfactory microanalysis. The *trans* isomer **5.05d** could not be isolated in pure form.

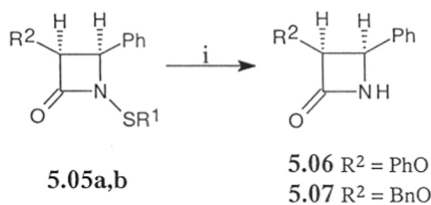
N1 Deprotection

Attempts made to cleave the thiophenyl substitution at N1 position with S-chlorination by NCS, SOCl_2 were failed. However, the thiophenyl moiety was successfully removed by reacting these compounds with thiophenol in presence of pyridine at room temperature for about 14 h to give N-unsubstituted β -lactams **5.06** & **5.07**.

Preparation of N-Unsubstituted β -lactam **5.06** & **5.07**.

To a solution of the β -lactam (0.3 mmol) in pyridine (5 mL), thiophenol (0.110 g, 1 mmol) was added and stirred for 14 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 . The reaction mixture after usual work-up gave the crude product. This crude product was column chromatographed to get the unsubstituted β -lactams **5.06** (55%) & **5.07** (97%).

Scheme 5.13



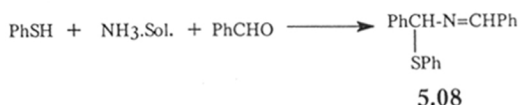
Reagents and Conditions : i) PhSH/Py, 14 h. r. t.

The ^1H NMR spectrum of **5.06** showed a doublet at 5.05 for C3 proton of the β -lactam ring with the coupling constant value of 4.8 Hz. A doublet of doublet was observed at 5.5 ($J = 4.8$ & 5.5 Hz) for the C4 proton of the β -lactam ring. A broad singlet appearing at 6.6 was assigned to the NH proton of the β -lactam. A doublet with J value of 9 Hz appearing at 6.8 and integrating for two protons, was assigned to the aromatic protons of the phenoxy group. Other aromatic protons appeared as multiplets in the region of 6.9 - 7.4, integrating for eight protons. The IR spectrum showed a broad band at 2800 - 3500 for NH stretching and a sharp band at 1770 for β -lactam carbonyl stretching. This compound gave satisfactory microanalysis. Similarly the compound **5.07** was characterized by spectral and analytical data.

Preparation of N-thiophenylbenzyl imine 5.08.

To aq. NH_3 solution (25 mL), thiophenol (1 mmol) was added dropwise at 0°C and stirred for 30 min. A solution of benzaldehyde (1.2 mmol) in CH_2Cl_2 (30 mL) was then added dropwise and the mixture was allowed to warmup to room temperature and stirred for an additional 28 h. It was then diluted with distilled water (20 mL) and extracted with CH_2Cl_2 . The usual workup procedure afforded the imine **5.08** as a pale yellow solid.

Scheme 5.14

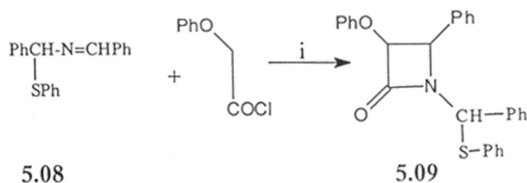


The ^1H NMR spectrum (90 MHz) of **5.08** showed a singlet at 6.0 for the methine proton adjacent to the thiophenyl group. Several multiplets appeared in between 7.3 and 7.95 which were interpreted for aromatic protons. A singlet was observed at 8.65 corresponding to the methine proton of the imine. The IR spectrum showed a band at 1630.

Preparation of β -lactam 5.09.

The imine **5.08** on treatment with phenoxyacetyl chloride in the presence of triethylamine at 0°C gave the β -lactam **5.09** in 42% yield. The crude product was purified by column chromatography and crystallized from acetone/pet. ether system.

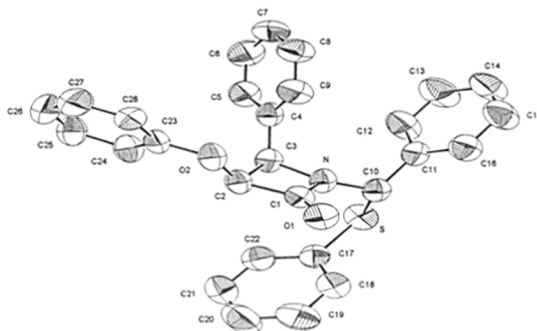
Scheme 5.15



Reagents and Conditions: i) $\text{RCH}_2\text{COCl}/\text{Et}_3\text{N}$, dry, CH_2Cl_2 .

The ^1H NMR spectrum of **5.09** showed doublets at 5.0 and 5.2 which corresponded to the C4 and C3 protons of the β -lactam ring. The coupling constant measurements ($J = 4.8$ Hz) showed that the C3 and C4 protons are *cis* to each other. A singlet appeared at 6.5 corresponded to the methine proton of the N-protective group. A doublet was observed at 6.65, integrating for two aromatic protons. A very complex multiplet appeared in the region 6.87 - 7.75 integrating for

eighteen aromatic protons. This compound gave satisfactory microanalysis. The IR spectrum showed bands at 1750 and 1440 for β -lactam carbonyl stretching and C-N stretching respectively. The structure of the compound **5.09** was also proved by single crystal X-ray analysis.



The ORTEP diagram of the β -lactam **5.09**

X-ray determination of **5.09** : Data was measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer with Mo-K α ($\lambda = 0.7093 \text{ \AA}$) radiation at 293 K. Crystal belongs to monoclinic, space group $P2_1/c$ with $a = 11.813(2)$, $b = 6.410(2)$, $c = 30.552(4) \text{ \AA}$; $V = 2312.6 \text{ \AA}^3$, $Z = 4$, $d_{\text{calc}} = 1.257 \text{ Mg m}^{-3}$, $\mu = 0.165 \text{ mm}^{-1}$. The structure was solved by direct methods using MULTAN-80 Least squares refinement of scale factor, positional and anisotropic thermal parameters for non hydrogen atoms converged to $R = 0.068$. Hydrogen atoms geometrically fixed and confirmed by difference fourier were held fixed during refinement. Structure solution and refinement were carried out using NRCVAX programs.

5.4 SUMMARY

The sulfenimines **5.02** & **5.03** derived from thiophenol and optically pure isborneol, on treatment with various acid chlorides afforded a mixture of *cis-trans* β -lactams in all the cases. The ratio of *cis-trans* isomer was determined from ^1H NMR spectral data. The N-thiophenyl group was removed by the treatment of thiophenol in pyridine at room temperature to afford N-unsubstituted β -lactams in good yield.

An imine **5.08** with N-thiophenylbenzyl group was also prepared and used for the synthesis of β -lactam **5.09** via cycloaddition reaction. The structure of the β -lactam **5.09** was established by single crystal X-ray analysis.

5.5 EXPERIMENTAL

5.5.1 Preparation of Sulfenimines 5.02.

To a 250 mL 3 necked round bottom flask fitted with a reflux condensor containing N-chlorosuccinamide (5.3 g, 40 mmol) in 150 mL of liquid NH_3 at -33°C , a solution of thiophenol (2.3 g, 21 mmol) in 5 mL of THF was added slowly and the reaction mixture was stirred at this temperature for 1 h. A solution of benzaldehyde (3.2 g, 30 mmol) in CH_2Cl_2 (10 mL) was then added and the reaction mixture was warmed to room temperature and stirred for 24 h. It was then diluted with distilled water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), washed with NaHCO_3 (15 mL), dried over Na_2SO_4 and concentrated to give viscous oil. The crude product was purified by fraction distillation to provide 4.3 g (96.5%) of pure sulfenimine 5.02, as a yellow viscous oil, b.p. $140^\circ\text{C}/3\text{ mm}$.

IR : 1610.

$^1\text{H NMR}$: 7.15 - 7.95 (m, 10H, Ar); 8.5 (s, 1H, CH).

5.5.1a Preparation of sulfenimines 5.03.

The optically pure thioborneol 5.01 was prepared in 62% yield by the reported procedure.¹⁴ To a suspension of N-chlorosuccinamide (3.2 g, 24 mmol) in liquid NH_3 (150 mL) at -33°C , a solution of thioborneol 5.01 (2.0 g, 12 mmol) in THF (5 mL) was added slowly and the reaction mixture was stirred at this temperature for 1 h. A solution of benzaldehyde (1.5 g, 15 mmol) in CH_2Cl_2 (10 mL) was then added and the reaction mixture was warmed up to the room temperature and stirred further for 24 h. After the usual workup as described for imine 5.02 and fractional distillation gave 1.2 g (37 %) of imine 5.03 as a pale yellow oil, b.p. $105\text{-}110^\circ\text{C}/8\text{ mm}$.

IR : 1600.

$^1\text{H NMR}$: 0.8 (s, 3H, CH_3); 0.9 (s, 3H, CH_3); 1.8 (s, 3H, CH_3); 1.1-3.4 (m, 8H, CH_2 & CH); 7.1-7.8 (m, 5H, Ar); 9.8 (s, 1H, CH).

5.5.2 General procedure for the preparation of β -lactams 5.04a-d & 5.05a-d.

A solution of the acid chlorides (4.5 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of imines 5.02 & 5.03 (3.5 mmol) and triethylamine (1.0 g, 10 mmol) in CH_2Cl_2 (15 mL) at -23°C . The reaction mixture was then allowed to warm to room temperature and stirred further for 15 h. It was then washed with water (2 x 15 mL), satd. NaHCO_3 (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated to give a mixture of *cis* and *trans* β -lactams 5.04a-d & 5.05a-d (0.510 g) in 39 - 54% yield. The ratio of these isomers was determined by ^1H NMR spectral data. The *cis* and *trans* mixture was separated by column chromatography and isolated as an oil.

cis-3-phenoxy-4-phenyl-1-thiophenylazetidin-2-one 5.04a.

^1H NMR : 5.05 (d, $J = 5.4$ Hz, 1H, C4H); 5.6 (d, $J = 5.4$ Hz, 1H, C3H); 6.75 (d, $J = 8$ Hz, 2H, Ar); 6.9 (t, $J = 8$ Hz, 1H, Ar); 7.05 - 7.60 (m, 12H, Ar).

^{13}C NMR : 66.9, 83.3, 115.8, 122.5, 128.3, 129.1, 129.2, 129.5, 130.6, 132.9, 135.7, 157.0, 169.8.

IR : 3040, 1760.

Analysis : M. F. $\text{C}_{21}\text{H}_{17}\text{NO}_2\text{S}$

Calculated : C, 72.60; H, 4.93; N, 4.03; S, 9.23.

Found : C, 72.35; H, 5.11; N, 3.87; S, 8.89.

trans-3-phenoxy-4-phenyl-1-thiophenylazetidin-2-one 5.05a.

^1H NMR : 4.75 (d, $J = 3$ Hz, 1H, C4H); 5.2 (d, $J = 3$ Hz, 1H, C3H); 6.85 (d, $J = 8$ Hz, 2H, Ar); 7.0 (t, $J = 8$ Hz, 1H, Ar); 7.15 - 7.50 (m, 12H, Ar).

^{13}C NMR : 67.6, 88.3, 115.7, 122.6, 127.5, 128.8, 129.3, 129.5, 129.8, 134.9, 135.4, 157.0, 169.0.

IR : 3040, 1760.

Analysis : M. F. $\text{C}_{21}\text{H}_{17}\text{NO}_2\text{S}$

Calculated : C, 72.60; H, 4.93; N, 4.03; S, 9.23.

Found : C, 72.68; H, 5.23; N, 4.31; S, 8.97.

5.5.2b Preparation of β -lactams 5.04b & 5.05b.

The imine **5.02** (0.630 g, 3 mmol) on treatment with benzyloxyacetyl chloride (0.640 g, 3.5 mmol) in the presence of triethylamine (0.900 g, 9 mmol) at -23°C , provided the β -lactam **5.04b** & **5.05b** (0.570 g, 53%) as a *cis* - *trans* mixture. The *cis* and *trans* isomers were separated by column chromatography.

cis-3-Benzyloxy-4-phenyl-1-thiophenylazetidin-2-one **5.04b**.

M. P. : $109 - 111^{\circ}\text{C}$.

^1H NMR : 4.27 (d, $J = 18$ Hz, 1H, CH_2); 4.31 (d, $J = 18$ Hz, 1H, CH_2); 4.9 (d, $J = 4.8$ Hz, 1H, C4H); 5.05 (d, $J = 4.8$ Hz, 1H, C3H); 6.90 - 7.05 (m, 2H, Ar); 7.15 - 7.45 (m, 13H, Ar).

^{13}C NMR : 66.7, 72.4, 84.6, 128.1, 128.2, 128.4, 128.7, 128.9, 129.0, 129.3, 129.9, 133.2, 135.8, 136.2, 170.3.

IR : 1760.

Analysis : M. F. $\text{C}_{22}\text{H}_{19}\text{NO}_2\text{S}$

Calculated : C, 73.10; H, 5.30; N, 3.88; S, 8.87.

Found : C, 73.36; H, 5.21; N, 3.60; S, 8.56.

trans-3-benzyloxy-4-phenyl-1-thiophenylazetidin-2-one **5.05b**.

M. P. : $138 - 140^{\circ}\text{C}$

^1H NMR : 4.65 (d, $J = 3.2$ Hz, 1H, CH) 4.68 (d, $J = 3.2$ Hz, 1H, CH) 4.65 (d, $J = 14.6$ Hz, 1H, CH_2); 4.85 (d, $J = 14.6$ Hz, 1H, CH_2); 7.05 - 7.20 (m, 2H, Ar); 7.25 - 7.5 (m, 13H, Ar).

^{13}C NMR : 67.5, 73.1, 90.1, 127.0, 128.3, 128.4, 128.5, 128.7, 128.9, 129.4, 135.5, 135.7, 136.6, 170.6.

IR : 1740.

Analysis : M. F. $\text{C}_{22}\text{H}_{19}\text{NO}_2\text{S}$

Calculated : C, 73.10; H, 5.30; N, 3.88; S, 8.87.

Found : C, 73.16; H, 5.45; N, 3.53; S, 8.96.

5.5.2c Preparation of β -lactams 5.04c & 5.05c.

The imine **5.02** (0.630 g, 3 mmol) on treatment with acetoxyacetyl chloride (0.470 g, 3.5 mmol) in the presence of triethylamine (0.900 g, 9 mmol) at -23°C , provided the β -lactam **5.04c** & **5.05c** (0.390 g) in 42% yield. The pure *trans* isomer **5.05c** was isolated as an oil by column chromatography.

trans-3-Acetoxy-4-phenyl-1-thiophenylazetidin-2-one **5.05c**.

^1H NMR : 2.15 (s, 3H, CH_3); 4.7 (d, $J = 2.7$ Hz, 1H, C4H); 5.5 (d, $J = 2.7$ Hz, 1H, C3H); 7.2 - 7.4 (m, 10H, Ar).

^{13}C NMR : 20.34, 66.84, 82.59, 127.2, 128.7, 128.9, 129.3, 129.9, 134.4, 135.3, 168.1, 169.2.

IR : 3020, 1750.

Analysis : M.F. $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$

Calculated : C, 65.16; H, 4.83; N, 4.47; S, 10.21.

Found : C, 65.43; H, 4.80; N, 4.23; S, 9.87.

5.5.2d Preparation of β -lactam 5.04d & 5.05d.

The imine **5.03** derived from the optically active isoborneol (0.682 g, 2.5 mmol) was treated with phenoxyacetyl chloride (0.510 g, 3 mmol) in the presence of triethylamine (0.910 g, 9 mmol) at 0°C , to give the β -lactams **5.04d** & **5.05d** (0.405 g, 39%) as a mixture. The pure *cis* isomer was isolated by column chromatography. However, the *trans* isomer could not be obtained in pure form.

cis-3-Phenoxy-4-phenyl-1-thiobornylazetidin-2-one **5.04d**.

M. P : $200 - 201^{\circ}\text{C}$

^1H NMR : 0.75 (s, 3H, CH_3); 0.8 (s, 3H, CH_3); 1.1 (s, 3H, CH_3); 1.55 - 1.65 (m, 7H, CH_2 & CH); 2.95 (t, $J = 7$ Hz, 1H, CH); 5.0 (d, $J = 4.8$ Hz, 1H, C4H); 5.5 (d, $J = 4.8$ Hz, 1H, C3H); 6.75 (d, $J = 9$ Hz, 2H, Ar); 6.85 (t, $J = 9$ Hz, 1H, Ar); 7.1 - 7.4 (m, 7H, Ar).

IR : 1760.

$[\alpha]_D^{27}$: +23.38 (c 1.3, CHCl_3).

Analysis : $\text{C}_{25}\text{H}_{29}\text{O}_2\text{NS}$

Calculated : C, 73.67; H, 7.17; N, 3.44; S, 7.87.

Found : C, 73.60; H, 7.26; N, 3.62; S, 8.06.

5.5.3a Preparation of 3-Phenoxy-4-phenylazetidin-2-one 5.06.

To a solution of β -lactam **5.04a** (0.100 g, 0.3 mmol) in pyridine (5 mL), thiophenol (0.110 g, 1 mmol) was added at room temperature and stirred for 14 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was washed with water (15 mL), brine (10 mL) and dried over Na_2SO_4 . It was filtered and filtrate on removal of solvent provided the crude product, which was column chromatographed to get 0.038 g (55%) of pure unsubstituted β -lactam **5.06**.

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

IR : 2800 - 3500, 1770.

Analysis : M. F. $\text{C}_{15}\text{H}_{13}\text{NO}_2$

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

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

5.5.3b Preparation of 3-Benzoyloxy-4-phenylazetidin-2-one 5.07.

To a solution of β -lactam **5.05b** (0.110 g, 0.3 mmol) in pyridine (5 mL), thiophenol (0.110 g, 1mmol) was added at room temperature and stirred for 14 h. The reaction mixture was diluted with distilled water (20 mL) and extracted with EtOAc (3 x 15 mL). The organic layer was washed with water (2 x 15 mL), brine (15 mL), dried over Na_2SO_4 . The removal of solvent by distillation furnished crude product, which was column chromatographed to provide 0.068 g (97%) of pure unsubstituted β -lactam **5.07**.

M. P. : 134 - 135°C.

^1H NMR : 4.5 (bs, 1H, CH); 4.61 (bs, 1H, CH); 4.65 (d, J = 12 Hz, 1H, CH_2); 4.85 (d, J = 12 Hz, 1H, CH_2); 6.7 (bs, 1H, OH); 7.2 - 7.5 (m, 10H, Ar).

IR : 3500 - 3000, 1770.

Analysis : M. F. $\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}$

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

Found : C, 75.58; H, 6.11; N, 5.36.

5.5.4 Preparation of the imine 5.08.

To a solution of thiophenol (0.110 g, 1 mmol) in dichloromethane (15 mL), aq. NH_3 solution (30%, 25 mL) was added drop by drop at 0°C and stirred for 30 min. Then, a solution of benzaldehyde (0.130 g, 1.2 mmol) in dichloromethane (15 mL) was added and stirred for an additional 28 h. The reaction mixture was then diluted with distilled water (20 mL) and extracted with dichloromethane (3 x 15), dried over Na_2SO_4 and concentrated to afford a pale yellow solid. This crude imine was used as such for the cycloaddition reaction.

5.5.5 Preparation of 1-(1'-thiophenylbenzy)-3-phenoxy-4-phenylazetidin-2-one 5.09.

To a mixture of imine 5.08 (0.450 g, 1.5 mmol), triethylamine (0.600 g, 6 mmol) and CH_2Cl_2 (10 mL), a solution of phenoxyacetyl chloride (0.320 g, 2 mmol) in CH_2Cl_2 (10 mL) was added with stirring at 0°C. The reaction mixture was warmed up to room temperature and stirred further for 14 h. It was diluted with CH_2Cl_2 (20 mL) and successively washed with water (2 x 15 mL), satd. NaHCO_3 (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated to crude product which was purified by column chromatography to give 0.265 g (42%) of pure β -lactam 5.09. It was crystallized from acetone/pet.ether to get analytical pure crystalline sample.

M. P. : 194°C.

^1H NMR : 5.0 (d, J = 4.8 Hz, 1H, C_4H); 5.2 (d, J = 4.8 Hz, 1H, C_3H); 6.5 (s, 1H, CH); 6.65 (d, J = 8 Hz, 2H, Ar); 6.87 (t, J = 8 Hz, 1H, Ar); 6.95 - 7.75 (m, 17H, Ar).

IR. : 1750, 1440.

Analysis : $\text{C}_{28}\text{H}_{23}\text{O}_2\text{NS}$

Calculated : C, 76.86; H, 5.30; N, 3.20; S, 7.33.

Found : C, 76.77; H, 5.36; N, 3.14; S, 7.47.

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