STEREOCONTROLLED SYNTHESIS OF SUBSTITUTED AZETIDIN-2-ONES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

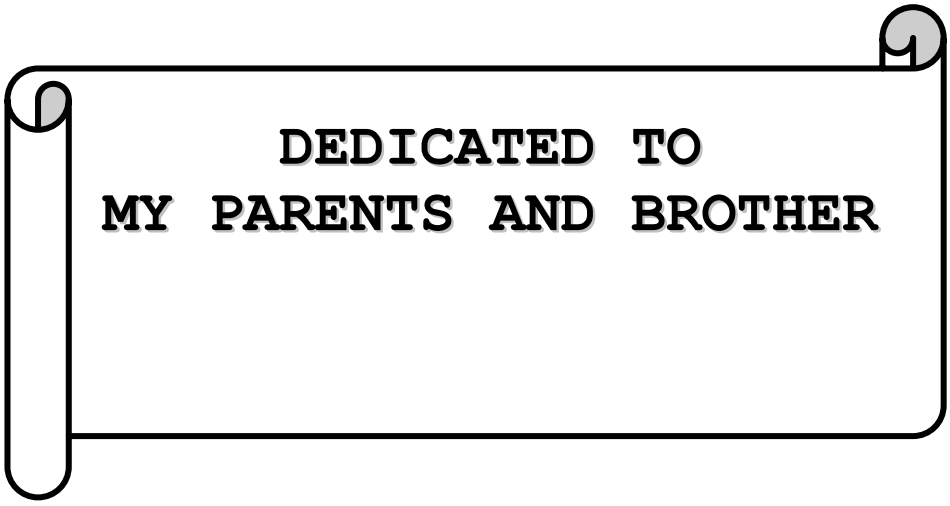
IN CHEMISTRY

D. KRISHNASWAMY

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE - 411 008


DEDICATED TO
MY PARENTS AND BROTHER

CERTIFICATE

*This is to certify that the work incorporated in the thesis entitled "**Stereocontrolled Synthesis of Substituted Azetidin-2-ones"** submitted by Mr. D. Krishnaswamy was carried out by him under my supervision at the National Chemical Laboratory. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

Date:

National Chemical Laboratory (Dr. A. R. A. S. Deshmukh)

Pune 411 008 Research Guide

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Whatever I am and whatever I intend to be in future is because of the goodwill and unstinted support that I have received from my family members, their constant encouragement helped me in pursuing the Ph.D study and no words are enough to acknowledge them

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(D. Krishnaswamy)

CONTENTS

Chapter-3

GENERAL REMARKS

1. All melting points (recorded on a Thermonik Campbell melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or chloroform, on a Perkin-Elmer Infrared Spectrometer Model 599-B and Shimadzu FTIR-8400, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200 spectrometer. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, bs = broad singlet and m = multiplet have been used to describe spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker DRX-500 instrument operating at 50.3 MHz and 125.8 MHz respectively.
5. Elemental analyses (C, H, N, S) were obtained on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer.
6. Optical rotation was measured on a JASCO-181 digital polarimeter using sodium line (5893 Å). Concentration is expressed in gm/100ml.
7. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system.
8. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck).
9. ^{1}H NMR & ^{13}C NMR spectra of the compounds are attached at the end of corresponding chapter.
10. Pet. ether refers to the petroleum fraction boiling between 60-80 °C.
11. All the dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents. Dichloromethane was dried over anhydrous P_2O_5 and stored over $4A^{o}$ molecular sieves. THF was freshly distilled over sodium benzophenone ketyl.

ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile [$(CH_3)_2C(CN)N=NC(CH_3)_2CN$]
Bn	Benzyl
CAN	Ceric Ammoniumnitrate
Cbz	Benzyloxycarbonyl
DAM	Bis(4-methoxyphenyl)methyl
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMAP	*N*, *N*'-Dimethylaminopyridine
DME	1, 2 Dimethoxyethane
DIEA	Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
Et	Ethyl
EtOAc	Ethylacetate
h	Hour
LDA	Lithium diisopropylamide
Me	Methyl
Mes	Methanesulfonyl
min	minute
MP	Melting point
Pet.ether	Petroleum ether
Ph	Phenyl
PhthN	Phthalimido
PMP	*p*-Methoxyphenyl
Pr	Propyl
PTSA	p-Toluenesulfonic acid
rt	Room temperature
TBDMS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran

TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
Bu_3SnH	Tributyltin hydride

Name of candidate : **D. Krishnaswamy**

Name of research Guide: Dr. A. R. A. S. Deshmukh

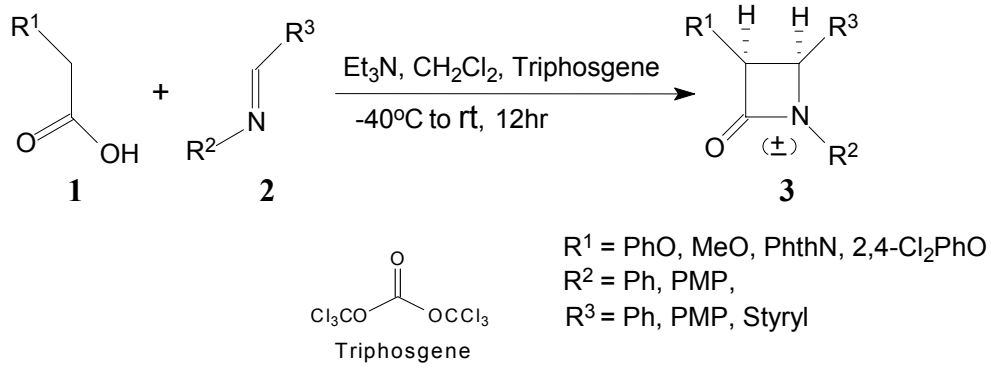
Synopsis of thesis entitled: **Stereocontrolled synthesis of substituted Azetidin-2-ones**

CHAPTER-1

Section A: Synthesis of azetidin-2-ones via Staudinger reaction using triphosgene as an acid activator

Staudinger reaction is a cycloaddition reaction between ketene and imine for synthesizing azetidin-2-ones (β-lactams). Among various methods available for β-lactam ring construction, this is the most widely used reaction. Ketenes can either be generated from acid chlorides or directly from acids using acid activators. Triphosgene, [bis (trichloromethyl) carbonate] has emerged as a very useful synthetic reagent for synthesis of various organic compounds. Being a solid, it is very easy and safe to handle compared to its gaseous congener, phosgene. We have made use of triphosgene as an acid activator for the synthesis of azetidin-2-ones (**3**) via Staudinger reaction starting form variety of acids (**1**) and imines (**2**). In all the cases the cycloaddition reaction was found to be stereoselective and gave exclusively cis β-lactams in good to excellent yields (65-95%) (**Scheme-1)**

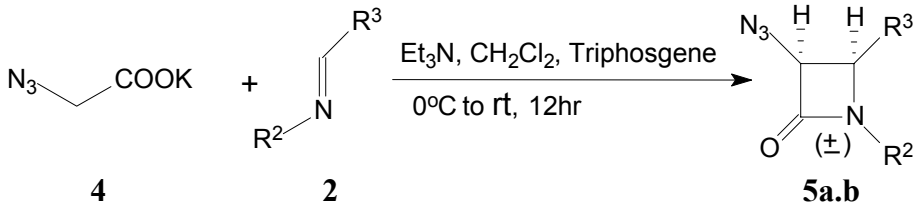
Scheme-1



Section B: Synthesis of 3-azido and 3-amino-azetidin-2-ones using triphosgene

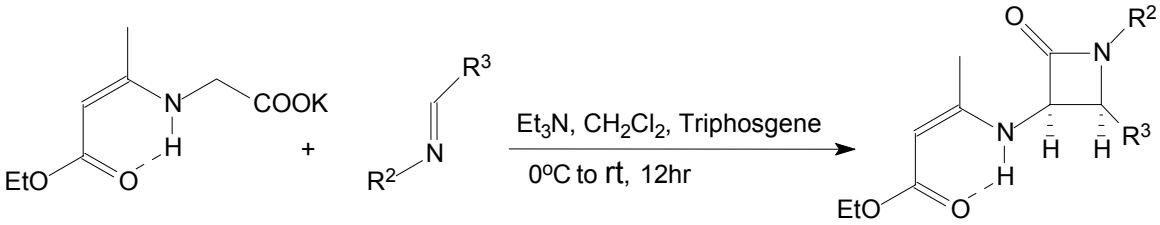
3-Azido (**5**) and 3-amino- β-lactams (**7**) were synthesized from azido acetic acid (**4**) and Dane's salt (**6**) using triphosgene as illustrated in **Scheme-2**. These β-lactams are important precursors for variety of β-lactam antibiotics.

Scheme-2



4 **2** **5a.b**

a. R^2 = Ph; R^3 = PMP
b. R^2 = PMP; R^3 = Styryl



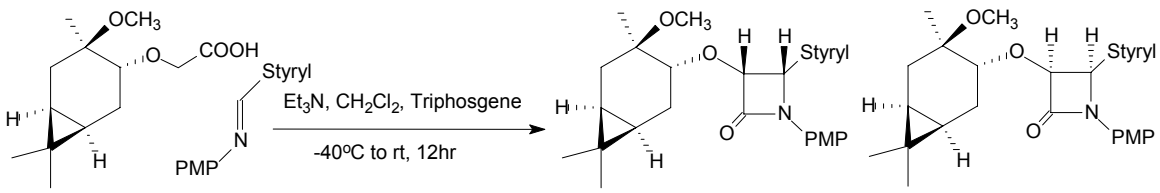
6 **2** **7a-c**

a. R^2 = PMP, R^3 = Ph
b. R^2 = PMP, R^3 = PMP
c. R^2 = PMP, R^3 = Styryl

Section C: Asymmetric synthesis of azetidin-2-ones from chiral acids using triphosgene

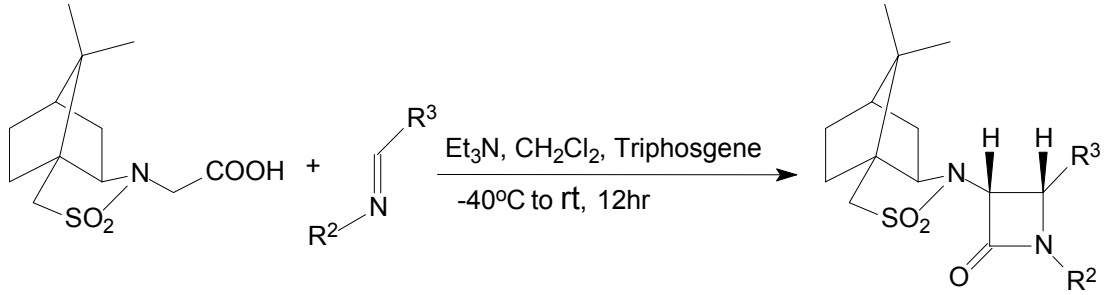
This section describes the asymmetric synthesis of azetidin-2-ones using chiral acids (**8**, **12**, **15**) derived from (+)-3-Carene, Camphorsultam, and Oxazolidinone respectively using triphosgene (**Scheme-3**, **Scheme-4** and **Scheme-5**). In case of carene acid (**8**), mixture of diastereomers (60:40) was obtained while in case of camphorsultam and oxazolidinone acids (**12** and **15**), the reaction was diastereospecific yielding single diastereomer of azetidin-2-ones (**14** and **17**)

Scheme-3



8 **9** **10** **11**

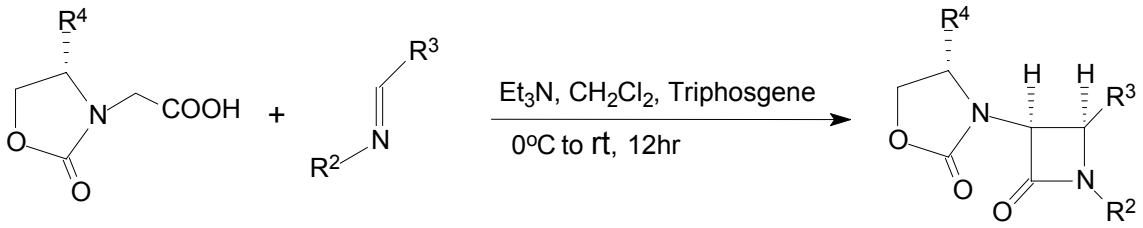
Scheme-4



12 **13** **14a-c**

a. R^2 = PMP, R^3 = Ph
b. R^2 = PMP, R^3 = PMP
c. R^2 = PMP, R^3 = Styryl

Scheme-5



15 **16** **17**

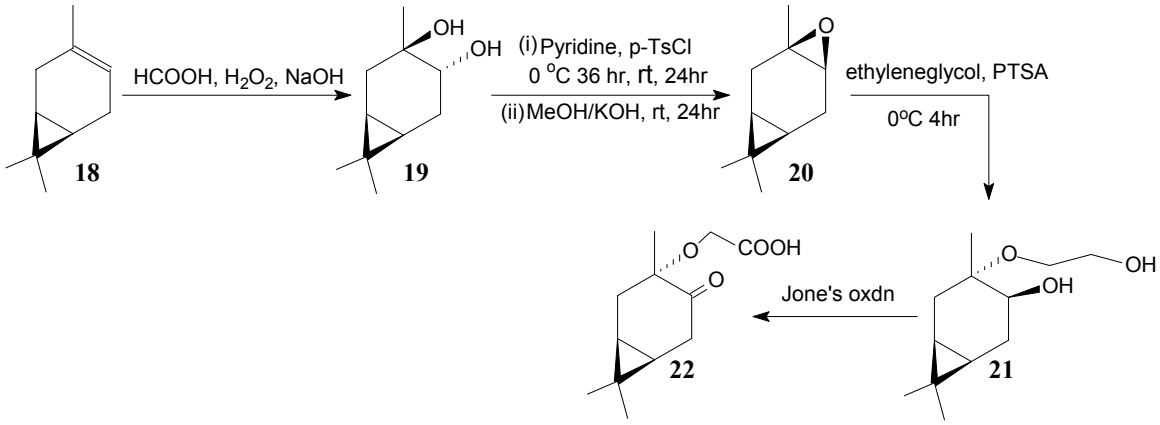
R^2 = CH_2Ph, PMP
R^3 = Ph, PMP
R^4 = Ph, CH_2Ph, *iso*-propyl

Chapter-2

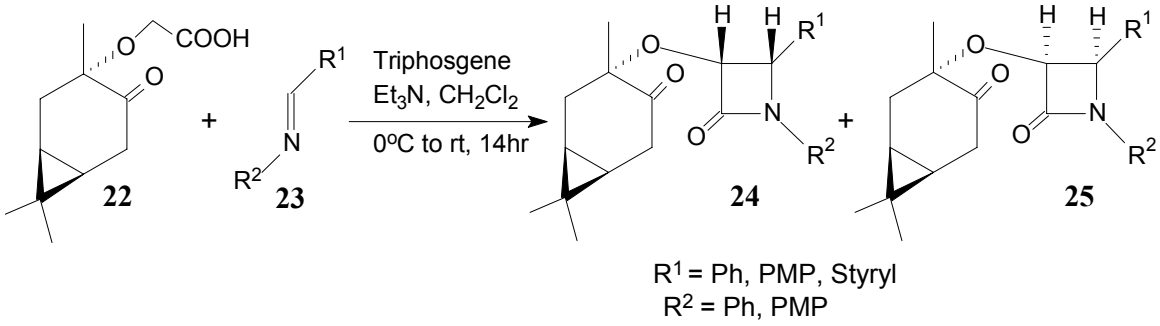
Section A: Synthesis of chiral acids from (+) 3 carene and their applications towards diastereoselective synthesis of azetidin-2-ones

This section deals with synthesize of chiral acids from (+) 3 carene. These acids were used as chiral ketene precursors to study the azetidin-2-one formation via the Staudinger reaction. β-carene oxide (**20**) obtained from (+) 3 carene (**18**) was opened with ethylene glycol to get the carene alcohol (**21**). This alcohol was transformed to chiral acid (**22**) which on treatment with imines (**23**) in presence of triphosgene underwent Staudinger reaction to give diastereomeric mixture (60:40) of azetidin-2-ones (**24** and **25**). In all cases only cis β-lactams were obtained with moderate diastereoselectivity (**Scheme-6** and **Scheme-7**)

Scheme-6

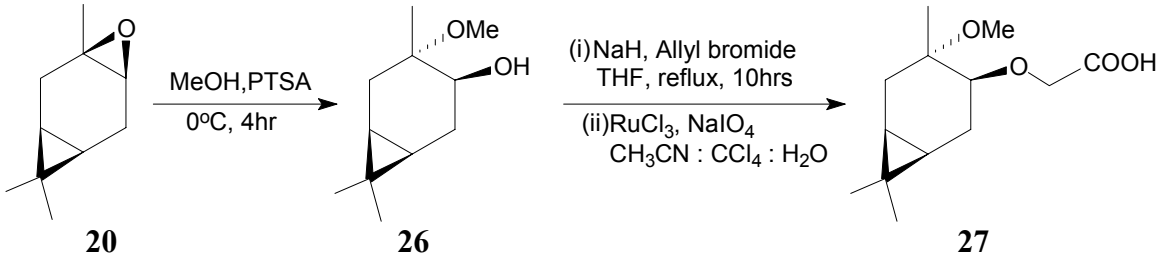


Scheme-7

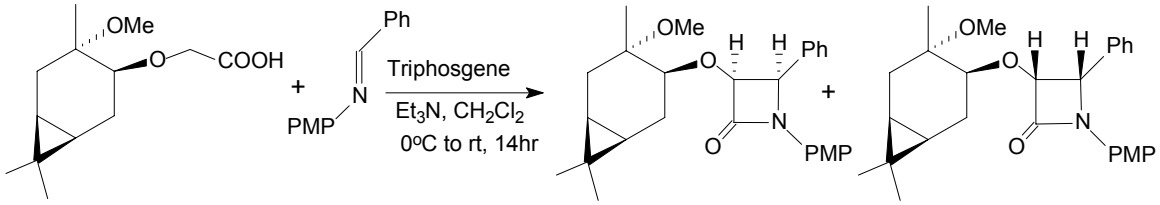


β-Carene oxide was opened with methanol to get the alcohol (**26**), which was converted to the chiral acid (**27**) as shown in **Scheme-8**. This acid when subjected to Staudinger reaction with the imine (**28**) in presence of triphosgene gave diastereomeric mixture of azetidin-2-ones (**29** and **30**) with moderate selectivity. (**Scheme-8** and **Scheme-9**)

Scheme-8



Scheme-9

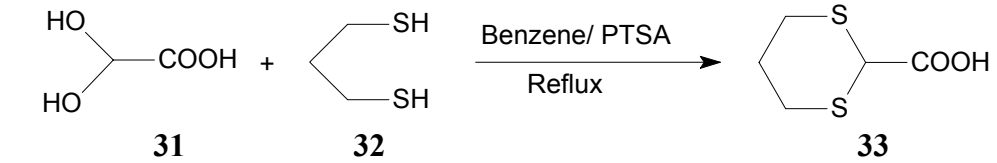


27 **28** **29** **30**

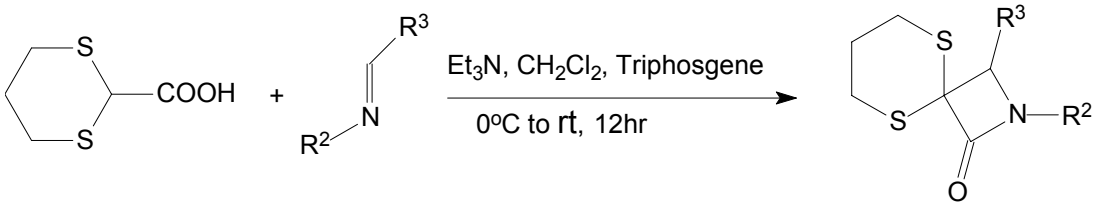
Section B: Synthesis of spiro azetidin-2-ones using acids derived from glyoxylic acid and camphor-10-sulphonic acid

This section describes the synthesis of spiro azetidin-2-ones from glyoxylic acid (**31)** and from (1S)-(+) Camphor-10-sulphonic acid (**36**). Glyoxylic acid was converted to protected acid (**33**) using propane dithiol. This acid (**33**) when subjected to Staudinger reaction with imines in presence of triphosgene gave good yields of spiro β-lactams **(35)** as illustrated in **Scheme-10**.

Scheme-10



31 **32** **33**



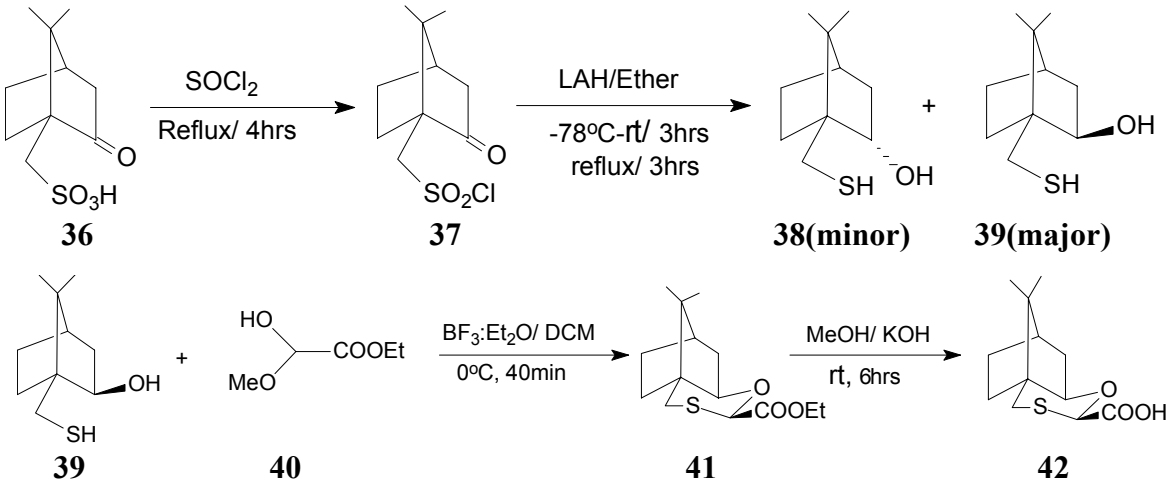
33 **34** **35**

R^2 = PMP, Ph, 4-Cl-Ph, α-MeCHPh
R^3 = Ph, PMP, Styryl

We then became interested in asymmetric synthesis of spiro β-lactams using chiral acid and to study the diastereoselectivity in the β-lactam formation. For this (1S)- (+) camphor-10-sulphonic acid **(36**) was chosen, as we thought it would provide the necessary steric bulk to give selectivity in β-lactam formation. It was converted to acid chloride (**37**) using thionyl chloride, which on reduction with LAH gave mixture of alcohols (**38** and

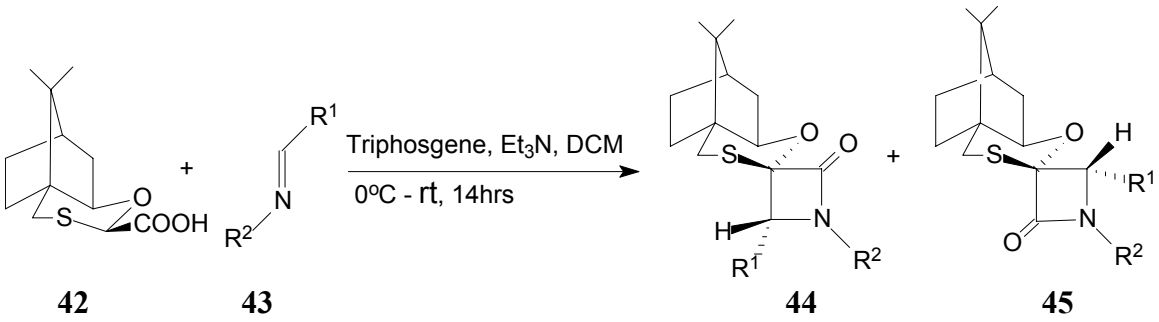
39). The major product (**39)** on treatment with the ester **(40**) in presence of BF_3: Et_2O gave the ester **(41**), which on hydrolysis yielded the chiral acid (**42**) as illustrated in **Scheme-11**

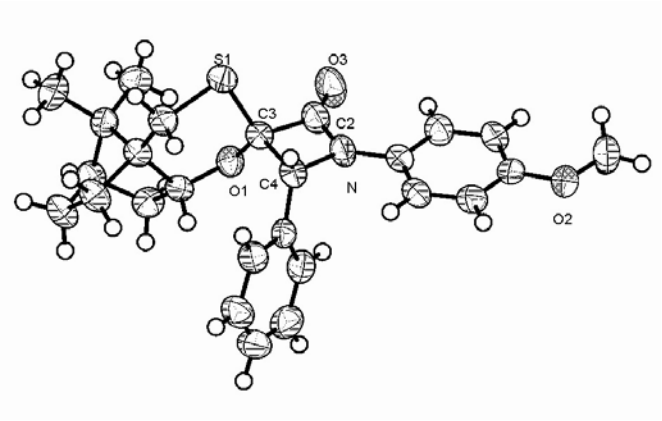
Scheme-11



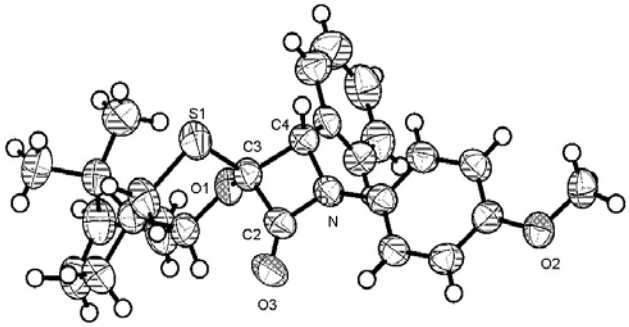
The acid (**42**), on treatment with imines (**43**) in presence of triphosgene gave a diastereomeric mixture of two β-lactams (**44** and **45**) as shown in **Scheme-12**. In one case where R^1 = Ph and R^2 = PMP, both the diastereomers (**44a** and **45a)** could be separated by column chromatography and crystallization. The stereochemistry of the newly formed centers were assigned as (3R, 4R) and (3S, 4S) based on the single crystal X-ray structure of the two representative diastereomers (**44a** and **45a)**.

Scheme-12





X-Ray structure of 44a



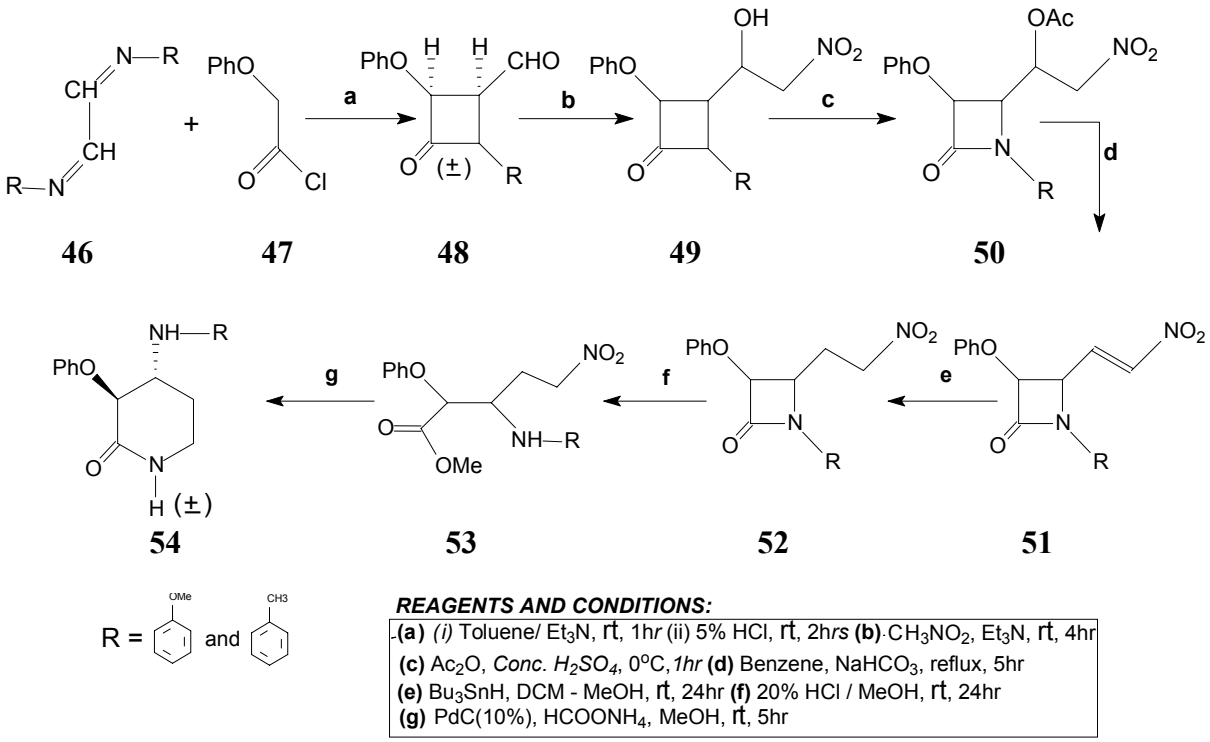
X-ray structure of 45a

Chapter 3

Section A: *4-formyl azetidin-2-one, synthon for the synthesis of 4-aminopiperidin-2-ones*

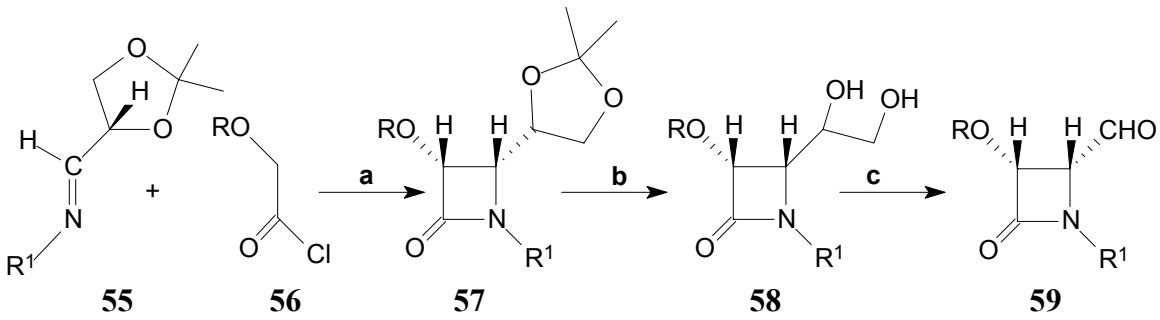
Piperidin-2-ones serve as very important synthetic intermediate for several piperidine alkaloids and azasugars. We have made use of 4-formyl-azetidin-2-one as a synthon for the synthesis of 4-aminopiperidin-2-ones. The starting 4-fomyl azetidin-2-one (**48**) was prepared from bisimine (**46**) and phenoxyacetyl chloride (**47**). The β-lactam (**48**) on treatment with nitromethane in presence of triethylamine underwent nitro aldol reaction to yield the nitroalcohol (**49**), which was converted to the acetate (**50**) followed by elimination using bicarbonate to get the nitro olefin (**51**). The double bond of the olefin was reduced using tributyltinhydride to get the nitroalkane (**52**), which was opened with methanolic HCl to β-amino ester (**53**). Reduction of the nitro group of the ester (**53**) by transfer hydrogenation using Pd/C gave the racemic 4-aminopiperidin-2-one (**54**). All the reaction sequences are given in **Scheme-13**

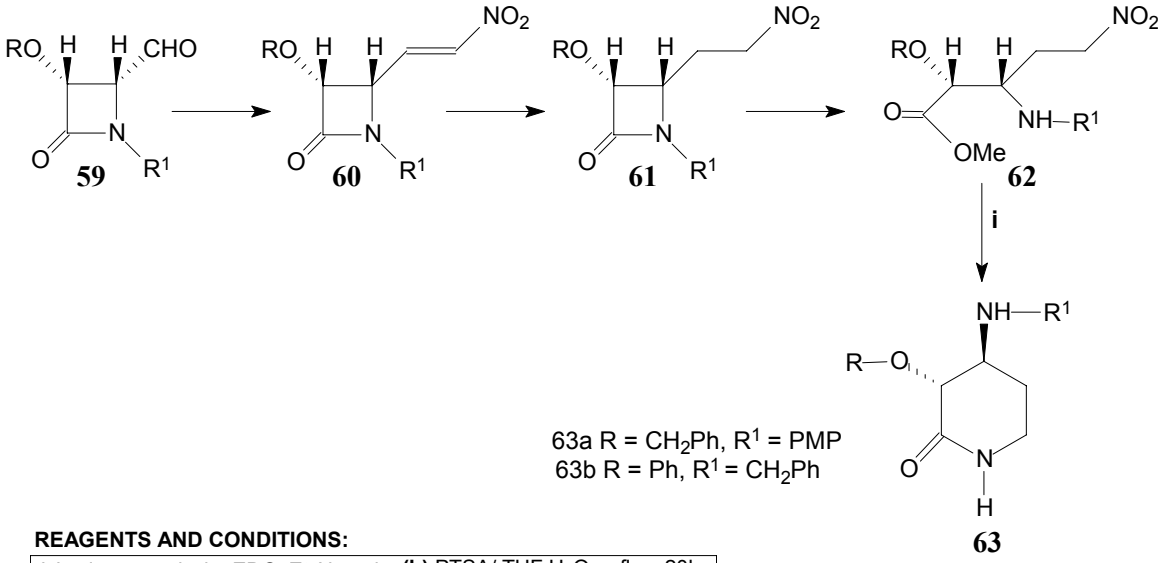
Scheme-13



In order to synthesize the optically pure 4-aminopiperidin-2-one (**63**), we used the optically pure 4-formyl azetidin-2-one (**59**) as the synthon. The azetidin-2-one (**59**) was obtained from the schiff's base (**55**) derived from D-glyceraldehyde acetonide and acid chloride (**56**) under microwave condition. Then by following the standardized protocol, the required optically pure 4-aminopiperidin-2-one (**63**) was obtained. (**Scheme-14**)

Scheme-14:

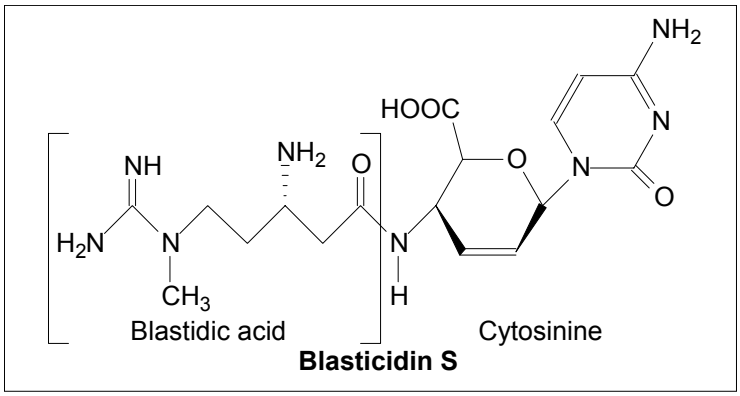




REAGENTS AND CONDITIONS:

(a) microwave irrdn, EDC, Et_3N, 5min. **(b)** PTSA/ THF:H_2O, reflux, 20hr
(c) $NaIO_4$, acetone:H_2O, rt, 1hr **(d)** CH_3NO_2, Et_3N, rt, 4hr
(e) Ac_2O, Conc.H_2SO_4, 0°C, 1hr **(f)** $NaHCO_3$, Benzene, reflux, 4hr
(g) Bu_3SnH, DCM:MeOH, rt, 24hr **(h)** 20% HCl/MeOH, rt, 24hr
(i) PdC(10%) $HCOONH_4$, MeOH, rt, 5hr

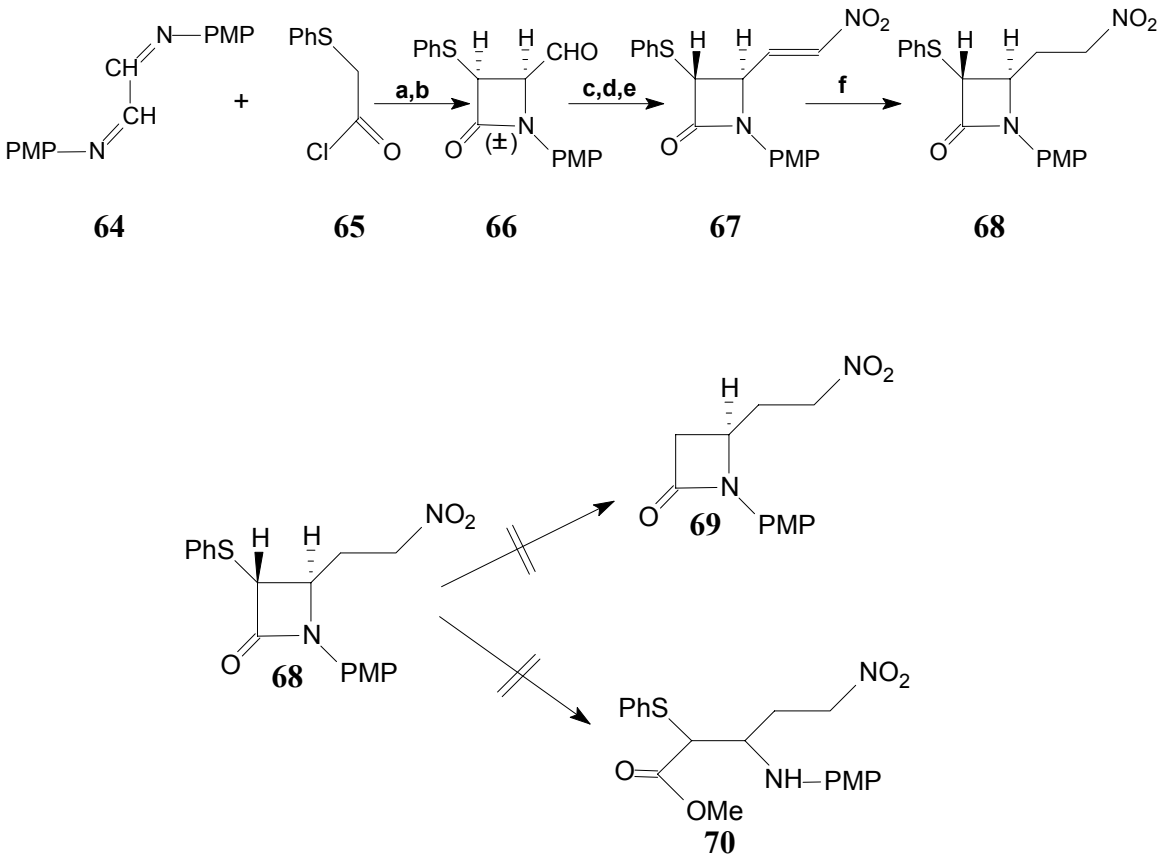
Section B: Studies towards synthesis of Blastidic Acid



Blasticidin S

Blastidic acid is an amino acid component of Blasticidin S, an antibiotic produced by *Streptomyces griseochromogenes,* which was used as a fungicide against rice blast disease in Japan. So far very few syntheses have been reported for blastidic acid and hence we were interested in achieving the synthesis of blastidic acid using 4-formyl-β-lactam as a synthon. Our initial strategy was to start the synthesis from 3-phenylthio-4-formyl-β-lactam (**66**) and later remove the –SPh group, but unfortunately the β-lactam (**66)** could not be desulfurised or cleaved. (**Scheme-15)**.

Scheme-15

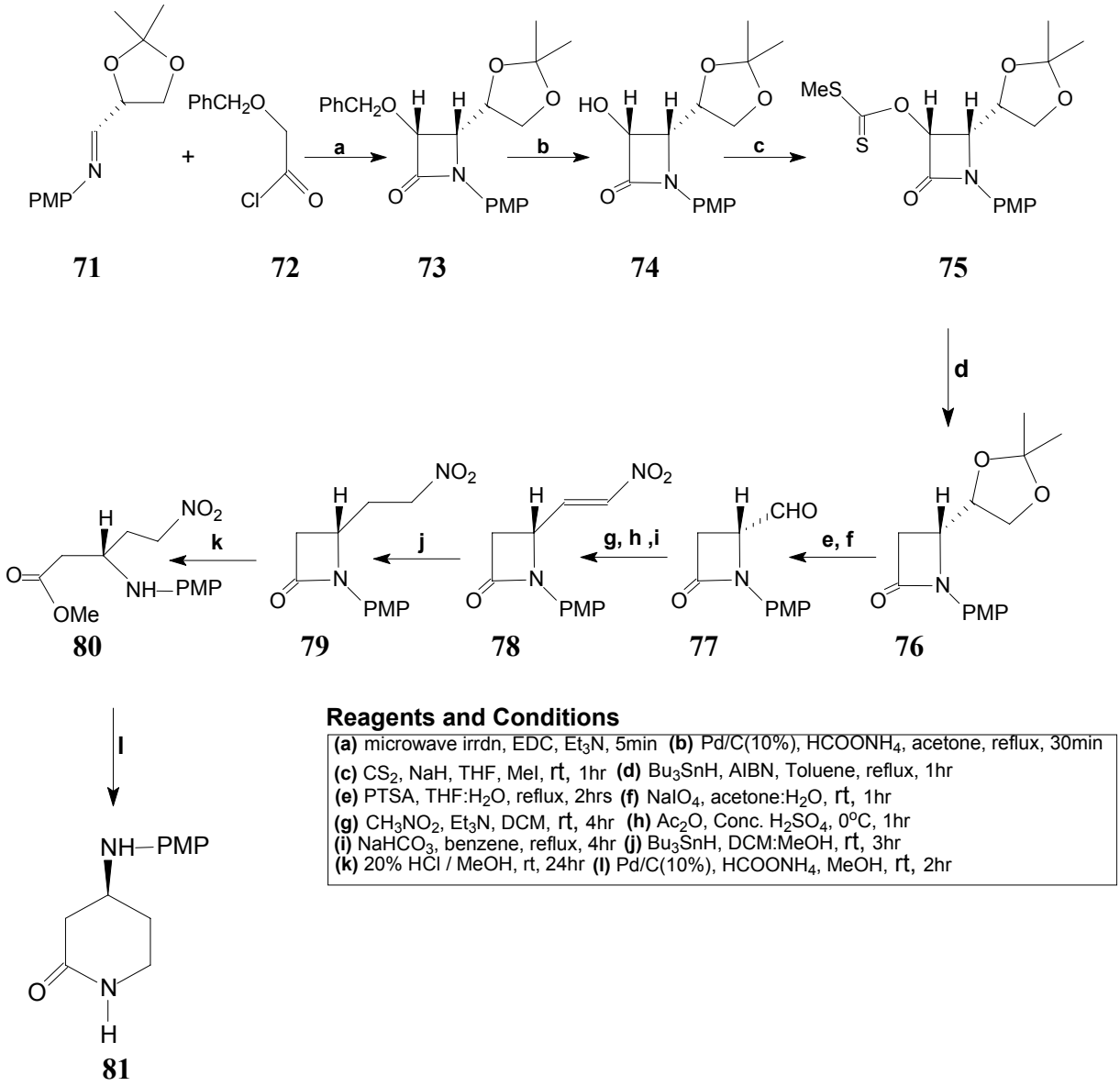


Reagents and Conditions

(a) Et_3N, Toluene, rt, 1hr **(b)** 5% HCl, rt, 2hr
(c) CH_3NO_2, Et_3N, rt, 4hr **(d)** Ac_2O, Conc. H_2SO_4, 0^oC, 30min
(e) $NaHCO_3$, Benzene, reflux, 4hr **(f)** Bu_3SnH, DCM:MeOH, rt, 26hr

As we were unsuccessful in our earlier strategy, we adopted another synthetic route starting with 3-benzyloxy β-lactam (**73**), prepared by known procedure. This β-lactam (**73**) was subsequently converted to 3-unsubstituted-4-formyl-β-lactam (**77**), which was utilized for the synthesis of the 4-aminopiperidin-2-one (**81**) following the reaction sequence shown in **Scheme-16**. This 4-aminopiperidin-2-one (**81**) is a precursor for Blastidic acid.

Scheme-16



Reagents and Conditions

(a) microwave irrdn, EDC, Et_3N, 5min **(b)** Pd/C(10%), $HCOONH_4$, acetone, reflux, 30min
(c) CS_2, NaH, THF, MeI, rt, 1hr **(d)** Bu_3SnH, AIBN, Toluene, reflux, 1hr
(e) PTSA, THF:H_2O, reflux, 2hrs **(f)** $NaIO_4$, acetone:H_2O, rt, 1hr
(g) CH_3NO_2, Et_3N, DCM, rt, 4hr **(h)** Ac_2O, Conc. H_2SO_4, 0^oC, 1hr
(i) $NaHCO_3$, benzene, reflux, 4hr **(j)** Bu_3SnH, DCM:MeOH, rt, 3hr
(k) 20% HCl / MeOH, rt, 24hr **(l)** Pd/C(10%), $HCOONH_4$, MeOH, rt, 2hr

Note: Compound numbers in the synopsis are different from the numbers in the chapters.

CHAPTER 1

SECTION A

SYNTHESIS OF AZETIDIN-2-ONES *VIA* STAUDINGER REACTION USING TRIPHOSGENE AS AN ACID ACTIVATOR

CHAPTER 1

SECTION B

SYNTHESIS OF 3-AZIDO AND 3-AMINO-AZETIDIN-2-ONES USING TRIPHOSGENE

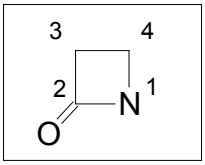
CHAPTER 1

SECTION C

ASYMMETRIC SYNTHESIS OF AZETIDIN-2-ONES FROM CHIRAL ACIDS USING TRIPHOSGENE

1. 1 : Introduction

Azetidin-2-one (β-lactam), a four membered cyclic amide (Fig. 1), is a part structure of many biologically important antibiotics. The unique structural feature and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of synthetic chemists, as they provide variety of synthetic challenges. Although the first synthesis of β-lactam ring was reported way back in 1907[1] by Staudinger, β-lactams as a class acquired immense importance only after the discovery of penicillin by Fleming in 1928[2] and its structural confirmation by X-ray crystallography[3] which unambiguously confirmed the presence of 4-membered amide ring (β-lactam). The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.



Azetidin-2-one
(β–Lactam ring)

Fig. 1

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

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

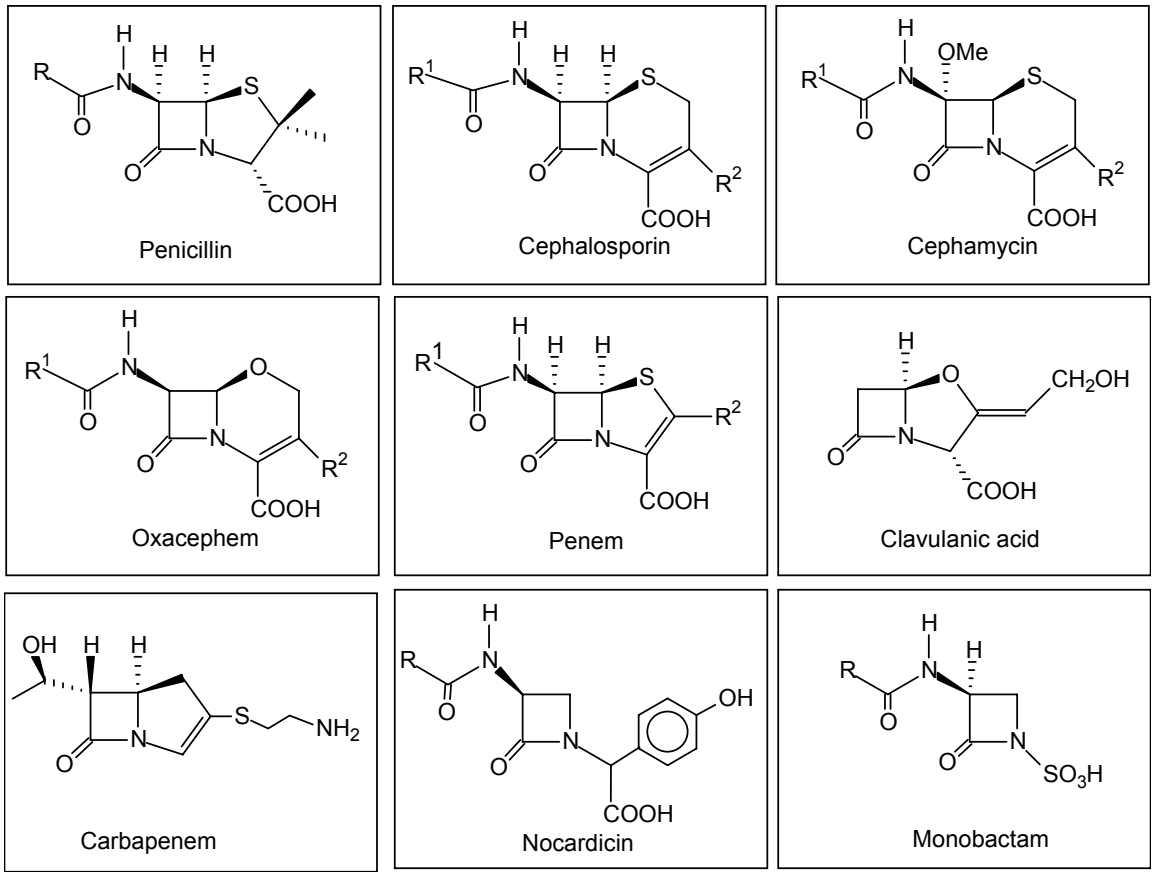


Fig. 2: Classification of β-Lactam antibiotics based on structure

Carbacephems,[6] which are carbon analogues of cephalosporins are also being used as antibiotics. It has superior stability over cephalosporin. Loracarbef (lorabid) is the first carbacephem approved for clinical use.

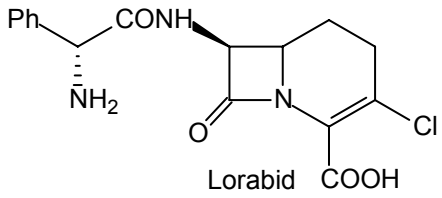
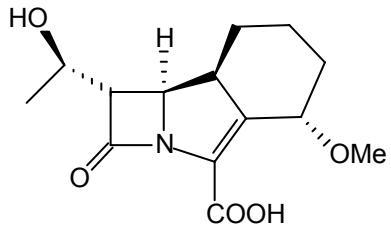


Fig. 3

Tricyclic β-lactam antibiotics called trinems[7] are also new class of tricyclic carbapenems. GV 104326, a highly potent, broad-spectrum antibacterial agent, effective against gram-positive, gram-negative and anaerobic pathogenic bacteria, is an example of tribactam antibiotic.



GV 104326 (tribactam)

Fig. 4

In 1995, a new class of compounds was reported in which the antibiotic property of β-lactams and the antiviral property of nucleosides were incorporated together to afford dual properties of the drug.[8] Kehagia et al.[9] reported a new class of β-lactams in which a steroidal and β-lactam units were coupled together via Ugi reaction in a one step process (Fig. 5)

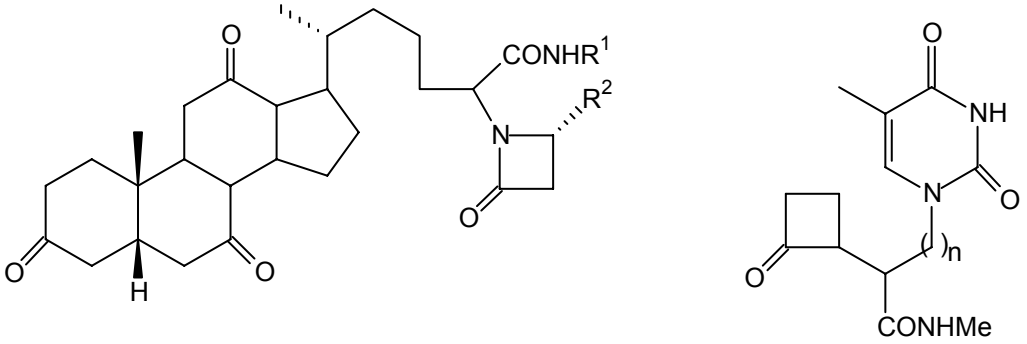


Fig. 5

Apart from their antibacterial activities, β-lactams also shows biological activities that include cholesterol absorption inhibition[10] and human leukocyte elastase[11] (HLE).

Mode of action:

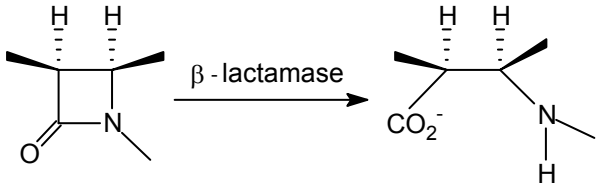
The biological activity of β-lactam antibiotics is mainly due to the presence of the azetidin-2-one ring (β-lactam ring). The SAR[12] studies have shown that the main requirement for the antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell wall and then bind in active form to the targets, which are the inner membrane enzymes that are responsible for the biosynthesis of the cell wall, thereby inactivating one or more enzymes involved in the cell wall synthesis. Penicillin binds to the so-called 'penicillin-binding proteins' (PCBs), which are specific molecules on the inner membrane of the cell wall. The binding of penicillin to the PCBs causes

termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[13]

β-lactamases and β-lactamase inhibitors:

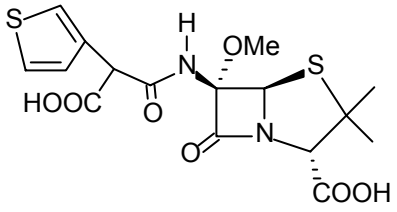
The β-lactamases[14] are group of bacterial enzymes that catalyze the hydrolysis of β-lactam antibiotics (Scheme 1.01). Since the hydrolyzed β-lactam has no antibiotic activity, the β-lactamases represents a source of bacterial resistance against β-lactam antibiotic.

Scheme 1.01

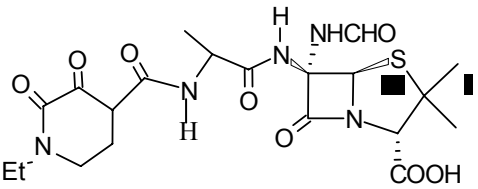


This phenomenon of bacterial resistance led to a serious research in this field and paved the way for development of novel β-lactams called β-lactamase inhibitors.[15] They are essentially structural variants of the classical β-lactams with modified skeleton. They may not have antibiotic activity of their own, but they are used in combination with the β-lactam antibiotic. Specifically they associate themselves with the β-lactamases, thereby protecting the antibiotic against the hydrolytic action of β-lactamase. Thus the antibiotic activity of the β-lactam is safeguarded and it can penetrate through the bacterial cell wall.

Temocillin and Formidacillin[15a] are some of the examples of β-lactamase inhibitors, which are the result of extensive SAR studies of penicillin.



Temocillin



Formidacillin

Fig. 6

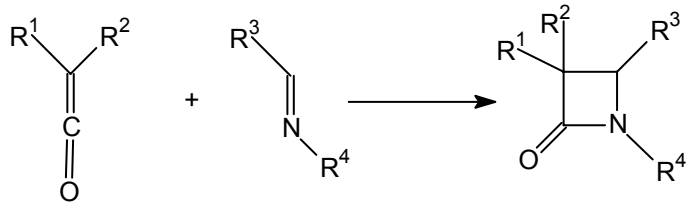
General methods for constructing azetidin-2-one (β-lactam) ring:

Over the past few decades, several methodologies[16] have been developed for the construction of the β-lactam ring. Few important methods will be discussed here.

Staudinger Reaction:

Staudinger achieved the first chemical synthesis of β-lactam ring in 1907 by [2+2] cycloaddition of ketenes with imines. This reaction is referred to as Staudinger reaction or ketene-imine cycloaddition reaction[17] (Scheme 1.02). Later it was modified, wherein acid chlorides or activated carboxylic acids were used in presence of a base as ketene precursor.

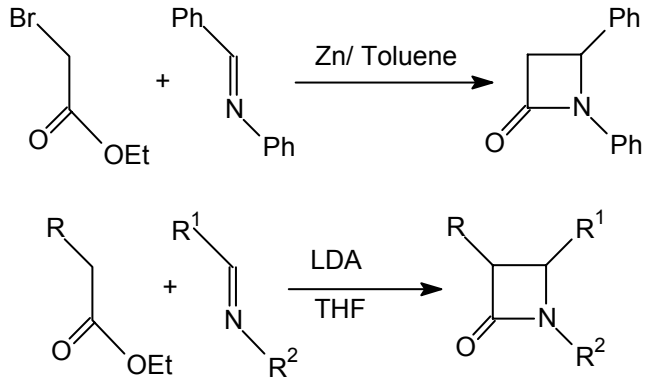
Scheme 1.02



Enolate-Imine condensation:

Gilman and Speeter first reported this reaction.[18] They constructed the β-lactam ring by condensation of Zn enolate (Reformatsky reagent) with imines. Later on, other metal enolates have also been used in the enolate imine condensation reaction to achieve good selectivities and yields in β-lactam formation[19] (Scheme 1.03).

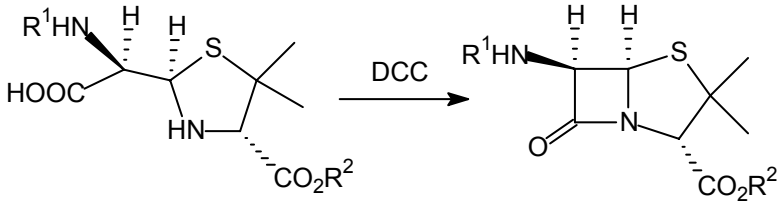
Scheme 1.03



Formation of N-C2 bond:

This approach was first reported by Staudinger, Klever and Kober in 1910.[20] Sheehan and Henery-Logan have used this method for their landmark synthesis of penicillin[21] by cyclization of β-amino acid using dicyclohexylcarbodiimide (DCC) as condensing reagent (Scheme 1.04).

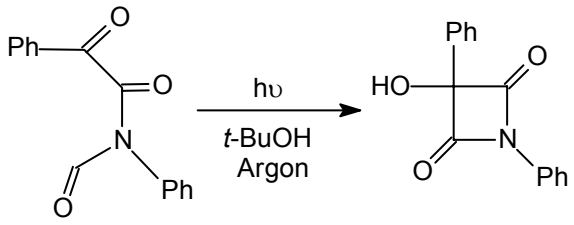
Scheme 1.04



Formation of C2-C3 bond:

Compared to the amide (N-C2) bond formation, azetidinone formation at the C2-C3 position is complicated by the difficulty in forming a C-C bond versus an amide bond. Hence this method is least used. A photochemical approach leading to formation of 4-keto-β-lactams has been developed[22] (Scheme 1.05).

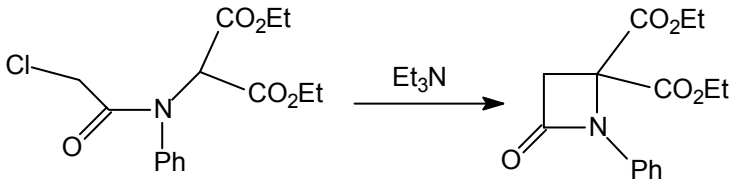
Scheme 1.05



Formation of C3-C4 bond:

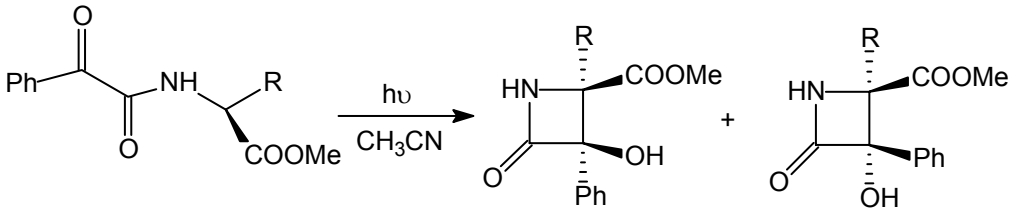
This involves formation of a nucleophilic center at C3 and an electrophilic center at C4 or *vice versa*. The first example of such an Intramolecular nucleophilic displacement reaction was reported by Sheehan and Bose[23] wherein haloacylamino malonate was cyclized in an intramolecular fashion in the presence of a base (Scheme 1.06).

Scheme 1.06



Recently, a photocyclization of phenylglyoxyamides of α-amino acid methyl esters to 3-hydroxy β-lactams has been reported,[24] which involves the formation of C3-C4 bond (Scheme 1.07).

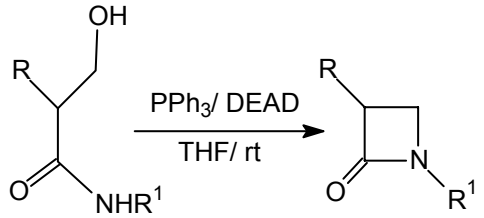
Scheme 1.07



Formation of C4 -N bond:

This is the route selected by nature for the biosynthesis of azetidinone containing antibiotics.[25] The essential strategy involved in the synthesis of β-lactams through C4 –N bond is the intramolecular displacement of a leaving group attached to C4 with an appropriately activated nitrogen. Miller and coworkers[26] have made significant contribution to this methodology. The key feature of the Miller's hydroxamate approach is the intramolecular cyclization of chiral β-hydroxy amides under Mitsunobu reaction conditions[27] (Scheme 1.08).

Scheme 1.08

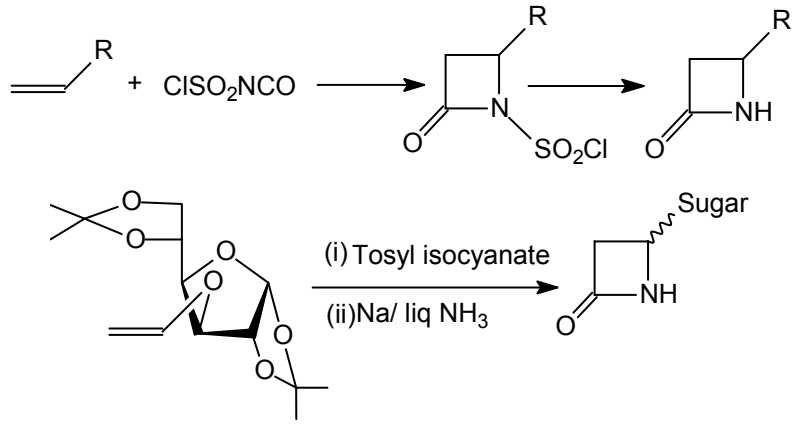


Isocyanate addition to alkenes:

Graf[28] reported the cycloaddition of N-chlorosulfonyl isocyanate (CSI) with alkenes to get 1-chlorosulfonyl azetidin-2-ones. Subsequent removal of the chlorosulfonyl group gave the NH β-lactam. The cycloaddition is promoted by activated

alkenes like vinyl acetates. Chmielewski and coworkers have used the cycloaddition reaction between tosyl isocyanate and sugar derived vinyl acetates to obtain good diastereoselectivities in β-lactam formation[29] (Scheme 1.09).

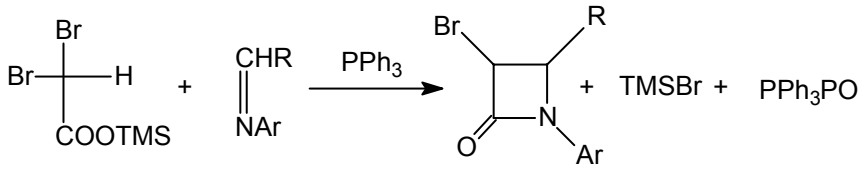
Scheme 1.09



Manhas's α-Bromo-β-Lactam approach:

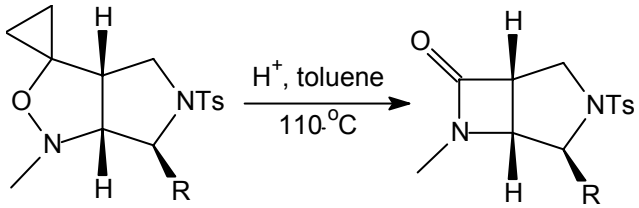
Manhas et al.[30] have developed this approach, which involves condensation of halo ester with imines in presence of triphenyl phosphine (Scheme 1.10).

Scheme 1.10



Recently, Cordero et al.[31] have reported that spirocyclopropane isoxazolidines undergo ring contraction to yield β-lactams on heating in the presence of protic acid (Scheme 1.11).

Scheme 1.11



R = Me, *iso*-propyl

Asymmetric Synthesis of β-lactams:

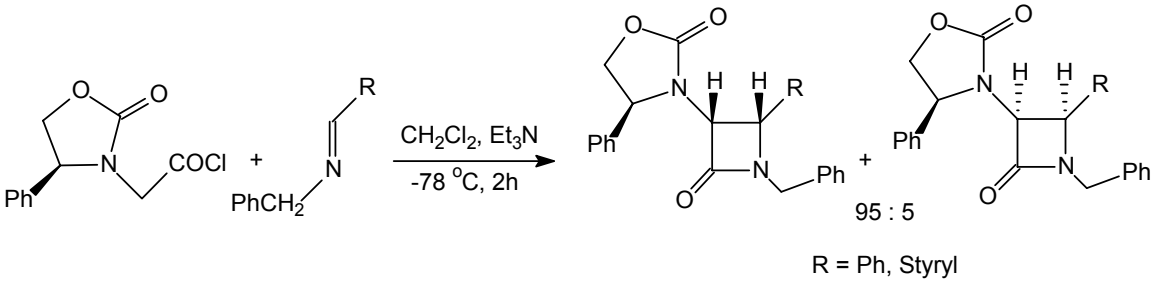
Asymmetric synthesis of β-lactams is an important area of research, as biological activity of β-lactam antibiotics is closely related to the stereochemistry. Among the various methods available for the asymmetric synthesis of β-lactams, the asymmetric Staudinger reaction[17,32] (ketene-imine cyclization) is the most widely used. This is mainly because of the simplicity in reaction procedures and versatility. Asymmetry can be induced in a ketene-imine cycloaddition reaction by using a chiral ketene or chiral imine or both (referred as double stereodifferentiation).

Asymmetric Staudinger reaction using chiral ketene precursors*:*

Various levels of diastereoselectivities in β-lactam formation using chiral auxiliary in the ketene component have been reported in literature. Following is a brief review of asymmetric Staudinger reaction using chiral ketenes.

Evans and Sjogren[33] developed a (*S*)-phenylglycine derived oxazolidinone as a chiral auxiliary attached to ketene component in the asymmetric Staudinger reaction and obtained very high diastereoselectivity (> 95%) in the *cis* β-lactam formation. No trace of the *trans* isomer was detected. (Scheme1.12).

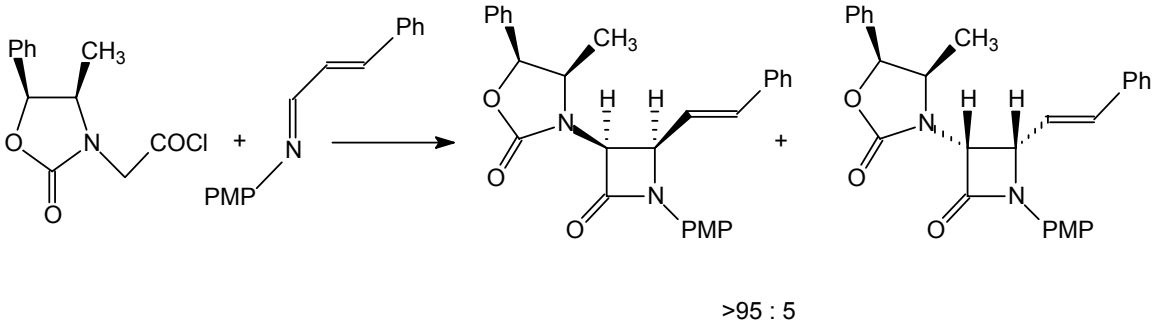
Scheme 1.12



Boger and Myers[34] used the enantiomeric oxazolidone to synthesize the other diastereomer of the β-lactam with very good diastereoselectivity.

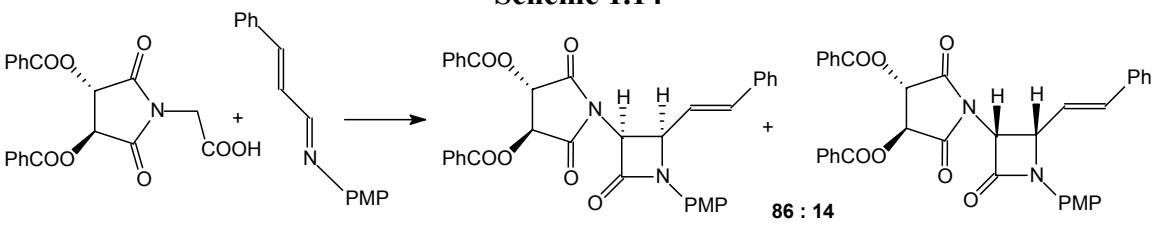
Cooper et al.[35] have used a norephedrine derived oxazolidinone as the chiral auxiliary in the ketene component and achieved very high diastereoselectivity (>95%) in the *cis* β-lactam formation *via* asymmetric Staudinger reaction (Scheme 1.13).

Scheme 1.13



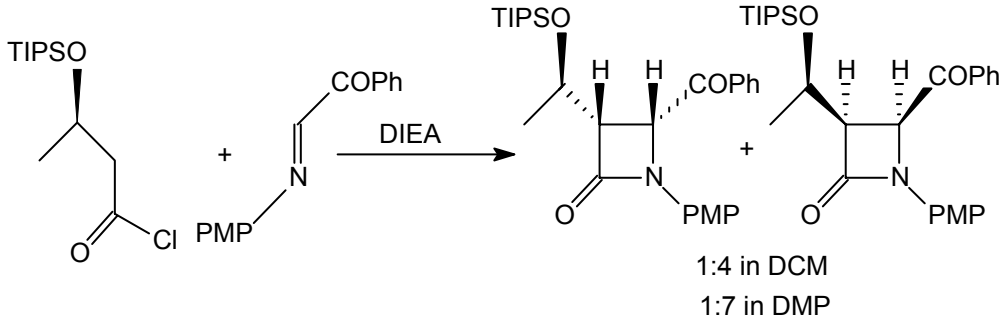
Cooper et al.[35] have also reported the use of a tartarimidoacetic acid derived from *S*, *S*-Tartaric acid as a chiral ketene precursor in the asymmetric Staudinger reaction. However, there was only moderate diastereoselectivity in the β-lactam formation (de upto 72%) as the chiral center is farther away from the amide nitrogen (Scheme 1.14).

Scheme 1.14



An acid chloride derived from *O*-protected 3-hydroxybutyric acid was used in the asymmetric Staudinger reaction, to yield diastereomeric mixture of β-lactams. The ratio depends on the solvent used. Increase in the diastereoselectivity was observed with the increase in bulkiness of the O- protecting group[36] (Scheme 1.15).

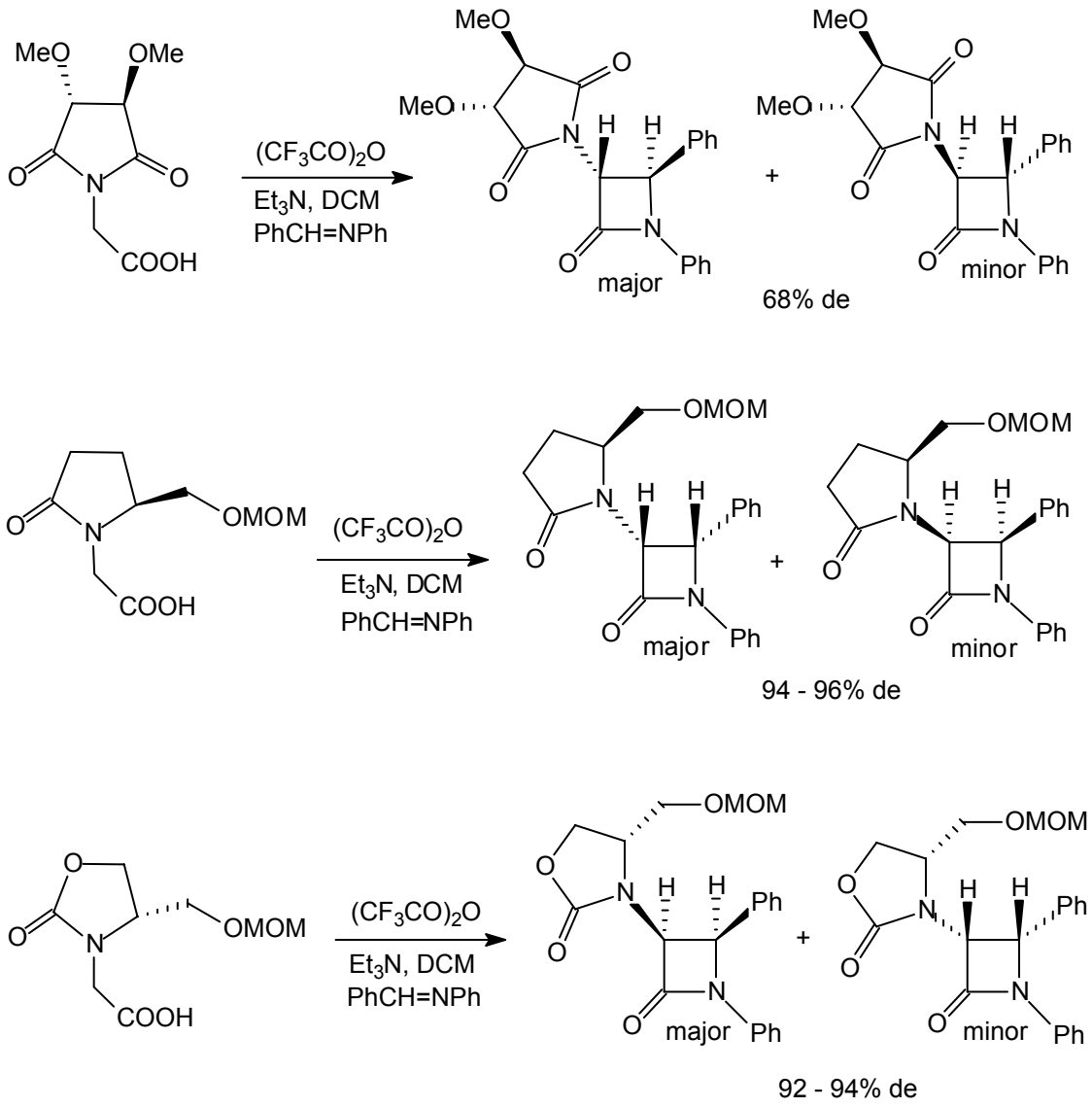
Scheme 1.15



Ikota et al.[37] have used mixed anhydride of acetic acid derived form (L)–(+)–Tartaric acid, (*S*)–Glutamic acid, and (*S*)–Serine as the chiral ketene precursor in the asymmetric Staudinger reaction with imines derived from benzylideneaniline and

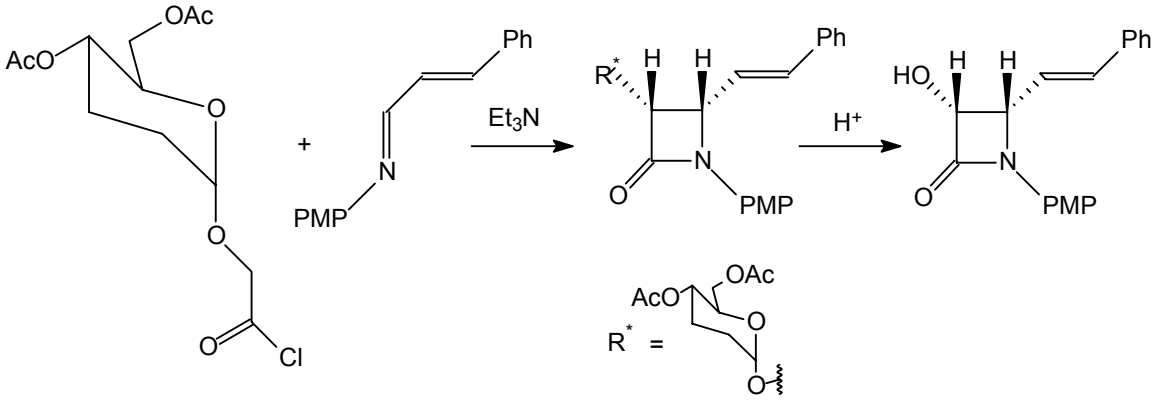
obtained very good diastereoselectivity in β-lactam formation (Scheme 1.16). The removal of the chiral auxiliary gave the 3-amino β-lactam derivatives

Scheme 1.16



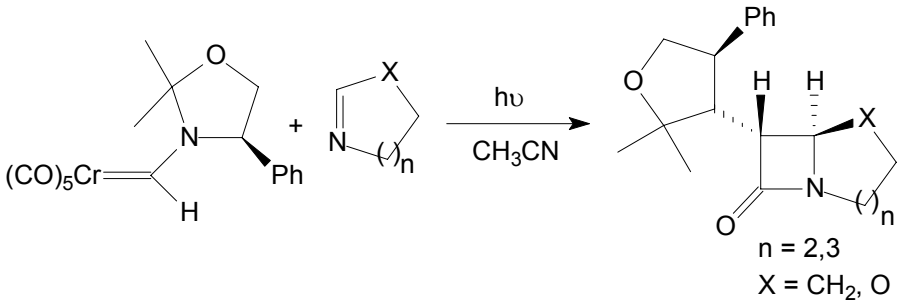
Borer and Balogh[38] have used a chiral ketene derived from carbohydrate (tri-O-acetyl-D-glucal) in the asymmetric Staudinger reaction to get *cis* β-lactams with good diastereoselectivity. Removal of the chiral auxiliary by hydrolysis using 4: 1: 1 THF/ H_2O/ HOAc gave the *cis* β-lactams with 70% enantiomeric excess (Scheme 1.17). An excellent review by Chemielewski, on the use of carbohydrates in β-lactam synthesis has appeared in 1994.[39]

Scheme 1.17



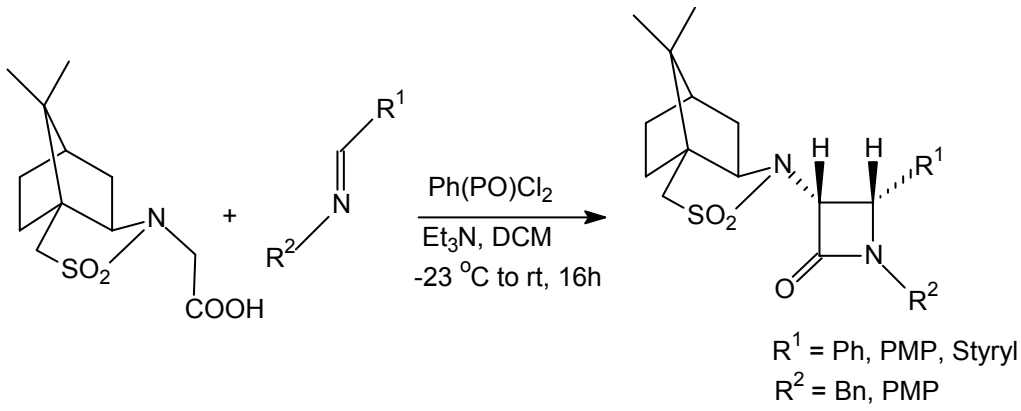
Hegedus et al.[40] have prepared *trans* β-lactams in excellent yields (75-95%) and diastereoselectivity (>95%) by the photolysis of optically active chromium carbene complexes with cyclic imines (Scheme 1.18).

Scheme 1.18



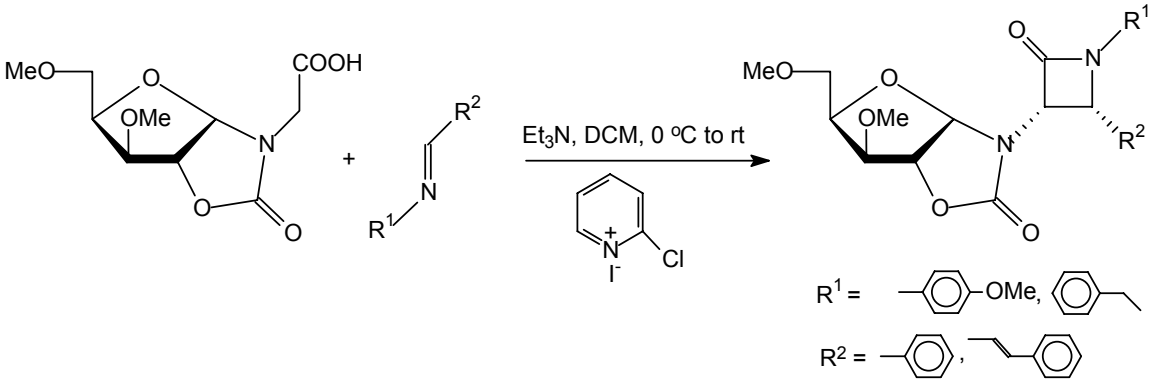
Chiral acid derived from Oppolzer's sultam has been used as chiral ketene precursor in the asymmetric Staudinger reaction to get diastereospecifically a single *cis* β-lactam[41] in good yields (Scheme 1.19)

Scheme 1.19



Recently Koll et al.[42] have achieved excellent diastereoselectivity (>99%) in β-lactam formation using a chiral oxazolidinone auxiliary based on D-Xylose as a ketene precursor in the asymmetric Staudinger reaction (Scheme 1.20).

Scheme 1.20



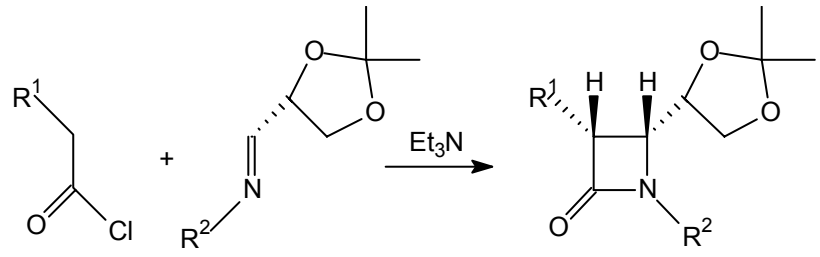
Asymmetric Staudinger reaction using chiral imines:

Asymmetric induction *via* chiral imines can be achieved by using either chiral aldehydes or chiral amines. The use of chiral aldehydes and chiral amines will be briefly discussed below.

Chiral Aldehydes:

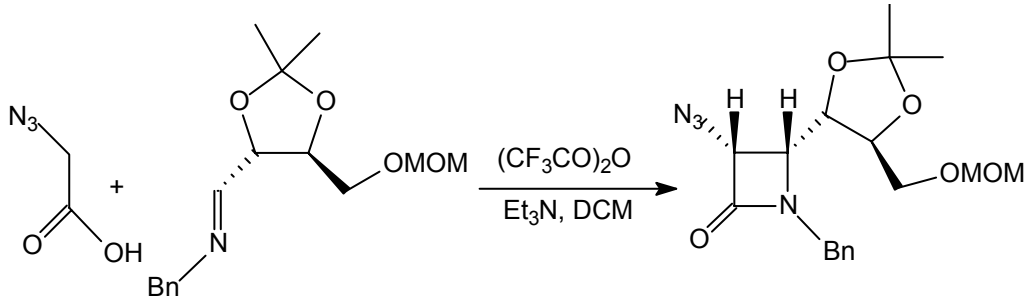
Imines derived from D and L glyceraldehyde acetonide[43] gave complete *cis* diastereoselectivity in β-lactam formation *via* asymmetric Staudinger reaction (Scheme 1.21). Bose and co-workers, in series of papers,[44] have reported similar observation.

Scheme 1.21



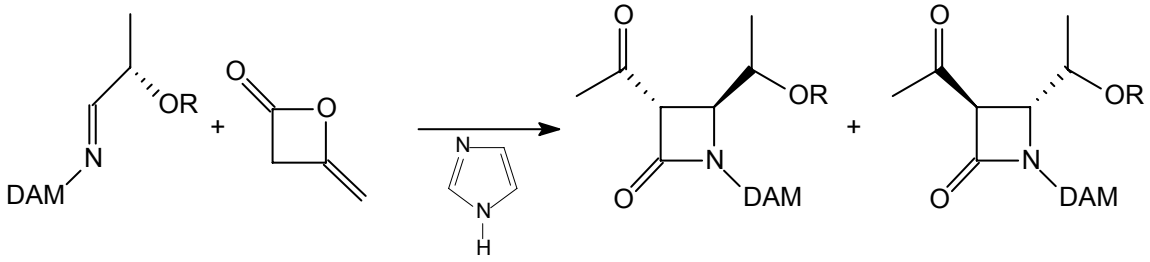
Ikota has reported the use of an imine derived from 2, 3-O-isopropylidene–L–threitol in the asymmetric Staudinger reaction and achieved very good diastereoselectivity[45] (Scheme 1.22).

Scheme 1.22



Terashima et al.[46] have used the diketenes along with the imine derived from commercially available (*S*)–ethyl lactate as the chiral aldehyde component in the asymmetric Staudinger reaction. The diastereoselectivities were solvent dependent, with acetonitrile giving the best results (90% de) (Scheme 1.23).

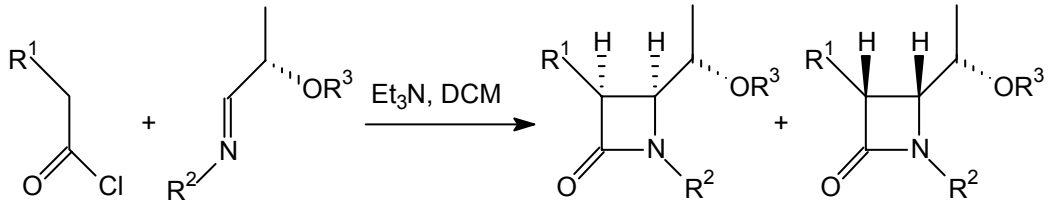
Scheme 1.23



R = Bn, TBDMS

Palomo et al.[47]and Brown[48] have also used the chiral aldehyde derived from (*S*)–ethyl lactate in the ketene-imine cycloaddition reaction and achieved excellent diastereoselectivity by careful optimization of the protecting groups (Scheme 1.24).

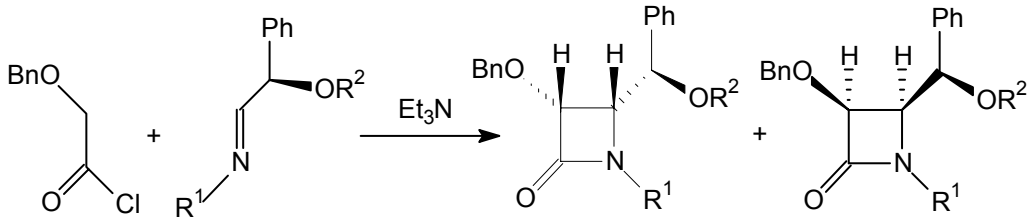
Scheme 1.24



R^1 = PhO, AcO, CH_3O, BnO. R^2 = PMP, Bn
R^3 = TBDMS

Terashima and co-workers[49] have reported the ketene-imine cycloaddition reaction with imines derived from optically active mandelate. The diastereoselectivity was dictated by the bulkiness of the protecting group (Scheme 1.25).

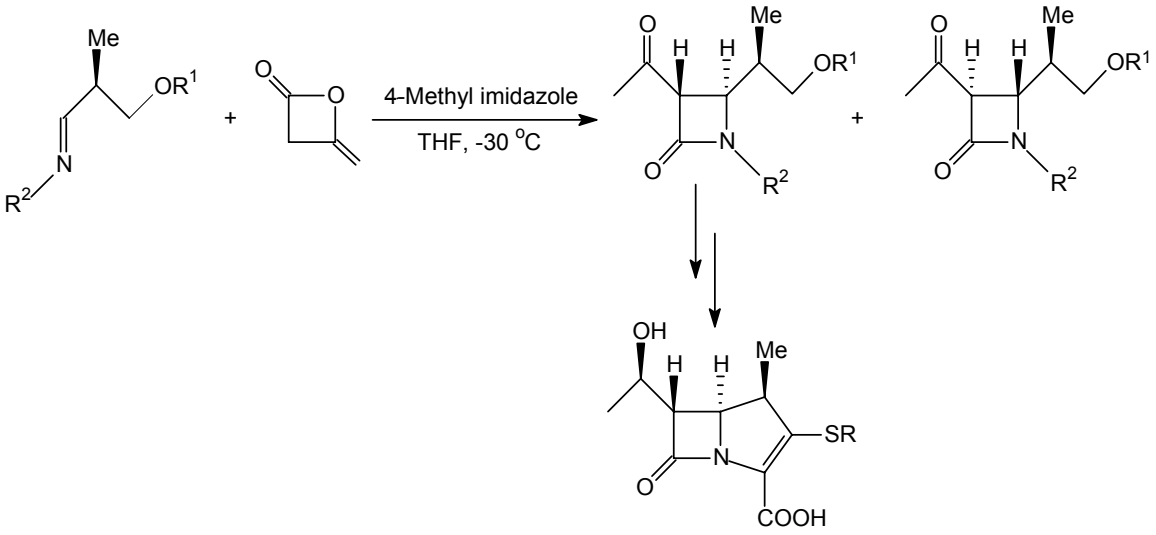
Scheme 1.25



R^1 = DAM, Bn
R^2 = TBDMS, *t*-Bu

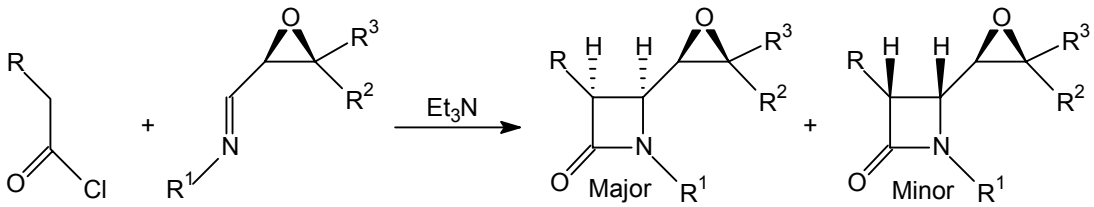
Imines derived from (*S*)–Methyl–3–hydroxy–2–methylpropionate were used in the asymmetric Staudinger reaction to synthesize important precursor of 1–β–methyl carbapenem[50] (Scheme 1.26). A careful optimization of the reaction condition and protecting groups gave 15:1 ratio in favor of the desired diastereomer.

Scheme 1.26



Imines derived from chiral α, β–epoxyaldehydes[51] have also been employed in Staudinger reaction to achieve very high diastereoselectivity. The epoxy aldehydes were synthesized from (*S*)–Malic acid[52], (+)–Tartaric acid[53] or Sodium erythorbate[51] (Scheme 1.27).

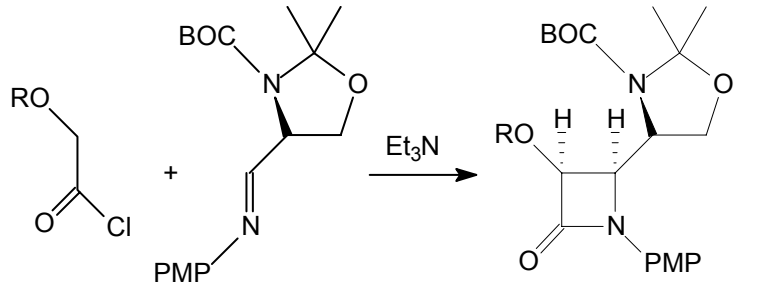
Scheme 1.27



R = PhthN, R^1 = PMP, Bn, R^2 = CH_3, H, R^3 = CH_3, Ph

Palomo et al.[54] have used the imines derived from N, O– diprotected L– Serinal in the asymmetric Staudinger reaction and diastereospecifically obtained a single cis β-lactam (Scheme 1.28).

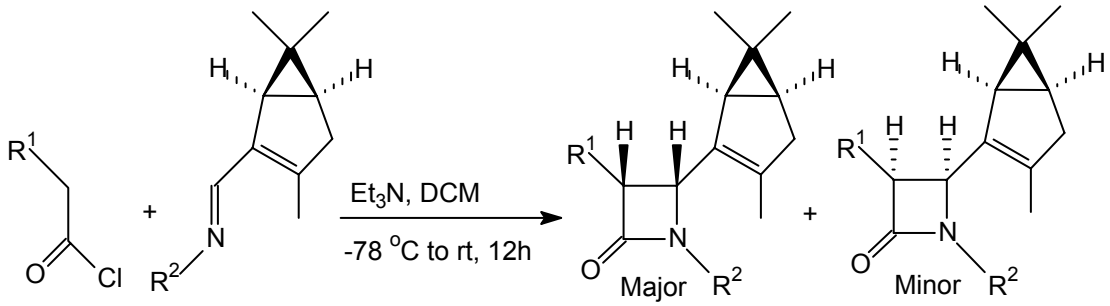
Scheme 1.28



R = CH_3CO, CH_3, Bn

Bhawal et al.[55] have utilized the imine prepared from chiral aldehyde derived from (+)–3–carene in the ketene-imine cycloaddition reaction. Good diastereoselectivity in the β-lactam formation was achieved, in spite of the chiral directing group being far away from the aldehyde carbon (Scheme 1.29).

Scheme 1.29



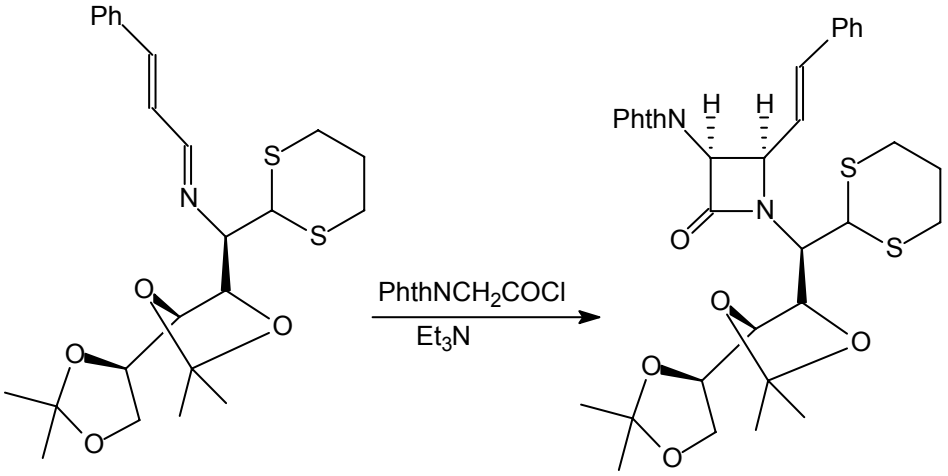
R^1 = PhthN, PhO, R^2 = PMP, Bn

Chiral Amines:

Asymmetric Staudinger reaction using imines derived from achiral aldehydes and chiral amines often result in poor diastereoselectivity in β-lactam formation. This is because the stereo directing group in the chiral amine is far away from the newly formed chiral center. However there are few reports on efficient use of chiral amines in the asymmetric Staudinger reaction, which will be discussed here.

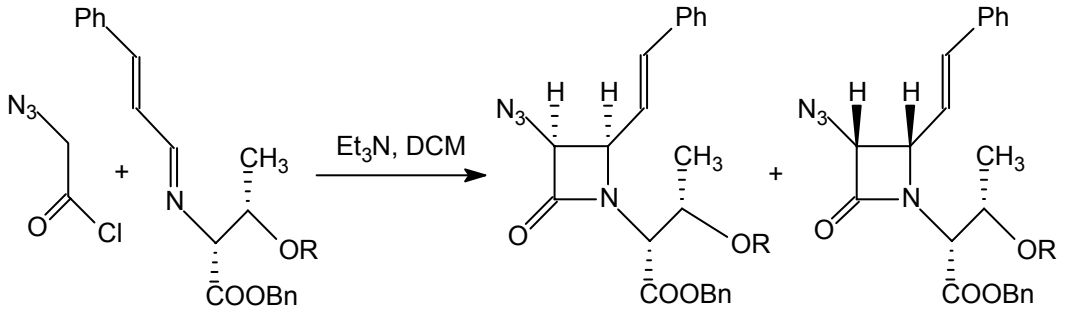
Asymmetric Staudinger reaction using imines derived from D–Glucosamine[56] and cinnamaldehyde have resulted in diastereospecific formation of single *cis* β-lactam (Scheme 1.30).

Scheme 1.30



D –Threonine has also been used as chiral auxiliary in the Staudinger reaction. In this case the diastereoselectivity was dependent on the bulkiness of the substituents[57] (Scheme 1.31).

Scheme 1.31

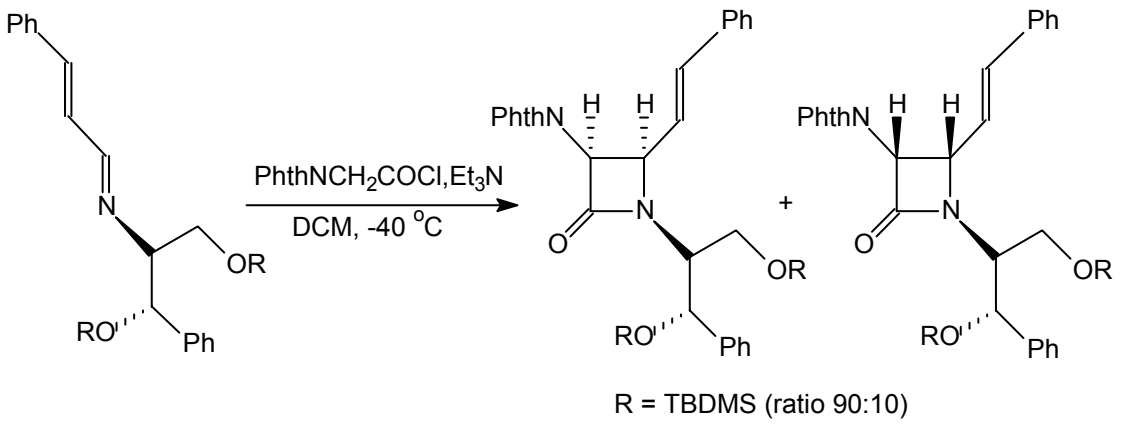


R = TBDMS (ratio 90:10)

R = H (ratio 1:1) R = $SiPh_3$ (ratio 95:5)

Gunda[58] has used a chiral imine derived from (1*S*, 2*S*)–2–Amino–1–phenyl–1,3-propanediol in the ketene-imine cycloaddition reaction and here too, the diastereoselectivity was dictated by the hydroxy protecting group (Scheme 1.32).

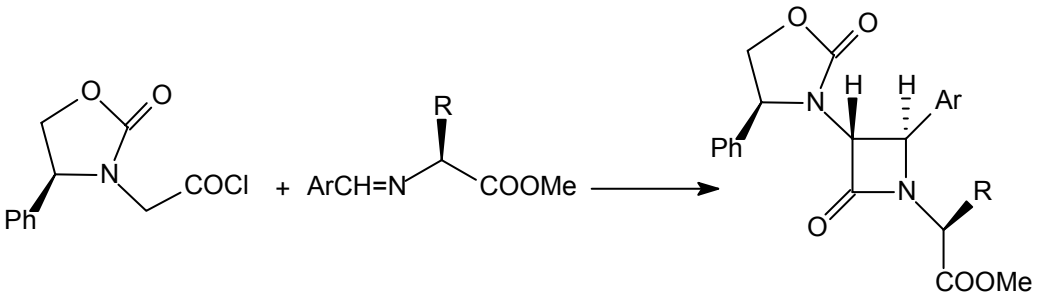
Scheme 1.32



Double Stereodifferentiation:

The concept of double asymmetric induction has been applied to Staudinger reaction with variable success. High levels of asymmetric induction has been achieved in Staudinger reaction between the Evans-Sjogrens ketene and imines derived from (*R*) and (*S*)-α-amino acid esters[59] (Scheme 1.33).

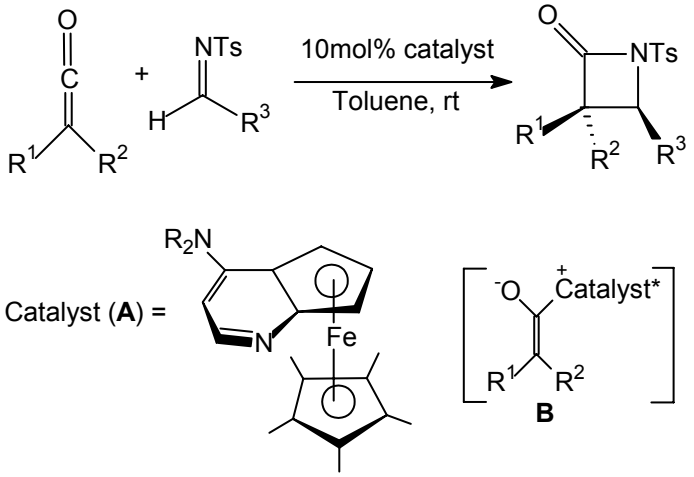
Scheme 1.33



Catalytic Asymmetric Staudinger reaction:

Recently Hodous and Fu[60] have reported a highly enantioselective synthesis of β-lactams catalyzed by a planar chiral nucleophile (**A**). This chiral catalyst (**A**) was found to be very effective in promoting the [2+2] cycloaddition reaction of symmetrical and unsymmetrical ketenes with variety of imines (Scheme 1.34). The reaction was proposed to proceed through the intermediate (**B**), similar to what Lectka[61] has observed.

Scheme 1.34



Mechanism of Staudinger reaction:

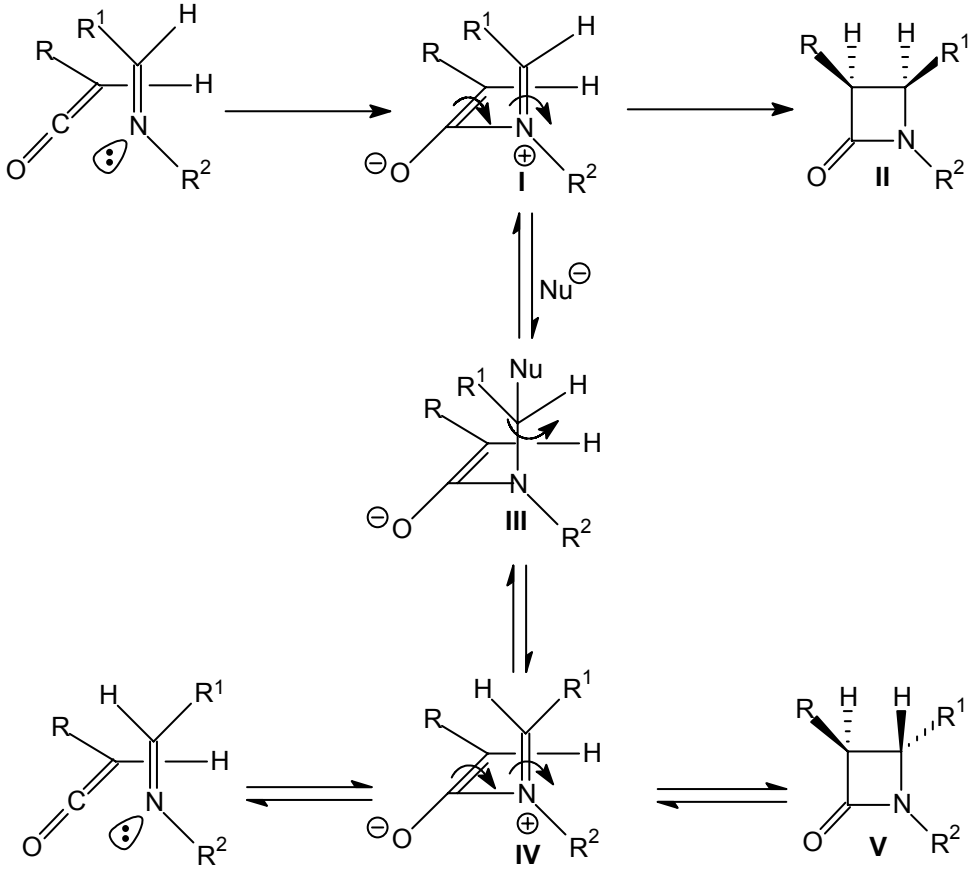
Although the ketene-imine cycloaddition reaction (Staudinger reaction) has been known for several decades, the mechanism and stereo chemical outcome of this reaction is still obscure. Efforts in this aspect have resulted in several papers by various groups.[62] Based on these results; a two-step zwitterionic mechanism has been preferred over a concerted [2+2] cycloaddition reaction. Lynch et al.[63] have established the formation of intermediate ketene. They found that the treatment of (*R*)-3-hydroxybutyric acid chloride with diisopropylamine in a FT-IR cell displayed a strong band at 2120, which they assigned to a ketene. The involvement of zwitterionic intermediate has also been proven by various spectroscopic methods and trapping experiments.[64] The possibility of acylation of imine with acid chloride under the reaction condition has been ruled out as the acid chloride when it reacts with imine in the absence of base leads to the formation of amide instead of β-lactam

It has been postulated that the LUMO of the ketene carbonyl is attacked by the HOMO of the imine in an orthogonal approach, in a plane perpendicular to the substituents of the ketene, resulting in the formation of the zwitterionic intermediate **I** (Scheme 1.35).[65] This hypothesis was supported by semi-empirical molecular orbital calculations (MNDO) of a transition intermediate between ketene and N-methyl-2-methylimine.[35] It is further believed that the attack of the imine occurs from the less hindered side of the ketene, resulting in the zwitterionic intermediate **I**. Rotation of the imine into the plane of the ketene followed by a conrotatory ring closure produces the

thermodynamically less stable *cis* β-lactam **II** in which the two hydrogens (or small substituents) are *cis* to each other. The well-known preference for the formation of *trans* β-lactams with cyclic imines can be explained similarly. An orthogonal approach between the ketene and imine will produce the zwitterionic intermediate **IV**, which on conrotatory ring closure will give *trans* β-lactam (Scheme 1.35).

This mechanism also successfully explains the formation of *cis-trans* mixture in the Staudinger reaction. A nucleophile can add to the zwitterionic intermediate **I** or **IV** to form intermediate **III**. The loss of nucleophile from intermediate **III** after C-N bond rotation can result in formation of **IV** and subsequent trans β-lactam **V**. The intermediate **III** can also revert back to **I** and form *cis* β-lactam **II**. Thus the ratio of *cis* and *trans* isomers depends upon the formation and stability of intermediate **I** and **IV** (Scheme 1.35). It was also observed that the initially formed *cis* product could undergo base catalyzed isomerisation to produce more stable *trans* product.[66]

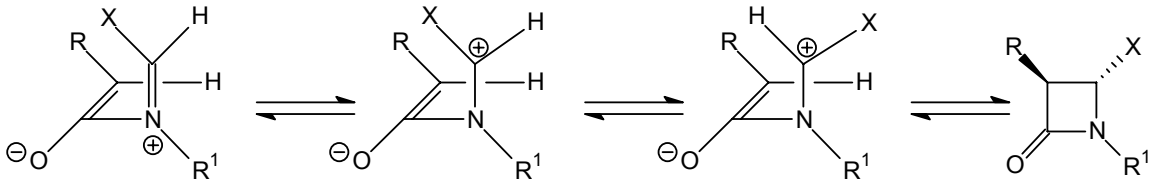
Scheme 1.35



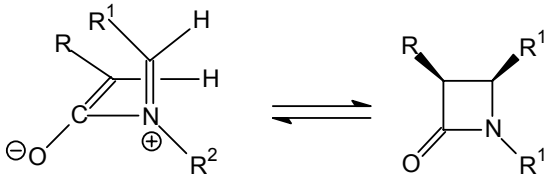
The formation of *trans* isomer by using imidates, thioimidates and sometimes C-aryl imines and potentially C-alkyl imines can be explained by the ability of these groups

to stabilize the positive charge of the zwitterionic intermediate by the inductive or mesomeric effect. This allows the isomerisation of *trans* iminium ion to the sterically less crowded *cis* iminium ion, which on ring closure will generate, *trans* β-lactam (Scheme 1.36). On the contrary, imine possessing electron withdrawing substituents on the imine carbon, like α-carbonyl group or halomethyl group, prevents the C-N bond rotation of the zwitterionic intermediate and produces *cis* isomer. A detailed account of semi-empirical calculation reported by Cossio et al.[62c] also supports the Ketene-Imine cycloaddition mechanism.

Scheme 1.36



X = OR, SR, aryl, alkyl



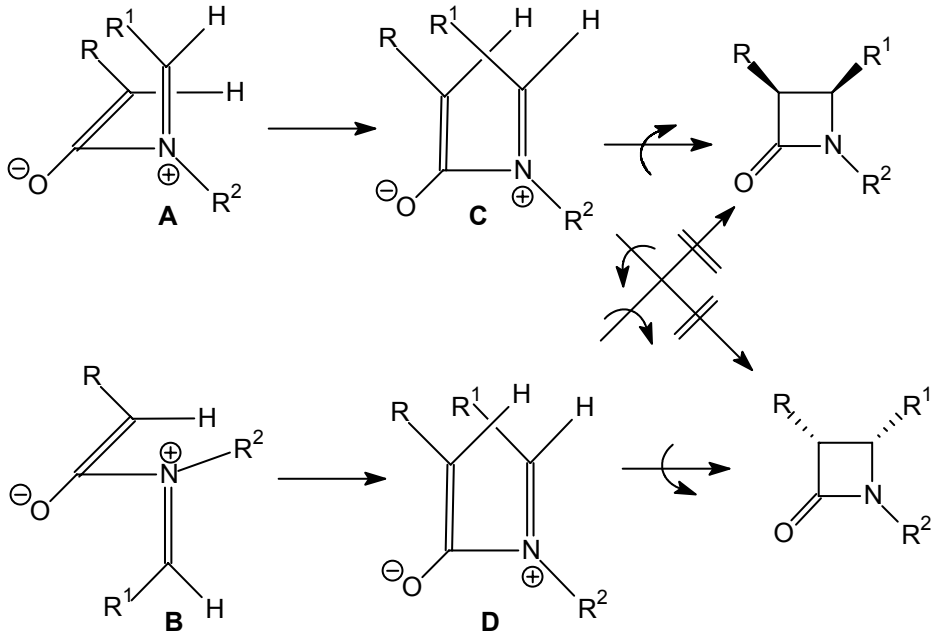
R^1 = COPh, $COOCH_3$, CH_2Cl, CH_2F

Asymmetric Induction:

Asymmetry can be induced in ketene-imine cycloaddition by controlling the orientation of the imine with respect to the plane of the ketene. The ketene can be approached by the imine either from the top face or from bottom face to produce two possible zwitterionic intermediates **A** and **B** respectively (Scheme 1.37). Before conrotatory ring closure can take place, the intermediates **A** and **B** have to undergo 90° rotation around the C-N bond to produce two more intermediates **C** and **D** respectively. The conrotatory ring closure of these intermediates **C** and **D** will produce enantiomeric *cis* β-lactams. These intermediates **C** and **D** can also be formed from **A** and **B** by rotating through 270° around the C-N bond. According to the principle of least motion, the transformation of **A** to **C** and **B** to **D** is favored, as this requires only 90° rotation.

It has been pointed out by Hegedus et al.[62a] that the conrotatory ring closure of the intermediate **C** can occur only in clockwise direction 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**, which can undergo only counterclockwise conrotatory ring closure.

Scheme 1.37



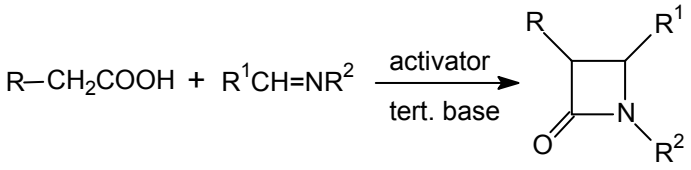
1. 2 : Background for the present work

Since the discovery of β-lactam antibiotics, the development of synthetic methods for the construction of azetidin-2-one ring has been the object of intense study by number of research groups. Among the various methods available for the synthesis of β-lactams, the Staudinger reaction has found wide acceptance.[17] This is mainly because of its simplicity, versatility and predictability of stereochemical outcome and typically proceeds with good stereoselectivity, depending on reaction condition[67] and substituents.[68]

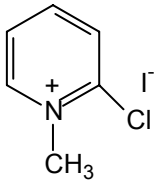
Ketenes can be generated thermally,[68] photochemically[40b] or from acid chlorides in presence of a tertiary base. The Staudinger reaction for the synthesis of β-lactams usually involves the reaction between an imino compound and an acid chloride in presence of a tertiary base. However, this method is not convenient when the acid chloride is not commercially available or difficult to prepare. In such cases, an alternate method is adopted which involves the use of carboxyl group activating agents called *acid activators* (Scheme1.38). The reaction carried out with acid activators essentially follows the same stereochemical pattern as observed in the reaction with acid chlorides.

Various reagents[17] like ethylchloroformate,[69] trifluoroacetic anhydride,[70] p-toluenesulphonyl chloride[71]and several phosphorous derived reagents[72] have been used as acid activators in the Staudinger reaction.

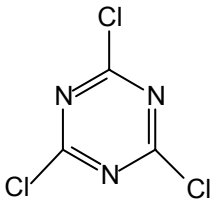
Scheme 1.38



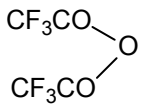
Some of the reagents used as acid activators in the Staudinger reaction for β-lactam synthesis are listed below (Fig.7).



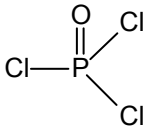
2-chloro-N-methylpyridinium iodide[66,73]



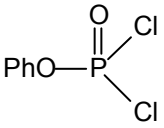
Cyanuric chloride[74]



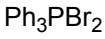
Trifluoroacetic anhydride[70]



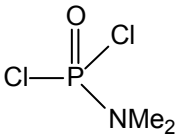
Phosphorous oxychloride[75]



Phenyl dichlorophosphate[72a,b,76]



Triphenylphosphine dibromide[77]

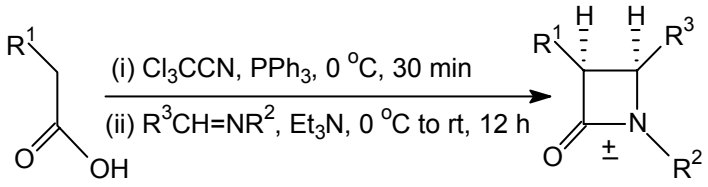


N, N-Dimethylphosporamide dichloride[72e]

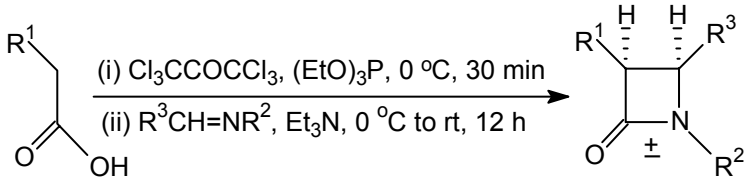
Fig. 7: Reagents used as acid activators in Staudinger reaction

Our group has reported the use of combination of Trichloroacetonitrile-Triphenylphosphine[78] and also a combination of Hexachloroacetone-Triethylphosphite,[79] as efficient acid activators for Staudinger reaction for azetidin-2-one synthesis. (Scheme 1.39 & Scheme 1.40).

Scheme 1.39



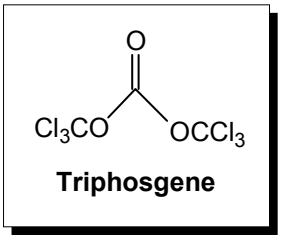
Scheme 1.40



R^1 = PhO, MeO, PhthN; R^2 = PMP, Ph, Benzyl; R^3 = PMP, Ph, Styryl

1. 3 : Present work

We were interested in developing a mild and efficient acid activator for the synthesis of azetidin-2-ones *via* the Staudinger reaction. Triphosgene [bis(trichloromethyl)carbonate] (BTC), has emerged as a versatile synthetic reagent for the synthesis of some important class of organic compounds.[80] This white crystalline solid has proved to be safe and advantageous over its gaseous congener, phosgene. As triphosgene was already employed in the preparation of acid chlorides and anhydrides from carboxylic acids,[80] we envisaged that it could as well function as an acid activator in the Staudinger reaction under mild reaction condition, for the synthesis of azetidin-2-ones. This section describes the synthesis of various substituted azetidin-2-ones under very mild reaction condition using triphosgene as an acid activator.



Triphosgene

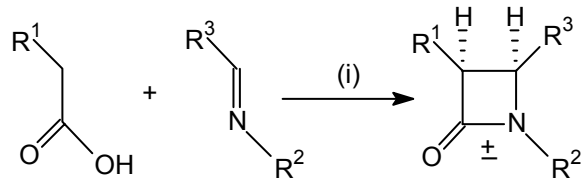
1. 4 : Results and Discussion

1. 4. 1 : Preparation of azetidin-2-ones 1.03a-j.

In a typical procedure, a solution of triphosgene (0.5 mmol) in dichloromethane was slowly added to a cooled (-40^{o}C) mixture of phenoxy acetic acid **1.01a** (1 mmol), imine **1.02a** (1 mmol), (derived from *p*-anisidine and benzaldehyde) and triethylamine (3 mmol) in dichloromethane. After the completion of addition, the reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 12h. After completion of reaction (by TLC), the reaction mixture was diluted with dichloromethane and the organic layer was washed successively with water, saturated sodium bicarbonate

solution and brine solution and dried over anhydrous sodium sulphate. Removal of solvent, followed by column chromatography of the residue gave a white solid **1.03a** (Scheme 1.41).

Scheme 1.41



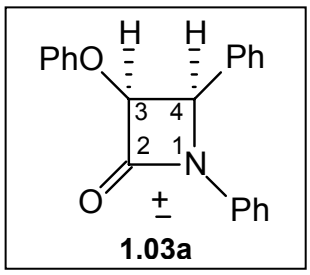
1.01 **1.02** **1.03a-j**

Reagents and condition: (i) NEt_3, triphosgene, CH_2Cl_2, -40 °C to rt, 12 h

The IR spectrum of the compound **1.03a** showed a strong band at 1755 cm^{-1} characteristic of the β-lactam carbonyl group. The ^1H NMR and ^{13}C NMR spectra of **1.03a** confirmed its structure. The ^1H and ^{13}C NMR spectra of **1.03a** are discussed below.

The ^1H NMR spectrum of **1.03a** showed doublets at 5.45 ppm and 5.60 ppm (J = 4.8 Hz) corresponding to the C-4 and C-3 β-lactam protons. The aromatic protons appeared as multiplets between 6.75 to 7.50 ppm. The *cis* stereochemistry of the C-3 and C-4 protons was confirmed from the coupling constant value of J = 4.8 Hz, which is characteristic of *cis* β-lactam.

The ^{13}C NMR spectrum of **1.03a** showed a peak at 162.80 ppm corresponding to β-lactam carbonyl carbon. The aromatic quaternary carbon bearing the –OMe group and the aromatic quaternary carbon attached to nitrogen of β-lactam ring appeared at 156.55 ppm and 136.60 ppm. The other aromatic quaternary carbon attached to the oxygen atom appeared at 132. 26 ppm. The remaining aromatic carbons resonated at 128.88, 128.40,128.07, 127.81, 124.32, 121.89, 117.26, 115.35. The C-3 and C-4 carbons of β-lactam ring appeared at 80.76 ppm and 61.61 ppm. This compound also gave satisfactory elemental analysis and the mass spectrum gave a molecular ion peak at (m/z) 315. The yield of β-lactam **1.03a** was also excellent (89%).



1.03a

In order to explore the generality of this method, several other substituted azetidin-2-ones (**1.03b-j**) were synthesized (Scheme 1.41) as summarized in Table 1. All

the compounds were characterized by spectral and analytical data. The IR spectrum of all the compounds **1.03b-j** showed the peaks in the expected region 1760 cm^{-1} to 1740 cm^{-1} corresponding to the β-lactam carbonyl and the ^1H NMR showed two sets of doublets in the region 4.80 ppm to 5.50 ppm for the C-3 and C-4 protons of the β-lactam ring with coupling constants 4.0 to 5.5 Hz indicating the *cis* stereochemistry. This method was found to be very clean and mild. Triphosgene was found to be better than other acid activators in terms of yields and simplicity of work up procedures. For example, the yields of azetidin-2-ones **1.03a** (95%) and **1.03f** (87%) were better than that of reported method using Mukaiyama's reagent[66] wherein the yields were 84% and 72% for **1.03a** and **1.03f**. It can be seen from the table that the yields were excellent in case of phenoxy and methoxy acetic acid but in case of dichloro phenoxyacetic acid, the yields were slightly low. However, in all the cases, the ketene-imine cycloaddition reaction was stereoselective, giving only *cis*-β-lactam.

Table 1: *Synthesis of azetidin-2-ones* **1.03a-j** *from acids* **1.01a-j** *and imines* **1.02a-j**.

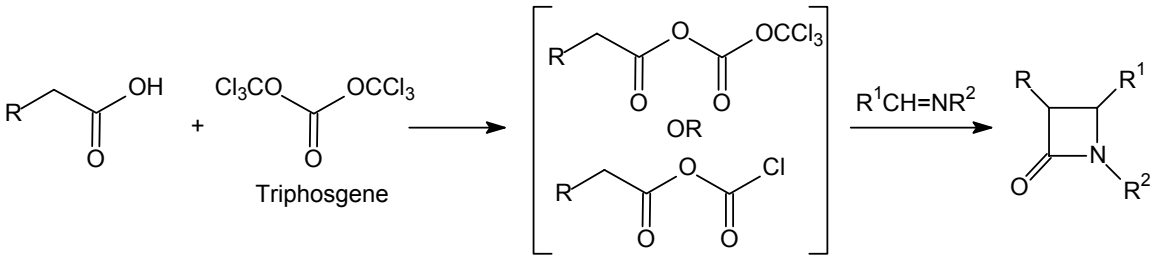
Compound	R^1	R^2	R^3	Yield (%)	MP (^{0}C)
1.03a	PhO	Ph	Ph	89	184
1.03b	PhO	PMP	Ph	95	186-188
1.03c	PhO	Ph	PMP	83	150
1.03d	PhO	PMP	PMP	82	166-167
1.03e	PhO	PMP	Styryl	93	178-180
1.03f	MeO	PMP	Ph	87	160-161
1.03g	MeO	Ph	PMP	86	129-130
1.03h	MeO	PMP	PMP	83	114-115
1.03i	2,4-Cl_2PhO	PMP	Ph	65	148-150
1.03j	2,4-Cl_2PhO	Ph	PMP	66	164-165

In all cases PMP = 4-$MeOC_6H_4$

Mechanism:

We envisage that, the reaction proceeds *via* initial formation of anhydride **A** that subsequently reacts with the imine to yield the azetidin-2-one (Scheme 1.42).

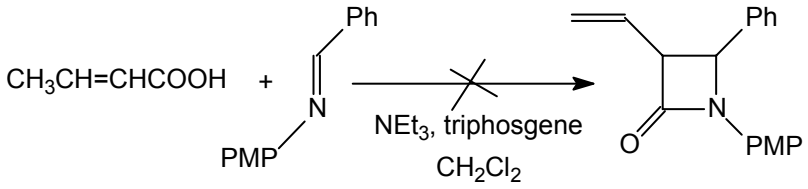
Scheme 1.42



A

We wanted to extend this methodology for synthesizing 3-vinyl-β-lactams[81] **1.06** from crotonic acid **1.04**. Reaction of crotonic acid with imine **1.05** and triethylamine, using triphosgene as acid activator however failed to give the expected 3-vinyl- β-lactam **1.06** (Scheme 1.43).

Scheme 1.43



1.04 **1.05** **1.06**

1. 5 : Summary

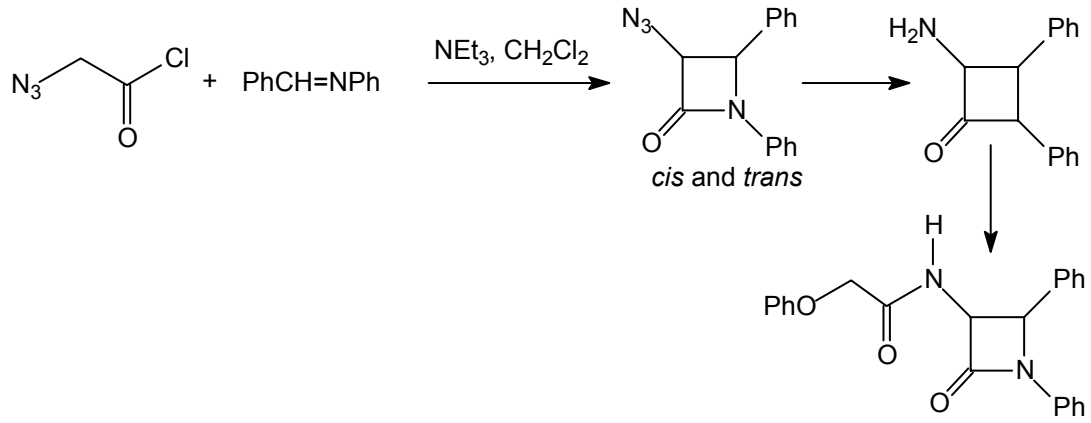
Triphosgene was successfully employed as acid activator for synthesis of azetidin-2-ones *via* Staudinger reaction. A series of azetidin-2-ones were synthesized in excellent yields. The reaction condition was very mild and in all the cases, the ketene imine cycloaddition reaction was stereoselective giving only *cis* β-lactams.

1. 6 : Background for the present work

Many β-lactam antibiotics like penicillin, cephalosporin contain 3-amido-azetidin-2-one unit as a part of their structure. Therefore, synthetic approaches towards such antibiotics and their analogues require an easy access to the 3-amido- β-lactams. As a result, the synthesis of 3-amino azetidin-2-ones has received much attention over the past several years.

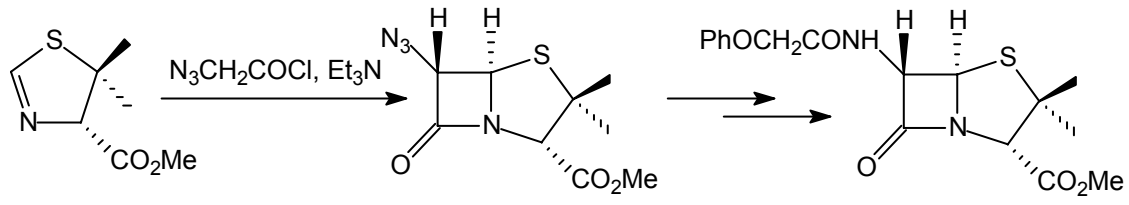
Bose et al.[67] have reported a method for the synthesis of 3-amido-β-lactam that utilizes an azido group as a latent amino function which can be reduced to amino group without affecting the β-lactam ring (Scheme 1.44).

Scheme 1.44



Later, Bose et al.[82] employed this method for the synthesis of 6-*epi*-penicillin (Scheme 1.45).

Scheme 1.45



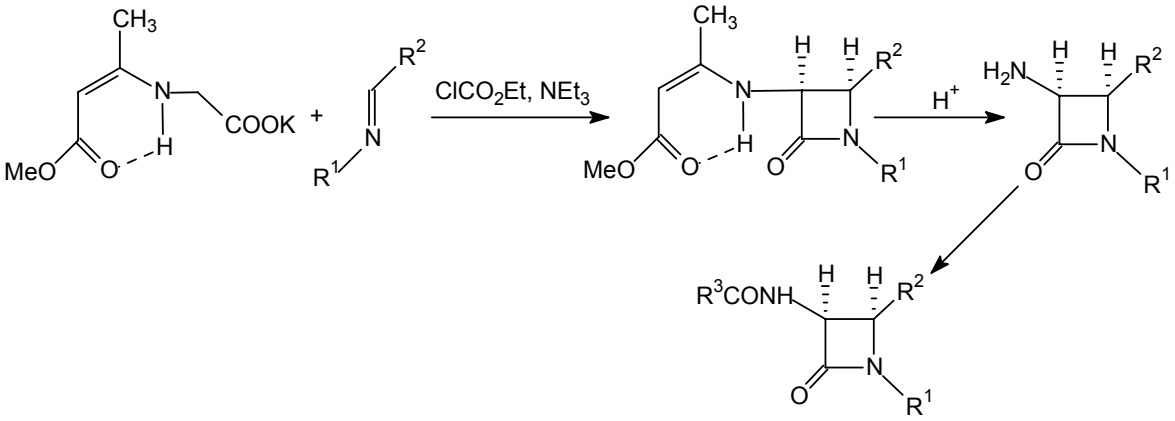
Several other research groups,[83] have also utilized the 3-azido-β-lactam for the total synthesis of various β-lactam antibiotics.

One drawback of the 3-azido-β-lactam approach is the potential explosive nature of azido acetic acid and its derivatives. To overcome this problem, other latent forms of

amino groups like activated phthalimidoacetic acid[84] and Dane salt[74,85] of amino acetic acid are also used.

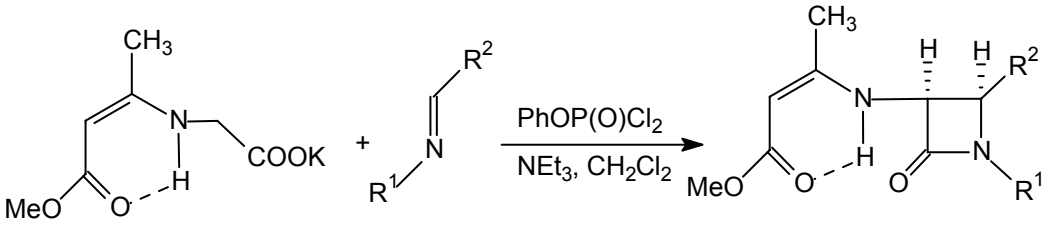
Bose et al.[69,85,86] have used Dane salt in presence of ethylchloroformate as an activating agent for the synthesis of 3-(β-carbonyl-vinyl amino)-azetidin-2-ones *via* Staudinger reaction in 40-60% yield. Removal of the protecting group with PTSA afforded the *cis* 3-amino-azetidin-2-ones, which was acylated to yield 3-amido-azetidin-2-ones (Scheme 1.46).

Scheme 1.46



Palomo et al.[87] have used phenyl dichlorophosphate as an efficient acid activator for Dane salt and obtained 3-vinylamino- azetidin-2-ones in 40-60% yields (Scheme 1.47)

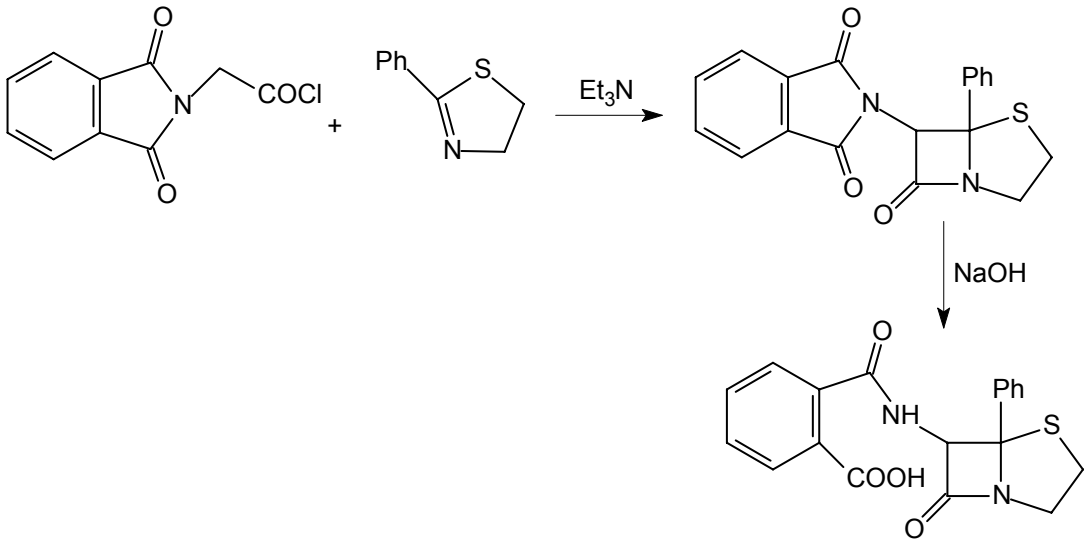
Scheme 1.47



Cyanuric chloride[74] and phosphorous oxychloride[88] have also been used as activators for Dane salt in the Staudinger reaction for the synthesis of β-lactams.

Sheehan et al.[89] have synthesized substituted penicillin and simpler analogs wherein the key step of the synthesis was the cycloaddition reaction between phthalimidoacetyl chloride and 2-phenyl-2-thiaozoline in presence of triethylamine to get 2-phenyl-2-phthalimido-2-thiazolidine acetic acid β-lactam (Scheme 1.48).

Scheme 1.48



1. 7 : Present work

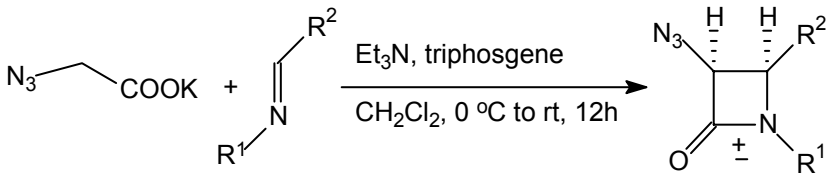
3-Amino-azetidin-2-ones serves as synthons for variety of β-lactam antibiotics and hence their synthesis has acquired immense importance over the years. In this section, we describe an efficient route for the synthesis of azetidin-2-ones from potassium salt of azido acetic acid, Dane salt and phthalimidoacetic acid *via* Staudinger reaction, using triphosgene as an activating agent. All these β-lactams serve as precursors for 3-amino-azetidin-2-ones.

1. 8 : Results and Discussion

1. 8. 1: Preparation of azetidin-2-ones 1.09a & 1.09b from potassium salt of azido acetic acid 1.07.

A solution of triphosgene in anhydrous CH_2Cl_2 was added to a well cooled (0 ^oC) CH_2Cl_2 solution of potassium salt of azido acetic acid **1.07**, imine **1.08a** and triethylamine. After completion of addition, the reaction mixture was warmed up to room temperature and stirred at room temperature for 12h. Usual work up, after the completion of reaction (by TLC) gave the crude product, which was purified by column chromatography to get white solid **1.09a** (melting point: 120-122 ^oC) (Scheme 1.49).

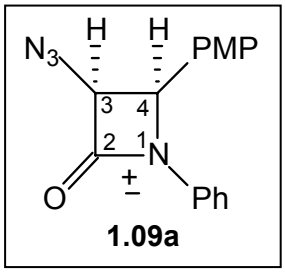
Scheme 1.49



1.07 **1.08** **1.09a,b**

a R^1 = Ph; R^2 = PMP
b R^1 = PMP; R^2 = Styryl

The IR spectrum of **1.09a** showed bands at 1740 cm^{-1} and at 2140 cm^{-1} corresponding to the β-lactam carbonyl and the azido group respectively. The ^1H NMR and ^{13}C NMR spectra of **1.09a** showed the characteristic peaks, confirming that **1.09a** is the required 3-azido-azitidin-2-one. The ^1H and ^{13}C NMR spectra of **1.09a** are discussed below.



1.09a

The ^1H NMR spectrum showed a singlet at 3.80 ppm corresponding to the -OMe protons. Doublets at 5.35 ppm with J = 5 Hz and at 5.00 ppm with J = 5.0 Hz corresponded to the C-3 and C-4 protons of the β-lactam ring. The coupling constant value (J = 5.0 Hz) confirmed the *cis* stereochemistry of the C-3 and C-4 protons. The aromatic protons appeared as multiplets between 6.90 ppm to 7.50 ppm.

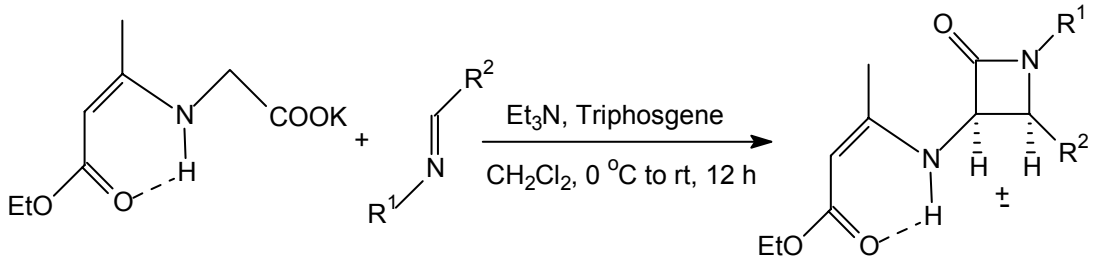
The ^{13}C NMR spectrum of **1.09a** showed a peak at 161.22 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbon bearing the –OMe group appeared at 160.10 ppm and the other aromatic quaternary carbon attached to the nitrogen of the β-lactam ring resonated at 136.99 ppm. The –OMe carbon appeared at 55.31 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 67.66 and 60.61 ppm. The other aromatic carbons appeared at 114.57, 117.62, 124.45, 124.75, 128.94 and 129.23 ppm respectively. This compound also gave satisfactory elemental analysis.

Similarly, the 3-azido-azetidin-2-one **1.09b** (Scheme 1.49) was also prepared by treating potassium salt of azido acetic acid **1.07** with imine **1.08b** (derived from trans-cinnamaldehyde and *p*-anisidine) in presence of NEt_3 using triphosgene as acid activator. It was characterized by spectral and analytical data

1. 8. 2: Preparation of azetidin-2-ones 1.12a-c from Dane salt 1.10.

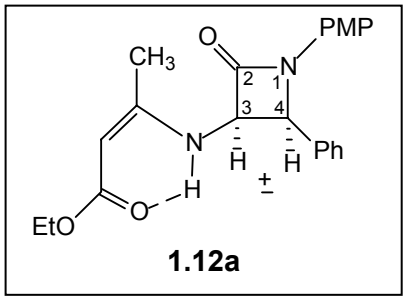
Dane salt **1.10** was prepared by reported procedure[85a,b] from glycine and ethylacetoacetate. Anhydrous dichloromethane solution of triphosgene was slowly added to a cooled (0 ^{o}C) CH_2Cl_2 solution of Dane salt **1.10**, imine **1.11a** (derived from benzaldehyde and *p*-anisidine) and triethylamine. After completion of addition, the reaction mixture was stirred at room temperature for 12h. Usual work up followed by purification by column chromatography, gave a white solid **1.12a** (melting point: 140 ^{o}C) (Scheme 1.50).

Scheme 1.50



1.10 **1.11** **1.12a-c**

The IR spectrum of **1.12a** showed a peak at 1753 cm^{-1} corresponding to the β-lactam carbonyl. The ^{1}H NMR and ^{13}C NMR spectra of **1.12a** showed the characteristic peaks thereby confirming the structure of **1.12a**. The ^{1}H and ^{13}C NMR spectra of **1.12a** are discussed below.



1.12a

The ^{1}H NMR spectrum showed a triplet (J = 7.1 Hz) at 1.10 ppm corresponding to the methyl protons of the –CO_2Et group. The protons of the –CH_3 group attached to the double bond appeared as a singlet at 1.85 ppm. The protons of the -OMe group attached to the aromatic ring gave a singlet at 3.75 ppm and the two –OCH_2 protons of the -CO_2Et group appeared as quartet (J =7.1 Hz) at 3.90 ppm. The olefinic proton appeared as singlet at 4.40 ppm. The C-3 proton appeared as doublet of doublet (J = 4.9 Hz, 8.8 Hz) at 5.15 ppm and the C-4 proton appeared as a doublet (J = 4.9 Hz) at 5.35 ppm The coupling constant value (J = 4.9 Hz) showed that the β-lactam protons are *cis* to each other. The aromatic protons appeared as multiplets between 6.80 ppm to 7.50 ppm. The –NH proton showed a doublet (J = 8.8 Hz) at 8.60 ppm.

The ^{13}C spectrum of **1.12a** showed a signal at 163.24 ppm corresponding to the β-lactam carbonyl. The ester carbonyl appeared at 169.13 ppm. The methyl carbon of the $–CO_2Et$ appeared at 14.19 ppm, the carbon of the methyl group attached to the double bond appeared at 19.45 ppm and the $-CH_2$ carbon of $–CO_2Et$ group appeared at 58.23 ppm. The carbon of the –OMe group appeared at 55.21 ppm and the two β-lactam carbons, C-3 and C-4 appeared at 63.30 and 61.61 ppm. The olefinic –CH appeared at 86.27 ppm and the olefinic quaternary carbon appeared at 132.77 ppm. The aromatic quaternary carbons appeared at 131.00, 156.22 and 158.21 ppm and other aromatic carbons appeared at 114.21, 118.55, 127.00, 128.69 and 128.91. This compound also gave satisfactory elemental analysis. The β-lactam **1.12a** was obtained in 70% yield.

Following the same procedure, azetidin-2-ones **1.12b-c** were prepared from Dane salt using triphosgene as acid activator (Scheme 1.50, Table 2). All the compounds were characterized by spectral (Table 3) and analytical techniques. The yields of the β-lactams were found to be better than other acid activators[87] and the reaction condition was also very mild. In all the cases, the reaction was stereoselective giving only *cis* β-lactams **1.12a-c**.

Table 2: *Synthesis of azetidin-2-ones* **1.12a-c** *from Dane salt* **1.10**

Compound	R^1	R^2	Yield (%)	MP (^oC)
1.12a	PMP	Ph	70	140
1.12b	PMP	PMP	65	118-120
1.12c	PMP	Styryl	73	115-116

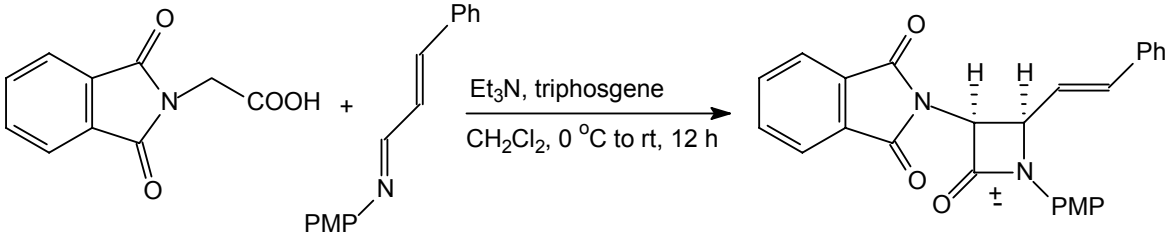
Table 3: *^1H NMR data for the azetidin-2-ones* **1.12a-c**

Compound No	Chemical shifts and *J* values of C-3 & C-4 protons of β-lactam **1.12**	
	C-3 H	C-4 H
1.12a	5.15 (dd, *J* = 4.9 & 8.8 Hz)	5.35 (d, *J* = 4.9 Hz)
1.12b	5.14 (dd, *J* = 5.4 & 8.8 Hz)	5.23 (d, *J* = 5.4 Hz)
1.12c	5.10 (dd, *J* = 5.1 & 9.5 Hz)	4.80 (dd, *J* = 5.1 & 8.1 Hz)

1. 8. 3: Preparation of azetidin-2-one 1.15 from Phthalimidoacetic acid 1.13.

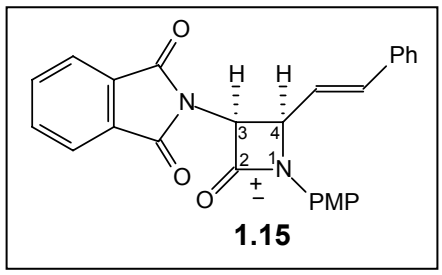
Anhydrous dichloromethane solution of triphosgene was added to a cooled (0 ^{o}C) CH_2Cl_2 solution of phthalimidoacetic acid **1.13,** imine **1.14** and triethylamine. After completion of addition, the reaction mixture was warmed up to room temperature and stirred for 12h. Usual work up gave the crude product, which was purified by column chromatography to obtain **1.15** as a white solid (melting point: 189-190 ^{o}C, Lit[72e] 192-194 ^{o}C) (Scheme 1.51).

Scheme 1.51



1.13 **1.14** **1.15**

The IR spectrum of **1.15** showed a band at 1728 cm^{-1} characteristic of β-lactam carbonyl group. The structure of **1.15** was further confirmed by the ^{1}H NMR and ^{13}C NMR spectra as discussed below.



1.15

The ^{1}H NMR spectrum of **1.15** showed a singlet at 3.75 ppm corresponding to the protons of –OMe group.The C-3 proton of the β-lactam ring appeared as a doublet at 5.70 ppm (J = 5.8 Hz) and the C-4 proton appeared as doublet of doublet at 5.00 ppm (J = 5.8 Hz, 8.45 Hz). The *cis* stereochemistry of the C-3 & C-4 protons of the β-lactam ring was confirmed from the coupling constant value of 5.8 Hz. The –CH proton of the styryl side chain at C-4 appeared as doublet of doublet at 6.40 ppm (J = 8.45 Hz, 16.1 Hz). The aromatic protons and the other styryl proton attached to the aromatic ring appeared as multiplets between 6.80 ppm to 7.90 ppm.

The ^{13}C NMR spectrum of **1.15** showed a peak at 160.69 ppm corresponding to the β-lactam carbonyl. The keto carbonyls of the phthalimido ring appeared at 167.34 ppm. The aromatic quaternary carbon bearing the –OMe group of the *p*-anisyl moiety appeared at 156.57 ppm. The aromatic quaternary carbon attached to the nitrogen of the

β-lactam ring appeared at 137.64 ppm. The other aromatic quaternary carbon appeared at 135.54 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 57.84 ppm and 61.11 ppm. The –OMe carbon appeared at 55.52 ppm. The other aromatic carbons and the two styryl carbons appeared at 134.55, 131.57, 131.35, 128.71, 126.80, 123.78, 123.01, 118.67 and 114.52 ppm. This compound also gave satisfactory microanalysis. The azetidin-2-one **1.15** was obtained in 78% yield, better than earlier reported method[72e] (55%).

In case of potassium salt of azido acetic acid, Dane salt and phthalimidoacetic acid, the addition of triphosgene was done at 0 ^{o}C. At lower temperature (-40 ^{o}C), there was a problem of solubility of these acids in dichloromethane.

1. 9 : Summary

Triphosgene was utilized as a very efficient acid activator for synthesis of azetidin-2-ones from potassium salt of azido acetic acid, Dane salt and phthalimido acetic acid *via* Staudinger reaction. In all the cases, the reaction was found to be stereoselective and gave only *cis* β-lactams in very good yields. The yields of β-lactams obtained by this method were better than those obtained by using other acid activators and reaction condition was also very mild. These β-lactams (**1.09**, **1.12** & **1.15**) serve as precursors for 3-amino-azetidin-2-ones, which are synthons for variety of β-lactam antibiotics.

1.10 : Present work

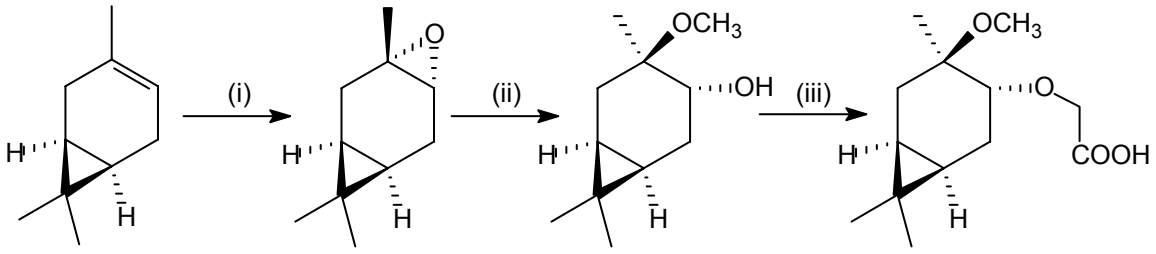
Asymmetric synthesis of β-lactams is an important area of research and of the various methods available; Staudinger reaction is the most preferred one. Both chiral acids and chiral imines have been used in the asymmetric Staudinger reaction (Asymmetric Staudinger reaction is discussed in detail in Introduction **1.1**). As triphosgene was found to be a very efficient acid activator for synthesis of azetidin-2-ones starting from various acids and also potassium salts of acids *via* Staudinger reaction (Section A & Section B), we were interested in extending this methodology to asymmetric synthesis of β-lactams starting from chiral acids. The chiral acids derived from (+)-3-carene, camphorsultam and oxazolidone were employed for this purpose.

1. 11 : Results and Discussion

1. 11. 1: Preparation of (+)-3-Carene derived chiral acid 1.19.

The (+)-3-carene derived chiral acid **1.19** was prepared from naturally occurring monoterpene, (+)-3-carene by the reaction sequence as shown below (Scheme 1.52). The carene epoxide **1.17**, prepared by known procedure[90] from carene, was regio and stereospecifically opened with methanol under acidic condition to get the methoxy alcohol[91] **1.18** in quantitative yield. The methoxy alcohol **1.18** was refluxed with Na and chloroacetic acid in toluene to get the required carene derived chiral acid **1.19**.

Scheme 1.52



Reagents and conditions: (i) $ClCO_2Et$, H_2O_2, Na_3PO_4, CH_2Cl_2. (ii) CH_3OH, PTSA, 2 h. (iii) Na, $ClCH_2CO_2H$, toluene.

The structure of the acid **1.19** was confirmed from the spectral and mass data, as discussed below.

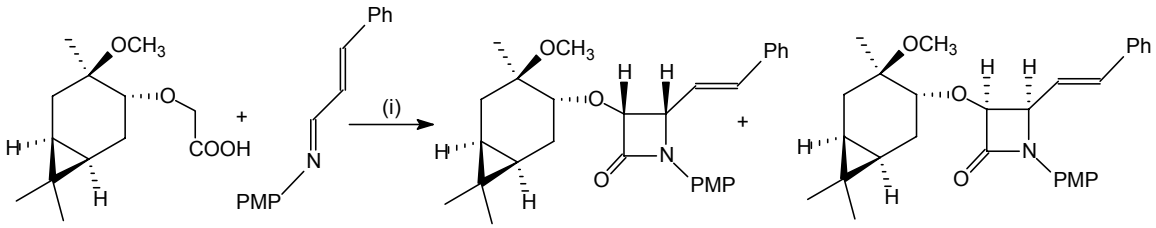
The IR spectrum of **1.19** showed bands at 1731 cm^{-1} and at 3600-2600 cm^{-1} characteristic of carboxylic acid.

The ^{1}H NMR spectrum of **1.19** showed two singlets at 0.95 ppm and at 1.05 ppm for the *gem* dimethyl groups of carane moiety. The –CH protons of the cyclopropyl ring of the carane system appeared as multiplets between 0.50 ppm to 0.60 ppm. The protons of the angular methyl and methoxy groups were observed at 1.25 ppm and 3.38 ppm respectively. The methylene protons of the carane ring appeared as multiplets between 1.20 ppm to 2.40 ppm. The –CH proton of the carane moiety attached to the oxygen of the acid side chain appeared as multiplets between 3.20 ppm to 3.40 ppm. The methylene protons attached to the –COOH group appeared as two doublets at 3.90 ppm (J = 17.6 Hz) and at 4.35 ppm (J = 17.6 Hz). The carboxylic acid proton appeared as broad singlet at 9.30 ppm. The mass spectrum of **1.19** showed a molecular ion peak at (m/z) 242.

1. 11. 2: Preparation of azetidin-2-ones 1.21 & 1.22 from (+)-3-carene derived acid 1.19.

An anhydrous solution of triphosgene in dichloromethane was slowly added to a cooled (-40 ^{o}C) dichloromethane solution of acid **1.19** and imine **1.20** in presence of triethylamine. After completion of addition, the reaction mixture was allowed to come to room temperature and stirred at this temperature for 12 h. After completion of reaction (TLC), the reaction mixture was diluted with dichloromethane and washed successively with water, saturated bicarbonate solution and brine and the organic layer was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product as thick brown oil. The IR spectrum of the crude product showed a band at 1745 cm^{-1} inferring the presence of β-lactam carbonyl. The ^{1}H NMR of the crude reaction mixture showed two sets of signal confirming the presence of diastereomeric mixture of β-lactams **1.21** and **1.22** in the ratio 60:40 (Scheme 1.53). The diastereomers could not be separated by column chromatography. However, the major diastereomer could be separated by crystallization.

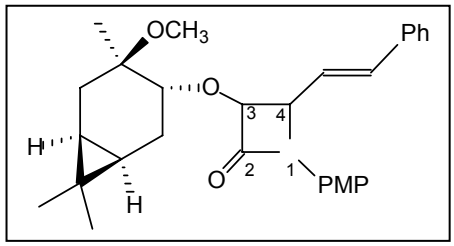
Scheme 1.53



1.19 **1.20** **1.21** **1.22**

Reagents and conditions: (i) Et_3N, triphosgene, CH_2Cl_2, -40 ^oC to rt, 12 h.

The major diastereomer was characterized by spectral and analytical data. The IR spectrum of the major diastereomer showed a band at 1740 cm^{-1} corresponding to the carbonyl of the β-lactam ring.



Major diastereomer

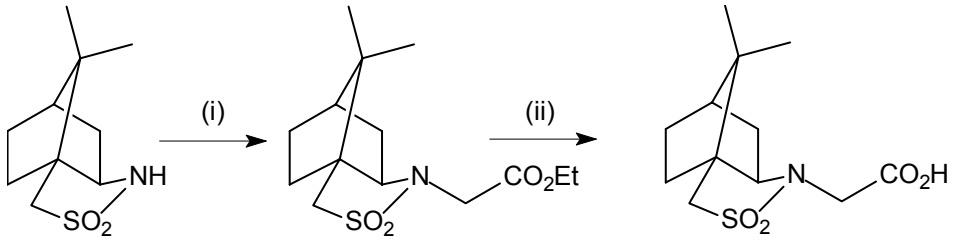
The ^1H NMR spectrum of major diastereomer showed singlets at 0.71 ppm and 0.87 ppm corresponding to the protons of *gem* dimethyl group. The protons of other methyl group and the –OMe group of the carane moiety appeared as singlets at 1.27 ppm and 3.27 ppm respectively. The –CH protons of the cyclopropyl ring of the carane system appeared as multiplets between 0.50 ppm and 0.65 ppm. The methylene protons of the carane system appeared as multiplets between 0.90 to 2.20 ppm. The –CH proton of the carane moiety attached to the oxygen atom of the acid side chain appeared as multiplets between 3.20 ppm to 3.40 ppm. The –OMe protons of the *p*-anisyl group appeared as singlet at 3.75 ppm. The C-4 proton of the β-lactam appeared as doublet of doublet at 4.70 ppm (J = 4.4 Hz, 8.7 Hz). The C-3 proton of the β-lactam ring appeared as doublet at 5.42 ppm (J = 4.4 Hz). The stereochemistry of the β-lactam protons was assigned as *cis* based on the coupling constant value of 4.4 Hz of C-3 and C-4 protons. One of the styryl protons appeared as doublet of doublet (J = 8.7 Hz, 16.0 Hz) at 6.37 ppm. Multiplets between 6.75 ppm to 6.95 ppm corresponded to the other styryl proton and two aromatic protons. The remaining aromatic protons appeared as multiplets between 7.15 ppm to 7.55 ppm.

The ^{13}C NMR spectrum of the major diastereomer showed a peak at 164 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbon bearing the methoxy group appeared at 156.10 ppm and the other aromatic quaternary carbon attached to the nitrogen atom of the β-lactam ring appeared at 135.90 ppm. The styryl olefinic carbon attached to the phenyl group appeared at 135.50 ppm. The quaternary aromatic carbon appeared at 131.50 ppm. The other styryl carbon and aromatic carbons appeared at 128.70, 128.20, 126.50, 125.10, 118.50 and 114.20 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 84.20 ppm and 81.90 ppm. The quaternary carbon of the carane ring bearing the methyl and methoxy group appeared at 78.20 ppm. The –CH carbon of the carane moiety attached to the oxygen atom appeared at 61.50 ppm. The –OMe carbon of the p-anisyl and the –OMe carbon of the Carane moiety appeared at 55.40 ppm and 48.90 ppm. The methylene carbons of the Carane ring appeared at 29.70 ppm and 26.20 ppm. The two methine carbons of the cyclopropyl group appeared at 28.20 ppm and 20.50 ppm. The $–CH_3$ carbon of the carane system appeared at 19.10 ppm. The quaternary carbon of the cyclopropyl group appeared at 17.60 ppm. The carbons of the gem dimethyl group appeared at 15.50 ppm and 14.80 ppm. This compound gave satisfactory elemental analysis.

1. 11. 3: Preparation of camphorsultam derived acid 1.25.

The camporsultam derived acid **1.25** was prepared by N-alkylation of Oppolzer's sultam[92] with ethylbromoacetate followed by hydrolysis using our earlier reported procedure[41] (Scheme 1.54).

Scheme 1.54



1.23 **1.24** **1.25**

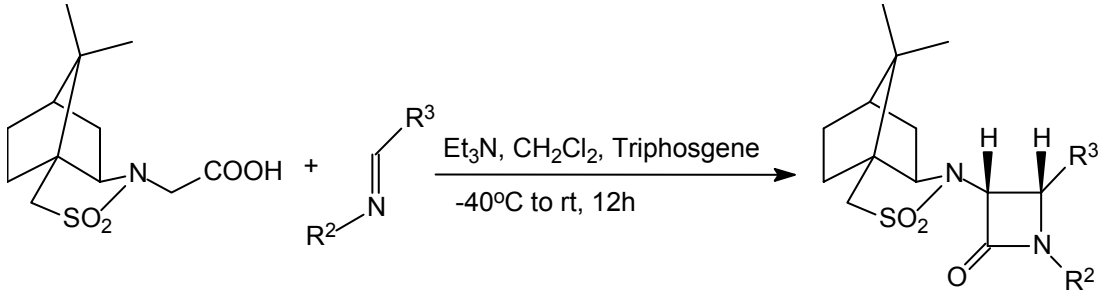
Reagents and conditions: (i) (a) NaH, THF, reflux, 1 h. (b) Bu_4NI, $BrCH_2CO_2Et$, rt, 3 h. (ii) MeOH, KOH, rt, 16 h.

1. 11. 4: Preparation of azetidin-2-ones 1.27a-c from Camphorsultam derived acid 1.25

An anhydrous solution of triphosgene in dichloromethane was slowly added to a cooled (-40 ^{o}C) dichloromethane solution of acid **1.25** and imine **1.26a** in presence of triethylamine. After completion of addition, the reaction mixture was allowed to come to room temperature and stirred at this temperature for 12 h. After completion of reaction (TLC), the reaction mixture was diluted with dichloromethane and washed successively with water, saturated bicarbonate solution and brine and the organic layer was dried over anhydrous sodium sulphate. The solvent was removed to get the crude product as brown solid (Scheme 1.55). The IR spectrum of the solid showed a band at 1753 cm^{-1} characteristic of β-lactam. The ^{1}H NMR spectrum of the crude product showed the presence of only one diastereomer and there was no trace of other diastereomer). Column purification gave **1.27a** as a white crystalline solid. The structure of **1.27a** was confirmed by comparing IR and NMR data, with the reported values.[41] The IR and NMR data of **1.27a** are discussed below.

The IR spectrum of **1.27a** gave a band at 1753 cm^{-1} corresponding to the β-lactam carbonyl.

Scheme 1.55

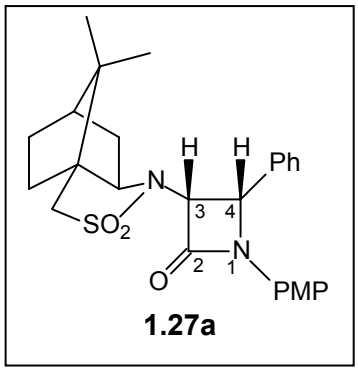


1.25 **1.26** **1.27a-c**

The ^{1}H NMR spectrum of **1.27a** gave singlets at 0.15 ppm and 0.70 ppm for the *gem* dimethyl groups of the sultam moiety. The multiplets between 1.25 ppm and 1.90 ppm corresponded to the methylene and methine protons of the chiral auxiliary. The methylene protons attached to the sulfonyl group of the sultam moiety appeared as doublets at 2.80 ppm and 3.10 ppm (J = 13.7 Hz). The methine proton of the chiral auxiliary bearing the nitrogen atom appeared as triplet with J = 7.5 Hz. The –OMe protons of the *p*-anisyl moiety appeared as a singlet at 3.75 ppm. The C-3 and C-4

protons of the β-lactam appeared as two merged doublets at 5.30 ppm. The two aromatic protons appeared as doublets at 6.85 ppm (J = 10.0 Hz). The remaining aromatic protons appeared as multiplets between 7.25 ppm and 7.50 ppm.

The ^{13}C NMR spectrum of **1.27a** showed a peak at 160.34 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbon bearing the –OMe group of the *p*-anisyl moiety appeared at 156.26 ppm. The aromatic quaternary carbon attached to the nitrogen of the β-lactam ring showed a peak at 133.47 ppm**.** The other aromatic quaternary carbon appeared at 130.64 ppm. The remaining aromatic carbons appeared at 114.17, 118.40, 127.48, 127.99 and 128.36 ppm respectively. The *gem* dimethyl carbons of the sultam moiety appeared at 18.75 ppm and 19.78 ppm. The four methylene carbons of the chiral auxiliary appeared at 26.51, 32.35, 37.24 and 48.19 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 65.28 ppm and 61.09 ppm. The two quaternary carbons of the sultam moiety appeared at 47.13 ppm and 49.70 ppm. The two methine carbons of the sultam moiety appeared at 44.74 ppm and 59.92 ppm. The –OMe carbon of the *p*-anisyl group appeared at 55.21 ppm. This compound also gave satisfactory elemental analysis.



1.27a

To ascertain the generality of this method, we prepared other substituted azetidin-2-ones **1.27 b** & **c**, using the same procedure, in very good yields (Scheme 1.55, Table 4). In all the cases **1.27a-c**, the reaction was diastereospecific giving only a single *cis* diastereomer

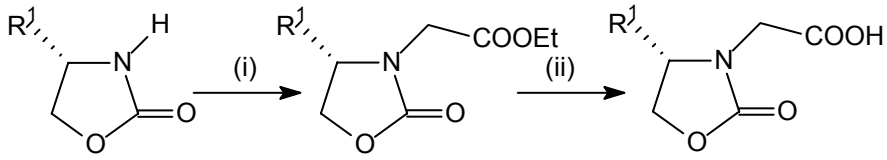
Table 4*: Synthesis of azetidin-2-ones* **1.27a-c** *from camphorsultam derived acid* **1.25**.

Compound	R^2	R^3	Yield (%)	MP (^{o}C)
1.27a	PMP	Ph	90	238-240
1.27b	PMP	PMP	90	210-212
1.27c	PMP	Styryl	82	204-206

1. 11. 5: Preparation of Oxazolidone derived chiral acids 1.30a-c.

The oxazolidone derived chiral acids (**1.30a-c**) were prepared by N-alkylation of chiral oxazolidones (**1.28a-c**) with ethyl bromoacetate followed by hydrolysis of the ester (**1.11a-c**) using a reported procedure[33] (Scheme 1.56).

Scheme 1.56



1.28a-c **1.29** **1.30a-c**

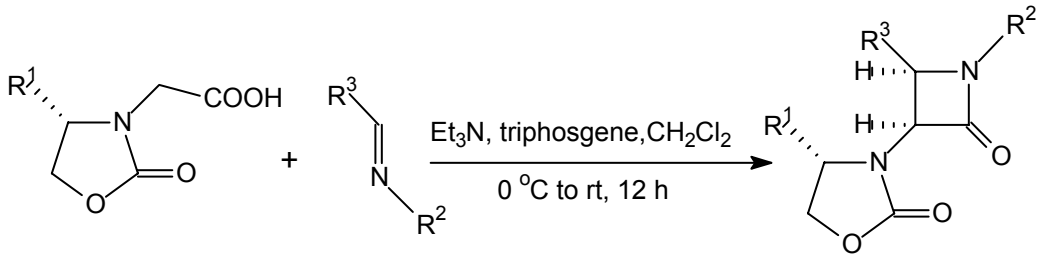
a R^1**=** Ph
b R^1**=** CH_2Ph
c R^1**=** *iso*-propyl

Reagents and conditions: (i) $BrCH_2CO_2Et$, NaH, THF, 0 ^oC. (ii) NaOH, THF-H_2O, 25 ^oC.

1. 11 .6: Preparation of azetidin-2-ones 1.32a-f from oxazolidone derived chiral acid 1.30.

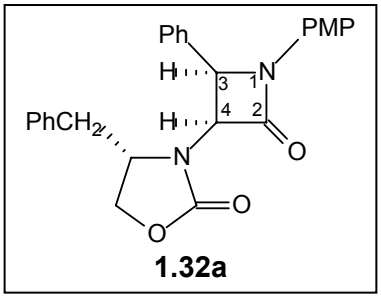
An anhydrous solution of triphosgene in dichloromethane was slowly added to a cooled (-40 ^oC) solution of acid **1.30** and imine **1.31a** in presence of triethylamine. After completion of addition, the reaction mixture was allowed to come to room temperature and stirred at this temperature for 12 h. After completion of reaction (TLC), the reaction mixture was diluted with dichloromethane and washed successively with water, saturated bicarbonate solution and brine and the organic layer was dried over anhydrous sodium sulphate. The solvent was removed to get the crude product as brown solid (Scheme 1.57). The IR spectrum of the brown solid showed a band at 1750 cm^{-1} characteristic of β-lactam. The ^1H NMR spectrum of the crude product showed the presence of only one diastereomer and there was no trace of other diastereomer. Column purification gave **1.32a** as a white crystalline solid. The structure of **1.32a** was confirmed from IR and NMR spectral data, as discussed below.

Scheme 1.57



1.30 **1.31** **1.32a-f**

The IR spectrum of **1.32a** showed a band at 1753 cm^{-1} corresponding to the β-lactam carbonyl.



1.32a

The ^{1}H NMR spectrum of **1.32a** showed a doublet of doublet with J = 13.2 Hz, 10.3 Hz at 1.80 ppm and a doublet of doublet (J = 13.2 Hz, 3.9 Hz) at 2.95 ppm (each doublet of doublet integrating for one proton) corresponding to the methylene protons of oxazolidone ring. The methylene protons of the benzylic group appeared as multiplets between 3.60 ppm and 3.90 ppm. The –OMe protons appeared as a singlet at 3.75 ppm. The -CH proton of oxazolidone group appeared as multiplets between 4.00 to 4.25 ppm. The C-3 and C-4 protons of the β-lactam ring appeared as doublets at 5.40 ppm (J = 4.9 Hz) and at 5.20 ppm (J = 4.9 Hz). The J value showed that the β-lactam protons are *cis* to each other. The aromatic protons appeared as multiplets between 6.85 ppm to 7.50 ppm.

The ^{13}C spectrum showed a peak at 160.34 ppm corresponding to β-lactam carbonyl and a peak at 157.47 ppm corresponding to the oxazolidone carbonyl. The aromatic quaternary carbon bearing the –OMe group appeared at 156.4 ppm and the aromatic quaternary carbon attached to nitrogen of the β-lactam ring appeared at 135.09 ppm. The other aromatic quaternary carbons appeared at 133.30 and 130.82 ppm. The methine and methylene carbons of the oxazolidone ring appeared at 55.29 and 67.60 ppm. The methylene carbon of the benzylic group appeared at 39.96 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 63.08 and 60.58 ppm. The carbon of the -OMe group appeared at 55.36 ppm. The other aromatic carbons appeared 114.28, 118.40, 127.00, 127.30, 128.25, 128.40 and 128.73 ppm respectively.

Following the optimized procedure, we made several β-lactams **1.30b-f** (Scheme 1.57, Table 5) from oxazolidone derived acid **1.30** using triphosgene as acid activator. All the β-lactams were completely characterized by spectral and analytical data. This method gave very good yields of β-lactams **1.32a-f**. In all the cases, the reaction was diastereospecific giving only single diastereomer of *cis* β-lactam.

Table 5: *Synthesis **of** azetidin-2-ones* **1.32a-f** *from oxazolidone derived acid* **1.30**

Compound	R^1	R^2	R^3	Yield (%)	MP (^oC)
1.32a	CH_2Ph	PMP	Ph	67	194
1.32b	Ph	CH_2Ph	Ph	70	220-222
1.32c	CH_2Ph	CH_2Ph	Ph	70	151
1.32d	*iso*-propyl	PMP	Ph	71	215-217
1.32e	*iso*-propyl	PMP	PMP	72	200-202
1.32f	*iso*-propyl	CH_2Ph	Ph	70	185

1.12 : Summary

Triphosgene was efficiently utilized as an acid activator in the asymmetric Staudinger reaction for the synthesis of β-lactams from chiral acids designed from (+)-3-carene, camphorsultam and oxazolidone. In case of carene derived acid, a diastereomeric mixture (60:40 ratio) of *cis* β-lactams were obtained. In case of sultam and oxazolidone derived acids, the reaction was diastereospecific giving single diastereomer of *cis* β-lactam. In all the cases, the yields of azetidin-2-ones were found to be very good.

Section A

1. 13 : Experimental

1. 13. 1 : General procedure for the synthesis of azetidin-2-ones 1.03a-j

A solution of triphosgene (0.148 g, 0.5 mmol), in anhydrous CH_2Cl_2 (10 ml), was added slowly to a solution of acid (**1.01**, 1 mmol), imine (**1.02**, 1 mmol) and triethylamine (0.42 ml, 3 mmol) in anhydrous CH_2Cl_2 (10 ml), at –40 ^oC. The reaction mixture was then allowed to warm up to room temperature and stirred further for 12 h. The reaction mixture was then washed with water (3 x 10 ml), saturated sodium bicarbonate solution (3 x 15 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and filtered through a short silica gel column to get pure β-lactams **1.03a-j**, which were recrystallized from methanol.

1. 13. 1a : Preparation of 1-phenyl-3-phenoxy-4-phenyl-azetidin-2-one 1.03a

Following the optimized procedure, treatment of phenoxyacetic acid (0.152 g, 1 mmol) with imine (0.181g, 1 mmol) derived from benzaldehyde and *p*-anisidine in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03a**, as a white solid (0.280 g, 89%).

MP : 184 ^oC.

IR ($CHCl_3$) : 1755 cm^{-1}.

^1H NMR ($CDCl_3$) (200MHz) : δ 5.45 (d, *J* = 4.8 Hz, 1H), 5.60 (d, *J* = 4.8 Hz, 1H), 6.75-7.50 (m, 15 H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 61.61, 80.76, 115.35, 117.26, 121.89, 124.32, 127.81, 128.07, 128.40, 128.88, 128.95, 132.26, 136.60, 156.55, 162.80.

MS (m/z) : 315 (M^+).

Analysis ($C_{21}H_{17}NO_2$) : Calculated: C, 79.98; H, 5.43; N, 4.44
Observed: C, 79.73; H, 5.20; N, 4.37.

1. 13. 1b : Preparation of 1-(4-methoxyphenyl)-3-phenoxy-4-phenylazetidin-2-one 1.03b

Following the optimized procedure, treatment of phenoxyacetic acid (0.152 g, 1 mmol) with imine (0.211 g, 1 mmol) derived from benzaldehyde and *p*-anisidine in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03b**, as a white solid (0.328 g, 95%).

MP : 186-188 ^{o}C.

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.74 (s, 3H), 5.35 (d, *J* = 4.0 Hz, 1H), 5.55 (d, *J* = 4.0 Hz, 1H), 6.70-7.40 (m, 14H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.20, 61.90, 80.98, 114.16, 115.47, 118.67, 121.92, 127.92, 128.14, 128.48, 129.00, 132.43, 156.27, 156.50, 163.00.

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

Analysis ($C_{22}H_{19}NO_3$) : Calculated: C, 76.52; H, 5.51; N, 4.06.
Observed: C, 76.41; H, 5.69; N, 3.93.

1. 13. 1c : Preparation of 4-(4-methoxyphenyl)-1-phenyl-3-phenoxy-azetidin-2-one 1.03c

Following the optimized procedure, treatment of phenoxyacetic acid (0.152 g, 1 mmol) with imine (0.211 g, 1 mmol) derived from *p*-anisaldehyde and aniline in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03c** as a white solid (0.286 g, 83%).

MP : 150 ^{o}C (Lit[93] 149-150 ^{o}C).

IR ($CHCl_3$) : 1739 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 3.75 (s, 3H), 5.4 (d, *J* = 4.9 Hz, 1H), 5.60 (d, *J* = 4.9 Hz, 1H), 6.70-7.40 (m, 14H,).

^{13}C NMR ($CDCl_3$) (50.3 MHz) **:** 55.06, 61.64, 81.19, 113.87, 115.71, 117.54, 122.10, 124.42, 129.01, 129.16, 129.31, 136.99, 157.02, 159.85, 163.16.

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

Analysis ($C_{22}H_{19}NO_3$) **:** Calculated: C, 76.52; H, 5.51; N, 4.06
Observed: C, 76.33; H, 5.61; N, 4.23.

1. 13. 1d : Preparation of 1,4-di(4-methoxyphenyl)-3-phenoxy-azetidin-2-one 1.03d

Following the optimized procedure, treatment of phenoxyacetic acid (0.152 g, 1 mmol) with imine (0.240 g, 1 mmol) derived from *p*-anisaldehyde and *p*-anisidine, in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03d** as a white solid (0.307 g, 82%).

MP **:** 166-167 ^oC.

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

^{1}H NMR ($CDCl_3$) (200 MHz) **:** 3.80 (s, 6H), 5.40 (d, J = 5.2 Hz, 1H), 5.50 (s, J = 5.2 Hz, 1H), 6.70-7.50 (m, 13H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) **:** 54.95, 55.19, 61.59, 81.04, 113.63, 114.13, 115.48, 118.70, 121.87, 124.28, 129.01, 129.21, 130.27, 156.22, 156.81, 159.63, 162.33.

MS (m/z) **:** 375 (M^+).

Analysis ($C_{23}H_{21}NO_4$) **:** Calculated: C, 73.58; H, 5.68; N, 3.73
Observed: C, 73.37; H, 5.81; N, 3.84.

1. 13. 1e : Preparation of 1-(4-methoxyphenyl)-3-phenoxy-4-styryl-azetidin-2-one 1.03e

Following the optimized procedure, treatment of phenoxyacetic acid (0.152 g, 1 mmol) with imine (0.237 g, 1 mmol) derived from cinnamaldehyde and *p*-anisidine, in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03e** as a white solid (0.345 g, 93%)

MP : 178-180 ^{o}C.

IR ($CHCl_3$) : 1749 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 3.75 (s, 3H), 5.00 (dd, *J* = 4.4 Hz, 5.1 Hz, 1H), 5.50 (d, *J* = 4.4 Hz, 1H), 6.35 (dd, *J* = 5.1 Hz, 16.1 Hz, 1H), 6.75-7.50 (m, 15H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 57.68, 63.36, 83.72, 116.63, 117.96, 121.04, 124.55, 124.92, 128.90, 130.61, 130.83, 131.74, 133.00, 138.80, 139.17, 158.00, 159.63, 164.90.

MS (m/z) : 371 (M^{+}).

Analysis ($C_{24}H_{21}NO_3$) : Calculated: C, 77.61; H, 5.70; N, 3.77
Observed: C, 77.46; H, 5.82; N, 3.93.

1. 13. 1f : Preparation of 1-(4-methoxyphenyl)-3-methoxy-4-phenyl-azetidin-2-one 1.03f

Following the optimized procedure, treatment of methoxyacetic acid (0.180 g, 2 mmol) with imine (0.422 g, 2 mmol) derived from benzaldehyde and *p*-anisidine, in presence of triethylamine (0.84 ml, 6 mmol) and triphosgene (0.296 g, 1 mmol) as acid activator, gave the β-lactam **1.03f** as a white solid (0.492 g, 87%).

MP : 160-161 ^{o}C

IR (Nujol) : 1741 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 3.15 (s, 3H), 3.75 (s, 3H), 4.80 (d, *J* = 5.0 Hz, 1H), 5.20 (d, *J* = 5.0 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.20-7.40 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 57.63, 60.61, 64.04, 87.03, 116.53, 120.98, 130.16, 130.78, 132.81, 135.59, 158.54, 166.40.

MS (m/z) : 283 (M^{+}).

Analysis : Calculated: C, 72.08; H, 6.01; N, 4.94.
($C_{17}H_{17}NO_3$) Observed: C, 72.32; H, 6.12; N, 5.15.

1. 13. 1g : Preparation of 1-phenyl-3-methoxy-4-(4-methoxyphenyl)-azetidin-2-one 1.03g

Following the optimized procedure, treatment of methoxyacetic acid (0.180 g, 2 mmol) with imine (0.422 g, 2 mmol) derived from *p*-anisaldehyde and aniline, in presence of triethylamine (0.84 ml, 6 mmol) and triphosgene (0.296 g, 1 mmol) as acid activator, gave the β-lactam **1.03g** as a white solid (0.485 g, 86%).

MP : 129-130 ^{o}C.

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

^{1}H NMR ($CDCl_3$) (200 MHz) : 3.20 (s, 3H), 3.80 (s, 3H), 4.80 (d, J = 4.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H), 6.80-7.40 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 54.98, 58.11, 61.05, 84.46, 113.83, 117.25, 124.09, 124.82, 128.83, 129.01, 136.95, 159.67, 164.23.

MS (m/z) : 283 (M^+).

Analysis : Calculated: C, 72.08; H, 6.00; N, 4.94
($C_{17}H_{17}NO_3$) Observed: C, 71.88; H, 5.80; N, 4.93.

1. 13. 1h : Preparation of 1,4-di(4-methoxyphenyl)-3-methoxy-azetidin-2-one 1.03h

Following the optimized procedure, treatment of methoxyacetic (0.180 g, 2 mmol) acid with imine (0.482 g, 2 mmol) derived from *p*-anisaldehyde and *p*-anisidine, in presence of triethylamine (0.84 ml, 6 mmol) and triphosgene (0.296 g, 1 mmol) as acid activator, gave the β-lactam **1.03h** as white needles (0.519 g, 83%).

MP : 114-115 ^{o}C.

IR (Nujol) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) **:** 3.15 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.70 (d, *J* = 4.4 Hz, 1H), 5.10 (d, *J* = 4.4 Hz, 1H), 6.70 (d, *J* = 10.0 Hz, 2H), 6.85 (d, *J* = 10.0 Hz, 2H), 7.10-7.40 (m, 4H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) **:** 55.02, 55.20, 58.11, 61.19, 84.61, 113.83, 114.13, 118.61, 125.01, 129.09, 130.48, 156.10, 159.67, 163.64

MS (m/z) **:** 313 (M^+).

Analysis ($C_{18}H_{19}NO_4$) **:** Calculated: C, 68.99; H, 6.11; N, 4.47.
Observed: C, 68.84; H, 6.00; N, 4.64.

1. 13. 1i : Preparation of 1-(4-methoxyphenyl)-3-(2,4-dichlorophenoxy)-4-phenyl-azetidin-2-one 1.03i

Following the optimized procedure, treatment of 2,4-dichlorophenoxyacetic acid (0.221 g, 1 mmol) with imine (0.211 g, 1 mmol) derived from benzaldehyde and *p*-anisidine, in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03i** as a white solid (0.270 g, 65%).

MP **:** 148-150 ^oC.

IR ($CHCl_3$) **:** 1731cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) **:** 3.75 (s, 3H), 5.40 (d, *J* = 4.9 Hz, 1H) 5.55 (d, *J* = 4.9 Hz, 1H), 6.80-7.50 (m, 12H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) **:** 55.18, 61.28, 81.38, 114.21, 116.34, 118.69, 123.91, 127.15, 127.88, 128.25, 128.69, 129.68, 130.02, 132.04, 151.22, 156.41, 161.48.

MS (m/z) **:** 413 (M^+).

Analysis ($C_{22}H_{17}NO_3Cl_2$) **:** Calculated: C, 63.77; H, 4.11; N, 3.38; Cl, 17.16.
Observed: C, 63.57; H, 4.06; N, 3.27; Cl, 17.31.

1. 13. 1j : Preparation of 1-phenyl-3-(2,4-dichlorophenoxy)-4-(4-methoxy-phenyl)-azetidin-2-one 1.03j

Following the optimized procedure, treatment of 2,4-dichlorophenoxyacetic acid (0.221 g, 1 mmol) with imine (0.211 g, 1 mmol) derived from *p*-anisaldehyde and aniline, in presence of triethylamine (0.42 ml, 1 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.03j** as a white solid (0.273 g, 66%).

MP : 164-165 ^{o}C

IR (Nujol) : 1747 cm^{-1}

^{1}H NMR ($CDCl_3$) (300 MHz) : 3.75 (s, 3H), 5.35 (d, *J* = 4.4 Hz, 1H), 5.50 (d, *J* = 4.4 Hz, 1H), 6.80-7.40 (m, 12H)

^{13}C NMR ($CDCl_3$) (75.48 MHz) : 55.01, 60.93, 81.35, 113.79, 116.32, 117.21, 123.65, 123.95, 124.53, 127.19, 128.96, 129.23, 129.78, 136.59, 151.27, 159.84, 142.13

MS (m/z) : 413 (M^{+}).

Analysis ($C_{22}H_{17}NO_3Cl_2$) : Calculated: C, 63.77; H, 4.11; N, 3.38; Cl, 17.16
Observed: C, 63.84; H, 4.39; N, 3.22; Cl, 17.31.

Section B

1. 14 : Experimental

1. 14. 1 : General procedure for the preparation of azetidin-2-ones 1.09a,b from potassium salt of azido acetic acid 1.07

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added to a mixture of potassium salt of azido acetic acid (**1.07**, 1 mmol), imine (**1.08**, 1 mmol) and Et_3N (0.42 ml, 3 mmol) in CH_2Cl_2 at 0 ^oC. After completion of addition, the reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 12 h. The reaction mixture was washed with water (3 x 10 ml), saturated sodium bicarbonate solution (3 x 15 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was purified by column chromatography (silica gel 60-120 mesh, pet. ether/ethyl acetate, 80:20) to get pure β-lactams **1.09a,b**.

1. 14. 1a : Preparation of 3-azido-4-(4-methoxyphenyl)-1-phenyl-azetidin-2-one 1.09a

The potassium salt of azido acetic acid **1.07** (0.140 g, 1 mmol) on treatment with imine **1.08** (0.211 g, 1 mmol) derived from aniline and *p*-anisaldehyde in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) at 0 ^oC gave the crude product, which was purified by column chromatography to get the pure β-lactam **1.09a**, as a white solid (0.200 g, 68%).

MP : 120-122 ^oC.

IR ($CHCl_3$) : 1740 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : 3.80 (s, 3H), 5.00 (d, J = 5.4 Hz, 1H), 5.35 (d, J = 5.4 Hz, 1H), 6.90-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 55.31, 60.61, 67.66, 114.57, 117.62, 124.45, 124.75, 128.94, 129.23, 136.99, 160.48, 161.84.

MS (m/z) : 413 (M^+).

Analysis : Calculated: C, 68.56; H, 5.03; N, 14.99.
($C_{16}H_{14}N_3O_2$) Observed: C, 68.42; H, 5.12; N, 15.10.

1. 14. 1b : Preparation of 3-azido-1-(4-methoxyphenyl)-4-styryl-azetidin-2-one 1.09b

The potassium salt of azido acetic acid **1.04** (0.140 g, 1 mmol) on treatment with imine (**1.05**, 0.237 g, 1 mmol) derived from aniline and *trans*-cinnamaldehyde in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) at 0 ^oC gave the crude product, which was purified by column chromatography to get the pure β-lactam **1.06b** as a white solid (0.267 g, 83%).

MP : 115-116 ^oC.

IR ($CHCl_3$) : 1739 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : 3.80 (s, 3H), 4.90 (dd, *J* = 5.30 Hz, 8.30 Hz, 1H), 5.00 (d, *J* = 5.30 Hz, 1H), 6.30 (dd, *J* = 8.30 Hz, 15.95 Hz, 1H), 6.80-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 55.27, 59.75, 67.26, 114.26, 118.50, 122.40, 126.70, 128.59, 130.53, 135.27, 137.04, 156.47, 160.56.

MS (m/z) : 320 (M^+).

Analysis : Calculated: C, 67.48; H, 5.03; N, 17.49.
($C_{18}H_{16}N_4O_2$) Observed: C, 67.72; H, 5.34; N, 17.66.

1. 14. 2 : General procedure for preparation of azetidin-2-ones 1.12a-c from Dane salt 1.10

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added to a mixture of Dane salt (**1.10**, 1 mmol), imine (**1.11**, 1 mmol) and Et_3N (0.42 ml, 3 mmol) in CH_2Cl_2 at 0 ^oC. After completion of addition, the reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 12 h. The reaction mixture was washed with water (2 x 10 ml), saturated sodium bicarbonate solution (2 x 15 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was purified by

column chromatography (silica gel, 60-120 mesh, pet. ether/ethyl acetate, 80:20) to get pure β-lactams **1.12a-c**.

1. 14. 2a : Preparation of 1-(4-methoxyphenyl)-3-(α-methyl-β-ethoxycarbonylamino)-4-phenyl-azetidin-2-one 1.12a

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added at 0 ^oC, to a mixture of Dane salt **1.10** (0.225 g, 1 mmol), imine **1.11** (0.211 g, 1 mmol) (derived from *p*-anisaldehyde and aniline) and triethylamine (0.42 ml, 3 mmol). After completion of addition, the reaction mixture was warmed up to room temperature and stirred at room temperature for 12 h. After usual work up, crude product was obtained, which was purified by column chromatography to afford the pure β-lactam **1.12a** as a white solid (0.266 g, 70%).

MP : 140 ^oC.

IR ($CHCl_3$) : 1753 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.10 (t, *J* = 7.1 Hz, 3H), 1.85 (s, 3H), 3.75 (s, 3H), 3.90 (q, *J* = 7.1 Hz, 2H), 4.40 (s, 1H), 5.15 (dd, *J* = 4.9 Hz, 8.8 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 6.80 (d, *J* = 9.3 Hz, 2H), 7.20-7.50 (m, 7H), 8.60 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 14.19, 19.45, 55.21, 58.23, 61.61, 63.30, 86.27, 114.21, 118.55, 127.00, 128.69, 128.91, 131.00, 132.77, 156.22, 158.21, 163.24, 169.13.

MS (m/z) : 380 (M^+).

Analysis ($C_{22}H_{24}N_2O_4$) : Calculated: C, 69.46; H, 6.36; N, 7.36.
Observed: C, 69.50; H, 6.45; N, 7.20.

1. 14. 2b : Preparation of 1-(4-methoxyphenyl)-3-(α-methyl-β-ethoxycarbonylamino)-4-(4-methoxyphenyl)-azetidin-2-one 1.12b

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added at 0 ^oC, to a mixture of Dane salt **1.10** (0.225 g, 1 mmol), imine **1.11** (0.241g, 1 mmol) (derived from *p*-anisaldehyde and *p*-anisidine) and triethylamine (0.42 ml, 3

mmol). After completion of addition, the reaction mixture was warmed up to room temperature and stirred at room temperature for 12 h. After usual work up, crude product was obtained, which was purified by column chromatography to afford the pure β-lactam **1.12b** as a white solid (0.266 g, 65%).

MP : 118-120 ^{o}C.

IR ($CHCl_3$) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.17 (t, *J* = 7.1 Hz, 3H), 1.87 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 3.95 (q, *J* = 7.1 Hz, 2H), 4.40 (s, 1H), 5.14 (dd, *J* = 5.4 Hz, 8.8 Hz, 1H) 5.23 (d, *J* = 5.4 Hz, 1H), 6.60-7.40 (m, 8H), 8.60 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 14.19, 19.41, 55.03, 55.18, 58.19, 61.20, 63.30, 86.16, 114.17, 114.47, 116.16, 118.58, 124.57, 128.36, 130.46, 156.19, 159.94, 163.32, 169.16.

MS (m/z) : 410 (M^{+}).

Analysis ($C_{23}H_{26}N_2O_5$) : Calculated: C, 67.30; H, 6.39; N, 6.83.
Observed: C, 67.60; H, 6.48; N, 6.59.

1. 14. 2c : Preparation of 1-(4-methoxyphenyl)-3-(α-methyl-β-ethoxycarbonylamino)-4-styryl-azetidin-2-one 1.12c

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added at 0 ^{o}C, to a mixture of Dane salt (**1.10**, 0.225 g, 1 mmol), imine (**1.11**, 0.237 g, 1 mmol) (derived from *trans*-cinnamaldehyde and *p*-anisidine) and triethylamine (0.42 ml, 3 mmol). After completion of addition, the reaction mixture was warmed up to room temperature and stirred at room temperature for 12 h. After usual work up crude product was obtained, which was purified by column chromatography to afford the pure β-lactam **1.12c** as a white solid (0.296 g, 73%).

MP : 115-116 ^{o}C.

IR ($CHCl_3$) : 1749 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.17 (t, *J* = 7.1 Hz, 3H), 1.87 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 2H), 4.60 (s, 1H), 4.85 (dd, *J* = 5.1 Hz, 8.1 Hz, 1H) 5.10 (dd, *J* = 5.1 Hz, 9.5 Hz, 1H), 6.25 (dd, *J* = 8.1 Hz, 15.7 Hz, 1H), 6.60-7.40 (m, 8H), 8.60 (d, *J* = 9.5 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 13.95, 19.17, 54.87, 58.03, 59.96, 62.53, 85.91, 113.83, 118.05, 122.38, 122.47, 126.38, 128.06, 134.41, 135.17, 136.69, 155.86, 158.97, 162.56, 169.41.

MS (m/z) : 405 (M^+-1).

Analysis ($C_{24}H_{26}N_2O_4$) : Calculated: C, 70.92; H, 6.45; N, 6.89.
Observed: C, 71.10; H, 6.75; N, 7.03.

1. 14. 3 : Preparation of 1-(4-methoxyphenyl)-3-phthalimido-4-styryl-azetidin-2-one 1.15

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added at 0 ^oC, to a mixture of phthalimidoacetic acid **1.13** (0.205 g, 1 mmol), imine **1.14** (0.237 g, 1 mmol) (derived from *trans*-cinnamaldehyde and *p*-anisidine) and triethylamine (0.42 ml, 3 mmol). After completion of addition, the reaction mixture was warmed up to room temperature and stirred at room temperature for 12 h. After usual work up crude product was obtained, which was purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate, 75:25), to afford the pure β-lactam **1.15** as a white solid (0.330 g, 78%).

MP : 189-190 ^oC (Lit[72e] 192-194 ^oC).

IR (Nujol) : 1728 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 3.75 (s, 3H), 5.00 (dd, *J* = 5.8 Hz, 8.45 Hz, 1H), 5.70 (d, *J* = 5.8 Hz, 1H), 6.4 (dd, *J* = 8.45 Hz, 16.1 Hz, 1H), 6.80-7.90 (m, 14H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 55.52, 57.84, 61.11, 114.52, 118.67, 123.01, 123.78, 126.80, 128.71, 131.35, 131.57, 134.55, 135.54, 137.64, 156.57,

160.69, 167.34.

MS (m/z) **:** 424 (M^+).

Analysis **:** Calculated: C, 73.57; H, 4.75; N, 6.60.

($C_{26}H_{20}N_2O_4$) Observed: C, 73.36; H, 4.92; N, 6.35.

Section C

1.15 : Experimental

1. 15. 1 : Preparation of (4-methoxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yloxy)-acetic acid 1.19

To a solution of methoxy alcohol **1.18** (1.84 g, 10 mmol) in dry toluene (25 ml), clean sodium pieces (0.5 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 was not vigorous. A heavy precipitate of sodium chloroacetate was formed immediately. The reaction mixture was refluxed under stirring for an additional 48 h. The reaction mixture was diluted with toluene (30 ml) and extracted with water (3 x 25 ml) and the aqueous layer was acidified with 20% HCl. The crude product, which collects as brown oil on the top, was extracted with diethyl ether. The organic extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude product as oil, which was purified by fractional distillation (B.p. 90–95 °C/ 5 mm) under reduced pressure to afford the acid **1.19** as pale yellow oil (1.5 g, 62%).

MP : Oil.

$[\alpha]^{28}_D$: –58.4 (c 1.05, $CHCl_3$).

IR (neat) : 1731 cm^{-1}, 3600-2600 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.50-0.60 (m, 2H), 0.95 (s, 3H, CH_3), 1.05 (s, 3H), 1.25 (s, 3H), 3.38 (s, 3H), 1.20-2.40 (m, 4H), 3.20-3.40 (m, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 4.35 (d, *J* = 17.6 Hz, 1H), 9.30 (bs, 1H).

MS (m/z) : 242 (M^+).

1. 15. 2 : Preparation of 3-(4-methoxy-4,7,7-trimethyl-bicyclo[4.1.0]hept-3-yloxy-4-styryl-1-(4-methoxyphenyl)azetidin-2-one 1.21 & 1.22

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 (10 ml) was added slowly to a solution of the acid **1.19** (0.242 g, 1mmol), imine **1.20** (0.237 g,

1mmol) and triethylamine (0.42 ml, 3 mmol) in anhydrous CH_2Cl_2 (10 ml) at –40 ^oC. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. It was then diluted with CH_2Cl_2 and washed successively with water (3 x 10 ml), saturated $NaHCO_3$ (3 x 10 ml), brine (20 ml), dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was passed through a short silica-gel column to afford the β-lactams **1.21** & **1.22** (0.30 g, 65%) as a diastereomeric mixture (60:40). The major diastereomer was separated as a white solid by crystallization from petroleum ether/acetone, which showed following spectral and analytical data.

MP : 232-234 °C.

$[\alpha]^{28}_D$ -3.3 (c 1.2, CH_2Cl_2).

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

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.50-0.65 (m, 2H), 0.71 (s, 3H), 0.87 (s, 3H), 0.90 - 1.10 (m, 1H), 1.27 (s, 3H), 1.55 - 2.20 (m, 3H), 3.27 (s, 3H), 3.20 - 3.40 (m, 1H), 3.75 (s, 3H), 4.70 (dd, *J* = 4.4 Hz, 8.7 Hz, 1H), 5.42 (d, *J* = 4.4 Hz, 1H), 6.37 (dd, *J* = 8.7 Hz, 16.0 Hz, 1H), 6.75-6.95 (m, 3H), 7.15 -7.55 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 14.80, 15.50, 17.60, 19.10, 20.50, 26.20, 28.20, 29.70, 48.90, 55.40, 61.50, 78.20, 81.90, 84.20, 114.20, 118.50, 125.10, 126.50, 128.20, 128.60, 131.50, 135.50, 135.90, 156.10, 164.00.

Analysis ($C_{29}H_{35}O_4N$) : Calculated: C, 75.46; H, 7.64; N, 3.03.
Observed: C, 75.72; H, 7.51; N, 3.14.

1. 15. 3 : General procedure for the preparation of azetidin-2-ones 1.27a-c from camphorsultam derived acid 1.25

A solution of triphosgene (0.148 g, 0.5 mmol), in anhydrous CH_2Cl_2 (10 ml), was added slowly to a solution of acid (**1.25**, 1 mmol), imine (**1.26**, 1 mmol) and triethylamine (0.42 ml, 3 mmol) in anhydrous CH_2Cl_2 (10 ml) at –40 ^oC. The reaction mixture was then allowed to warm up to room temperature and stirred further for 12 h. The reaction mixture was then washed with water (3 x 10 ml), saturated sodium bicarbonate solution (3 x 10 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was

purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate, 80:20), to get pure β-lactams **1.27a-c**.

1. 15. 3a : Preparation of (2*R*,3*S*,6*R*,3'*S*,4'*S*)-*N*-[1'-(*p*-anisyl)-4'-phenylazetidin-2'-one-3'-yl]-2,10-camphorsultam 1.27a

Following the general procedure, treatment of sultam-derived acid **1.25** (0.273 g, 1 mmol) with imine **1.26** (0.211 g, 1 mmol) (derived from *p*-anisidine and benzaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.27a** as a white crystalline solid (0.420 g, 90%).

MP : 238-240 ^{o}C (Lit[41] 242-243 ^{o}C)

$[\alpha]^{28}_{D}$ +37.6 (c 1, CH_2Cl_2) (Lit[41] $[\alpha]^{25}_{D}$ = +39.2, c 1, CH_2Cl_2)

IR ($CHCl_3$) : 1753 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.15 (s, 3H), 0.70 (s, 3H), 1.25-1.50 (m, 2H), 1.60-1.90 (m, 5H), 2.80 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 3.70 (t, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 5.30 (m, 2H), 6.85 (d, *J* = 10 Hz, 2H), 7.25-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 18.75, 19.78, 26.51, 32.35, 37.24, 44.74, 47.13, 48.19, 49.70, 55.21, 59.92, 61.09, 65.28, 114.17, 118.40, 127.48, 127.99, 128.36, 130.64, 133.47, 156.26, 160.34.

MS (m/z) : 466 (M^+).

Analysis ($C_{26}H_{30}N_2O_4S$) : Calculated: C, 66.93; H, 6.48; N, 6.00; S, 6.87
Observed: C, 66.62; H, 6.19; N, 5.83; S, 6.70.

1. 15. 3b : Preparation of (2*R*,3*S*,6*R*,3'*S*,4'*S*)-*N*-[1'-(*p*-anisyl)-4'-*p*-anisylazetidin-2'-one-3'-yl]-2,10-camphorsultam 1.27b

Following the general procedure, treatment of sultam derived acid **1.25** (0.273 g, 1 mmol) with imine **1.26** (0.241 g, 1 mmol) (derived from *p*-anisidine and *p*-anisaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.27b** as a white crystalline solid (0.446 g, 90%).

MP : 210-212 ^{0}C (Lit[41] 215-216 ^{o}C).

$[\alpha]^{28}_D$: +58.4 (c 1, CH_2Cl_2) (Lit[41] $[\alpha]^{25}_D$ = +60.63, c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1753 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.20 (s, 3H), 0.75 (s, 3H), 1.20-1.50 (m, 2H), 1.60-1.85 (m, 5H), 2.90 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 3.70 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 6H), 5.25 (two merged doublets, 2H), 6.80-7.00 (m, 4H), 7.15-7.40 (m, 4H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 18.75, 19.74, 26.54, 32.35, 37.28, 44.74, 47.16, 48.23, 49.74, 55.21, 59.55, 60.98, 65.28, 113.88, 114.17, 118.40, 125.35, 128.66, 130.64, 156.22, 159.50, 160.41.

MS (m/z) : 496 (M^+).

Analysis ($C_{27}H_{32}N_2O_5S$) : Calculated: C, 65.30; H, 6.49; N, 5.64; S, 6.46
Observed: C, 65.42; H, 6.37; N, 5.86; S, 6.26.

1. 15. 3c : Preparation of (2*R*,3*S*,6*R*,3'*S*,4'*S*)-*N*-[1'-(*p*-anisyl)-4'-styrylazetidin-2'-one-3'-yl]-2,10-camphorsultam 1.27c

Following the general procedure, treatment of sultam derived acid **1.25** (0.273 g, 1 mmol) with imine **1.26** (0.237 g, 1 mmol) (derived from *p*-anisidine and *trans*-cinnamaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.27c** as a white crystalline solid (0.400 g, 82%).

MP : 204-206 ^{0}C (Lit[41] 208-210 ^{o}C).

$[\alpha]^{28}_D$: +59.0 (c 1, CH_2Cl_2) (Lit $[\alpha]^{25}_D$ = +60.89, c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1751 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 0.90 (s, 3H), 1.00 (s, 3H), 1.30-1.65 (m, 2H), 1.75-2.00 (m, 5H), 3.20 (q, *J* = 14.0 Hz, 2H), 3.70 (dd, *J* = 4.9 Hz, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 4.90 (m, 1H), 5.10 (d, *J* = 5.3 Hz, 1H), 6.35 (dd, *J* = 5.3 Hz, *J* = 16.1 Hz, 1H), 6.60 (d, *J* = 16.1 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.25-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) : 19.73, 20.06, 26.49, 32.38, 38.00, 44.69, 47.37, 48.66, 50.13,

(50.3 MHz) 55.20, 58.18, 60.53, 65.90, 114.16, 118.28, 123.83, 126.44, 127.80, 128.24, 130.96, 133.61, 135.74, 156.25, 159.71

MS (m/z) : 492 (M^+).

Analysis ($C_{28}H_{32}N_2O_4S$) : Calculated: C, 68.27; H, 6.55; N, 5.69; S, 6.51.
Observed: C, 68.23; H, 6.66; N, 5.97; S, 6.49.

1. 15. 4 : General procedure for preparation of azetidin-2-ones 1.32a-f from acids 1.30 derived from oxazolidone

A solution of triphosgene (0.148 g, 0.5 mmol) in anhydrous CH_2Cl_2 was slowly added to a mixture of acid (**1.30**, 1 mmol), imine (**1.31**, 1 mmol) and Et_3N (0.42 ml, 3 mmol) in CH_2Cl_2 at 0 ^oC. After completion of addition, the reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 12 h. The reaction mixture was washed with water (3 x 10 ml), saturated sodium bicarbonate solution (3 x 15 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether/ethyl acetate, 80:20) to get pure β-lactams **1.32a-f**.

1. 15. 4a : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(phenyl)-1'-(4-methoxy-phenyl)-3'-azetidinyl]-4-phenylmethyl-2-oxazolidone 1.32a

Following the general procedure, treatment of oxazolidone derived acid **1.30b** (0.235 g, 1 mmol) with imine **1.31** (0.211 g, 1 mmol) (derived from *p*-anisidine and benzaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32a** as a white solid (0.286 g, 67%).

MP : 194 ^oC.

$[\alpha]^{25}_D$: –80.2 (c 1, $CHCl_3$).

IR ($CHCl_3$) : 1753 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.80 (dd, *J* = 13.2 Hz & 10.3 Hz 1H), 2.95 (dd, *J* = 13.2 Hz, 3.9 Hz, 1H), 3.60-3.90 (m, 2H), 3.75 (s, 3H), 4.00-4.25 (m, 1H), 5.20 (d, *J* = 4.9 Hz, 1H), 5.40 (d, *J* = 4.9 Hz, 1H), 6.85-7.50 (m, 14H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 39.96, 55.29, 55.36, 60.58, 63.08, 67.60, 114.28, 118.40, 127.00, 127.30, 128.25, 128.40, 128.73, 130.82, 133.03, 135.09, 156.41, 157.47, 160.34.

MS (m/z) : 428 (M^+).

Analysis ($C_{26}H_{24}N_2O_4$) : Calculated: C, 72.88; H, 5.65; N, 6.54.
Observed: C, 72.67; H, 5.63; N, 6.52.

1. 15. 4b : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(phenyl)-1'-(phenyl)-3'-azetidinyl]-4-phenyl-2-oxazolidone 1.32b

Following the general procedure, treatment of oxazolidone derived acid **1.30a** (0.221 g, 1 mmol) with imine **1.31** (0.195 g, 1 mmol) (derived from benzylamine and benzaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32b** as a white solid (0.278 g, 70%).

MP : 220-222 ^{0}C (Lit[33] 228-230 ^{0}C)

$[\alpha]^{25}_D$: –73.4 (c 1, $CHCl_3$).

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.87-4.02 (m, 2H), 4.10-4.38 (m, 2H), 4.42 (d, *J* = 4.6 Hz, 1H), 4.55 (d, *J* = 4.6 Hz, 1H), 4.95 (d, *J* = 14.7 Hz, 1H), 7.00-7.50 (m, 15H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 44.96, 59.40, 60.43, 63.48, 69.92, 127.22, 127.52, 127.63, 128.36, 128.58, 129.17, 132.96, 134.65, 136.34, 156.63, 163.10

MS (m/z) : (M^+-133)

Analysis ($C_{25}H_{22}N_2O_3$) : Calculated: C, 75.36; H, 5.56; N, 7.03
Observed: C, 75.15; H, 5.45; N, 7.32.

1. 15. 4c : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(phenyl)-1'-(phenylmethyl)-3'-azetidinyl]-4-phenylmethyl-2-oxazolidone 1.32c

Following the general procedure, treatment of oxazolidone derived acid **1.30b** (0.235 g, 1 mmol) with imine **1.31** (0.195 g, 1 mmol) (derived from benzylamine and benzaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32c** as a white solid (0.288 g, 70%).

MP : 151 ^{0}C.

[α]$^{25}_D$: –44.0 (c 1, $CHCl_3$).

IR (Nujol) : 1745 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.90 (dd, *J* = 13.1 Hz, 9.7 Hz, 1H), 2.95 (dd, *J* = 13.1 Hz, *J* = 3.9 Hz, 1H), 3.60-3.80 (m, 2H), 3.80-4.10 (m, 1H), 4.25 (d, *J* = 14.7 Hz, 1H), 4.80 (d, *J* = 5.3 Hz, 1H), 5.00 (d, *J* = 5.3 Hz, 1H), 5.10 (d, *J* = 14.7 Hz, 1H), 7.00-7.50 (m, 15H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 39.87, 45.68, 55.53, 60.28, 64.10, 67.44, 127.03, 127.25, 127.95, 128.28, 128.46, 128.79, 133.75, 134.60, 135.11, 157.39, 163.71.

MS (m/z) : 412 (M^+).

Analysis ($C_{26}H_{24}N_2O_3$) : Calculated: C, 75.71; H, 5.87; N, 6.79.
Observed: 75.56; H, 5.81; N, 6.82.

1. 15. 4d : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(phenyl)-1'-(4-methoxyphenyl)-3'-azetidinyl]-4-isopropyl-2-oxazolidone 1.32d

Following the general procedure, treatment of oxazolidone derived acid **1.30c** (0.187 g, 1 mmol) with imine **1.31** (0.211 g, 1 mmol) (derived from *p*-anisidine and benzaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32d** as a white solid (0.270 g, 71%).

MP : 215-217 ^{0}C.

[α]$^{25}_D$: –17.2 (c 1, $CHCl_3$).

IR ($CHCl_3$) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.40 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H), 1.60-1.90 (m, 1H), 3.60-3.80 (m, 1H), 3.75 (s, 3H), 3.85-3.95 (m, 2H), 5.00 (d, *J* = 5.4 Hz, 1H), 5.30 (d, *J* = 5.4 Hz, 1H), 6.80-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.20, 17.72, 28.67, 55.18, 58.67, 61.09, 63.04, 63.19, 114.10, 118.33, 127.30, 128.21, 128.47, 130.82, 132.70,

156.19, 157.44, 160.27.

MS (m/z) : 380 (M^+).

Analysis : Calculated: C, 69.47; H, 6.36; N, 7.36.
($C_{22}H_{24}N_2O_4$) Observed: C, 69.19; H, 6.13; N, 7.16.

1. 15. 4e : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(4-methoxyphenyl)-1'-(4-methoxyphenyl)-3'-azetidinyl]-4-isopropyl-2-oxazolidone 1.32e

Following the general procedure, treatment of oxazolidone derived acid **1.30c** (0.187 g, 1 mmol) with imine **1.31** (0.241 g, 1 mmol) (derived from *p*-anisidine and *p*-anisaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32e** as a white solid (0.288 g, 72%).

MP : 200-202 ^{0}C.

[α]$^{25}_D$: –24.4 (c 1, $CHCl_3$).

IR ($CHCl_3$) : 1753 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.50 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H), 1.60-1.90 (m, 1H), 3.60-3.80 (m, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 3.85-3.95 (m, 2H), 5.00 (d, *J* = 5.4 Hz, 1H), 5.30 (d, *J* = 5.4 Hz, 1H), 6.80-7.50 (m, 8H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.42, 17.68, 28.45, 55.03, 55.18, 58.78, 60.84, 62.97, 63.19, 113.92, 114.06, 118.36, 124.39, 128.66, 130.86, 156.11, 157.36, 159.50, 160.38

MS (m/z) : 410 (M^+).

Analysis : Calculated: C, 67.30; H, 6.39; N, 6.83
($C_{23}H_{26}N_2O_5$) Observed: C, 67.21; H, 6.42; N, 6.75.

1. 15. 4f : Preparation of (4*S*,3'*S*,4'*R*)-3-[2'-oxo-4'-(phenyl)-1'-(phenylmethyl)-3'-azetidinyl]-4-isopropyl-2-oxazolidone 1.32f

Following the general procedure, treatment of oxazolidone derived acid **1.30c** (0.187 g, 1 mmol) with imine **1.31** (0.195 g, 1 mmol) (derived from benzylamine and bezaldehyde), in presence of triethylamine (0.42 ml, 3 mmol) and triphosgene (0.148 g, 0.5 mmol) as acid activator, gave the β-lactam **1.32f** as a white solid (0.254 g, 70%).

MP : 185 ^{0}C

[α]$^{25}_{D}$: –40.0 (c 1, $CHCl_3$).

IR (Nujol) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.40 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H), 1.60-1.90 (m, 1H), 3.40-3.50 (m, 1H), 3.65-3.75 (dd, *J* = 8.8 Hz, 11.5 Hz, 1H), 3.85-3.95 (dd, *J* = 8.8 Hz, *J* = 4.4 Hz, 1H), 4.15 (d, *J* = 14.7 Hz, 1H), 4.70 (d, *J* = 4.9 Hz, 1H), 4.90 (d, *J* = 4.9 Hz, 1H), 5.05 (d, *J* = 14.7 Hz, 1H), 7.10-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 13.46, 17.57, 28.20, 45.14, 58.71, 60.54, 62.97, 63.92, 127.33, 127.70, 128.21, 128.32, 128.62, 133.29, 134.72, 157.22, 163.61.

MS (m/z) : 364 (M^{+}).

Analysis ($C_{22}H_{24}N_2O_3$) : Calculated: C, 72.51; H, 6.64; N, 7.69.
Observed: C, 72.33; H, 6.53; N, 7.76.

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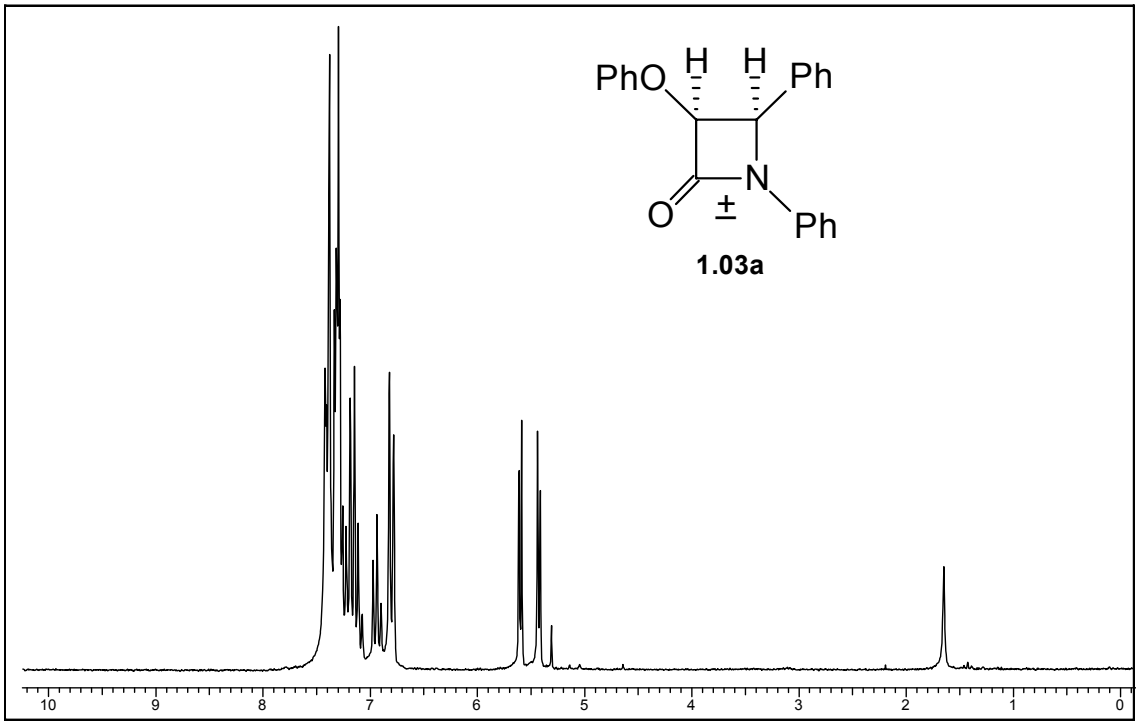
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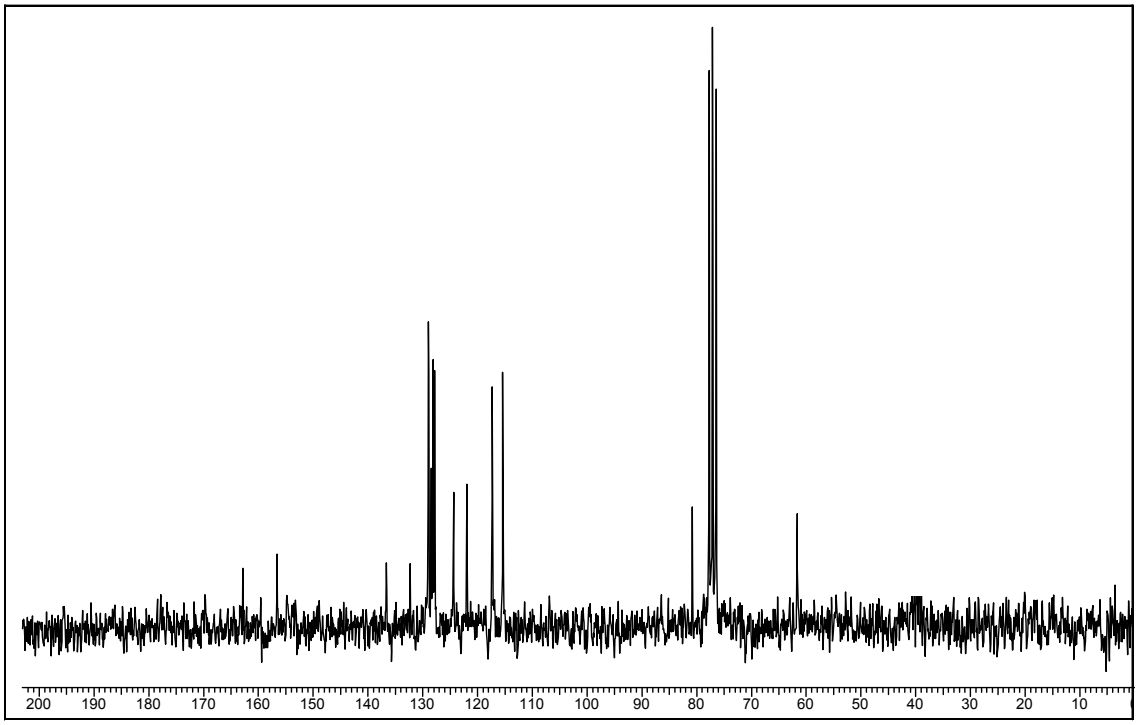
1.03a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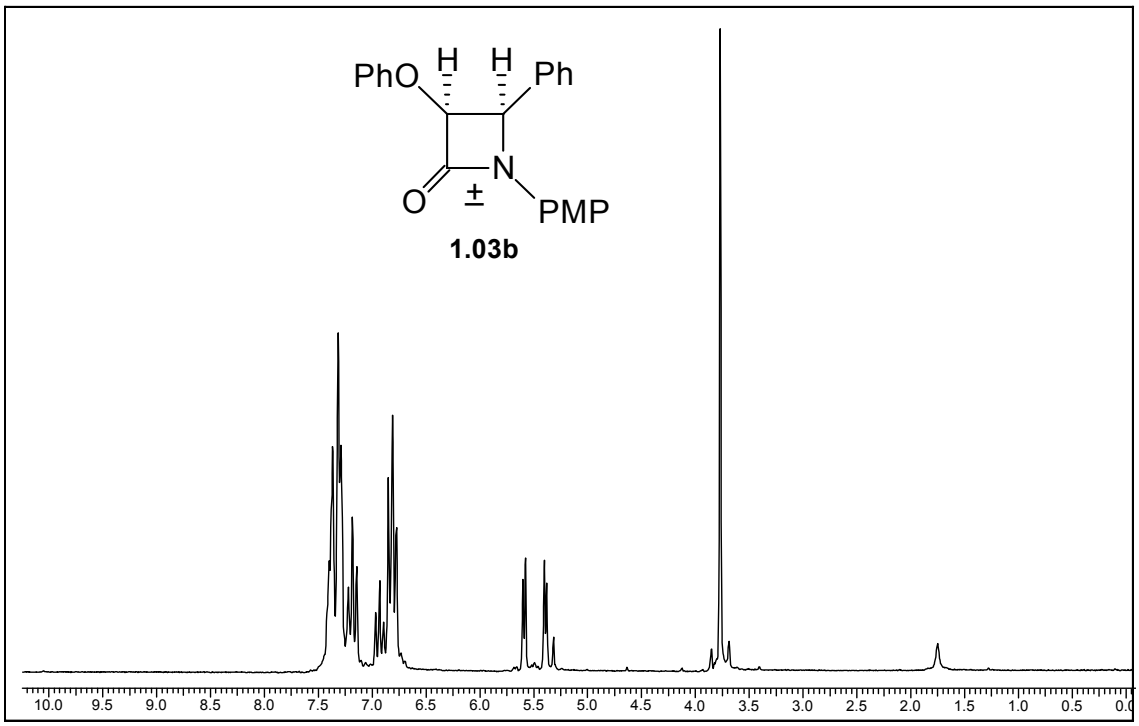
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±
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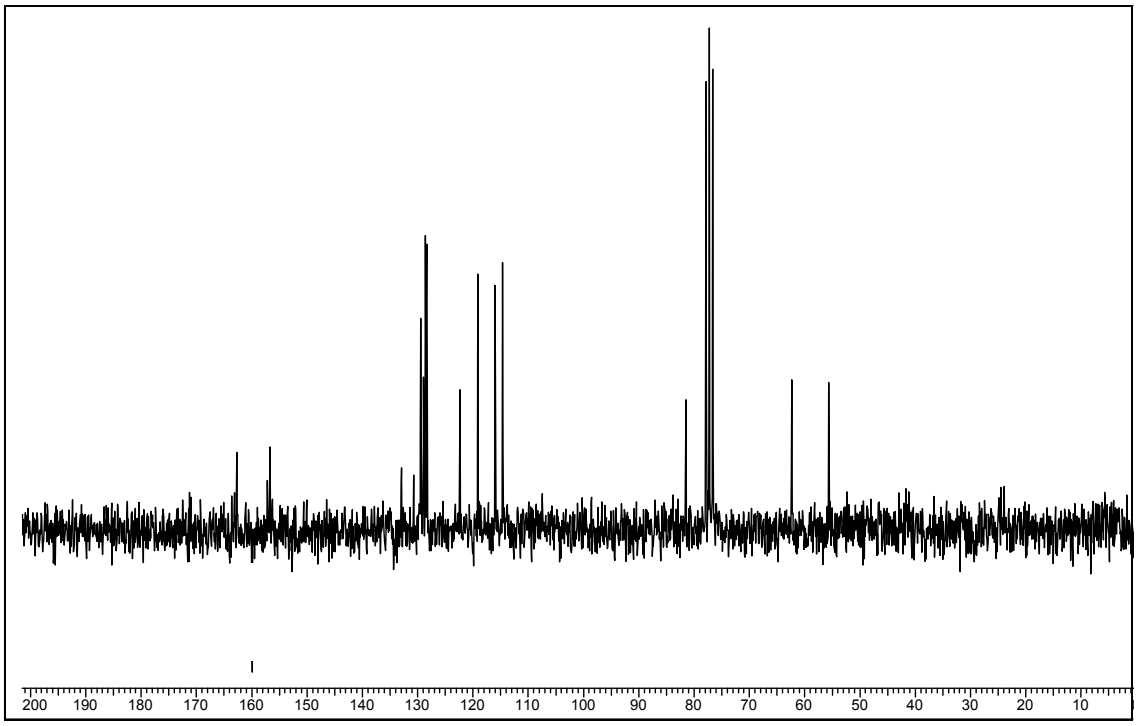
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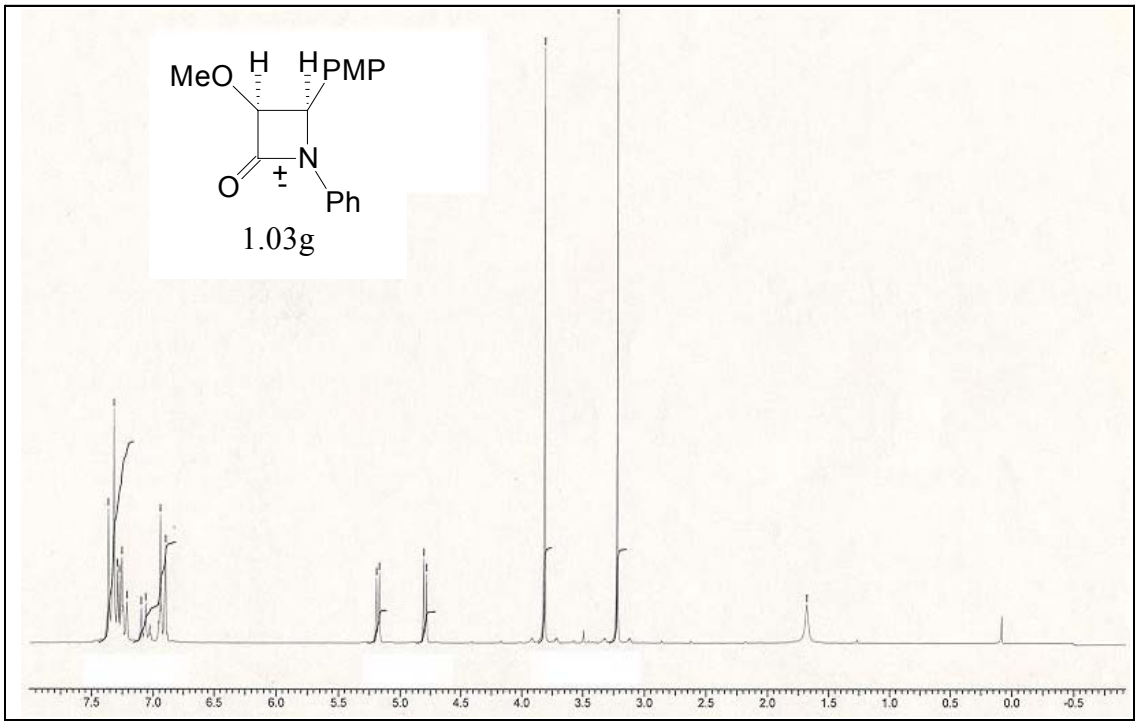
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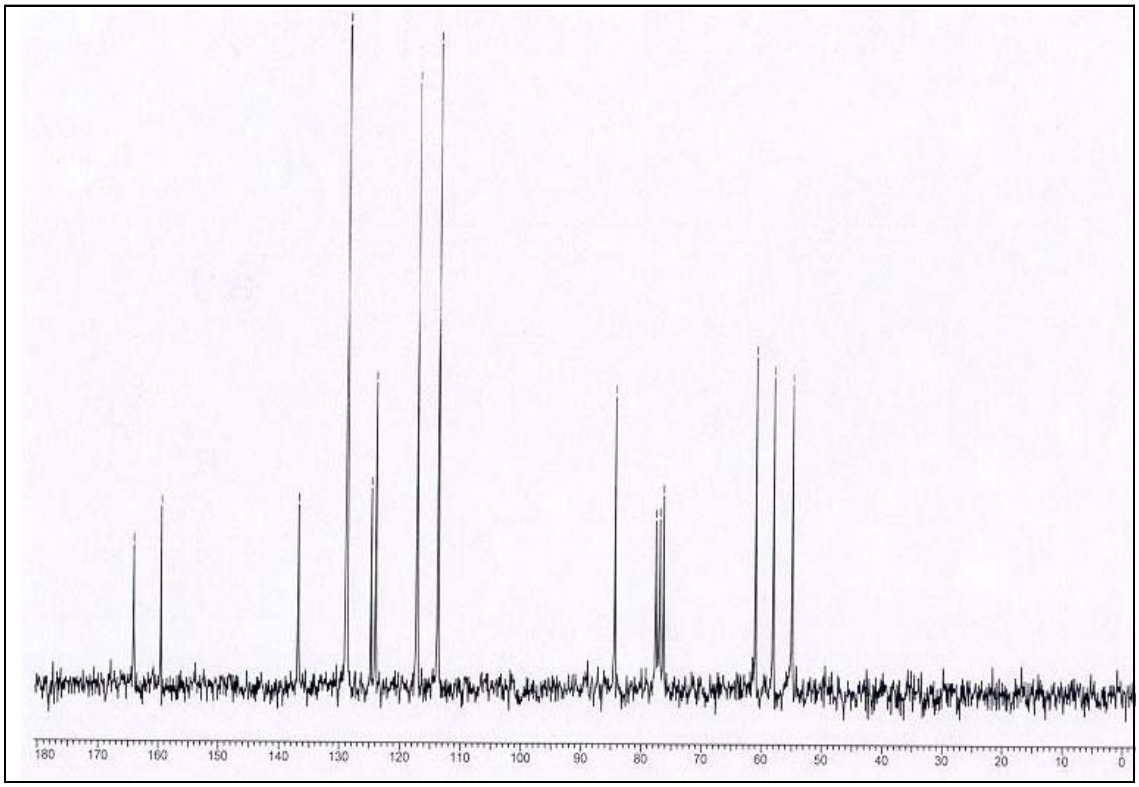
0.0
-0.5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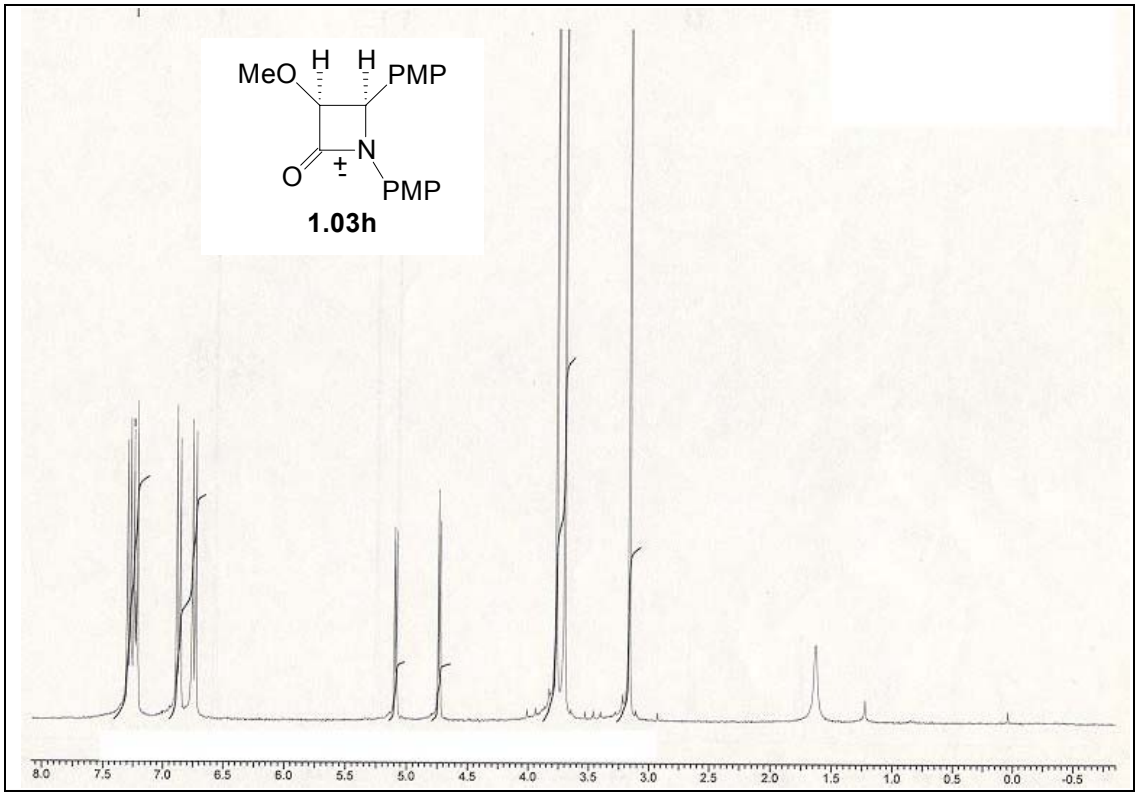
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H
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O
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7.5
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6.5
6.0
5.5
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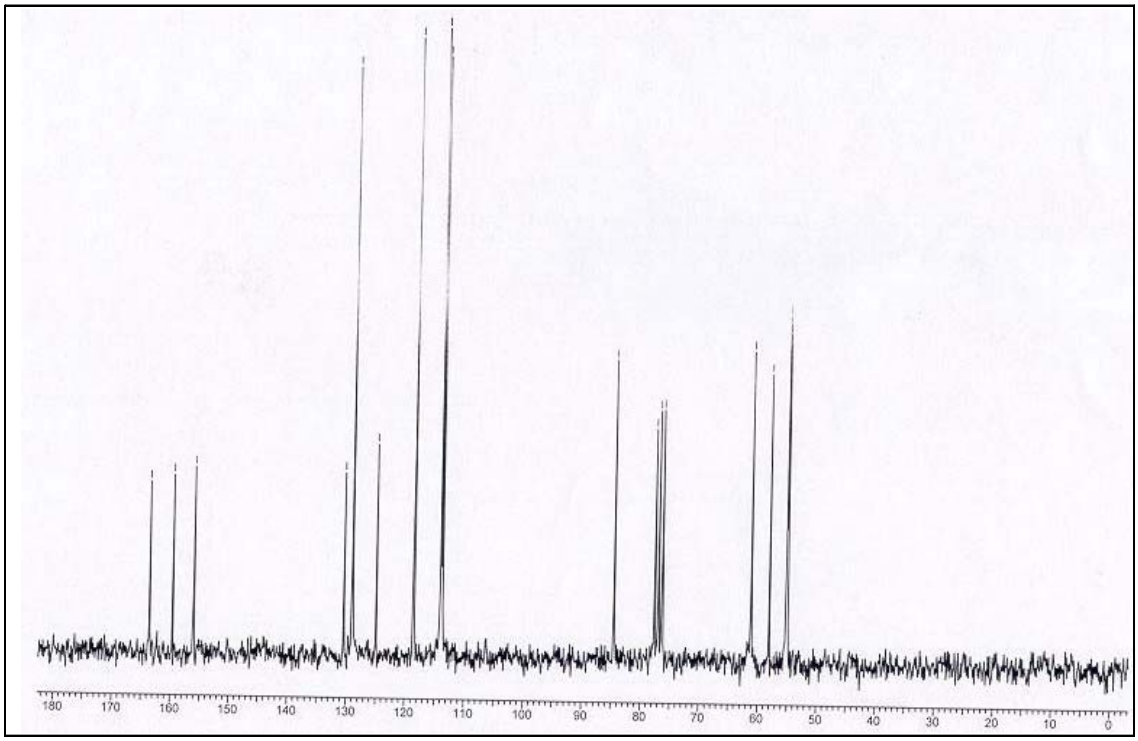
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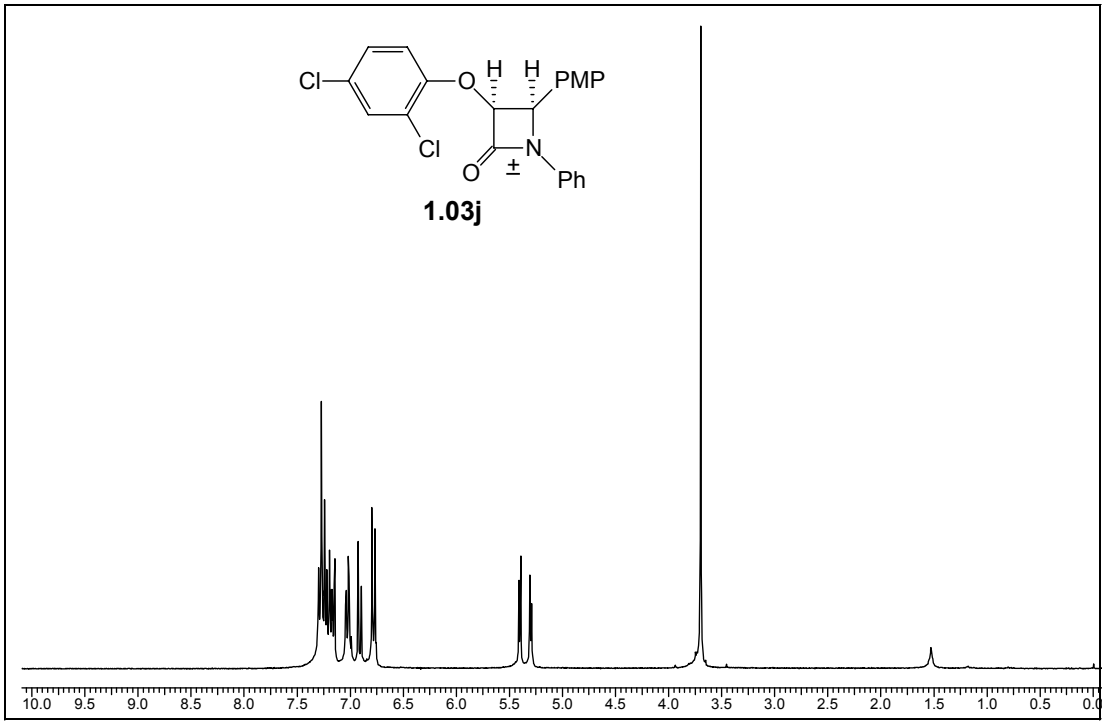
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O
H
H
PMP
Cl
O
±
N
Ph
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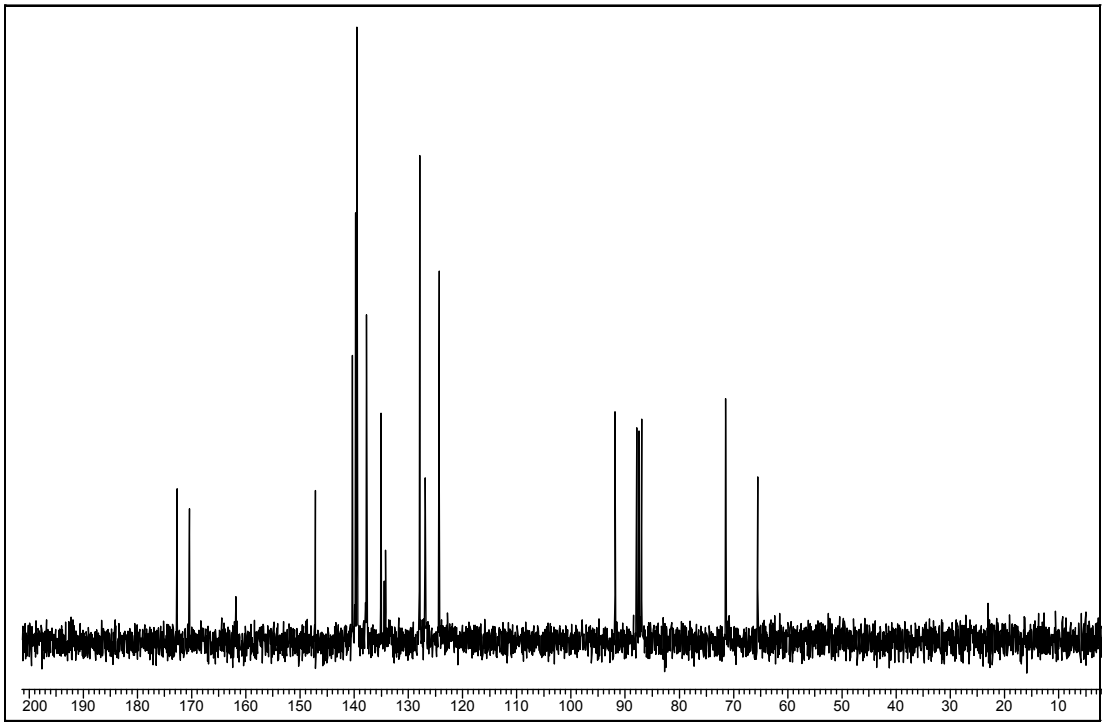
1.03j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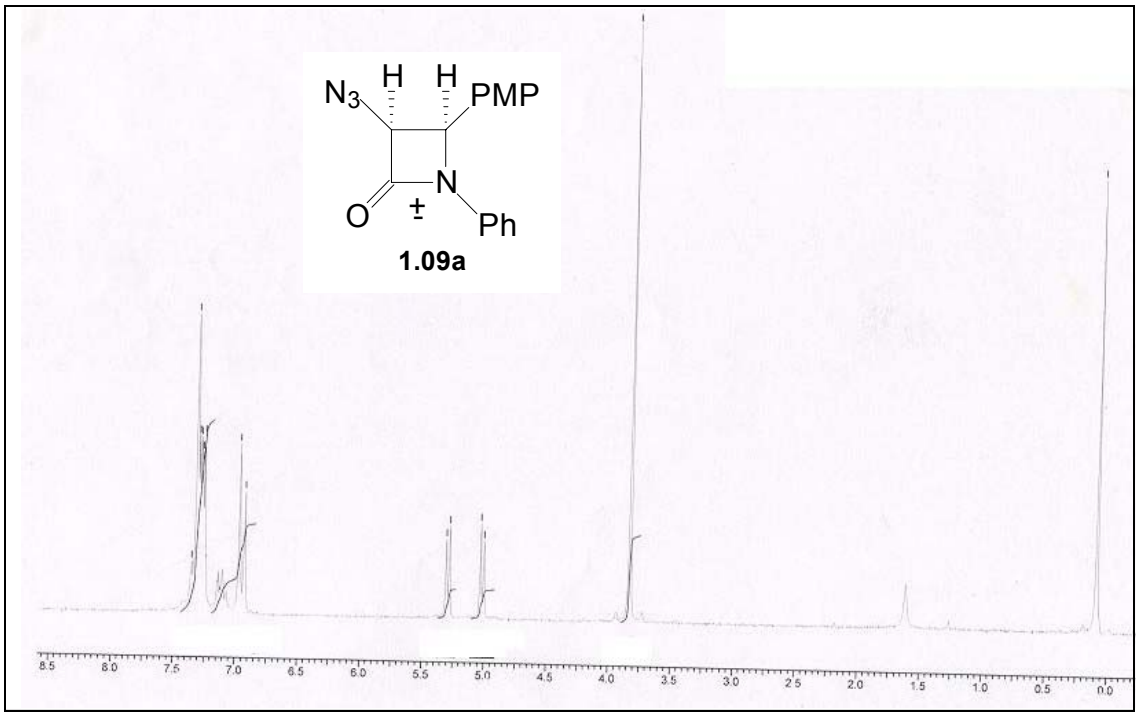
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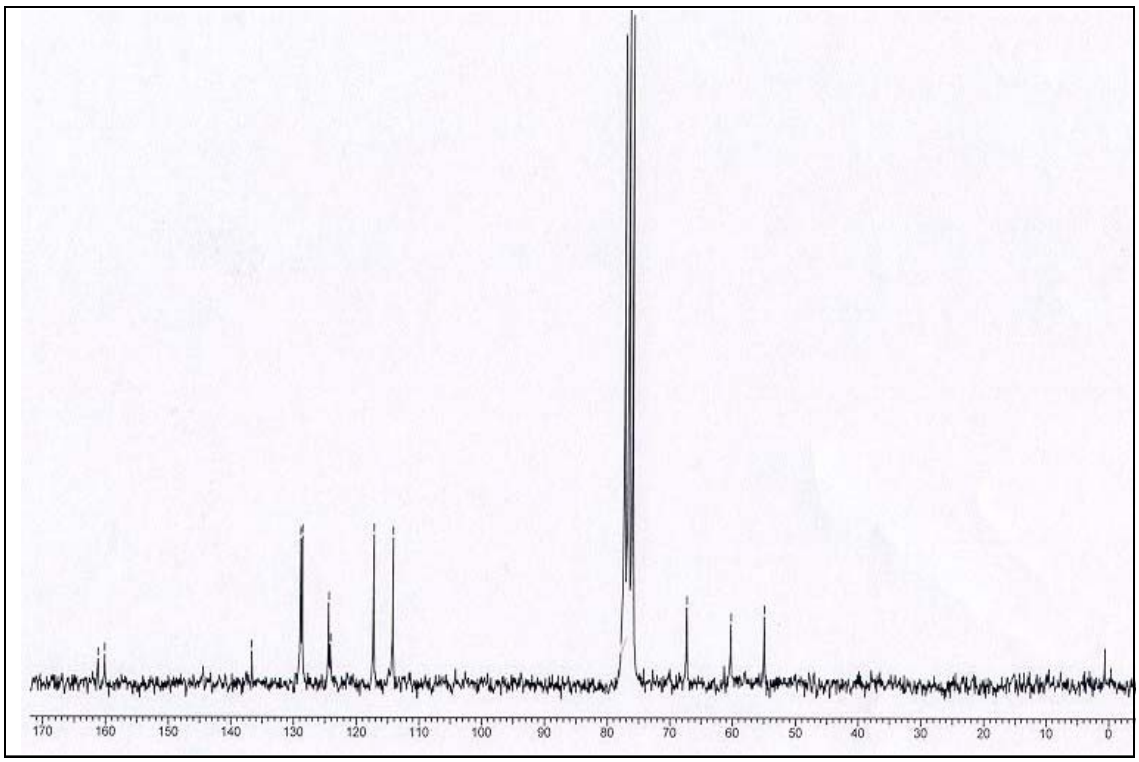
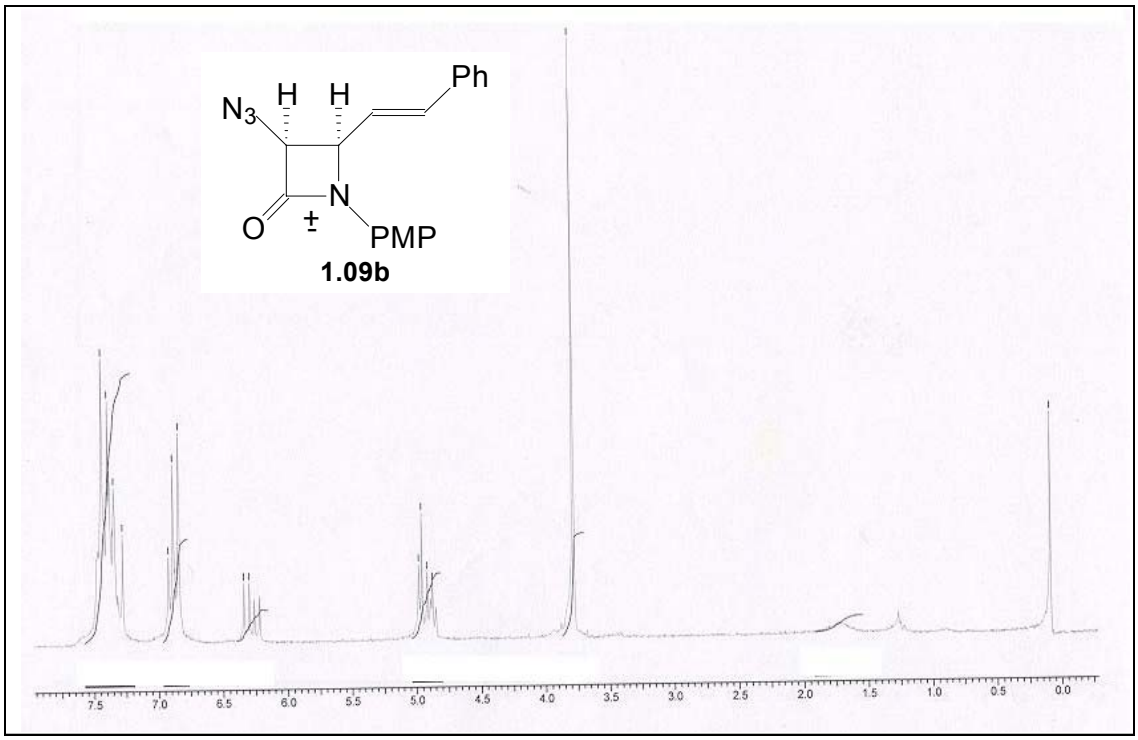
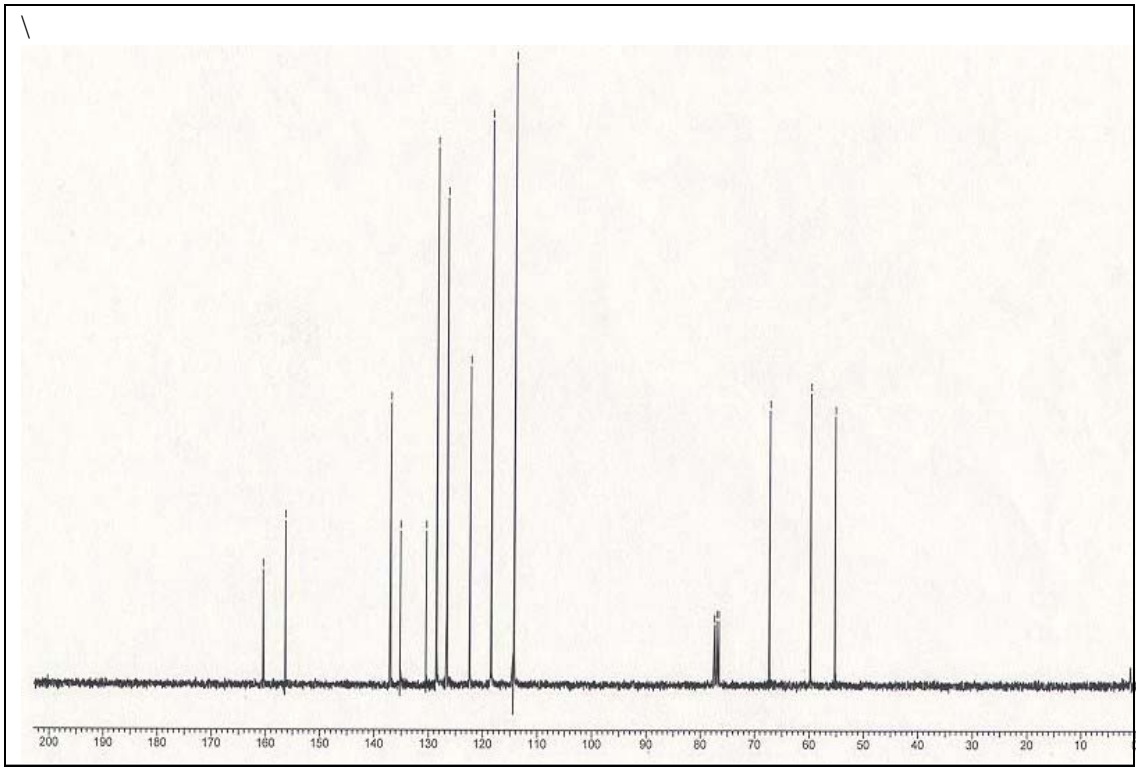
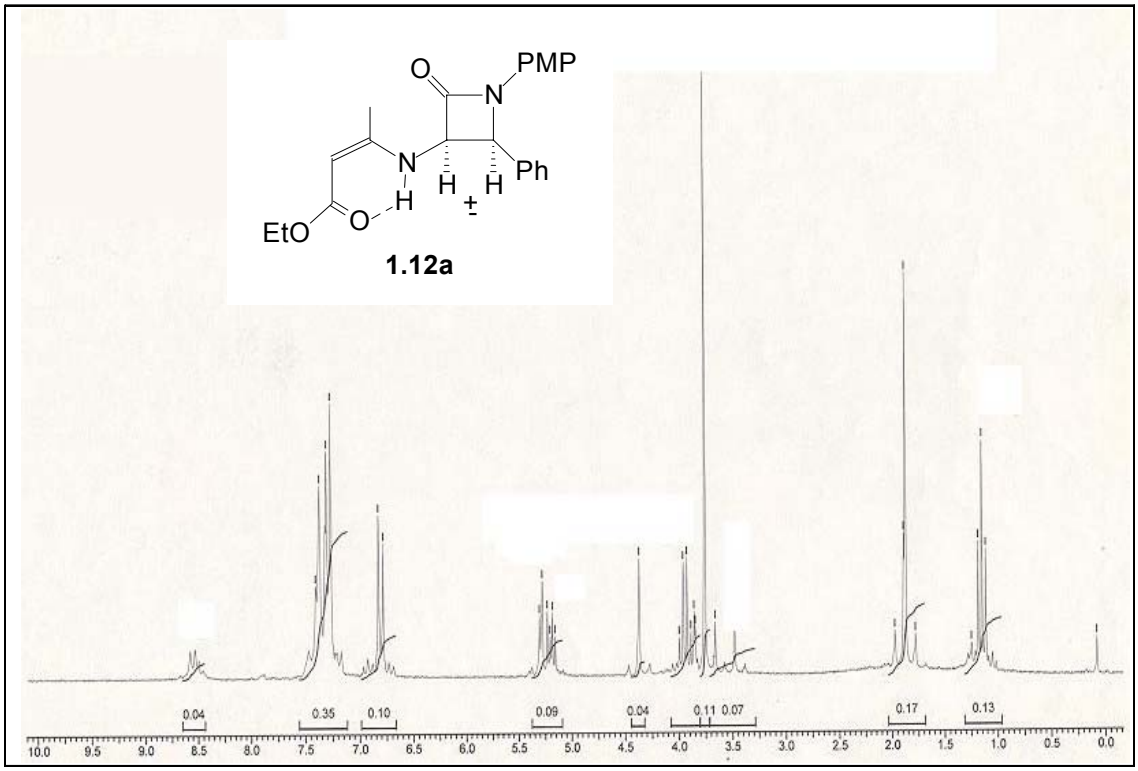
PMP
N
O
±
Ph
1.09a




N3
H
H
Ph
N
O
±
PMP
1.09b

\

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H
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0.10
0.09
0.04
0.11
0.07
0.17
0.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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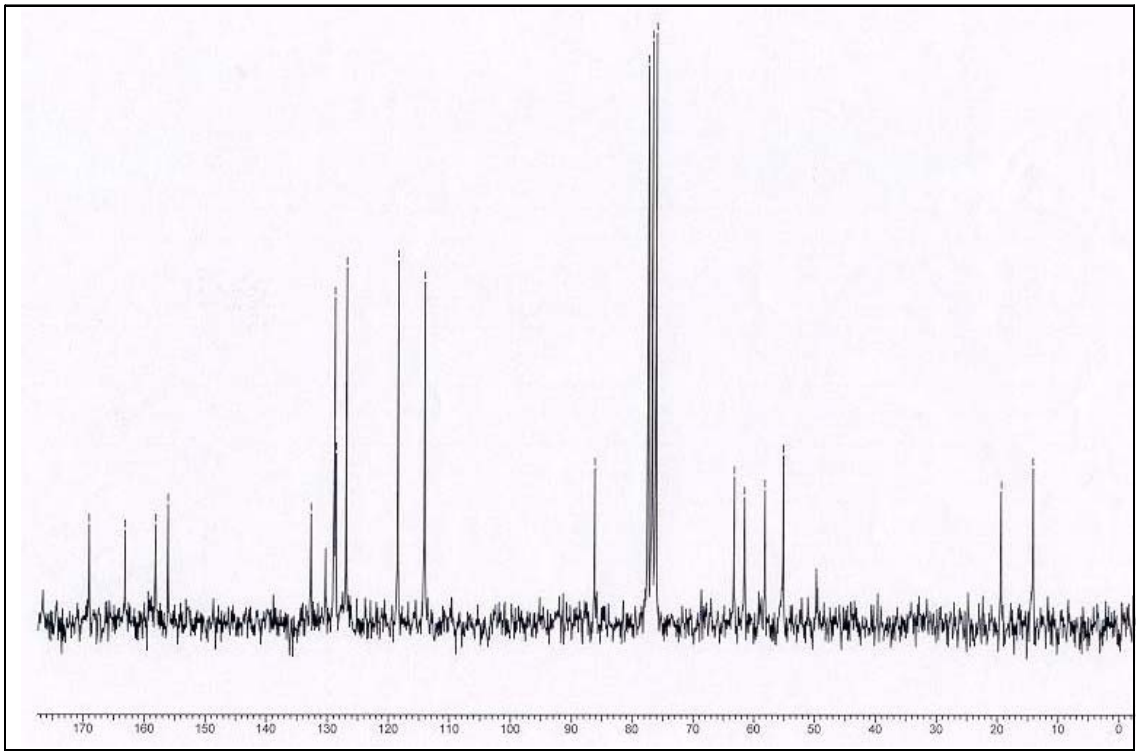
1.12a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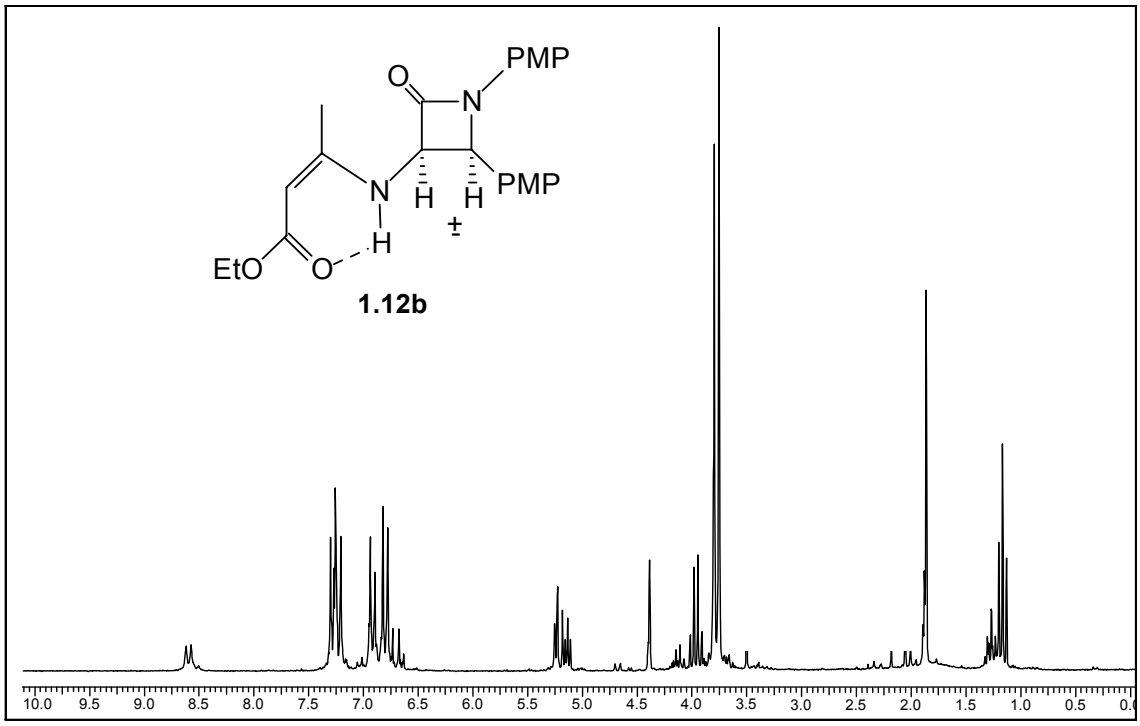
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H
H
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±
H
EtO
O
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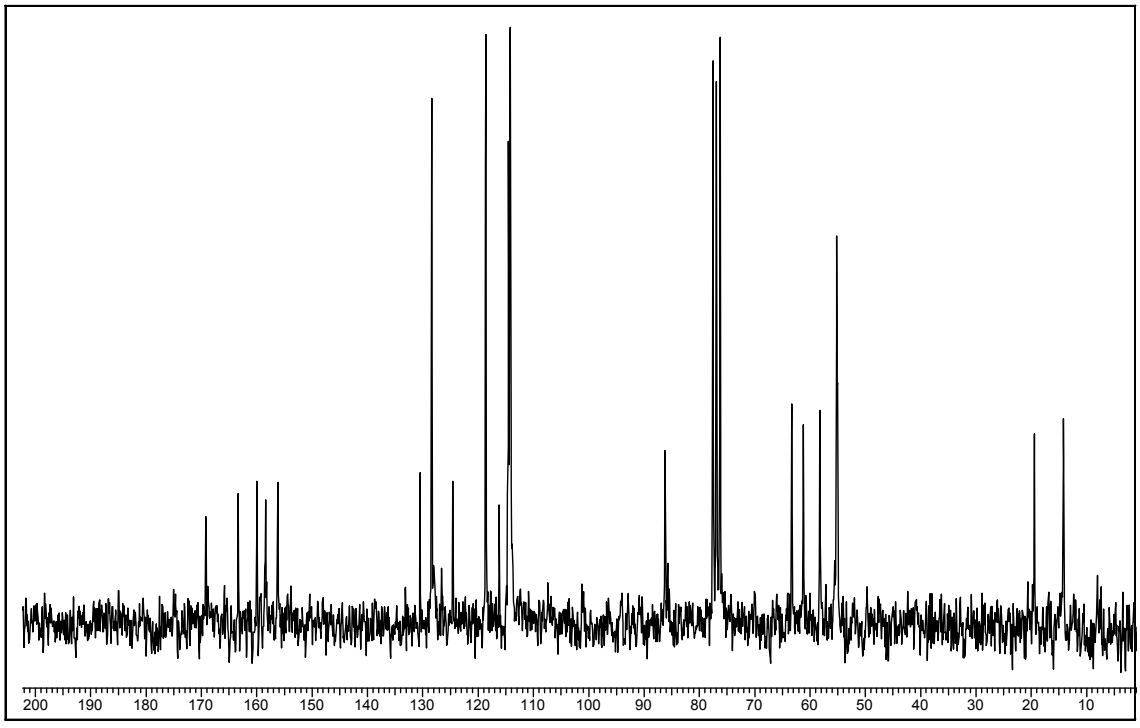
1.12b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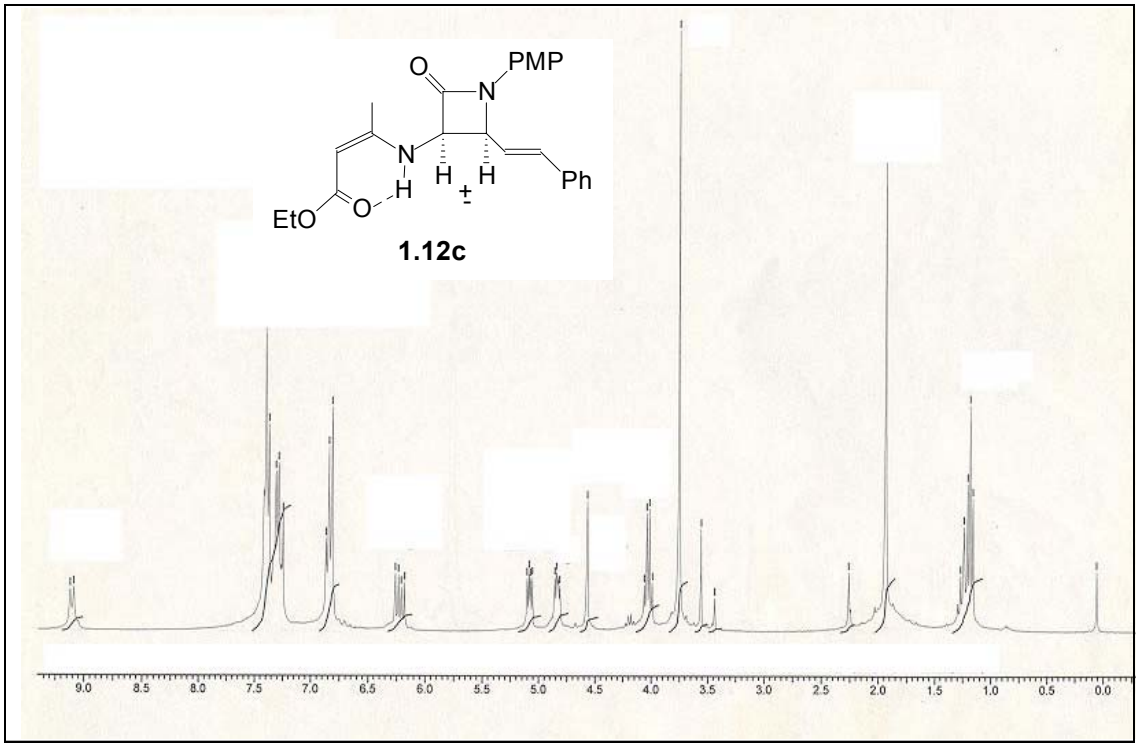
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H
Ph
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7.5
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6.0
5.5
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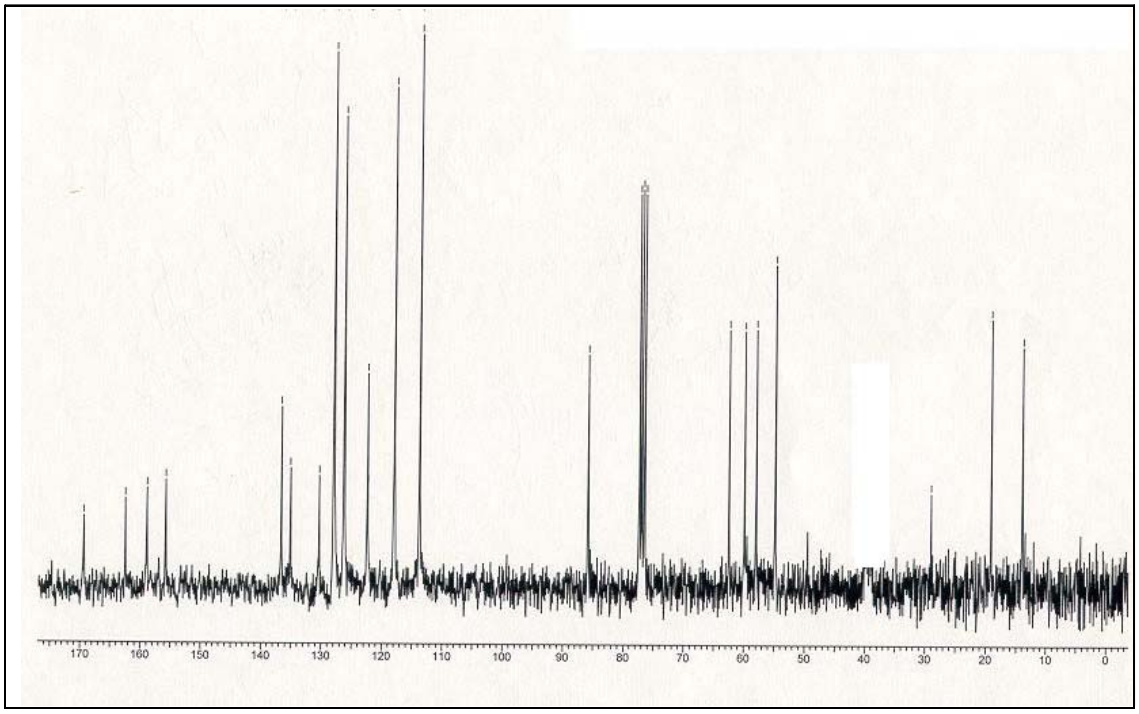
0.0

1.12c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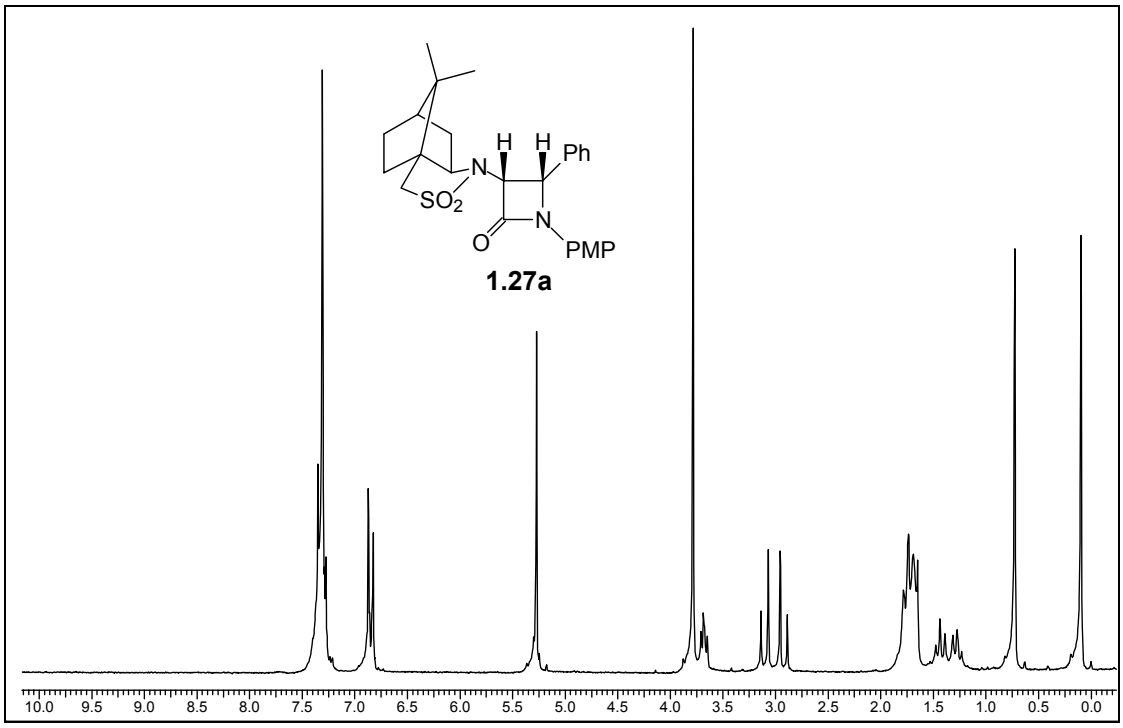
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N
SO2
O
N
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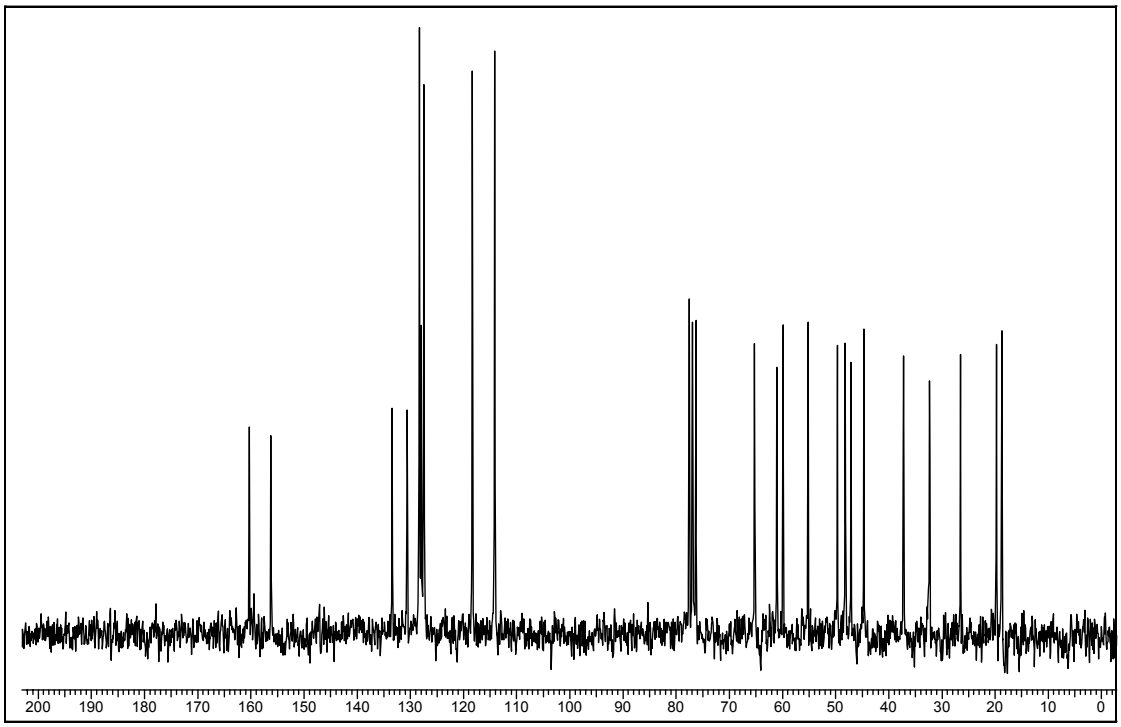
1.27a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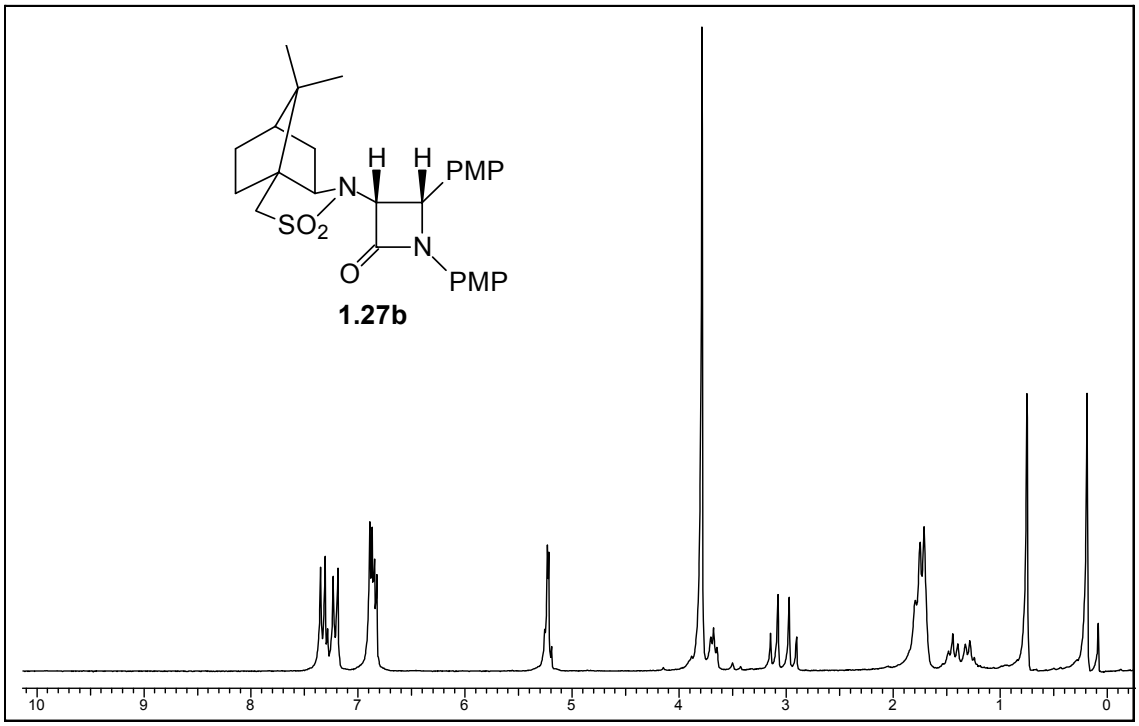
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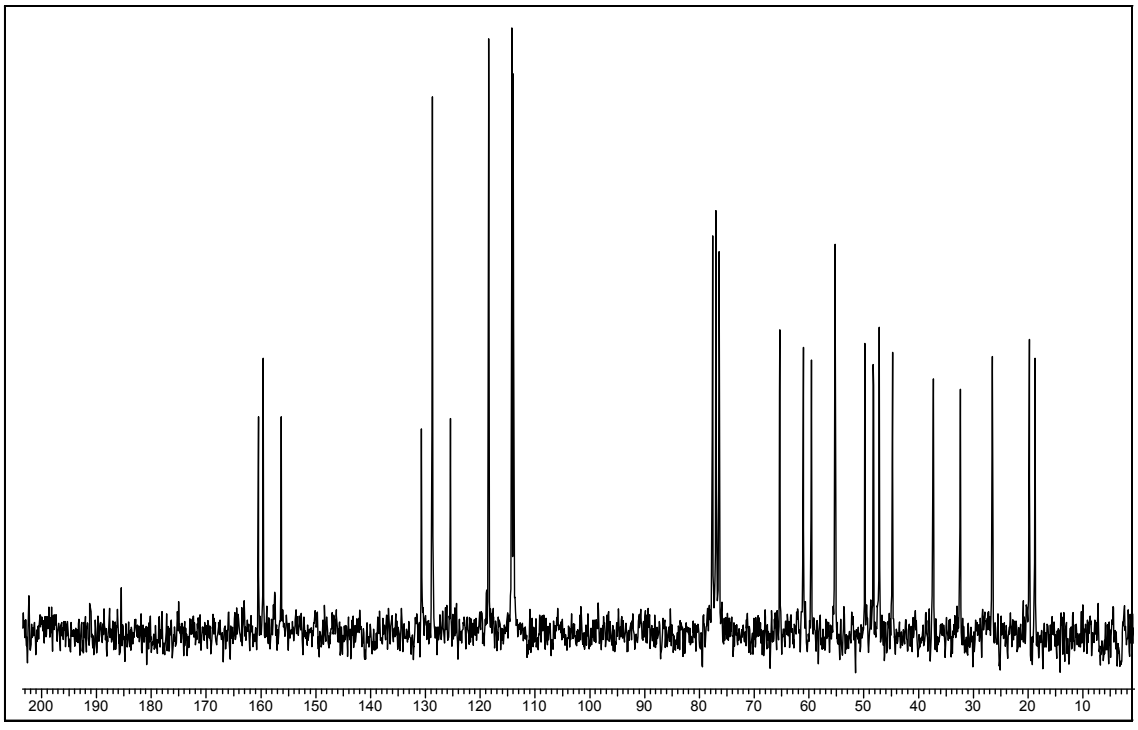
1.27b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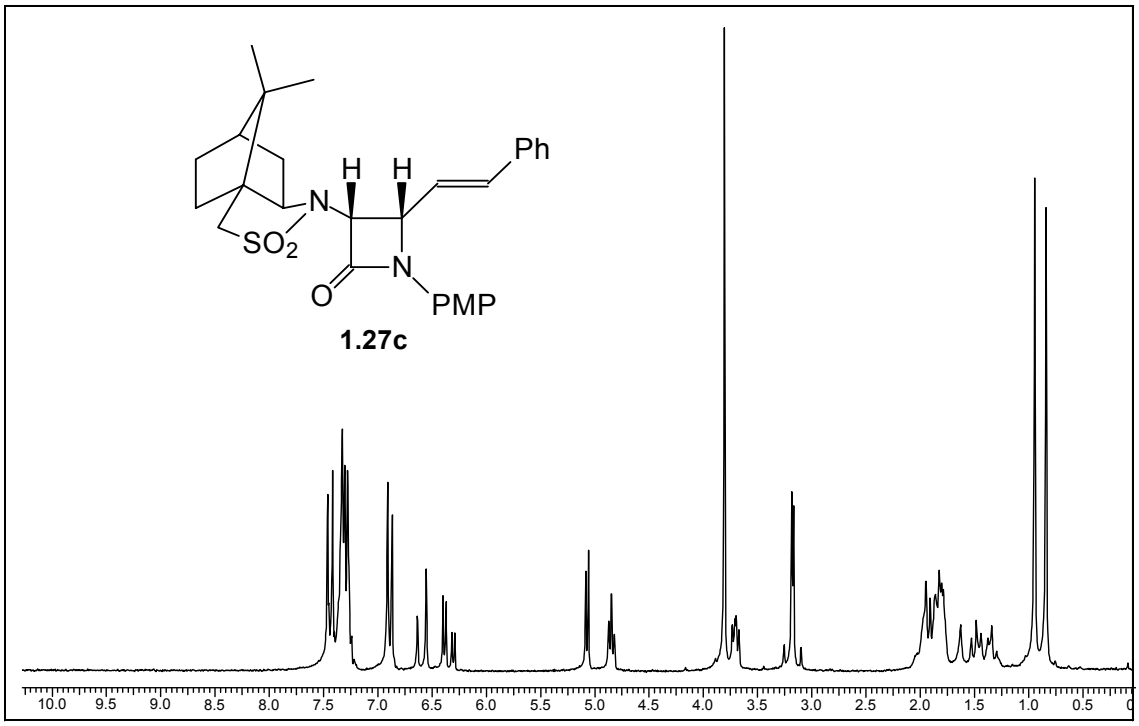
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N
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N
O
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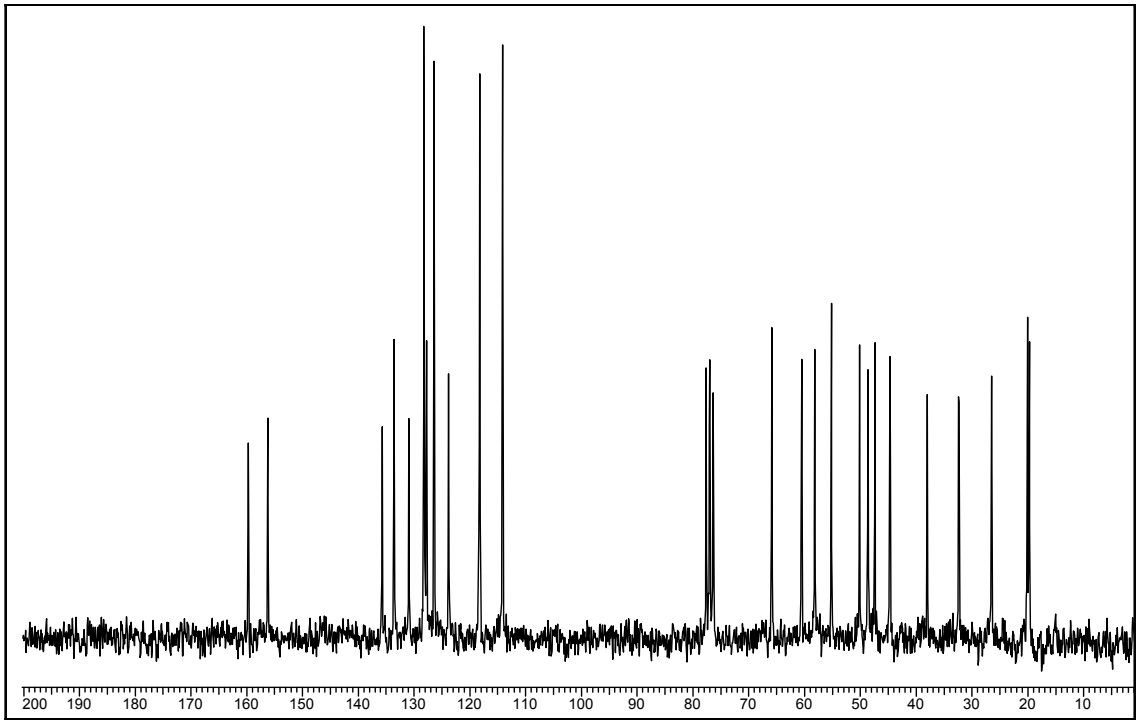
1.27c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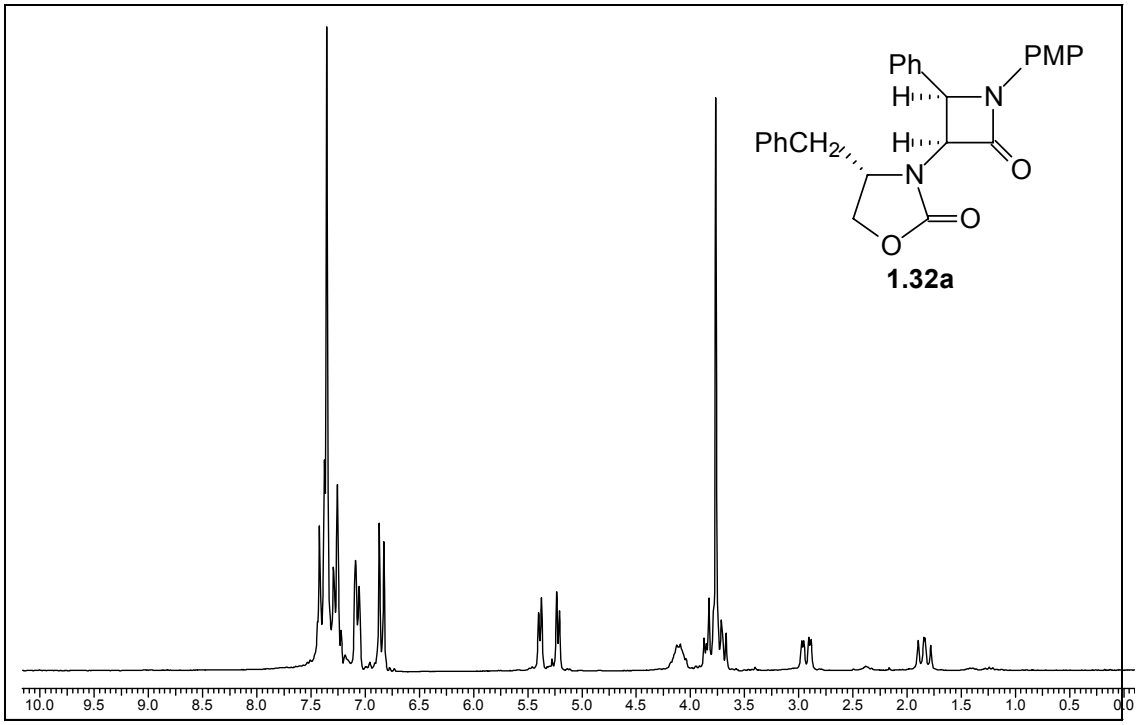
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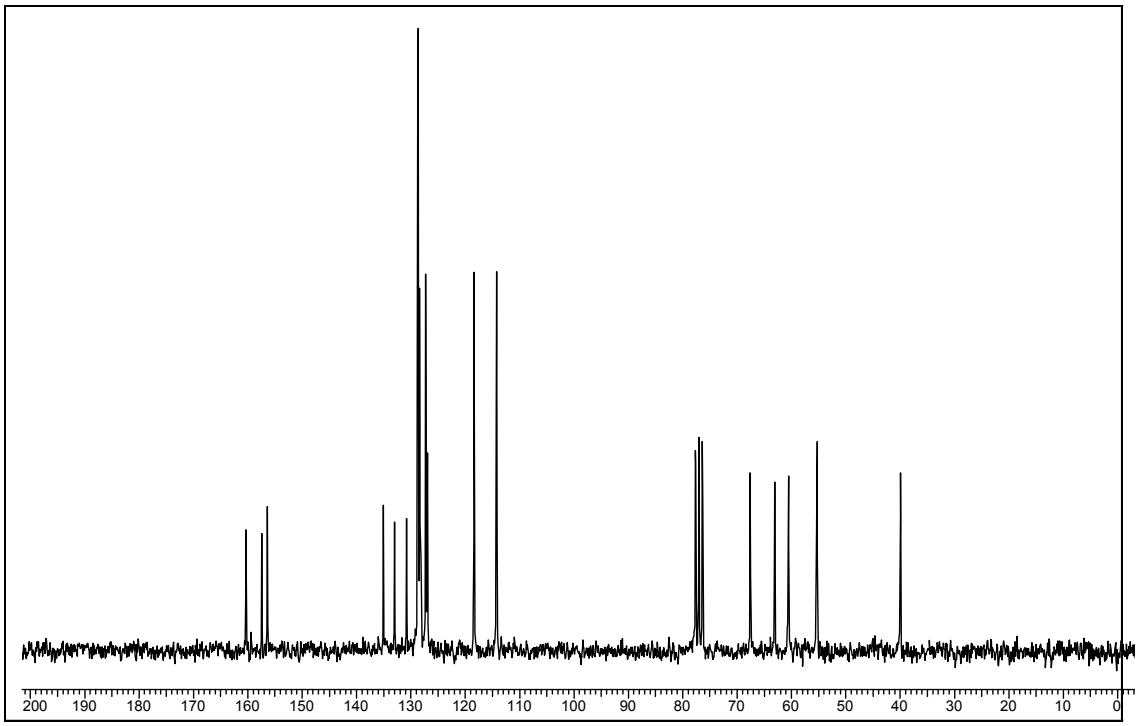
1.32a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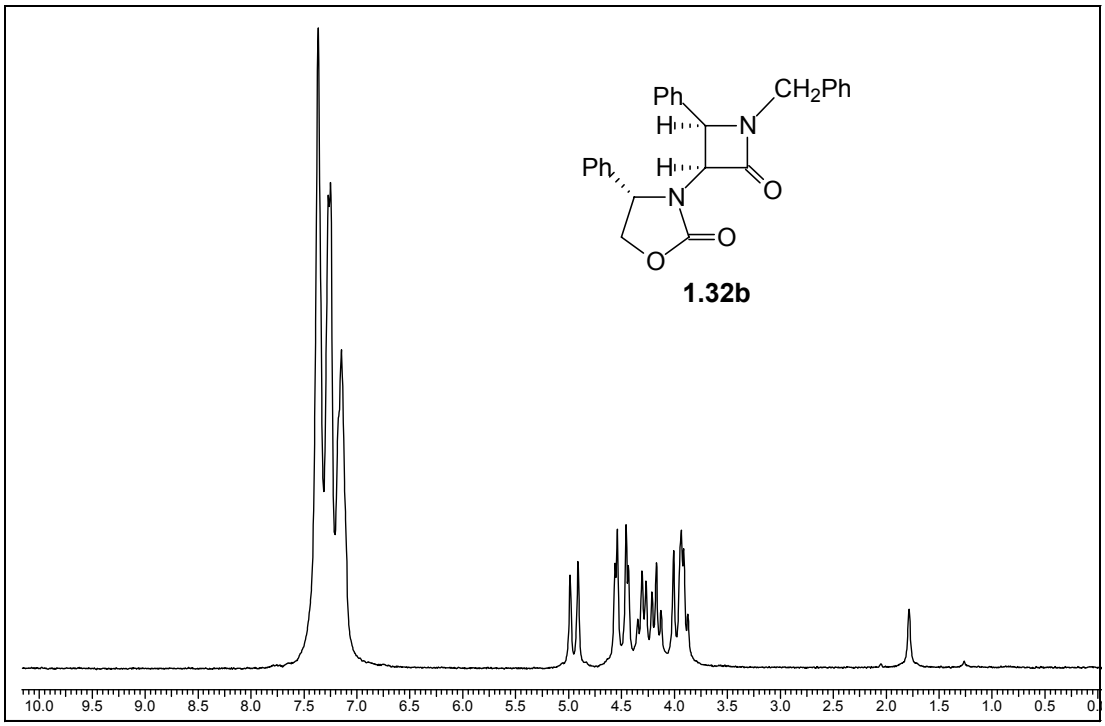
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N
H
Ph
N
O
O
O
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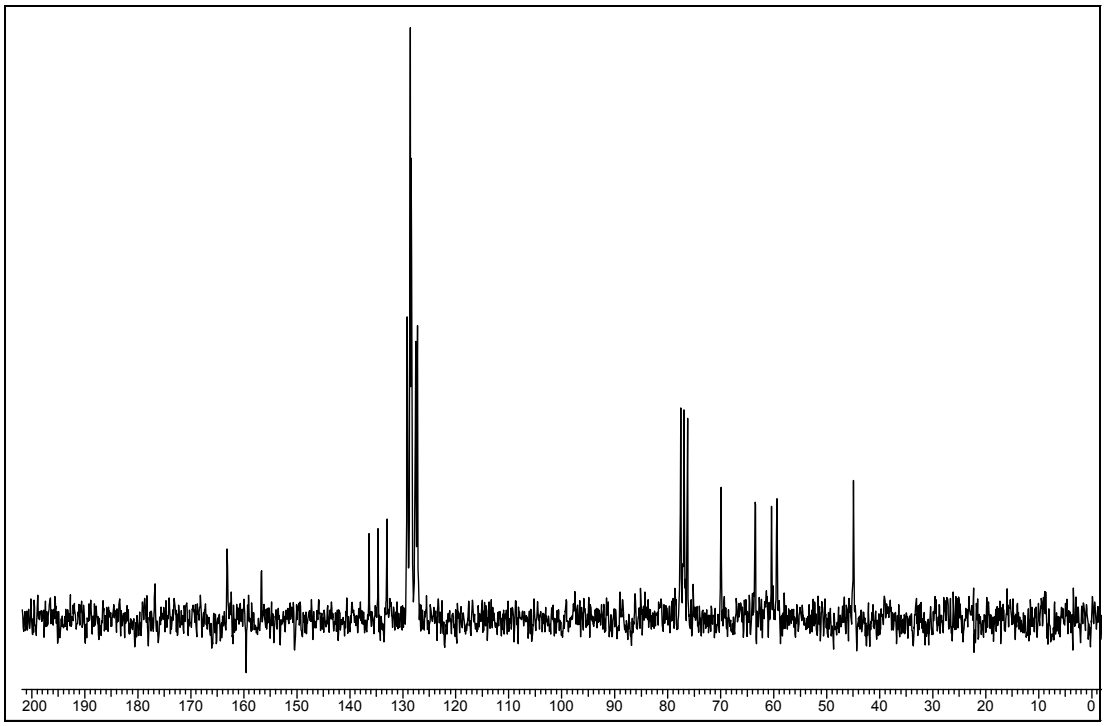
1.32b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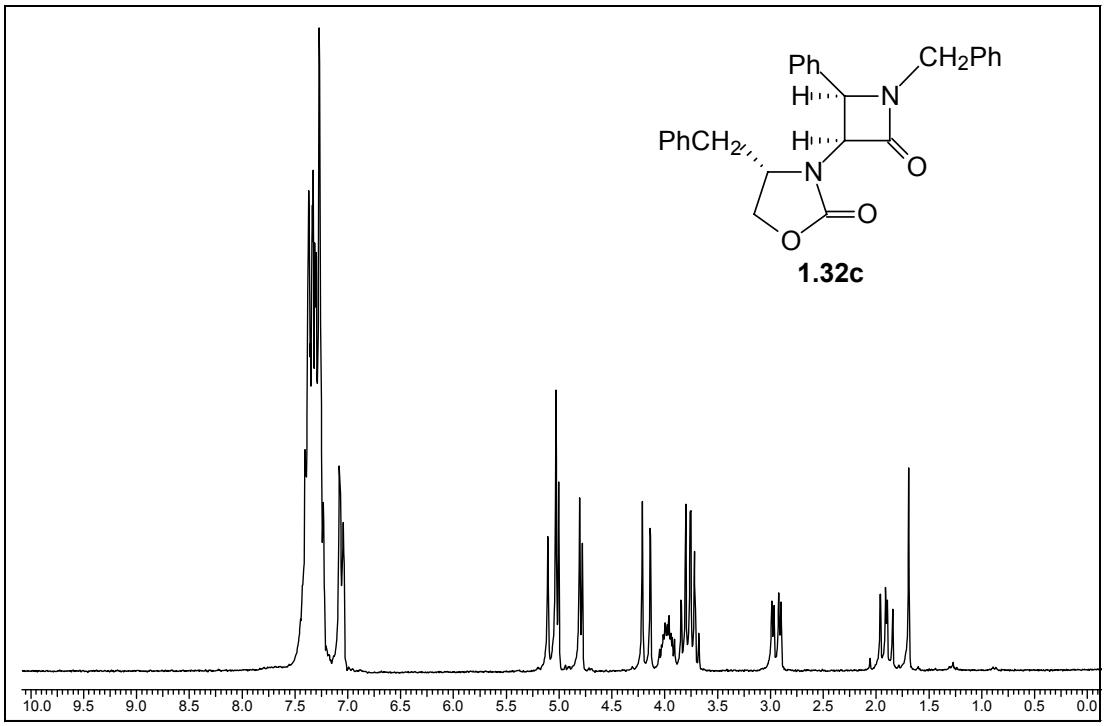
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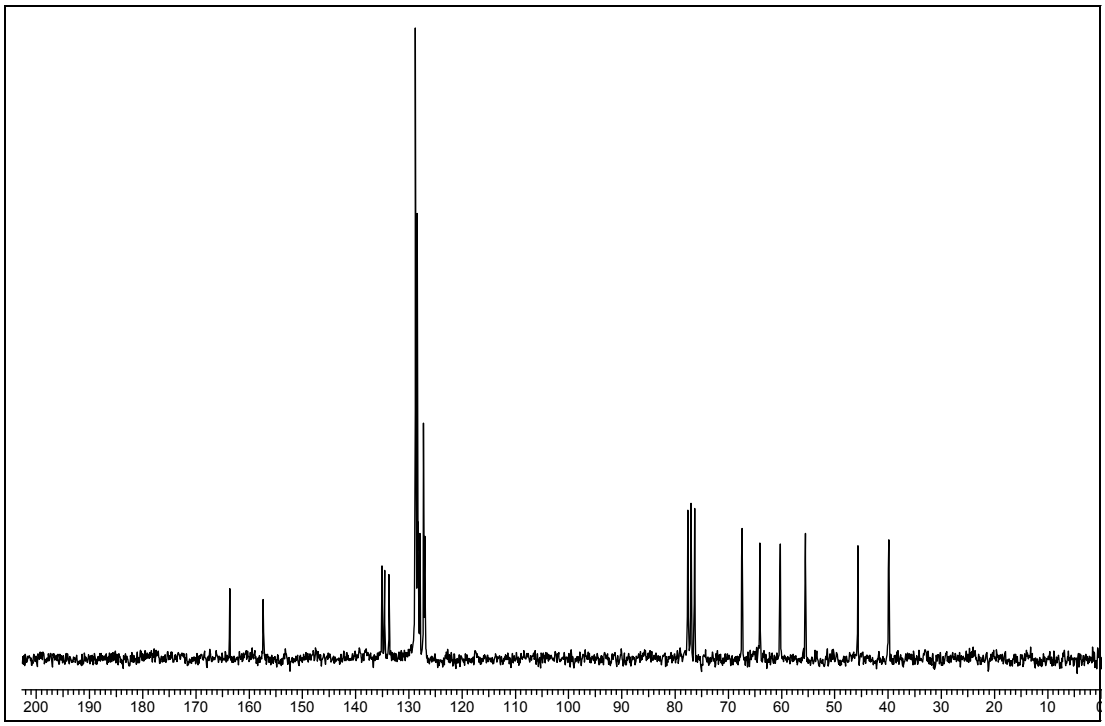
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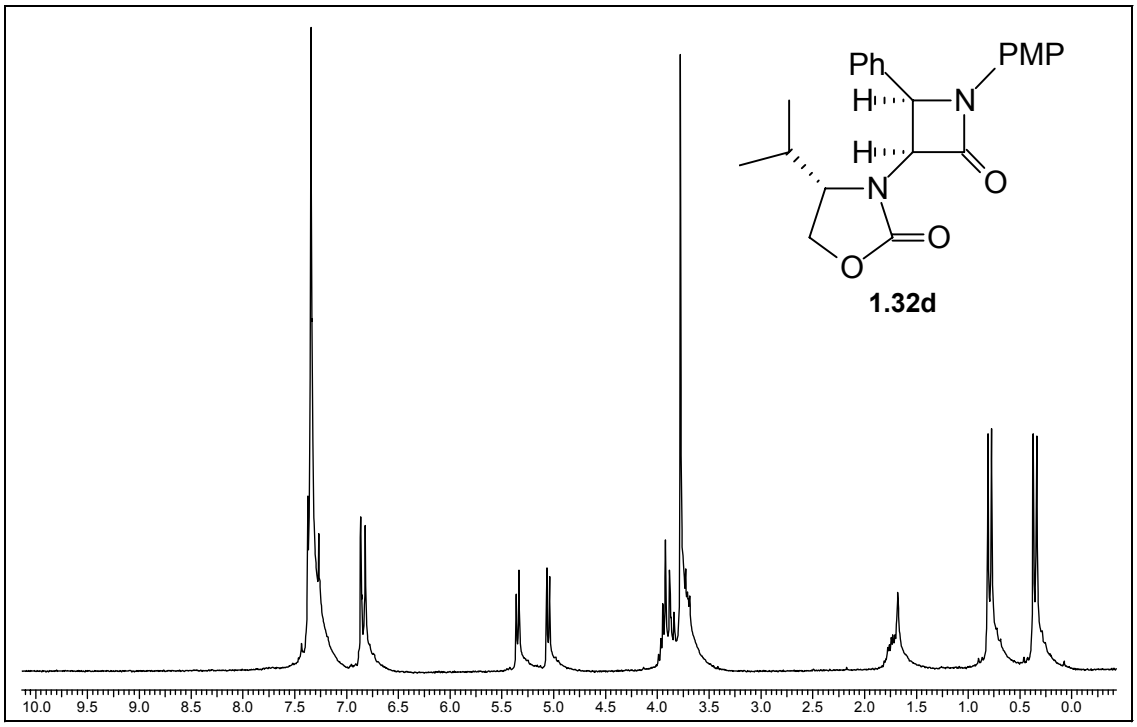
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H
N
O
O
O
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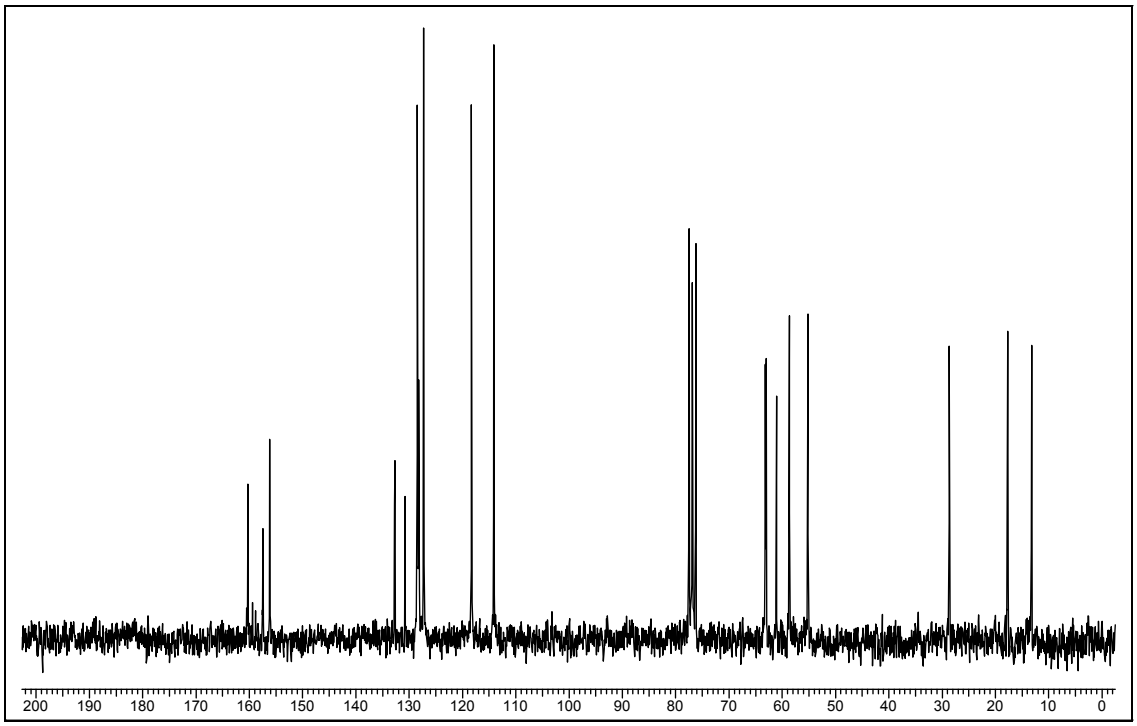
1.32d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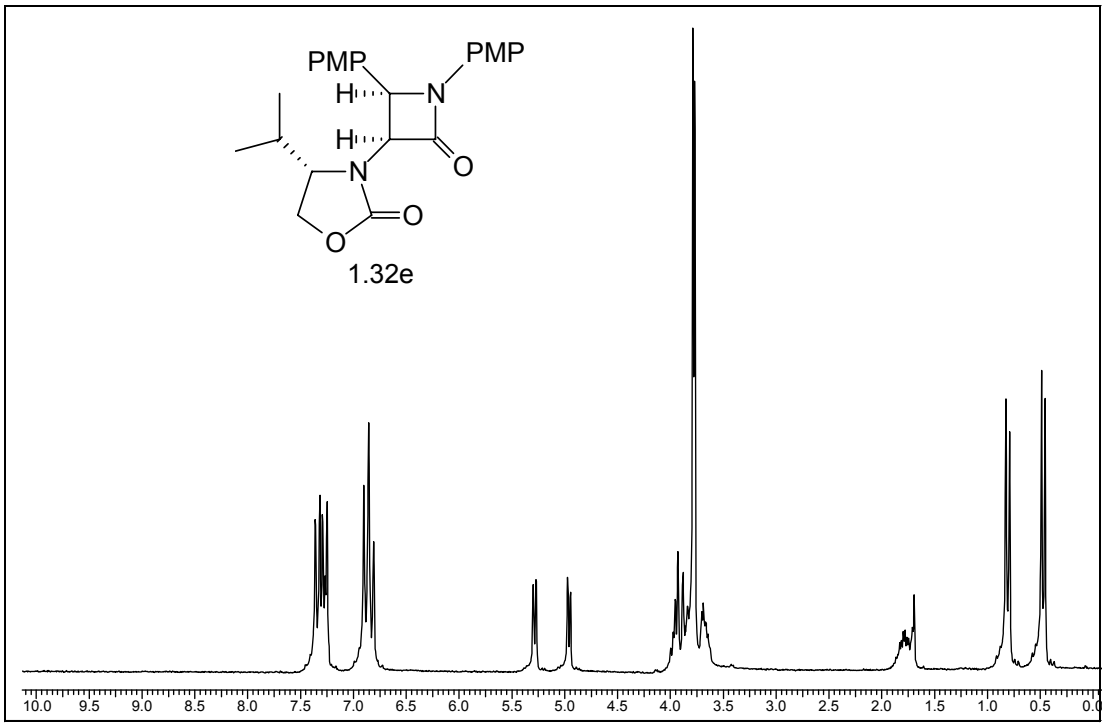
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PMP
H
H
N
N
O
O
O
1.32e
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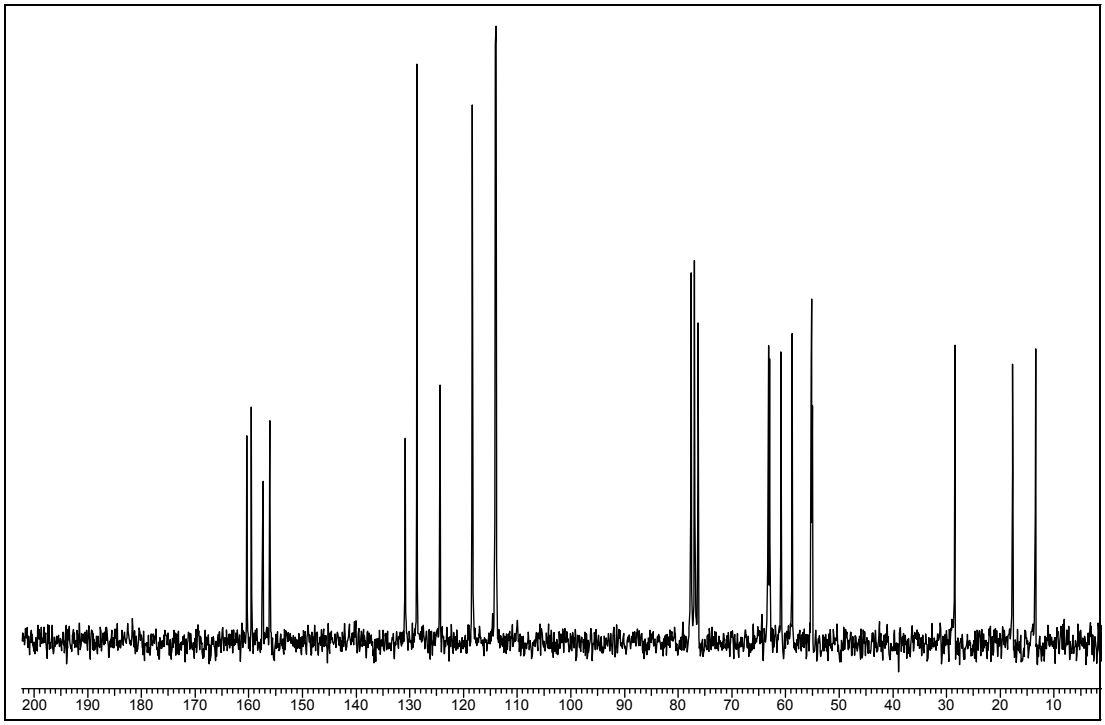
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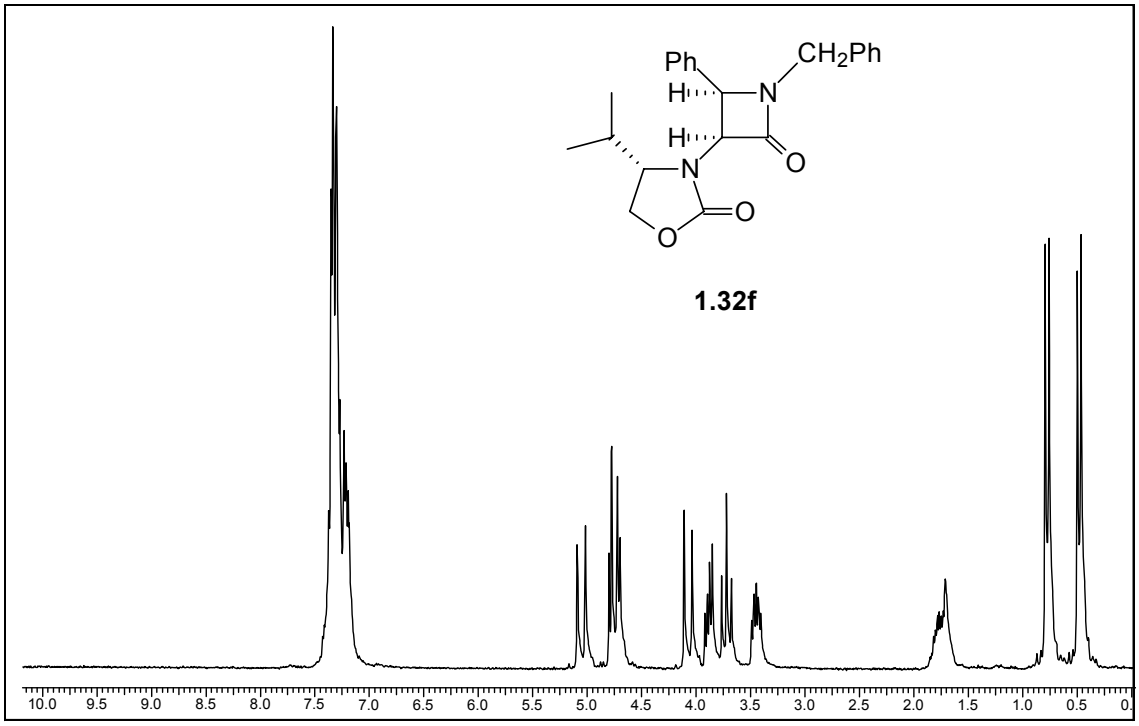
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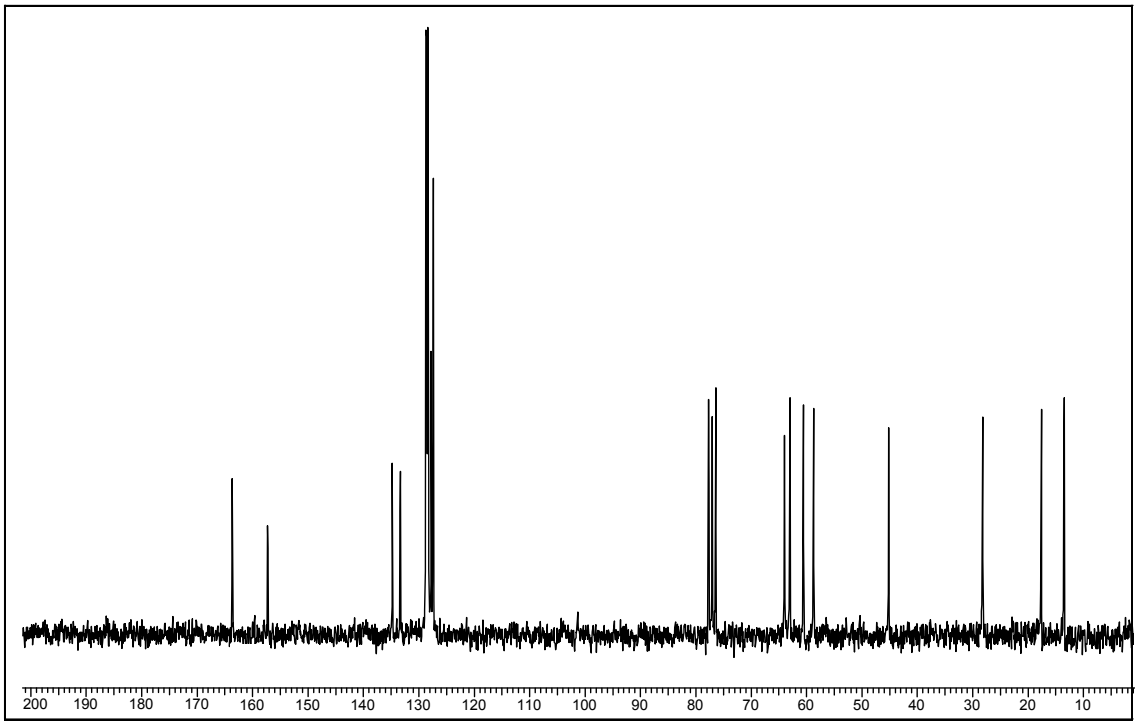
H
N
H
N
O
O
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

1.32f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CHAPTER 2

SECTION A

SYNTHESIS OF CHIRAL ACIDS FROM (+)-3-CARENE AND THEIR APPLICATIONS TOWARDS DIASTEREOSELECTIVE SYNTHESIS OF AZETIDIN-2-ONES

CHAPTER 2

SECTION B

SYNTHESIS OF SPIRO AZETIDIN-2-ONES USING ACIDS DERIVED FROM GLYOXYLIC ACID AND CAMPHOR-10-SULPHONIC ACID

2.1: Introduction

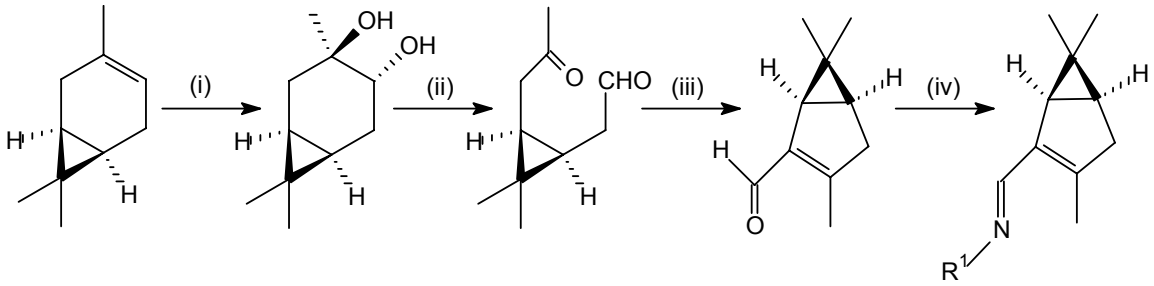
Asymmetric synthesis of azetidin-2-ones has become a major area of research over the past few decades. Of the various methods available for the synthesis of β-lactam ring, Staudinger reaction is the most preferred method due to its simplicity and versatility. Various chiral acid derivatives (as ketene precursors) and chiral amines (as chiral imine precursors) have been reported to effect moderate to very high diastereoselectivity in β-lactam ring construction *via* asymmetric Staudinger reaction (a brief review of various chiral acids and chiral imines used in asymmetric Staudinger reaction is presented in Chapter 1, introduction).

(+)-3-Carene, a bicyclic monoterpene is an inexpensive natural product abundantly available form Indian turpentine oil. The ketenes or imines derived form (+)-3-carene retains the imposing *gem* dimethyl group in the fused cyclopropane ring, which can effectively shield one face of the molecule from the reagent approach. Our group has effectively employed (+)-3-carene derived ketene precursors as well as imines, for the diastereoselective synthesis of β-lactams. Some of the results obtained earlier in our laboratory are reviewed below.

(+)-3-Carene derived chiral imines:

(+)-3-Carene was converted to a six membered bicyclic aldehyde, which on treatment with various amines gave the required imines in good yields (Scheme 2.01). These imines on treatment with acid chlorides gave good diastereoselectivity in β-lactam formation *via* ketene-imine cycloaddition reaction[1] (Scheme 2.02). In all the cases only *cis* β-lactams were obtained in very good yields. Maximum diastereoselectivity of 90:10 was obtained in the case of R^2 = PhthN and R^1 = PMP. The steric bulk of the imine was effective in inducing the diastereoselectivity even though the nearest chiral center was at the β-carbon from the aldehyde end.

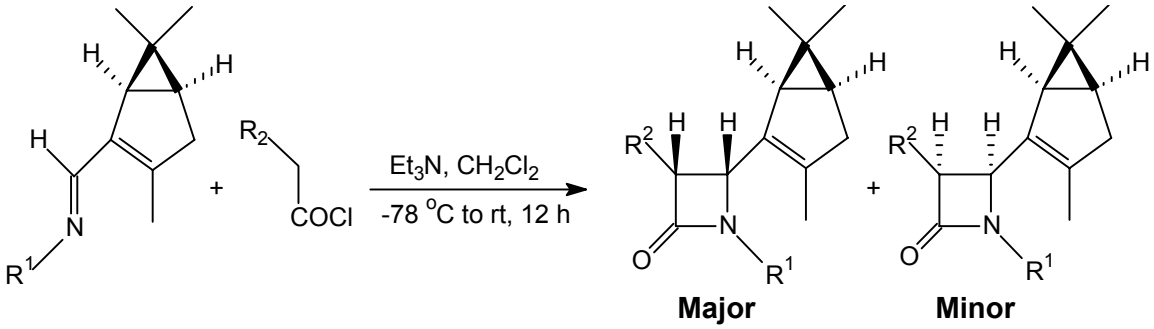
Scheme 2.01



(+)-3-Carene

Reagents and conditions: (i) a) H_2O_2, HCO_2H b) NaOH. (ii) $NaIO_4$, H_2O (iii) Piperidine, AcOH/benzene reflux, 5h. (iv) R^1NH_2, CH_2Cl_2, $MgSO_4$, rt, 24 h.

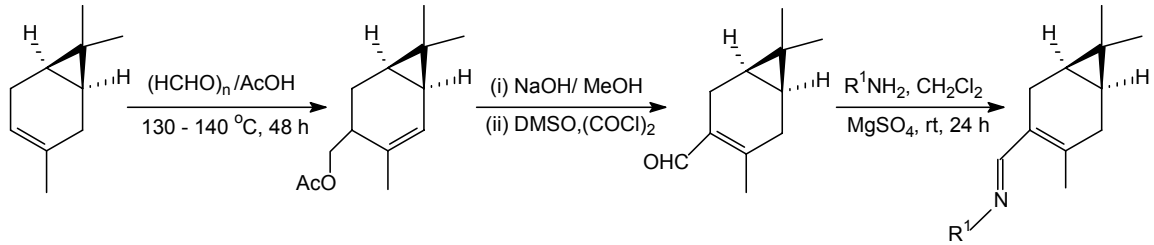
Scheme 2.02



R^1 = Ph, PMP, Bn; R^2 = PhO, BnO, PhthN, N_3, AcO.

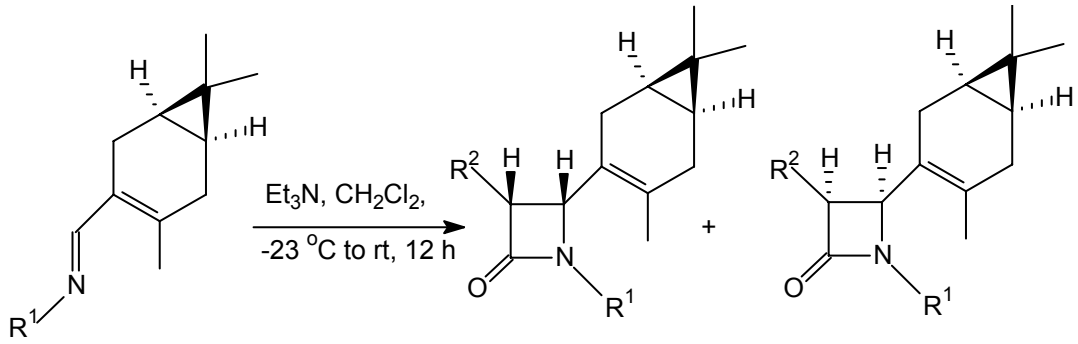
Our group has also examined the diastereoselectivity in β-lactam formation by using imines derived from (+)-3-carene, where the chiral center is located at γ position from the aldehyde end. The imine was prepared from seven membered bicyclic aldehyde, which was obtained from (+)-3-carene by Prins reaction followed by hydrolysis of acetate and Swern oxidation (Scheme 2.03)

Scheme 2.03



These imines on cycloaddition reactions with ketenes generated *in situ* from acid chlorides in presence of triethylamine gave 50:50 diastereomeric mixture of β-lactams (Scheme 2.04).[2]

Scheme 2.04

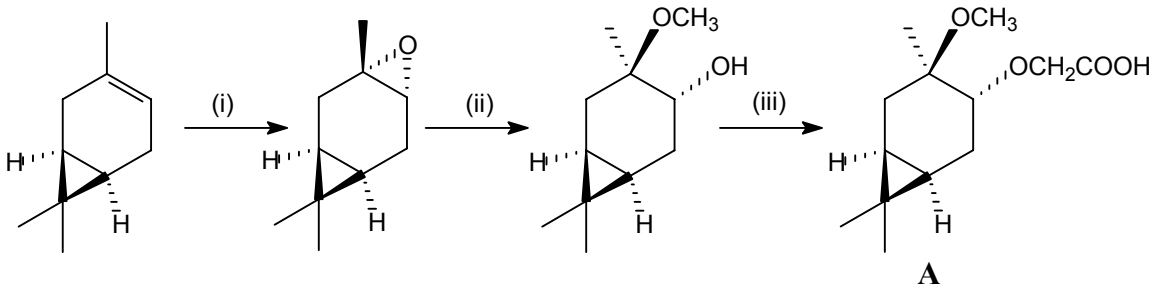


R^1= PMP, Bn. R^2= PhO, BnO, PhthN

(+)-3-Carene derived chiral ketene precursor:

Our group has also investigated the diastereoselectivity in β-lactam formation by making use of methoxy acid **A**, derived from (+)-3-carene (Scheme 2.05). Cycloaddition of ketene generated *in situ* from the acid **A** with imine at 0 °C gave diastereomeric mixture of *cis* β-lactams with diastereomeric ratio of 60:40 (Scheme 2.06).[3]

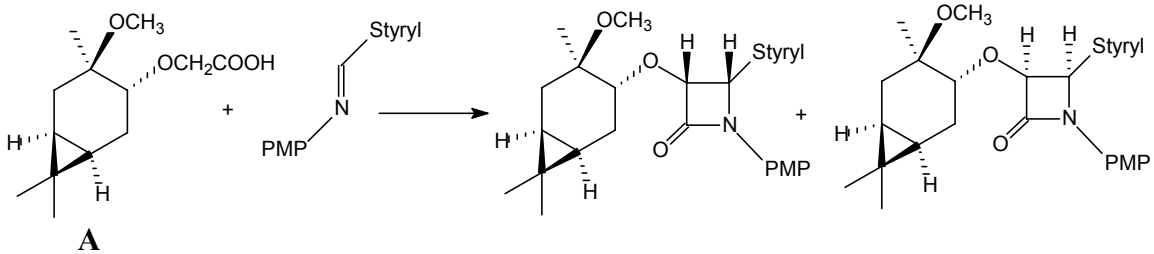
Scheme 2.05



A

Reagents and conditions: (i) H_2O_2 $ClCO_2Et$, Na_3PO_4, CH_2Cl_2; (ii) MeOH, PTSA 2 h; (iii) Na, $ClCH_2CO_2H$, Toluene.

Scheme 2.06



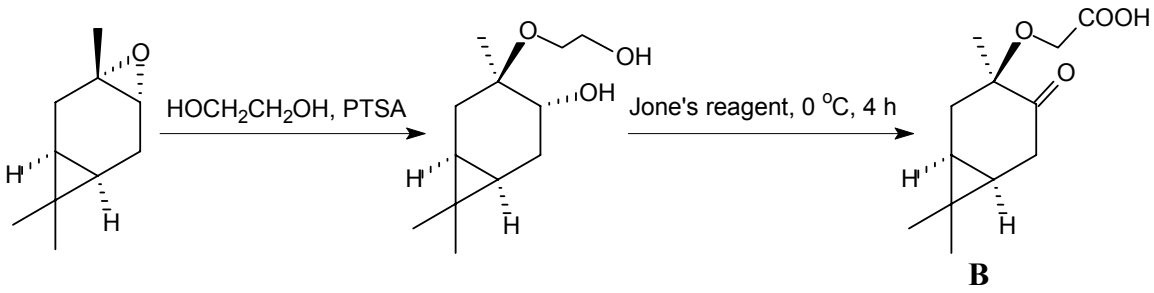
A

Reagents and condition: Et_3N, $PhOP(O)Cl_2$, CH_2Cl_2, 0 °C to rt, 14 h.

The use of acid **A**, which was derived from carene, with the –OCH_2COOH side chain at the secondary carbon (C-4) of the carane ring, as chiral ketene precursor in Staudinger reaction resulted in only moderate diastereoselectivity in β-lactam formation

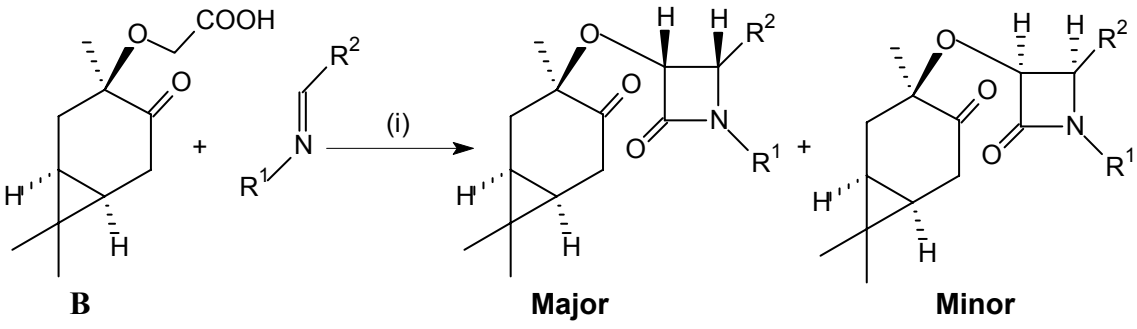
(Scheme 2.06). Therefore, the acid **B** was prepared from α-Carene oxide by opening it with ethylene glycol followed by Jones oxidation of the resulting diol (Scheme 2.07). This acid **B** has -OCH_2COOH side chain at tertiary carbon (C-3) of the carane ring.

Scheme 2.07



This acid **B** was expected to give good diastereoselectivity in β-lactam formation *via* cycloaddition reaction with imine. However, a maximum diastereoselectivity of 70:30 was obtained (Scheme 2.08). The mixture of diastereomers could be separated and the major diastereomer was transformed to optically pure 3-hydroxy-4-phenyl-β-lactam C, which is a synthetic equivalent of phenyl isoserine unit of taxol side chain (Scheme 2.09).[4]

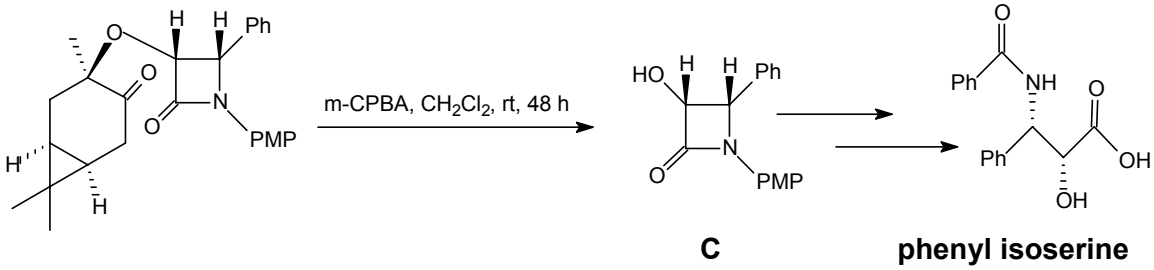
Scheme 2.08



R^1= PMP, Bn; R^2 = Styryl, Ph

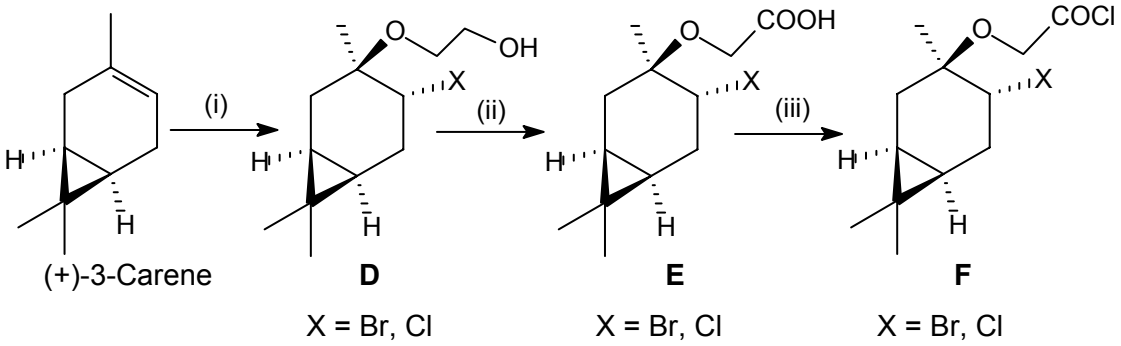
Reagents and condition: Et_3N, CH_2Cl_2, $PhOP(O)Cl_2$, 0 °C to rt, 15 h.

Scheme 2.09



Our group has also developed a complementary method for the synthesis of 3-hydroxy-β-lactams[5] **G** and **H** *via* halo acids **E** derived from (+)-3-carene. The halo acids **E** were prepared by NBS or NCS reaction with (+)-3-carene in the presence of ethylene glycol followed by Jones oxidation of halohydrins **D** in moderate yield. These acids were converted to corresponding acid chlorides **F** with thionyl chloride (Scheme 2.10).

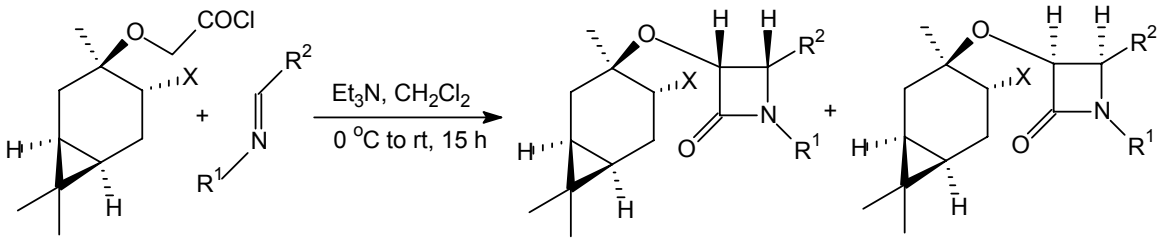
Scheme 2.10



Reagents and conditions: (i) NBS or NCS/$HOCH_2CH_2OH$, 0 °C, 4 h. (ii) Jones' reagent, 0 °C, 4 h. (iii) $SOCl_2$, benzene, reflux, 3 h.

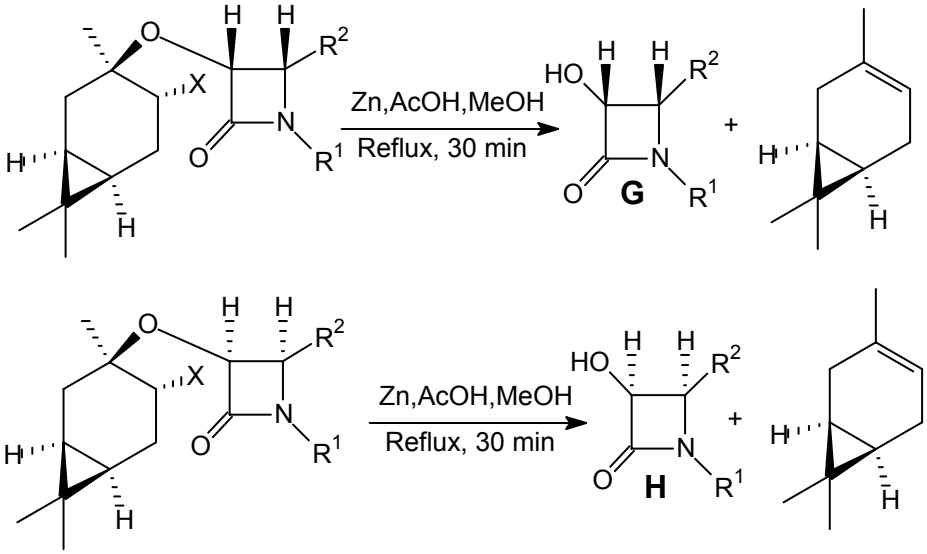
These acid chlorides **F** underwent cycloaddition reaction with imines to give good yield of diastereomeric mixture of *cis*-β-lactams (Scheme 2.11).

Scheme 2.11



The mixture of diastereomers were separated and converted to optically pure 3-hydroxy-β-lactams **G** and **H** by Zn induced cleavage of the chiral auxiliary (Scheme 2.12). (+)-3-Carene formed during the cleavage was also isolated and characterized.

Scheme 2.12



2.2 : Present work

In continuation of the earlier work reported in our laboratory, we were interested in making use of (+)-3-carene derived chiral auxiliaries in the asymmetric Staudinger reaction for the synthesis of β-lactams. Design and synthesis of chiral acids as ketene precursors, from readily available (+)-3-carene and their studies towards diastereoselective synthesis of azetidin-2-ones *via* Staudinger reaction is discussed in this section.

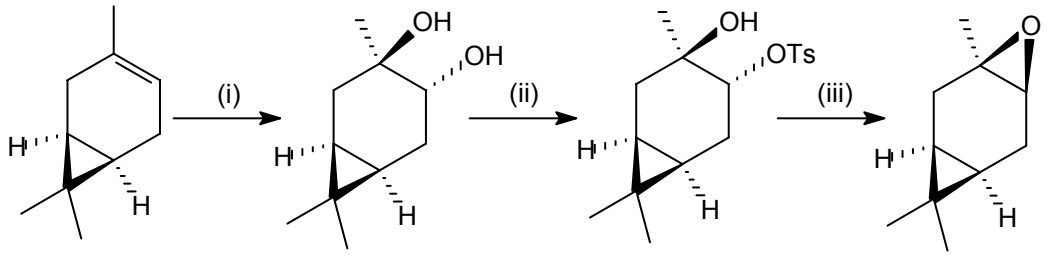
2.3 : Results and Discussion

As described in the introduction, earlier work in our laboratory had shown that, use of acids **A** and **B** as chiral ketene precursors in asymmetric Staudinger reaction resulted in moderate diastereoselectivity in azetidin-2-one formation We were interested to see the effect of inversion of the stereocenter carrying the acid side chain in the keto acid **B** and the methoxy acid **A** on the diastereoselectivity in β-lactam formation *via* Staudinger reaction. These acids **2.06** and **2.12** were synthesized from (+)-3-carene and were employed as a chiral ketene precursor in the asymmetric Staudinger reaction to study the diastereoselectivity in azetidin-2-one formation.

2.3.1 : Preparation of β-Carene oxide 2.04.

(+)-3-Carene **2.01** was converted to the trans diol[6] **2.02** using formic acid and hydrogen peroxide. Following a reported procedure,[7] the diol **2.02** on mono tosylation followed by treatment with base offered the β-Carene oxide **2.04** in good yield (Scheme 2.13).

Scheme 2.13



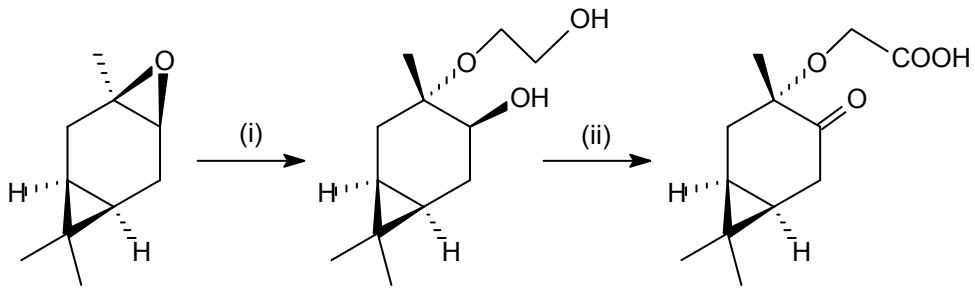
2.01 **2.02** **2.03** **2.04**

Reagents and conditions: (i) HCOOH, H_2O_2, NaOH <40 °C, 28 h. (ii) *p*-TsCl, pyridine, 0 °C (36 h), rt (24 h). (iii) MeOH, KOH, 48 h.

2.3.2 : Preparation of keto-acid 2.06.

The β-carane epoxide **2.04** was opened with ethylene glycol in presence of catalytic amount of PTSA to get the diol **2.05** quantitatively. To a solution of diol **2.05** in acetone, Jones reagent was slowly added dropwise at 0 °C until the color of the reagent persisted. The reaction mixture was stirred at room temperature for 4 h. After completion of reaction (TLC), the excess reagent was destroyed by adding isopropanol at 0 °C. The solution was concentrated under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous. Sodium sulphate. Removal of solvent under reduced pressure gave the acid **2.06** as pale yellow oil (Scheme 2.14).

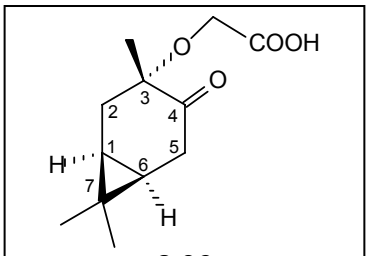
Scheme 2.14



2.04 **2.05** **2.06**

Reagents and conditions: (i) $HOCH_2CH_2OH$, PTSA, 0 °C, 4 h. (ii) Jones reagent, 0 °C to rt, 4 h.

The IR spectrum of **2.06** showed a broad band at 3500-3200 cm^{-1} and a sharp band at 1720 cm^{-1} characteristic of –OH and the carbonyl group of carboxylic acid.



2.06

The ^{1}H NMR spectrum showed two singlets at 0.85 ppm and at 1.05 ppm for the two *gem* dimethyl groups, each integrating for three protons. The two –CH protons of the carene ring appeared as multiplets between 0.70 and 0.95 ppm. The protons of C-3 methyl group of the carene ring, appeared as a singlet at 1.15 ppm. The four methylene protons (C-2 and C-5) of the carane ring appeared as three doublet of doublet at 1.53 ppm (J = 5.1 Hz, 15.9 Hz), 2.54 ppm (J = 9.3 Hz, 16.6 Hz), 2.75 ppm (J = 8.7 Hz, 17.5 Hz) and as multiplets between 2.05 ppm to 2.40 ppm respectively. Due to the diastereotopic nature, the methylene protons attached to the carboxylic acid group appeared as doublets at 3.90 ppm and 4.10 ppm with coupling constant of J = 16.6 Hz. A broad singlet at 6.25 ppm corresponded to the carboxylic acid proton. The ^{1}H NMR peak assignments thus confirmed the structure of **2.06**.

The ^{13}C NMR spectrum showed a peak at 213.33 ppm and at 173.20 ppm corresponding to the carbons of the keto and carboxylic acid group. The methylene carbons appeared at 34.51, 34.88 and 61.56 ppm. The methyl carbons of the carene system appeared at 14.47, 16.57 and 17.93 ppm. The methine carbons of the carene moiety appeared at 23.48 ppm and 27.60 ppm. The C-3 quaternary carbon appeared at 78.14 ppm and the C-7 quaternary carbon bearing the gem dimethyl groups appeared at 19.14 ppm. The mass spectrum gave a molecular ion peak at (m/z) 226.

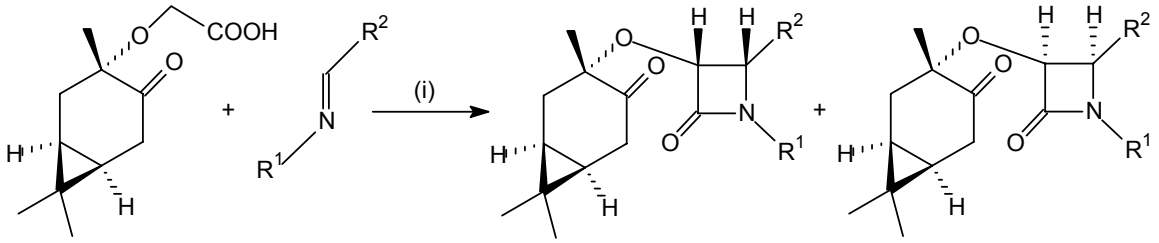
2.3.3 : Preparation of azetidin-2-ones 2.08a-c & 2.09a-c.

Having prepared the chiral acid **2.06**, we wanted to utilize this acid as a chiral ketene precursor in the asymmetric Staudinger reaction with imines, in order to investigate the diastereoselectivity in azetidin-2-one formation. The typical experimental procedure and results obtained are discussed below.

An anhydrous solution of triphosgene in dichloromethane was slowly added to a cooled (0 ^{o}C) dichloromethane solution of acid **2.06**, imine **2.07a** and triethylamine. After completion of addition, the reaction mixture was allowed to attain room

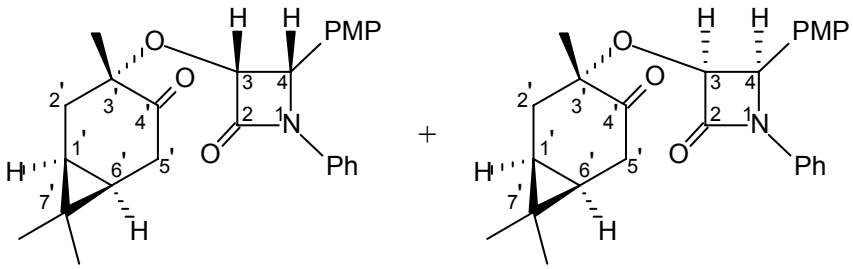
temperature and stirred at this temperature for 12 h. It was diluted with dichloromethane and successively washed with water, saturated bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to get the crude product as dark brown oil. The IR spectrum of the crude product showed a peak at 1760 cm^{-1} characteristic of β-lactam carbonyl. The ^1H NMR spectrum of the crude product also confirmed the presence of β-lactam. The ^1H NMR spectrum showed two sets of signals, indicating the presence of diastereomeric mixture of two azetidin-2-ones **2.08a** & **2.09a** (in the ratio 65:35) (Scheme 2.15). The diastereomeric mixture of **2.08a** & **2.09a** was isolated by flash column chromatography in 68% yield. Attempts to separate the two diastereomers by column chromatography/crystallization were unsuccessful. The IR and ^1H NMR spectra of the diastereomeric mixture of **2.08a** and **2.09a** are discussed below.

Scheme 2.15



Reagents and conditions: (i) Et_3N, CH_2Cl_2, triphosgene, 0 °C to rt, 12 h.

The IR spectrum of the mixture **2.08a** & **2.09a** showed bands at 1760 cm^{-1} and at 1730 cm^{-1} characteristic of β-lactam carbonyl and keto carbonyl.



Diastereomeric mixture of azetidin-2-ones **2.08a** and **2.09a**

The ^1H NMR spectrum of the mixture **2.08a** & **2.09a** showed two sets of signals confirming the presence of two diastereomers in the mixture. The protons of *gem* dimethyl groups of the two diastereomers appeared singlets at 0.65 ppm, 0.70 ppm, 0.75 ppm and 0.80 ppm. The protons of C-3' methyl groups of the two diastereomers appeared

as singlets at 0.95 ppm and 1.10 ppm. One of the C-5' methylene protons (for one of the diastereomer) of the carene system appeared as doublet of doublet at 3.00 ppm (J = 17.6 Hz, 8.8 Hz). The remaining methylene and methine protons of the carene system appeared as multiplets between 0.35 ppm and 2.50 ppm. The protons of –OMe group attached to the aromatic ring appeared as singlets at 3.70 and 3.75 ppm (for the two diastereomers). The C-4 protons of the minor and major diastereomers appeared as doublets at 4.65 ppm and 4.95 ppm with coupling constants J = 4.9 Hz and J = 5.4 Hz respectively. The C-3 protons of the two diastereomers appeared as two merged doublets at 5.05 ppm. The *cis* stereochemistry at C-3 and C-4 centers of the major and minor diastereomers was established based on the coupling constant value (J = 4.9 Hz) of these protons. The aromatic protons appeared as multiplets between 6.70 ppm to 7.50 ppm.

The ^{13}C NMR spectrum of the diastereomeric mixture of **2.08a** & **2.09a** showed peaks at 165.40 ppm and 164.92 ppm corresponding to the β-lactam carbonyl of the major and minor diastereomer. The carbon of the keto carbonyl of the chiral auxiliary resonated at 212.71 and 214.29 ppm (for the two diastereomers). The aromatic quaternary carbon bearing the –OMe group of the *p*-anisyl moiety appeared at 159.78 ppm and the aromatic carbon attached to the nitrogen of the β-lactam moiety appeared at 137.03 ppm. The other quaternary carbon of the *p*-anisyl moiety appeared at 129.86 ppm. The other aromatic carbons resonated at 128.90, 125.59, 125.41, 124.12, 119.53, 117.32 and 113.57 ppm. The C-3 carbon of major and minor isomer appeared at 77.99 ppm and 78.62 ppm. The C-4 carbon of the major and minor isomer appeared at 61.93 ppm and 62.55 ppm. The methoxy carbon of the –OMe group appeared at 55.09 ppm. The methylene carbon (C-2' and C-5') of the carane moiety appeared at 34.95, 34.77, 34.58 and 34.10 ppm. The quaternary carbon (C-7') of the cyclopropyl ring appeared at 19.18 ppm and 18.92 ppm. The methine carbon (C-1' and C-6') of the cyclopropyl ring resonated at 24.29 ppm and 21.3 ppm. The carbon of *gem* dimethyl groups appeared at 14.29, 14.59, 16.61 and 17.08 ppm. The carbon of the other methyl group at C-3' appeared at 27.67 ppm and 27.52 ppm. The C-3' carbon appeared at 79.28 ppm. The mass spectrum of the diastereomeric mixture showed a molecular ion peak at (m/z) 419.

Following the same procedure, the acid **2.06** was treated with other substituted imines **2.07b-c** to get a diastereomeric mixture of azetidin-2-ones **2.08b-c** & **2.09b-c** (Scheme 2.15). In these cases also, separation of diastereomers was not possible. The

isolated diastereomeric mixtures **2.08b-c** & **2.09b-c** were characterized by IR and ^{1}H NMR data, which showed the characteristic peaks of β-lactam. In all the cases, only *cis* azetidin-2-ones were obtained, with moderate diastereoselectivity (Table 1). When the reaction was carried out at lower temperature (-40 ^{o}C), there was no change in the diastereomeric ratio. However, there was considerable drop in the yield of azetidin-2-ones.

Table 1 *Synthesis of azetidin-2-ones* **2.08a-c** & **2.09a-c** *via cycloaddition reaction of imines* **2.07** *with chiral ketene derived from acid* **2.06**.

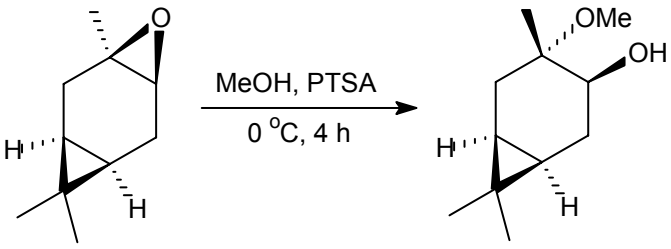
β-lactams 2.08 & 2.09	R^1	R^2	Ratio of 2.08 & 2.09	Yield (%)[a]
a	Ph	PMP	65:35	68
b	PMP	Ph	60:40	70
c	PMP	PMP	60:40	60

[a] Isolated yield of diastereomeric mixture

2.3.4 : Preparation of methoxy alcohol 2.10.

β-Carane oxide **2.04** was reacted with methanol in presence of PTSA at 0 ^{o}C to get the methoxy alcohol **2.10** in quantitative yield (Scheme 2.16).

Scheme 2.16



2.04 **2.10**

The structure of the methoxy alcohol **2.10** was confirmed from IR and ^{1}H NMR data. The IR spectrum gave a broad band at 3500-3300 cm^{-1} corresponding to hydroxy group of alcohol.

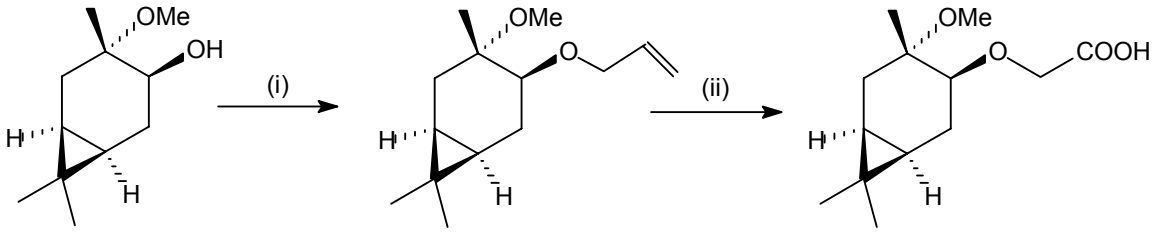
The ^{1}H NMR spectrum of **2.10** showed multiplets between 0.55 ppm and 0.65 ppm corresponding to the –CH of the cyclopropane ring of the carane system. The *gem* dimethyl protons appeared as singlets at 0.95 ppm and 0.96 ppm. The protons of the C-3 methyl group of carane ring appeared as singlet at 1.10 ppm. The methylene protons of

the carane ring appeared as multiplets between 0.90 ppm and 2.20 ppm. The protons of the –OMe group appeared as a singlet at 3.25 ppm. The –CH proton attached to the hydroxyl group appeared as a triplet at 3.75 ppm (J = 5.8 Hz). The –OH proton appeared as a broad singlet at 1.90 ppm.

2.3.5 : Preparation of methoxy acid 2.12.

The hydroxyl group of the methoxy alcohol **2.10** was allylated using NaH and allyl bromide in THF to get the allyl ether **2.11**. To a solution of ether **2.11** in the solvent system containing CH_3CN:CCl_4:H_2O (ratio 2:2:3), powdered $NaIO_4$ was added followed by catalytic amount of $RuCl_3$ at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 4 h. After completion of reaction (TLC), the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was concentrated under reduced pressure to get crude product. The crude product was basified with saturated $NaHCO_3$ solution and extracted with dichloromethane. The aqueous layer was acidified with dil. HCl at 0 ^oC and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get pure acid **2.12** as pale yellow oil (Scheme 2.17).

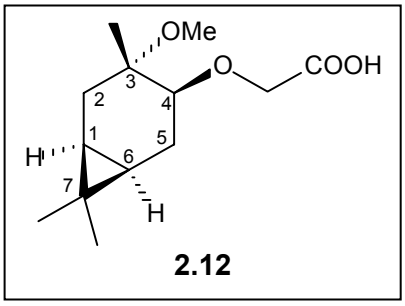
Scheme 2.17



2.10 **2.11** **2.12**

Reagents and conditions: NaH, Allyl bromide, THF, reflux, 16 h. (ii) CH_3CN:CCl_4:H_2O (2:2:3), $NaIO_4$, $RuCl_3$, 0 ^oC, 4 h.

The IR spectrum of **2.12** showed a broad band at 2800-3200 cm^{-1} and a band at 1730 cm^{-1} characteristic of carboxylic acid.



2.12

The ^1H NMR spectrum of acid **2.12** showed multiplets for the two –CH protons of the cyclopropyl ring between 0.50 ppm and 0.75 ppm. The *gem* dimethyl protons appeared as singlets at 0.90 ppm and 0.95 ppm.

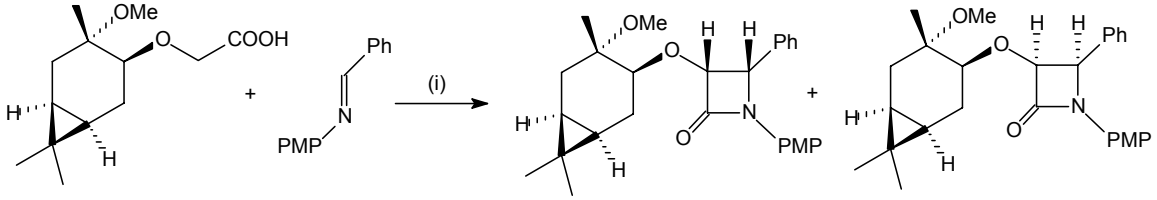
The protons of the -CH_3 group attached to the C-3 carbon of the carane ring, appeared as singlet at 1.15 ppm. The methylene protons of the carane ring appeared as multiplets between 1.10 ppm and 2.15 ppm. The methine proton of the C-4 carbon attached to the oxygen atom of acid side chain appeared as multiplets between 3.15 ppm and 3.40 ppm. The –OMe protons appeared as a singlet at 3.25 ppm. The methylene protons attached to the –COOH group appeared as two doublets at 4.02 ppm (J = 17.0 Hz) and at 4.20 ppm (J = 17.0 Hz). A broad singlet at 7.80 ppm corresponded to the carboxylic acid proton. The mass spectrum of **2.12** gave a molecular ion peak at (m/z) 242.

2.3.6 : Preparation of azetidin-2-ones 2.14 & 2.15.

The acid **2.12** was used as a chiral ketene precursor in the asymmetric Staudinger reaction for the synthesis of azetidin-2-one. Typical experimental procedure and the result obtained is discussed below.

In a typical experimental procedure, an anhydrous dichloromethane solution of triphosgene was slowly added to a cooled (0 ^{o}C) dichloromethane solution of the acid **2.12**, imine **2.13** and triethylamine (Scheme 2.18). After completion of addition, the reaction mixture was allowed to attain room temperature and stirred at this temperature for 12 h. It was diluted with dichloromethane and successively washed with water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to get the crude product as a dark brown oil. The IR spectrum of the crude product showed a peak at 1760 cm^{-1} characteristic of β-lactam carbonyl. The ^{1}H NMR spectrum of the crude product also confirmed the presence of azetidin-2-one. There were two sets of signals, indicating the presence of diastereomeric mixture of two azetidin-2-ones **2.14** & **2.15** (in the ratio 64:36). The diastereomeric mixture of azetidin-2-ones **2.14** & **2.15** was isolated by flash column chromatography (silica gel 230-400 mesh, pet. ether/ethyl acetate, 90:10) in 54% yield. Attempts to separate the two diastereomers by column chromatography/crystallization were unsuccessful. The IR and ^{1}H NMR spectra of the isolated diastereomeric mixture are discussed below.

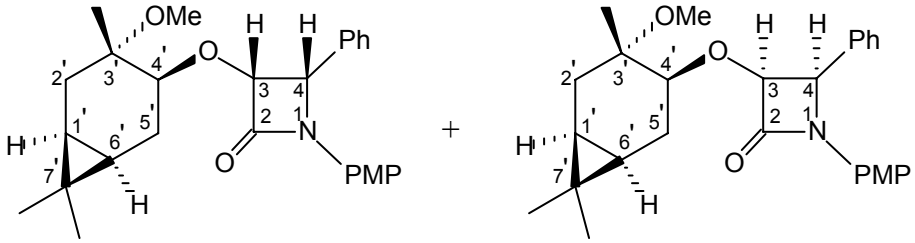
Scheme 2.18



2.12 **2.13** **2.14** **2.15**

Reagents and condition: (i) NEt_3, triphosgene, CH_2Cl_2, 0 °C to rt, 12 h

The IR spectrum of the diastereomeric mixture **2.14** and **2.15** showed sharp peak at 1745 cm^{-1} characteristic of β-lactam carbonyl.



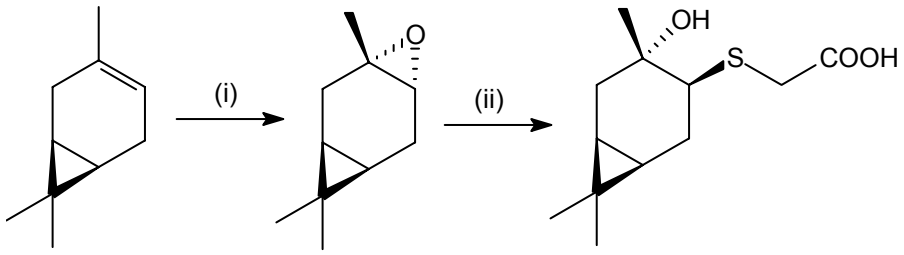
2.14 **2.15**

Mixture of diastereomers **2.14** and **2.15**

The ^{1}H NMR spectrum of the mixture **2.14** & **2.15** showed two sets of signals indicating the presence of two diastereomers. The protons of *gem* dimethyl groups appeared as two sets of singlets at 0.65, 0.90, 0.95 and 1.00 ppm (for the two diastereomers). The C-3' methyl appeared as singlet at 1.12 ppm and 1.26 ppm. The C-4' methine proton of the carane system attached to the oxygen atom appeared as multiplets between 3.10 ppm and 3.50 ppm. The remaining ring protons of the carane system appeared as multiplets between 0.40 ppm and 2.20 ppm. The protons of C-3' methoxy group and the –OMe protons of the PMP group appeared as singlets at 3.04, 3.23 and 3.75 ppm respectively. The C-4 protons of the minor and major diastereomers appeared as doublets at 4.90 ppm (J = 5.4 Hz) and at 5.10 ppm (J = 4. 8 Hz). The doublets due to the C-3 protons of the two diastereomers merged together at 5.20 ppm. The *cis* stereochemistry at C-3 and C-4 centers of the major and minor diastereomers was established based on the coupling constant value (J = 4.8 Hz and J = 5.4 Hz) of C-4 protons. The aromatic protons appeared as multiplets between 6.70 and 7.50 ppm.

Since the chiral acids, **2.06** and **2.12** derived from (+)-3-carene gave poor diastereoselectivity in azetidin-2-one formation, we were interested to see whether there can be any improvement in the diastereoselectivity by replacing the oxygen atom of the acid side chain by sulphur atom. With this idea in mind, the acid **2.17** was prepared by opening the α-carane epoxide **2.16** (prepared from (+)-3-carene by reported procedure[8]) with mercaptoacetic acid and NaOH (Scheme 2.19).

Scheme 2.19



(+)-3-carene **2.16** **2.17**

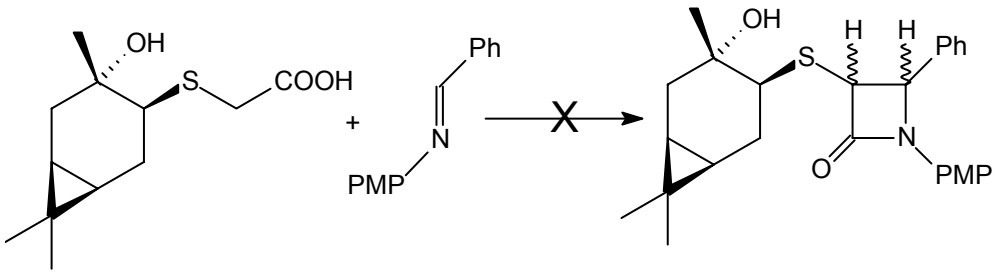
Reagents and conditions: (i) H_2O_2 $ClCO_2Et$, Na_3PO_4, CH_2Cl_2. (ii) $HSCH_2COOH$, NaOH, EtOH-H_2O, reflux, 24 h.

The structure of **2.17** was confirmed by IR and ^1H NMR spectra. The IR spectra of **2.17** showed a sharp peak at 1720 cm^{-1} and a broad peak at 3000-3400cm^{-1} characteristic of acid.

The ^1H NMR of **2.17** showed singlets at 0.90 ppm, 0.95 ppm and 1.26 ppm for the methyl groups of the carane system. The methine and methylene protons of the carane system appeared as multiplets between 0.65 ppm to 2.35 ppm. The methine proton of the carbon attached to the sulphur atom of the acid side chain appeared as doublet of doublet at 2.90 ppm (J = 4.4 Hz, 11.2 Hz). The methylene protons of the acid side chain appeared as a singlet at 3.40 ppm. A broad singlet at 6.50 ppm corresponded to the hydroxyl and the acid protons.

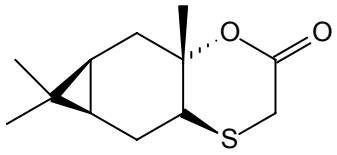
The acid **2.17**, when subjected to Staudinger reaction with imine **2.13** using triphosgene as activator, did not yield the desired azetidin-2-one **2.18**. Instead, the acid lactonised under the reaction condition to yield the lactone **2.19** (Scheme 2.20).

Scheme 2.20



2.17 **2.13** **2.18**

Reagents and condition: Et_3N, triphosgene, CH_2Cl_2, 0 °C to rt, 12 h.

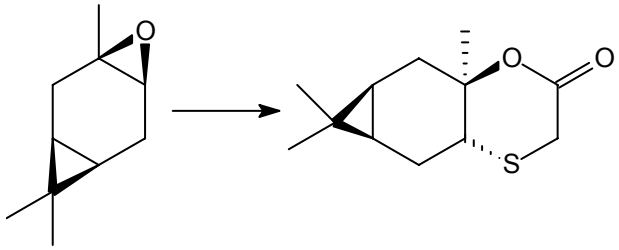


2.19

The structure of **2.19** was ascertained by IR and ^{1}H NMR spectra. The IR spectrum showed a sharp band at 1700 cm^{-1} corresponding to the lactone carbonyl. The ^{1}H NMR spectra showed singlets at 0.90, 1.10 ppm and 1.50 ppm corresponding to the methyl groups of the carane ring. The methylene and cyclopropyl protons of the carane ring appeared as multiplets between 0.75 ppm to 2.40 ppm. The methine proton of the carane ring attached to the carbon bearing the sulphur atom, appeared as a doublet of doublet at 3.15 ppm (J = 3.4 Hz, 13.7 Hz). The methylene proton of the lactone ring appeared as doublets at 3.45 ppm (J = 19.3 Hz) and at 3.65 ppm (J = 19.3 Hz).

Similarly when we tried to open the β-carene oxide **2.04** with mercapto acetic acid, we could get only the lactone **2.20** (Scheme 2.21).

Scheme 2.21



2.04 **2.20**

Reagents and condition: $HSCH_2COOH$, NaOH, EtOH-H_2O, reflux, 24 h.

The structure of lactone **2.20** was ascertained by IR and 1H NMR spectra.

2.4 : Summary

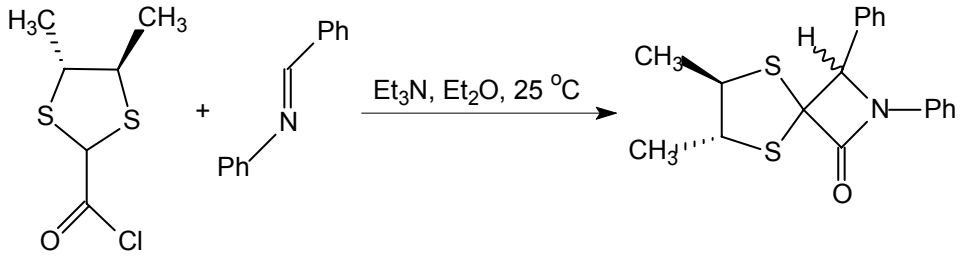
Chiral acids **2.06** and **2.12** were synthesized from (+)-3-carene and utilized as chiral ketene precursors in the asymmetric Staudinger reaction to study the diastereoselectivity in azetidin-2-one formation. These acids underwent Staudinger reaction with imines to afford a diastereomeric mixture of *cis* β-lactams **2.08a-c** and **2.09a-c**. The diastereoselectivity was found to be only around 60:40 ratio. Mercaptoacetic acid derivative **2.17** was prepared from α-carene oxide **2.16** and this acid **2.17** under Staudinger reaction conditions with imine gave the cyclised lactone **2.19** instead of the required β-lactam. Similarly the reaction of β-carene oxide **2.04** with mercaptoacetic acid also resulted in formation of the lactone **2.20**.

2.5 : Introduction

The construction of azetidin-2-one ring with attendant control of functional groups and stereochemistry has been the focus of several research groups over the past few decades. Although, a great deal of functionalized monocyclic azetidin-2-ones has been reported in the literature, relatively few efforts have been devoted towards synthesis of spiro azetidin-2-ones.

Chemielewski et al.[9] have synthesized spiro β-lactams using chiral cyclic ketenes derived from dithiolane carboxylic acid with moderate diastereoselectivity (Scheme 2.22).

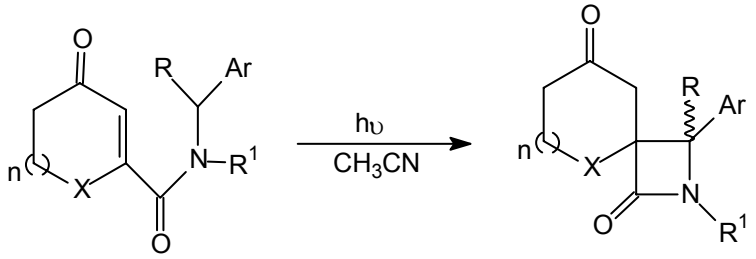
Scheme 2.22



Mixture of diastereomers in 60:40 ratio

Piva et al.[10] have developed an efficient method for synthesis of spiro β-lactam by photochemical cyclization of α, β-unsaturated cyclic oxoamides (Scheme 2.23).

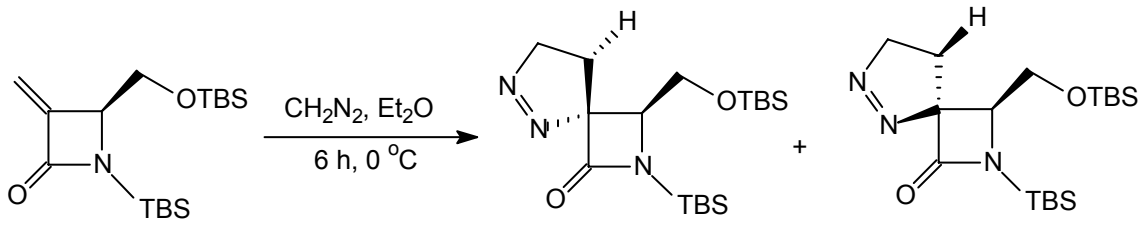
Scheme 2.23



X= CH_2, X= O

Diastereoselective synthesis of spiro β-lactams has also been achieved by cycloaddition to α-alkylidene-β-lactams[11] (Scheme 2.24). In this case, an *anti* addition with respect to the $–CH_2OTBS$ substituent was preferred.

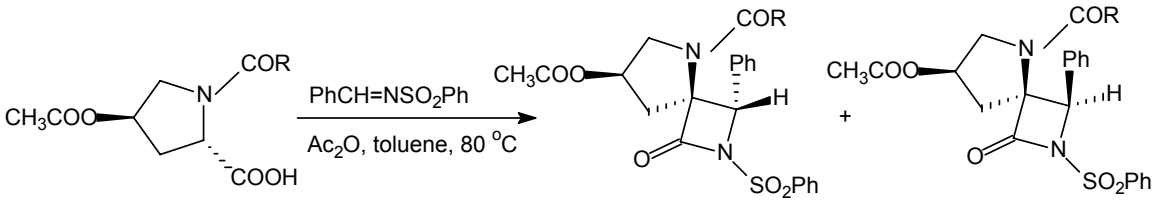
Scheme 2.24



Diastereomeric ratio 87:13

Croce and Rosa[12] have reported a stereoselective synthesis of *N*-phenylsulfonyl substituted spiro β-lactams. The reaction of substituted *N*-acyl proline with imines derived from benzaldehyde and benzene sulfonamide in presence of acetic anhydride afforded a diastereomeric mixture of spiro β-lactams (Scheme 2.25).

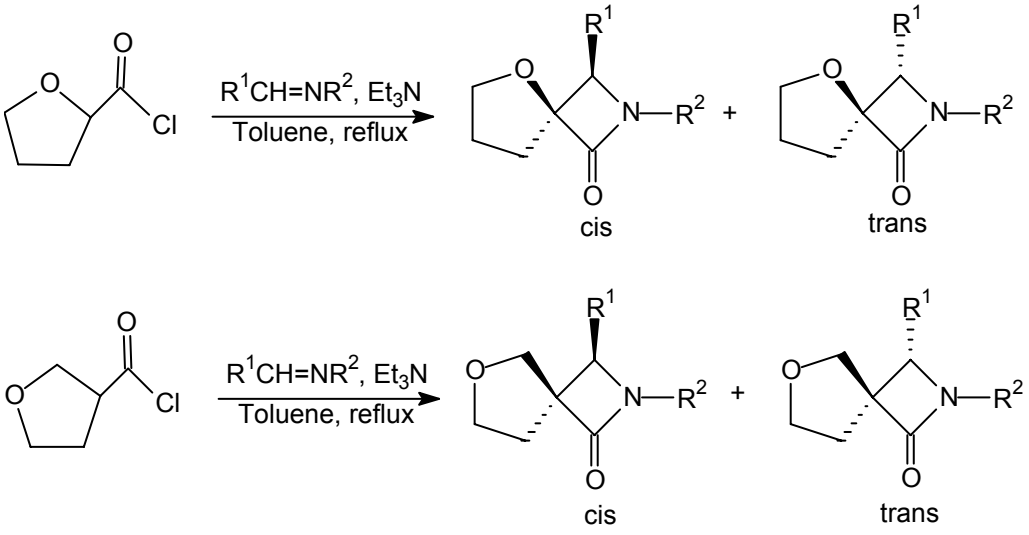
Scheme 2.25



Diastereomeric ratio 60 :40

Recently, Gonzalez et al.[13] have utilized ketene derived from tetrahydrofuroic acid in the Staudinger reaction for the synthesis of spiro β-lactams. A diastereomeric mixture of *cis* and *trans* spiro β-lactams was obtained and the nature of the imine substituents controlled the diastereoselectivity. This paper also gives a theoretical insight into the electronic effects controlling the stereochemical course of the reaction (Scheme 2.26)

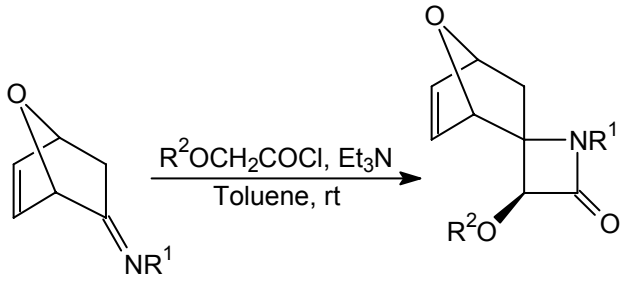
Scheme 2.26



R^1= Ph, PMP, *p*-$NO_2C_6H_4$; R^2= Ph, CH_3, PMP, *p*-$NO_2C_6H_4$

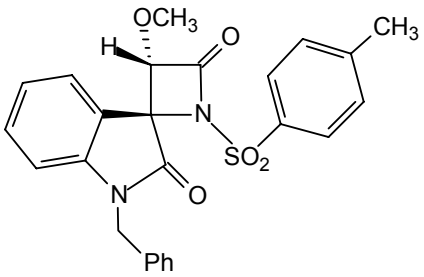
Arjona et al.[14] have made use of imines derived from 7-oxanorbornenone in the Staudinger reaction to get a single diastereomer of spiro β-lactam (Scheme 2.27).

Scheme 2.27

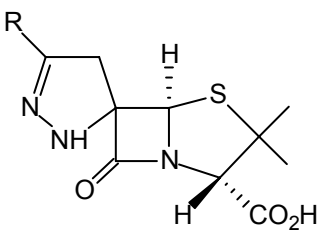


Single diastereomer

Some spiro β-lactams are also reported to show antiviral[15] and antibacterial properties[16] (Fig 1).



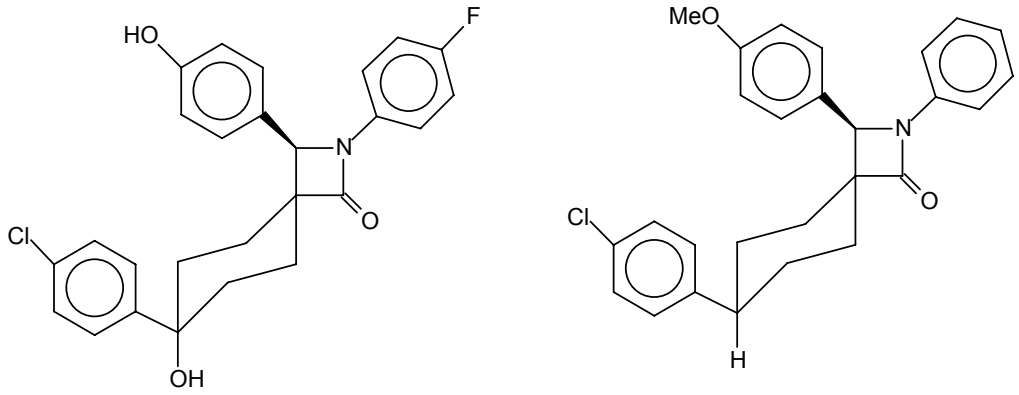
Antiviral (poliovirus and human rhinovirus inhibitor)



Antibacterial (spiro penicillin)

Fig. 1: spiro β-lactams with anti viral and anti bacterial properties

Recent investigations have revealed that some spiro β-lactams can serve as potent cholesterol absorption inhibitors[17]. SCH 58053[18] and SCH54016[19] are typical examples of cholesterol absorption inhibitors (Fig. 2).

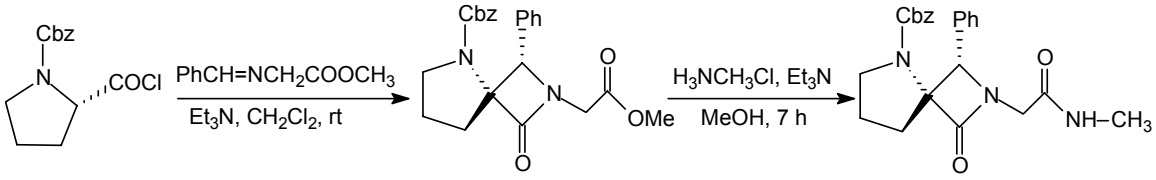


SCH 5053 SCH 54061

Fig. 2: Spiro β-lactams as potent cholesterol inhibitors

Recent studies by Alonso et al.[20] have shown that certain spiro β-lactams (like **D**) can adopt β-turn conformation, making them very useful precursor for development of new peptidomimetics (Scheme 2.28).

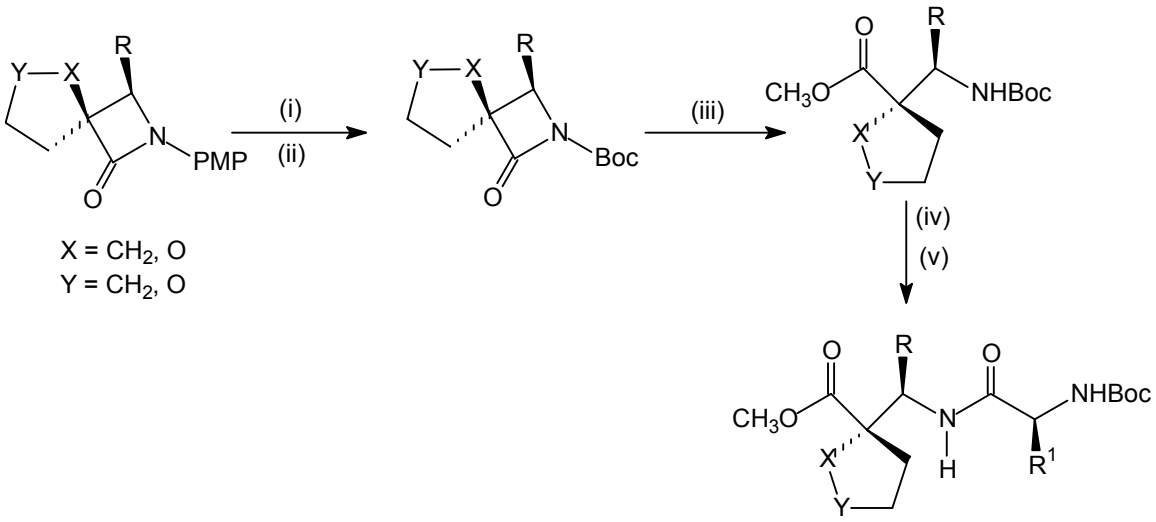
Scheme 2.28



D

Alonso et al.[21] have also recently reported that Spiro β-lactams can be utilized in the synthesis α, α-cyclic disubstituted β-amino esters and peptide derivatives, which are useful precursor for the construction of β-peptides with new folding patterns (Scheme 2.29).

Scheme 2.29



Reagents and conditions: (i) CAN, H_2O/ CH_3CN, 0 ^oC 30 min; (ii) $(Boc)_2O$, DMAP, CH_3CN, 0 ^oC to rt, 16 h; (iii) KCN (cat) MeOH, rt, 16 h; (iv) TFA, CH_2Cl_2, 0 oC, to rt, 2 h; (v) HOBT, DCC, BocNH-CH(R^1)COOH, THF, 0 ^oC to rt, 16 h.

2.6 : Present work

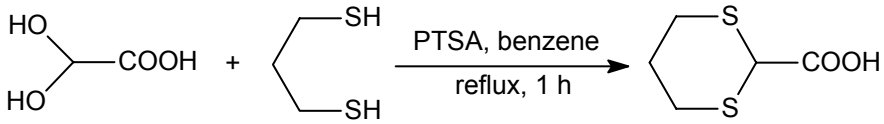
Due to the importance and relatively few reports on synthesis of spiro azetidin-2-ones, we became interested in utilizing Staudinger reaction for the synthesis of spiro azetidin-2-ones. The acids **2.22** and **2.32**, synthesized from glyoxylic acid monohydrate and camphor-10-sulphonic acid respectively, were chosen as appropriate ketene precursors. The synthesis of the acids **2.22** and **2.32** and their application towards stereoselective synthesis of spiro azetidin-2-ones *via* Staudinger reaction is discussed in this section.

2.7 : Results and Discussion

2.7.1 : Preparation of 1, 3-dithiane-2-carboxylic acid 2.23.

The dithio carboxylic acid **2.22**, was prepared following a reported precedure.[22] Glyoxylic acid monohydrate **2.21** on refluxing in benzene with 1,3-propanedithiol and PTSA furnished the required acid **2.22**, in 70% yield (Scheme 2.30).

Scheme 2.30



2.21 **2.22**

The acid was characterized by IR and ^{1}H NMR spectral data. The IR spectrum of the acid **2.22** showed bands at 3200-2500 cm^{-1} and at 1720 cm^{-1} characteristic of the carboxylic acid.

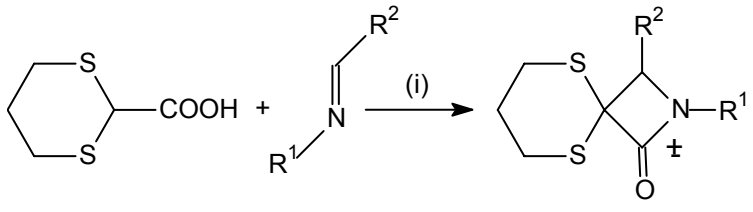
The ^{1}H NMR spectrum of **2.22** showed multiplets between 2.00 ppm and 3.50 ppm corresponding to the six-methylene protons. The methine proton appeared as a singlet at 4.15 ppm. A broad singlet at 9.10 ppm corresponded to the carboxylic proton.

2.7.2 : Preparation of spiro azetidin-2-ones 2.24a-g.

Having prepared the dithiolane carboxylic acid **2.22**, we were interested to investigate whether the acid **2.32** can undergo cycloaddition reaction with imines in presence of triphosgene as an acid activator (methodology developed by us) to give spiro azetidin-2-ones.

An anhydrous dichloromethane solution of triphosgene was added slowly to a cooled (0 ^oC) dichloromethane solution of acid **2.22**, imine **2.23a** and triethylamine. After completion of addition, the reaction mixture was warmed up to room temperature and stirred at this temperature for 12 h. It was diluted with dichloromethane and washed successively with water, saturated bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude product **2.24a**. It was purified by column chromatography (silica gel 60-120 mesh, pet. ether/ ethyl acetate) to get pure **2.24a** as white solid. (Scheme 2.31). The structure of **2.24a** was unambiguously confirmed by spectral and analytical data. The IR and NMR spectra of **2.24a** are discussed below.

Scheme 2.31

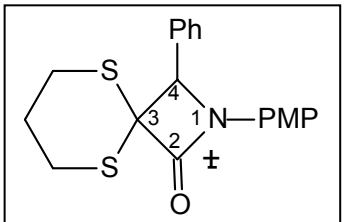


2.22 **2.23a-f** **2.24a-f**

Reagents and condition: (i) NEt_3, triphosgene, CH_2Cl_2, 0 ^oC to rt, 12 h.

The IR spectrum of **2.24a** showed a band at 1735 cm^{-1} indicating the presence of β-lactam carbonyl.

The ^{1}H NMR spectrum of **2.24a** showed three sets of multiplets between 1.80 and 2.30 ppm, between 2.60 and 2.90 ppm, between 3.50 and 3.90 ppm, each corresponding to two methylene protons (accounting for six -CH_2 protons). The –OMe protons of *p*-anisyl group appeared as a singlet at 3.70 ppm. The C-4 proton of the β-lactam ring appeared as a singlet at 4.90 ppm. Two aromatic protons of PMP group appeared as a doublet at 6.85 ppm (J = 9.3 Hz, 2H), while the remaining aromatic protons appeared as multiplets in the region between 7.10 ppm to 7.50 ppm



2.24a

The ^{13}C spectrum of compound **2.24a** showed a peak at 164.62 ppm corresponding to the carbonyl carbon of the β-lactam ring. The aromatic quaternary carbon bearing the -OMe group of the *p*-anisyl moiety appeared at 156.47 ppm and the aromatic quaternary carbon attached to the nitrogen of β-lactam ring appeared at 131.99 ppm. The other aromatic quaternary carbon appeared at 130.89 ppm. The remaining aromatic carbons appeared at 126.38, 128.54, 127.90, 118.75 and 114.60 ppm. The –OMe carbon appeared at 55.63 ppm. The C-3 spiro carbon appeared at 60.55 pm and the C-4 carbon of the β-lactam ring appeared at 66.86 ppm. The –CH_2 carbons of the 1,3 dithiane moiety appeared at 28.56, 28.18 and 25.39 ppm. The spiro β-lactam **2.24a** gave satisfactory elemental analysis.

Following similar procedure, several substituted spiro azetidin-2-ones **2.24b-g,** were synthesized by Staudinger reaction of acid **2.22** with various imines **2.23b-g** in presence of triphosgene (Scheme 2.31, Table 2). In all the cases, very good yields of spiro β-lactams were obtained and they were characterized by spectral and analytical data. When a chiral imine derived from *R*-(+)-phenyl ethylamine was used, a 50:50 diastereomeric mixture of spiro β-lactam **2.24g** was obtained (The diastereomeric ratio was calculated from the ^{1}H NMR data).

Table 2: *Synthesis of spiro azetidin-2-ones* **2.24a-g** *from acid* **2.22**.

Compound No.	R^1	R^2	Yield (%)	M.P (^oC)
2.24a	PMP	Ph	70	186
2.24b	Ph	PMP	71	155-156
2.24c	PMP	PMP	75	130
2.24d	PMP	Styryl	70	122-124
2.24e	Ph	Ph	72	173-174
2.24f	4-Cl-C_6H_4	Styryl	69	154
2.24g	α-MeCHPh	Ph	69[a]	oil

[a] Isolated yield of diastereomeric mixture

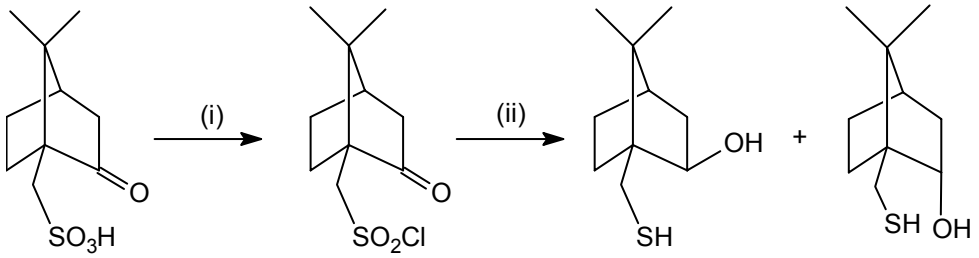
These spiro azetidin-2-ones **2.24** can also serve as precursors for 3-keto-β-lactams, which are important intermediates for biologically important compounds, having β-lactamase inhibition activity.[23]

2.7.3 : Preparation of camphor derived thiols 2.27 and 2.28.

Encouraged by the success achieved in getting the spiro β-lactams **2.24a-g** in very good yields, we focused our efforts towards asymmetric synthesis of spiro azetidin-2-ones *via* Staudinger reaction, using a chiral acid as ketene precursor. Earlier work in our group has shown that camphor derived chiral auxiliary results in very high diastereoselectivity in azetidin-2-one formation.[24] We, therefore decided to design a chiral acid derived from camphor-10-sulphonic acid as a convenient chiral auxiliary for diastereoselective synthesis of spiro azetidin-2-ones by asymmetric Staudinger reaction.

(1S)-(+)-10-Camphorsulphonic acid **2.25** was converted to acid chloride[25] **2.26**, which was reduced using LAH (by following a reported procedure[26]) to get a mixture of thiols **2.27** and **2.28** (Scheme 2.32). The major *exo*-thiol **2.27** was separated by column chromatography and used for further reaction.

Scheme 2.32



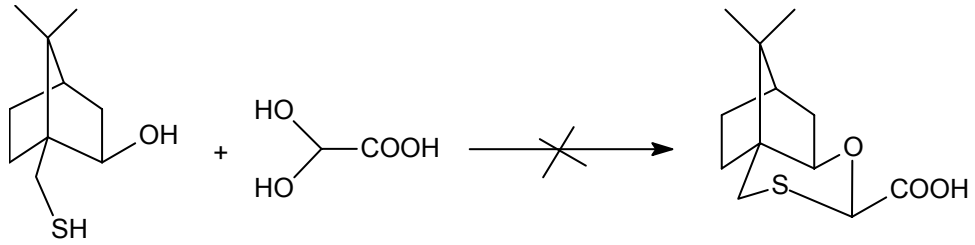
2.25 **2.26** **2.27(major)** **2.28(minor)**

Reagents and conditions: (i) $SOCl_2$, reflux, 4 h. (ii) LAH, ether -78 ^oC to rt, 3 h, reflux, 8 h.

2.7.4 : Preparation of camphor derived oxathio acid 2.32.

Our initial attempts to synthesize the chiral acid **2.32** from the *exo*-thiol **2.27** and glyoxylic acid monohydrate **2.21** were unsuccessful, as we got very poor yields of product or complex reaction mixtures (Scheme 2.33).

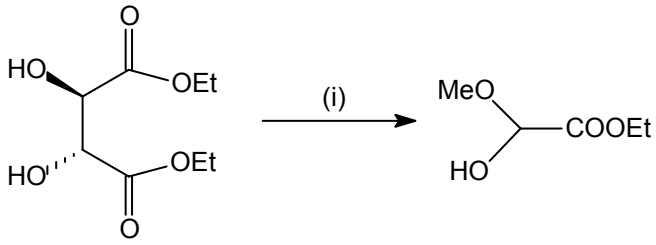
Scheme 2.33



2.27 **2.21** **2.32**

Hence we changed our strategy and decided to use the hemi-acetal of ethyl glyoxylate **2.30**, instead of glyoxylic acid monohydrate **2.21**. The glyoxylate **2.30** was obtained in very good yield by the $NaIO_4$ cleavage of L-diethyl tartrate **2.29** in methanol (Scheme 2.34).

Scheme 2.34



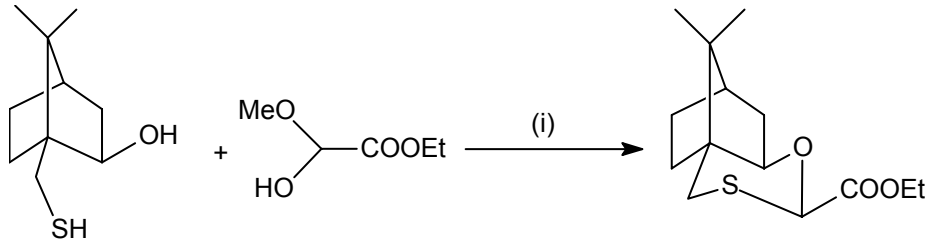
2.29 **2.30**

Reagents and condition: (i) $NaIO_4$, MeOH, rt, 4 h.

The ethyl glyoxylate **2.30** was then reacted with the *exo*-thiol **2.27** to get the desired camphor derived chiral ester **2.31**. Typical experimental procedure and characterization of the ester **2.31** is discussed below.

To a solution of *exo*-thiol **2.27** and ethylglyoxylate **2.30** in anhydrous dichloromethane was added BF_3 Etherate[27] at 0 ^oC and the reaction mixture was stirred for 30 min. After completion of reaction (TLC)**,** the reaction mixture was passed through column (silica gel, 60-120, pet. ether/ dichloromethane, 50:50) and the solvent was removed under reduced pressure to get pure chiral ester **2.31** as single diastereomer (Scheme 2.35). The product **2.31** was characterized by IR and NMR data.

Scheme 2.35



2.27 **2.30** **2.31**

Reagents and condition: (i) $BF_3.Et_2O$, CH_2Cl_2, 0 ^oC, 30 min

The IR spectrum of **2.31** showed a sharp peak at 1755 cm^{-1} corresponding to the carbonyl group of the ester.

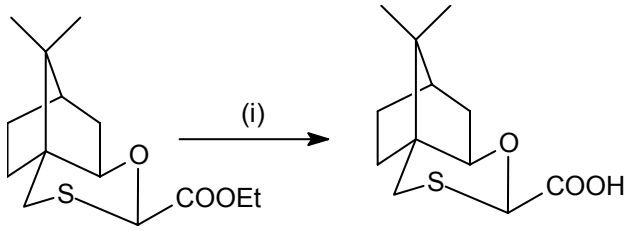
The ^1H NMR spectrum of **2.31** showed singlets at 0.92 ppm and 1.33 ppm corresponding to the protons of *gem* dimethyl groups of the camphor moiety. The methyl and the methylene protons of the ester group appeared at 1.30 ppm and 4.25 ppm as triplet (J = 7.3 Hz) and quartet (J = 7.3 Hz) respectively. The protons of $–CH_2$ group attached to sulphur atom, appeared as doublets at 2.85 ppm (J = 14.2 Hz) and at 3.10 ppm (J = 14.2 Hz). The methine proton of the carbon attached to the oxygen atom appeared as a doublet of doublet at 3.65 ppm (J = 3.4 Hz, 7.8 Hz). The remaining protons (one methine and six methylene protons) of the camphor moiety appeared as multiplets between 0.90 ppm to 2.10 ppm. The methine proton of the carbon bearing the -COOEt group appeared as a singlet at 5.30 ppm.

The ^{13}C NMR spectrum of **2.31** showed a peak at 167.80 ppm corresponding to the ester carbonyl carbon. The carbons of the *gem* dimethyl group of the camphor system

appeared at 22.90 ppm and 20.26 ppm respectively. The –CH carbon of the chiral auxiliary bearing the ester group appeared at 85.28 ppm. The –CH carbon of the camphor moiety attached to oxygen atom of the ring, appeared at 78.59 ppm. The methine carbon at the bridgehead of the camphor system appeared at 45.33 ppm. The quaternary carbons of the camphor system appeared at 46.76 ppm and 43.05 ppm respectively. The methylene carbons of the chiral auxiliary appeared at 37.53, 33.78,28.75 and 27.09 ppm. The methylene and the methyl carbon of the ester group appeared at 61.72 ppm and 14.01 ppm respectively.

The ester **2.31** was then hydrolyzed using methanolic KOH to get the required chiral acid **2.32** (Scheme 2.36) as thick colorless oil.

Scheme 2.36



2.31 **2.32**

Reagents and condition: (i) MeOH/KOH, rt, 5 h.

The IR spectrum of **2.32** showed a sharp peak at 1730 cm^{-1} and a broad band between 3300-3500 cm^{-1} characteristic of carboxylic acid.

The ^1H NMR spectrum of **2.32** showed singlets at 0.95 ppm and 1.30 ppm corresponding to the protons of the *gem* dimethyl groups of the camphor moiety. The protons of $–CH_2$ group attached to sulphur atom, appeared as doublets at 2.85 ppm (J = 14.2 Hz) and at 3.10 ppm (J = 14.2 Hz). The methine proton of the carbon attached to the oxygen atom appeared as a doublet of doublet at 3.65 ppm (J = 3.4 Hz, 7.8 Hz). The remaining protons (one methine and six methylene protons) of the camphor moiety appeared as multiplets between 0.80 ppm to 2.10 ppm. The methine proton of the carbon containing the -COOH group appeared as singlet at 5.35 ppm.

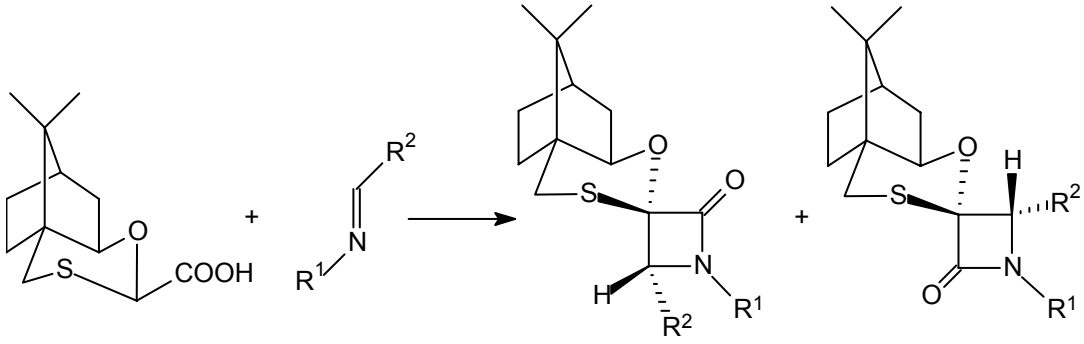
The rigid bicyclic structure of the chiral acid **2.32** was expected to provide the necessary steric bulk in the facial discrimination of the ketene in the asymmetric Staudinger reaction for β-lactam synthesis. Hence we decided to employ the chiral acid **2.32** along with triphosgene as acid activator in the asymmetric Staudinger reaction to

study the diastereoselectivity in spiro β-lactam formation. Typical experimental procedure and the results obtained are discussed below.

2.7.5 : Preparation of spiro azetidin-2-ones 2.34a-c and 2.35a-c.

An anhydrous dichloromethane solution of triphosgene was slowly added at 0 ^{o}C to a dichloromethane solution of acid **2.32**, imine **2.33a** and triethylamine. After completion of addition, the reaction mixture was allowed to attain room temperature and then stirred at this temperature for 12h. The reaction mixture was then diluted with dichloromethane and washed successively with water, saturated bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to get the crude product. The IR spectrum of the crude product showed a peak at 1745 cm^{-1}, indicating the presence of β-lactam carbonyl. The ^{1}H NMR of the crude reaction mixture showed the presence of two diastereomers **2.34a** and **2.35a** in almost 50:50 ratio (Scheme 2.37). The two diastereomeric azetidin-2-ones were separated by flash column chromatography and crystallization.

Scheme 2.37



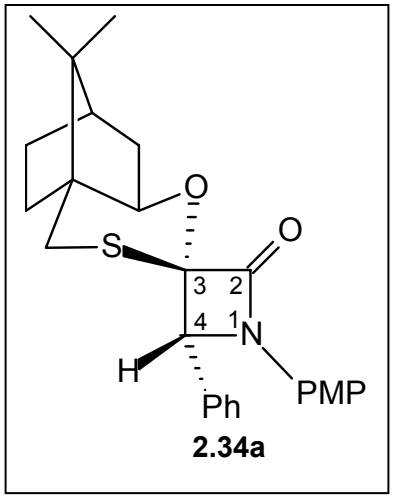
2.32 **2.33** **2.34a-c** **2.35a-c**

Reagents and conditions: Et_3N, triphosgene, CH_2Cl_2, 0 ^{o}C to rt, 12 h

The diastereomeric azetidin-2-ones **2.34a** and **2.35a** were characterized by spectral and analytical techniques. The IR and NMR spectra of **2.34a** and **2.35a** are discussed below.

The IR spectrum of **2.34a** showed a sharp band at 1747 cm^{-1} characteristic of β-lactam carbonyl.

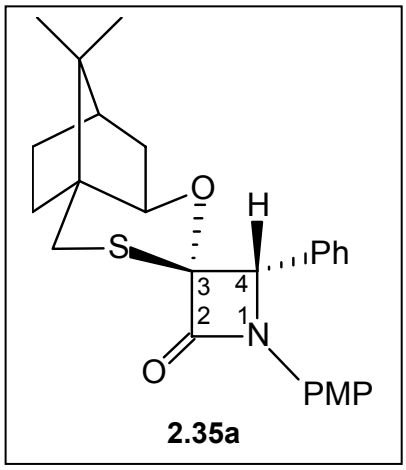
The ^{1}H NMR spectrum of **2.34a** showed singlets at 0.83 ppm and 1.15 ppm corresponding to the protons of the *gem* dimethyl groups. The methine proton of the chiral auxiliary bearing the oxygen atom appeared as doublet of doublet at 3.10 ppm (J = 3.2 Hz, J = 8.5 Hz). The protons of the methylene group of the chiral moiety, attached to sulphur atom appeared as two doublets at 2.60 ppm (J = 13.7 Hz) and at 3.30 ppm (J = 13.7 Hz). The remaining protons of the camphor moiety appeared as multiplets between 0.95 ppm and 1.70 ppm. The C-4 β-lactam proton appeared as a singlet at 4.93 ppm. The methoxy proton of the PMP group appeared as a singlet at 3.70 ppm. Two aromatic protons of PMP group appeared as a doublet at 6.80 ppm (J = 9.3 Hz) and remaining aromatic protons appeared as multiplets between 7.15 ppm to 7.50 ppm.



2.34a

The ^{13}C NMR spectrum showed a peak at 164.26 ppm corresponding to the β-lactam carbonyl. The peak at 156.41 ppm corresponded to the aromatic quaternary carbon bearing the –OMe group of the *p*-anisyl moiety. The aromatic quaternary carbon attached to the nitrogen atom of the β-lactam ring appeared at 133.64 ppm. The other aromatic quaternary carbon appeared at 130.84 ppm. The remaining aromatic carbons appeared at 128.64, 128.39, 127.94 118.96 and 114.39 ppm. The carbons of the *gem* dimethyl group of the chiral auxiliary appeared at 20.51 ppm and 19.66 ppm respectively. The methylene carbons of the chiral auxiliary appeared at 26.61, 27.04, 30.95 and 36.10 ppm. The –CH carbon of the camphor moiety attached to oxygen atom appeared at 80.69 ppm. The quaternary carbons of the chiral auxiliary appeared at 29.69 ppm and 47.06 ppm. The methine carbon at the bridgehead of the camphor system appeared at 44.47 ppm. The carbon of the –OMe group appeared at 55.42 ppm. The C-3 quaternary spiro carbon appeared at 92.35 ppm. The C-4 carbon of the β-lactam ring appeared at 71.48 ppm. The compound **2.34a** gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 435.

The IR spectrum of **2.35a** showed a sharp peak at 1750 cm^{-1} corresponding to the β-lactam carbonyl.



2.35a

The ^{1}H NMR spectrum of **2.35a** showed singlets at 0.90 ppm and at 1.15 ppm corresponding to the protons of *gem* dimethyl groups of the chiral auxiliary. The –CH proton of the chiral auxiliary attached to oxygen atom appeared as dd at 4.45 ppm (J = 3.9 Hz and J = 6.8 Hz). The -OMe protons of the PMP group appeared as singlet at 3.75 ppm. One of the proton of the $–CH_2$ group attached to the sulphur atom appeared as doublet at 2.75 ppm (J = 14.2 Hz). The doublet due to the other $–CH_2$ proton merged with the peak due to –OMe proton at 3.50 ppm. The C-4 proton of the β-lactam appeared as singlet at 4.91 ppm. Remaining protons of the chiral auxiliary appeared as multiplets between 0.80 ppm to 1.75 ppm. The aromatic protons appeared as multiplets between 6.75 ppm and 7.50 ppm.

The ^{13}C NMR spectrum showed a peak at 163.85 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbon bearing the –OMe group appeared at 156.40 ppm and the aromatic quaternary carbon attached to the nitrogen atom of the β-lactam appeared at 132.82 ppm. The other aromatic quaternary carbon appeared at 131.02 ppm. The remaining aromatic carbons appeared at 128.33, 128.15, 127.93, 118.81 and 114.44 ppm. The *gem* dimethyl carbons of the chiral auxiliary appeared at 20.31 ppm and 22.97 ppm. The methylene carbons of the auxiliary appeared at 26.49, 27.18, 33.64, 37.71 ppm. The –CH carbon of the camphor moiety attached to oxygen atom appeared at 82.27 ppm. The quaternary carbons of the chiral auxiliary appeared at 42.67 ppm and 46.98 ppm. The methine carbon at the bridgehead of the camphor system appeared at 45.41 ppm. The carbon of the –OMe group appeared at 55.46 ppm. . The C-3 quaternary spiro carbon appeared at 88.51 ppm. The C-4 carbon of the β-lactam ring appeared at 68.19 ppm. The compound **2.35a** gave satisfactory elemental analysis.

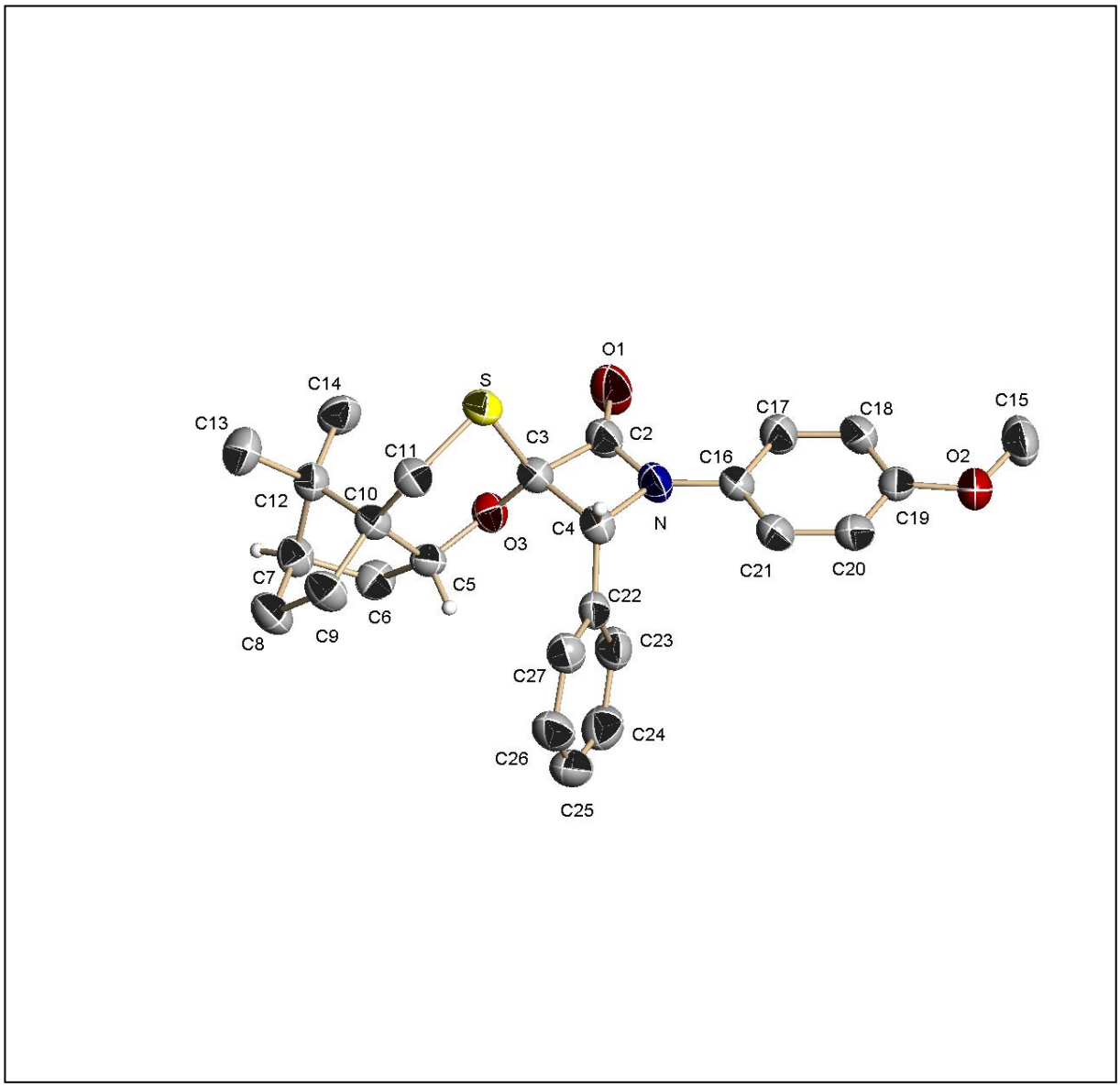
2.7.6 : X-ray structure determination of 2.34a and 2.35a:

The stereochemistry of the newly formed centers (C-3 and C-4) of the spiro azetidin-2-ones **2.34a** and **2.35a** was ascertained from the single crystal X-ray analysis. X-ray quality crystals of **2.34a** and **2.35a** were obtained by careful crystallization from methanol. The data were collected on SMART APEX CCD Single Crystal X-ray diffractometer. Based on the X-ray structure, the stereochemistry was assigned as 3*R*, 4*R* for the diastereomer **2.34a** and 3*S*, 4*S* for the diastereomer **2.35a**

Table 3: Crystal data and structure refinement for **2.34a**

Empirical formula	$C_{26}H_{29}NO_3S$
Formula weight	435.56
Temperature	293(2) K
Wavelength	0.71073 A^o
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 6.4422(4) A^o b = 18.0909(12) A^o c = 19.3926(13) A^o
Volume	2260.1(3) A^{o3}
Z, Calculated density	4, 1.280 Mg/m^3
Absorption coefficient	0.171 mm^{-1}
F(000)	928
Crystal size	0.40 x 0.28 x 0.09 mm
Theta range for data collection	1.54 to 25.00 deg.
Limiting indices	-7<=h<=7, -21<=k<=21, -23<=l<=23
Reflections collected / unique	17680 / 3982 [R (int) = 0.0357]
Completeness to theta = 25.00	100.0 %
Max. and min. transmission	0.9856 and 0.9347
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3982 / 0 / 283

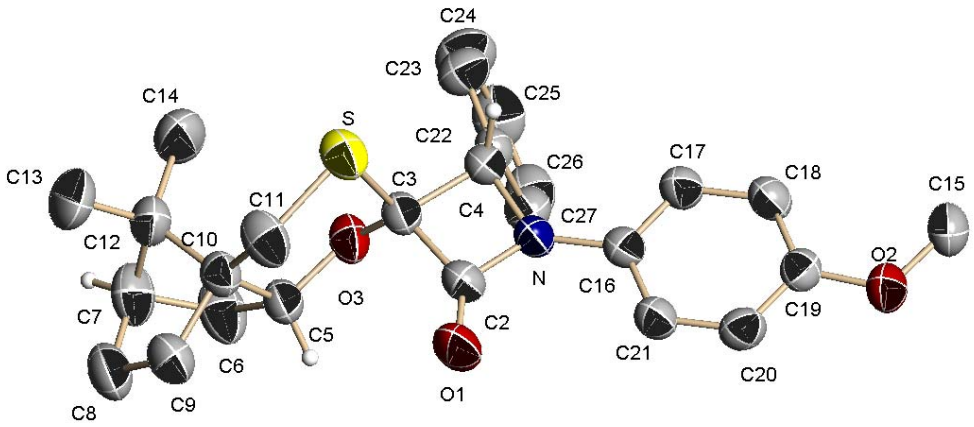
Goodness-of-fit on F^2	0.986
Final R indices [I>2sigma(I)]	R1 = 0.0328, wR2 = 0.0795
R indices (all data)	R1 = 0.0373, wR2 = 0.0815
Absolute structure parameter	0.05(7)
Largest diff. peak and hole	0.156 and -0.114 e. A^{o-3}



X-ray structure of 2.34a

Table 4: Crystal data and structure refinement for **2.35a**

Empirical formula	$C_{26}H_{29}NO_3S$
Formula weight	435.56
Temperature	293(2) K
Wavelength	0.71073 A^o
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 11.655(5) A^o b = 8.810(4) A^o beta = 111.465(7) deg. c = 12.312(5) A^o
Volume	1176.5(8) A^{o3}
Z, Calculated density	2, 1.230 Mg/m^3
Absorption coefficient	0.164 mm^{-1}
F(000)	464
Crystal size	0.48 x 0.26 x 0.10 mm
Theta range for data collection	1.78 to 23.28 deg.
Limiting indices	-12<=h<=12, -9<=k<=9, -13<=l<=13
Reflections collected / unique	9603 / 3370 [R (int) = 0.0216]
Completeness to theta = 23.28	99.8 %
Max. and min. transmission	0.9846 and 0.9253
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3370 / 1 / 283
Goodness-of-fit on F^2	1.136
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0876
R indices (all data)	R1 = 0.0371, wR2 = 0.0882
Absolute structure parameter	-0.04(8)
Largest diff. peak and hole	0.186 and -0.120 $e.A^{o-3}$



X-ray structure of 2.35a

From the X-ray structure, it is clear that both the spiro β-lactams **2.34a** and **2.35a** are *trans* β-lactams (with respect to C-4 aryl group and sulphur atom).

Following the same procedure, diastereomeric mixture of spiro azetidin-2-ones **2.34b,c** and **2.35b,c** (Scheme 2.37, Table 3) was obtained by cycloaddition of ketenes derived from acid **2.32** with imines **2.33b,c**. In these cases also the diastereomeric ratio was almost 50:50 (as determined from ^{1}H NMR of crude reaction mixture). In case of the diastereomeric mixture **2.34b** & **2.35b**, one of the diastereomer could be separated by crystallization from methanol. However, in case of diastereomeric mixture **2.34c** &

2.35c, the separation of diastereomers was not possible either by extensive column chromatography or crystallization.

Table 5: *Synthesis of spiro azetidin-2-ones* (**2.34a-c** & **2.35a-c**) *via cycloaddition reaction of imines* **2.33** *with chiral ketene derived from acid* **2.32**.

β-lactams 2.34 & 2.35	R^1	R^2	Ratio of 2.35 & 2.36	Yield (%)[a]
a	PMP	Ph	50:50	40
b	PMP	Styryl	50:50	41
c	*p*-Cl C_6H_4	Styryl	50:50	38

[a] Isolated yield of diastereomeric mixture

2.8 : Summary

Synthesis of spiro azetidin-2-ones **2.24** was achieved in very good yields, starting from dithiane carboxylic acid **2.22** (using triphosgene as acid activator). A novel chiral acid **2.32** was designed and synthesized from (1S)-(+)-10-camphorsulphonic acid. This acid was employed as a chiral ketene precursor in the asymmetric Staudinger reaction for the synthesis of diastereomeric spiro azetidin-2-ones **2.34** and **2.35**. The stereochemistry at the newly formed centers C-3 and C-4 of the spiro azetidin-2-ones was established from the single crystal X-ray structure of the two representative diastereomers of spiro azetidin-2-ones **2.34a** and **2.35a**.

Section A

2.9 : Experimental

2.9.1 : Preparation of (+)-3-carene diol 2.02

In a 1 L round bottom flask, formic acid (250 ml, 6.6 mmol) was taken and (+)-3-carene (55 g, 0.4 mol) was added 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 ^oC and it was stirred overnight. A solution of NaOH (80 g) in water (200 ml) was then added dropwise, without allowing the temperature to rise above 40 ^oC. The reaction mixture was stirred for 0.5 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 and the combined formate ester layer was taken in a 1 L round bottom flask attached with an overhead 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 rise above 40 ^oC. The white crystalline solid obtained was separated out, filtered, washed with cold water and dried to get 34.5 g (50%) of diol **2.02**.

2.9.2 : Preparation of β-carene oxide 2.04

Carene diol **2.02** (6.5 g, 38.2 mmol) was dissolved in pyridine (15 ml) and cooled to 0 ^oC. Then *p*-toluenesulfonyl chloride (8 g, 42 mmol) was added in portions and the reaction mixture was stirred at 0 ^oC for 36 h and at room temperature for 24 h. Then 150 ml of H_2O was added and extracted with ethyl acetate (4 x 20 ml). The organic layer was washed successively with ice water, dil. HCl, saturated bicarbonate solution and brine solution. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to afford the monosulfonated product **2.03**, which was treated with KOH (4 g) in MeOH (25 ml) and the reaction mixture was stirred at room temperature for 48 h. Then it was diluted with water and extracted with ether (4 x 15 ml). The solvent was removed under reduced pressure to get the crude epoxide, which was vacuum distilled (30 ^oC / 5 mm) to afford pure β-Carene oxide **2.04** (5.6 g, 86%) as a colourless oil.

MP : Oil.

$[\alpha]^{28}_D$: -7.2 (c 2, C_6H_6). (Lit.[7] $[\alpha]^{23}_D$ = –7.98, c 2, C_6H_6).

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.45-0.55 (m, 2H), 0.90 (s, 3H), 1.00 (s, 3H), 1.35 (s, 3H), 1.70-2.40 (m, 4H), 2.85 (d, *J* = 5.4 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.59, 17.20, 18.15, 19.62, 23.77, 24.55, 28.99, 55.57, 57.92.

2.9.3 : Preparation of diol 2.05

To a solution of β-Carene oxide **2.04** (0.760 g, 5 mmol) in ethylene glycol (5 ml), PTSA (0.020 g) was added at 0 ^oC and the reaction mixture was stirred at 0 ^oC for 4 h. After completion of reaction (TLC), the reaction mixture was diluted with water (40 ml) and was extracted with EtOAc (3 x 20 ml). The combined organic layer was washed with brine (20 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the diol **2.05** as colourless oil (1.0 g, 93%).

IR ($CHCl_3$) : 3500-3200 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.55-0.75 (m, 2H), 1.01 (s, 3H), 1.02 (s, 3H), 1.14 (s, 3H), 1.10-2.30 (m, 4H), 2.60 (bs, 2H), 3.40-3.75 (m, 5H).

2.9.4 : Preparation of (1′*S*,3′*S*,6′*R*)-2-[4′-oxo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]acetic acid 2.06

To a solution of diol **2.05** (0.535 g, 2.5 mmol) in acetone (10 ml), Jones reagent was added dropwise at 0 ^oC until the colour of the reagent persists. The reaction mixture was stirred at room temperature for 4 h. The green precipitate formed was filtered off and the excess reagent was destroyed by adding isopropyl alcohol at 0 ^oC to avoid the exothermic reaction. The solution was concentrated under reduced pressure and extracted with EtOAc (3 x 15 ml). The organic layer was washed with brine (20 ml), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was basified with saturated $NaHCO_3$ solution and extracted with dichloromethane (1 x 10 ml). The aqueous layer was acidified with dil. HCl at 0 ^oC and extracted with EtOAc (3 x 15 ml). The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the pure keto acid **2.06**, as pale yellow oil (0.400 g, 70%)

MP : Pale yellow oil.

IR ($CHCl_3$) : 3500-3200 cm^{-1}, 1720 cm^{-1}.

$[\alpha]^{28}_D$: -4.9 (c 1.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.70-0.95 (m, 2H), 0.85 (s, 3H), 1.05 (s, 3H), 1.15 (s, 3H), 1.53 (dd, *J* = 5.1 Hz, 15.9 Hz, 1H), 2.54 (dd, *J* = 9.3 Hz, 16.6 Hz, 1H), 2.75 (dd, *J* = 8.7 Hz, 17.5 Hz, 1H), 2.05-2.40 (m, 1H), 3.90 (d, *J* = 16.6 Hz, 1H), 4.10 (d, *J* = 16.6 Hz, 1H), 6.25 (bs, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.47, 16.57, 17.93, 19.14, 23.48, 27.60, 34.51, 34.88, 61.56, 78.14, 173.20, 213.33.

MS (m/z) : 226 (M^+).

Analysis ($C_{12}H_{18}O_4$) : Calculated: C, 63.68; H, 8.01.
Observed : C, 63.57; H, 8.08.

2.9.5 : General procedure for the synthesis of azetidin-2-ones 2.08a-c & 2.09a-c

To a stirred solution of the acid **2.06** (0.226 g, 1 mmol), imine **2.07a-c** (1 mmol) and triethylamine (0.42 ml, 3 mmol) in anhydrous dichloromethane (15 ml), a solution of triphosgene (0.148 g, 0.5 mmol) in dry dichloromethane was added slowly dropwise at 0 ^oC. The reaction mixture was allowed to attain room temperature and stirred at room temperature for 12 h. It was then diluted with dichloromethane and successively washed with water (3 x 10 ml), saturated sodium bicarbonate (3 x 15 ml) and brine (15 ml). The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to get the crude product, which was flash column chromatographed (silica gel, 230-400 mesh, pet. ether/EtOAc, 90:10) to get a diastereomeric mixture of azetidin-2-ones **2.08a-c** and **2.09a-c**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. In all the cases, attempts to separate the two diastereomers by column chromatography/crystallization were unsuccessful.

2.9.5a : Preparation of (3*R*,4*S*,1'*S*,3'*S*,6'*R*) and (3*S*,4*R*,1'*S*,3'*S*,6'*R*)-1-phenyl-4-(*p*-anisyl)-3-[3',7',7'-trimethylbicyclo(4.1.0)hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.08a & 2.09a

Following the general procedure, an anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.06** (0.226g, 1

mmol), imine **2.07a** (0.211 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish a diastereomeric mixture (65:35 ratio) of azetidin-2-ones **2.08a** and **2.09a** as a pale yellow oil (0.285 g, 68%). The diastereomers could not be separated either by chromatography or crystallization. The data for the isolated diastereomeric mixture of azetidin-2-ones **2.08a** & **2.09a** is as follows.

MP : Oil.

$[\alpha]^{28}_D$: +7.4 (c 1, $CHCl_3$)

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.35-0.70 (m, 2H), 0.65 & 0.70 (2s, total 3H), 0.75 & 0.80 (2s, total 3H), 0.95 & 1.10 (2s, total 3H), 0.80-2.50 (m, 3H), 3.00 (dd, *J* = 8.8 Hz, 17.6 Hz, 1H), 3.70 & 3.75 (2s, total 3H), 4.65 & 4.95 (d, *J* = 4.9 Hz & d, *J* = 5.4 Hz respect., total 1H, C-4 H of minor and major diastereomer), 5.05 (two merged doublets, total 1H, C-3 H of minor and major diastereomer), 6.70-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.29, 14.59, 16.61, 17.08, 18.92, 19.00, 19.18, 19.47, 21.35, 24.29, 27.52, 27.67, 34.10, 34.58, 34.77, 34.95, 55.09, 61.93, 62.55, 77.99, 78.62, 79.28, 113.57, 117.32, 119.53, 124.12, 125.41, 125.59, 128.90, 129.71, 129.86, 137.03, 159.78, 164.92, 165.40, 212.71, 214.29.

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

Analysis ($C_{26}H_{29}NO_4$) : Calculated: C, 74.43; H, 6.97; N, 3.34.
Observed: C, 74.28; H, 6.76; N, 3.23.

2.9.5b : Preparation of (3*R*,4*S*,1'*S*,3'*S*,6'*R*) and (3*S*,4*R*,1'*S*,3'*S*,6'*R*)-1-(*p*-anisyl)-4-phenyl-3-[3',7',7'-trimethylbicyclo(4.1.0)hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.08b & 2.09b

Following the general procedure, an anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.06** (0.226g, 1 mmol), imine **2.07b** 0.211 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish a diastereomeric mixture of β-lactams **2.08b** and **2.09b** (0.290 g, 70%) in 60:40 ratio, which was determined from ^{1}H NMR spectral data. The diastereomers could not be

separated by chromatography or crystallization. The data for the isolated diastereomeric mixture of β-lactams **2.08b** & **2.09b** is as follows.

MP : Pale yellow oil.

$[\alpha]^{28}_{D}$: +18.5 (c 1, $CHCl_3$).

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.30-0.75 (m, 2H), 0.75 (2s, total 3H), 0.82 (2s, total 3H), 0.95 & 1.24 (2s, total 3H), 1.00-1.40 (m, 1H), 1.50-1.70 (m, 1H), 1.90-2.50 (m, 1H), 3.00 (dd, *J* = 9.0 Hz, 13.4 Hz, total 1H), 3.75 (s, 3H), 4.75 & 5.05 (d, *J* = 4.9 Hz & d, *J* = 5.3 Hz respect., total 1H, C-4 H of minor and major diastereomer), 5.15 (two merged doublets, total 1H, C-3 H of minor and major diastereomers), 6.80 (d, *J* = 8.8 Hz, 2H), 7.20-7.45 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 16.73, 17.09, 18.97, 19.19, 19.46, 21.57, 24.35, 27.49, 27.70, 29.54, 34.26, 34.52, 34.69, 34.90, 55.27, 62.48, 63.10, 78.24, 78.73, 79.25, 114.26, 118.67, 128.16, 128.30, 128.47, 128.60, 128.82, 130.66, 133.89, 134.11, 156.23, 164.23, 164.66, 212.47, 213.85.

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

Analysis ($C_{26}H_{29}NO_4$) : Calculated: C, 74.43; H, 6.97; N, 3.34.
Observed: C, 74.50; H, 6.77; N, 3.28.

2.9.5c : Preparation of (3*R*,4*S*,1'*S*,3'*S*,6'*R*) and (3*S*,4*R*,1'*S*,3'*S*,6'*R*)-1-(*p*-anisyl)-4-(*p*-anisyl)-3-[3',7',7'-trimethylbicyclo(4.1.0)hept-4'-oxo-3'-yloxy]-azetidin-2-one 2.08c & 2.09c

Following the general procedure, an anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.06** (0.226 g, 1 mmol), imine **2.07c** (0.241 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish a diastereomeric mixture of azetidin-2-ones **2.08c** and **2.09c** (0.270 g, 60%) in 60:40 ratio, which was determined from ^{1}H NMR spectral data. The diastereomers could not be separated by chromatography or crystallization. The data for the isolated diastereomeric mixture of β-lactams **2.08c** & **2.09c** is as follows.

MP : Pale yellow oil.

$[\alpha]^{28}_D$: +25.4 (c 1, $CHCl_3$)

IR ($CHCl_3$) : 1745 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.40-0.75 (m, 2H), 0.70 & 0.75 (2s, total 3H), 0.80 &0.85 (2s, total 3H), 1.00 & 1.25 (2s, total 3H), 1.10-2.50 (m, 3H), 3.05 (dd, *J* = 9.0 Hz & 17.7 Hz, 1H), 3.75 (s, 3H), 3.80 & 3.84 (2s, total 3H), 4.70 & 5.00 (d, *J* = 4.4 Hz & d, *J* = 4.8 Hz respect., total 1H, C-4 H of minor and major diastereomer), 5.05 (merged doublets, total 1H, C-3 H of minor and major diastereomer), 6.70-7.50 (m, 8H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 14.22, 14.51, 16.53, 17.01, 18.92, 19.07, 19.40, 21.35, 24.25, 27.45, 27.60, 34.03, 34.65, 34.88, 55.09, 61.97, 62.55, 77.99, 78.58, 79.17, 113.50, 114.05, 118.57, 125.67, 129.64, 129.82, 130.48, 130.63, 155.96, 159.63, 159.71, 164.23, 164.70, 212.71, 214.25.

MS (m/z) : 449 (M^+).

2.9.6 : Preparation of (1*S*,3*S*,4*S*)-3-methoxy-3,7,7-trimethylbicyclo(4.1.0)heptan-4-ol 2.10

To a solution of β-Carene oxide **2.04** (1.0 g, 6.6 mmol) in anhydrous methanol (25 ml), PTSA (0.030 g) was added at 0 ^oC and the reaction mixture was stirred at 0 ^oC for 2 h. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3 x 20 ml). The combined extracts were washed with brine (2 x 20 ml), dried over Na_2SO_4 and concentrated under reduced pressure to get the methoxy alcohol **2.10** as colourless oil (1.1 g, 90%).

MP : Colourless oil.

$[\alpha]^{28}_D$: +45.7 (c 1.05, $CHCl_3$).

IR (Neat) : 3500-3300 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.55-0.65 (m, 2H), 0.95 (s, 3H), 0.96 (s, 3H), 1.10 (s, 3H), 0.90-2.20 (m, 4H), 1.90 (bs, 1H), 3.25 (s, 3H), 3.75 (t, *J* = 5.8

Hz, 1H).

MS (m/z) : 184 (M^+).

2.9.7 : Preparation of (1*S*,3*S*,4*S*)-3-methoxy-4-allyloxy-3,7,7-trimethylbicyclo(4.1.0)heptane 2.11

To a suspension of NaH (50% dispersion in oil, 0.230 g, 4.8 mmol) in anhydrous THF (5 ml) cooled to 15 ^{0}C, a solution of alcohol **2.10** (0.736 g, 4 mmol) in anhydrous THF (10 ml) was slowly added. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. Then it was cooled to 15 ^{o}C and allyl bromide (0.68 ml, 8 mmol) was added slowly over 10 min. The reaction mixture was then refluxed for 16 h. After completion of reaction, ice-cold water (3 ml) was added and the solvent removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 15 ml) and the organic layer was washed with water (2 x 10 ml), brine (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product, which was chromatographed (silica gel 60-120, pet. ether/ethyl acetate, 95:5) to get **2.11** as colourless oil (0.537 g, 60%).

IR (Neat) : 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.50-0.60 (m, 2H), 0.95 (s, 3H), 0.96 (s, 3H), 1.15 (s, 3H), 0.85-2.10 (m, 4H), 3.00-3.10 (m, 1H) 3.25 (s, 3H), 3.85-4.00 (m, 2H), 5.00-5.40 (m, 2H), 5.80-6.05 (m, 1H).

2.9.8 : Preparation of (1′*S*,3′*S*,4′*S*,6′*R*)-2-[3′-methoxy-3′,7′,7′-trimethylbicyclo(4.1.0)hept-4′-yloxy]acetic acid 2.12

To a solution of the ether **2.11** (0.448 g, 2 mmol) in the solvent system of CH_3CN: CCl_4: H_2O (ratio 2: 2: 3, 14 ml), powdered $NaIO_4$ (1.28 g, 6 mmol) was added followed by catalytic amount of $RuCl_3$ (5 mg) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 4 h. After completion of reaction (TLC), the reaction mixture was diluted with water and extracted with dichloromethane (3 x 10 ml). The organic layer was concentrated under reduced pressure to get crude product. The crude product was basified with saturated $NaHCO_3$ solution (20 ml) and extracted with dichloromethane (10 ml). The aqueous layer was acidified with dil. HCl at 0 ^{o}C and extracted with EtOAc (3 x 10 ml). The organic layer was washed with water, brine and dried over anhydrous.

Na_2SO_4 .The solvent was removed under reduced pressure to get pure **2.12**, as pale yellow oil (0.240 g, 50%).

MP : Oil

$[\alpha]^{28}_D$: -42.9 (c 1.25, $CHCl_3$).

IR ($CHCl_3$) : 3100-2800 cm^{-1}, 1730 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 0.50-0.75 (m, 2H), 0.90 (s, 3H), 0.95 (s, 3H), 1.10-2.15 (m, 4H), 3.15-3.40 (m, 1H), 3.25 (s, 3H), 4.02 (d, *J* = 17.1Hz, 1H), 4.20 (d, *J* = 17.1, 1H), 7.75 (bs, 1H).

MS (m/z) : 242 (M^+).

2.9.9 : Preparation of (3*R*,4*S*,1'*S*,3'*S*,6'*R*) and (3*S*,4*R*,1'*S*,3'*S*,6'*R*)-1-(*p*-anisyl)-4-phenyl-3-[3',7',7'-trimethylbicylco(4.1.0)hept-3'-methoxy-4'-yloxy]-azetidin-2-one 2.14 & 2.15

To a stirred solution of the acid **2.12** (0.242 g, 1 mmol), imine **2.13** (0.211 g, 1 mmol), triethylamine (0.42 ml, 3 mmol) in anhydrous dichloromethane (15 ml), a solution of triphosgene (0.148 g, 0.5 mmol) in dry dichloromethane was added slowly in drops at 0 ^oC. The reaction mixture was allowed to attain room temperature and stirred at room temperature for 12 h. It was then diluted with CH_2Cl_2 and successively washed with water (3 x 10 ml), saturated sodium bicarbonate (3 x 15 ml) and brine (15 ml). The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to get the crude product, which was column chromatographed (silica gel, 230-400 mesh, Pet. ether/EtOAc.) to get the diastereomeric mixture (64:36 ratio) of azetidin-2-ones **2.14** & **2.15** as a pale yellow oil (0.235 g, 54%) The diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. Attempts to separate the two diastereomers by column chromatography/crystallization were not successful. The data for the isolated diastereomeric mixture of azetidin-2-ones **2.14** and **2.15** is as follows.

MP : Oil

$[\alpha]^{28}_D$ +9.6 (c 0.75, $CHCl_3$).

IR (neat) : 1745 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) **:** δ 0.35-0.60 (m, 2H), 0.65 & 0.90 (2s, total 3H), 0.95 & 1.00 (2s, total 3H), 1.12 & 1.26 (2s, total 3H), 0.75-2.20 (m, total 4H), 3.00-3.50 (m, total 1H), 3.04 & 3.25 (2s, total 3H), 3.75 (s, total 3H), 4.90 & 5.10 (d, J = 5.4 Hz & d, J = 4.8 Hz respect., total 1H, C-4 H of minor and major diastereomers), 5.20 (two merged doublets, total 1H, C-3 H of major and minor diastereomers), 6.70-7.50 (m, 9H).

MS (m/z) **:** 435 (M^+).

2.9.10 : Preparation of (1′*S*,3′*S*,4′*S*,6′*R*)-2-[3′-hydroxy-3′,7′,7′-trimethylbicyclo(4.1.0)hept-4′-mercapto]acetic acid 2.17

To a solution of α-carene epoxide **2.16** (1.520 g, 10 mmol) in ethanol (10 ml), was added an aqueous solution of NaOH (1.2 g in 10 ml H_2O) followed by a solution of mercapto acetic acid (1.300 g, 10 mmol) in ethanol (10 ml) and the contents were refluxed for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the residue was taken in water (25 ml). It was extracted with dichloromethane (10 ml) and the aqueous layer was carefully acidified with cold dilute HCl at 0 ^oC. The aqueous layer was then extracted with dichloromethane (3 x 10 ml). The organic layer was washed with saturated brine solution (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the pure mercapto acid **2.17** as pale yellow oil (2.192 g, 90%)

$[\alpha]^{28}_D$ +56.7 (c 1.05, $CHCl_3$).

IR (neat) **:** 3400-3000 cm^{-1}, 1720 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) **:** δ 0.65-2.35 (m, 6H), 0.95 (s, 3H), 1.00 (s, 3H), 1.25 (s, 3H), 2.90 (dd, *J* = 4.4 Hz, 11.2 Hz, 1H), 3.40 (s, 2H), 6.50 (bs, 2H).

2.9.11: Data for lactone 2.19

Following the same procedure as **2.9.5** the mercapto acid **2.17** (0.244 g, 1 mmol) was treated with imine 2.13 (0.211 g, 1 mmol) and triethylamine (0.42 ml. 3 mmol) using triphosgene (0.148 g, 0.5 mmol) as acid activator. The IR and ^{1}H NMR of the crude reaction mixture showed the presence of the lactone. The crude mixture was

column chromatographed (silica gel 60-120, pet.ether/ethyl acetate, 90:10) to get the lactone **2.19** as thick colourless oil (0.130 g, 60%)

IR (neat) : 1700 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.70-2.40 (m, 6H), 0.90 (s, 3H), 1.10 (s, 3H), 1.50 (s, 3H), 3.15 (dd, *J* = 3.4 Hz, *J* = 13.7 Hz, 1H), 3.45 (d, *J* = 19.3 Hz, 1H), 3.65 (d, *J* = 19.3 Hz, 1H)

MS (m/z) : 226 (M^+).

2.9.12: Data for the lactone 2.20

Isolated as Thick oil

IR ($CHCl_3$) : 1700 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.60-0.95 (m, 2H), 1.02 (s, 3H), 1.04 (s, 3H), 1.35-1.47 (m, 1H), 1.55 (s, 3H), 1.62-1.80 (m, 1H), 2.10-2.35 (m, 2H), 2.80 (dd, *J* = 7.0 Hz, 11.9 Hz, 1H), 3.35 (d, *J* = 17.6 Hz, 1H), 3.65 (d, *J* = 17.6 Hz, 1H)

MS (m/z) : 226 (M^+).

Section B

2.10 : Experimental

2.10.1 : Preparation of 1, 3-dithiane-2-carboxylic acid 2.22

A solution of glyoxylic acid monohydrate **2.21** (0.92 g, 10 mmol), 1,3-propanedithiol (1.11 ml, 11 mmol) and PTSA (0.19 g, 1 mmol) in benzene (25 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature and the organic phase was extracted with saturated $NaHCO_3$ (3 x 10 ml). The aqueous layer was washed with ether (1 x 10 ml) and then carefully acidified with 6 N HCl and finally extracted with EtOAc (4 x 50 ml). The organic layer was dried over anhyd. Na_2SO_4 and the solvent was removed under reduced pressure to afford **2.22** as a pale yellow solid (1.30 g, 79%).

MP : 113-114 ^oC (Lit[21] 115-116 ^oC).

IR ($CHCl_3$) : 3200-2500 cm^{-1}, 1720 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.90-2.25 (m, 2H), 2.45-2.75 (m, 2H), 3.25-3.55 (m, 2H), 4.15 (s, 1H).

2.10.2 : General procedure for the synthesis of spiro azetidin-2-ones 2.24a-f

An anhydrous solution of triphosgene (0.148 g, 0.5 mmol) in dichloromethane was added dropwise at 0 ^oC to a dichloromethane solution (10 ml) of acid **2.24** (0.164 g, 1mmol), imine (**2.23a-f,** 1 mmol) and triethylamine (0.42 ml, 3 mmol). After completion of addition, the reaction mixture was warmed up to room temperature and stirred at this temperature for 12 h. It was then diluted with CH_2Cl_2 and washed successively with water (3 x 10 ml), saturated sodium bicarbonate solution (3 x 10 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude product, which was purified by column chromatography (silica gel 60-120 mesh, pet. ether/ ethyl acetate, 75:25) to get pure spiro azetidin-2-ones **2.24a-f**.

2.10.2a : Preparation of 2-(4-methoxyphenyl)-3-phenyl-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24a

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23a** (0.211 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24a** as a white solid (0.250 g, 70%).

MP : 186 ^oC.

IR ($CHCl_3$) : 1735 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.80-2.30 (m, 2H), 2.60-2.90 (m, 2H), 3.50-3.90 (m, 2H), 3.70 (s, 3H), 4.90 (s, 1H), 6.80 (d, *J* = 9.3 Hz, 2H), 7.10-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.39, 28.18, 28.56, 55.63, 60.55, 66.86, 114.60, 118.75, 127.90, 128.54, 126.38, 130.89, 131.99, 156.47, 164.62

MS (m/z) : 357 (M^+).

Analysis ($C_{19}H_{19}NO_2S_2$) : Calculated: C, 63.83; H, 5.36; N, 3.92; S, 17.94.
Observed: C, 63.62; H, 5.50; N, 3.73; S, 18.04.

2.10.2b : Preparation of 2-phenyl-3-(4-methoxyphenyl)-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24b

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23b** (0.211 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24b** as a white solid (0.253 g, 71%).

MP : 155-156 ^oC.

IR ($CHCl_3$) : 1737 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.80-2.30 (m, 2H), 2.60-2.90 (m, 2H), 3.50-3.90 (m, 2H), 3.70 (s, 3H), 4.90 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.00-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.33, 28.02, 28.42, 55.33, 60.66, 66.43, 113.92, 117.41, 123.55, 124.28, 129.17, 137.44, 160.42, 165.12

MS (m/z) : 357 (M^+).

Analysis ($C_{19}H_{19}NO_2S_2$) : Calculated: C, 63.83; H, 5.36; N, 3.92; S, 17.94.
Observed: C, 63.65; H, 5.60; N, 4.10; S, 17.75.

2.10.2c : Preparation of 2,3-di(4-methoxyphenyl)-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24c

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23c** (0.241 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24c**, as a white solid (0.290 g, 75%).

MP : 130 ^oC.

IR ($CHCl_3$) : 1745 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.80-2.30 (m, 2H), 2.60-2.90 (m, 2H), 3.50-3.90 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 4.90 (s, 1H), 6.80 (d, J = 9.3 Hz, 2H), 6.90 (d, J = 8.8Hz, 2H), 7.15-7.40 (m, 4H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.11, 27.76, 28.16, 55.03, 55.25, 60.58, 66.46, 113.66, 114.28, 118.47, 123.58, 128.91, 130.71, 156.19, 160.19, 164.38.

MS (m/z) : 387 (M^+).

Analysis ($C_{20}H_{21}NO_3S_2$) : Calculated: C, 61.90; H, 5.46; N, 3.61; S, 16.40.
Observed: C, 61.60; H, 5.72; N, 3.40; S, 16.54.

2.10.2d : Preparation of 2-(4-methoxyphenyl)-3-styryl-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24d

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23d** (0.237 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24d**, as a white solid (0.268 g, 70%)

MP : 122-124 ^oC.

IR ($CHCl_3$) : 1745 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.80-2.30 (m, 2H), 2.60-2.90 (m, 2H), 3.50-3.90 (m, 2H),

(200 MHz) 3.75 (s, 3H), 4.50 (d, J = 8.3 Hz, 1H), 6.40 (dd, J = 8.3 Hz, 16.0 Hz, 1H), 6.75-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) : δ 25.27, 27.56, 28.11, 55.33, 60.58, 65.77, 114.26, 118.38, 121.96, 126.81, 128.36, 128.58, 130.93, 135.26, 137.46, 156.20, 163.98.
(50.3 MHz)

MS (m/z) : 383 (M^+).

Analysis : Calculated: C, 65.79; H, 5.48; N 3.65; S, 16.72.
($C_{21}H_{21}NO_2S_2$) Observed: C, 65.50; H, 5.68; N, 3.40; S, 16.64.

2.10.2e : Preparation of 2,3-diphenyl-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24e

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23e** (0.181 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24e**, as a white solid (0.235 g, 72%).

MP : 173-174 ^oC (Lit[28] 175-176 ^oC).

IR ($CHCl_3$) : 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.80-2.30 (m, 2H), 2.60-2.90 (m, 2H), 3.50-3.90 (m, 2H), 5.00 (s, 1H), 7.00-7.75 (m, 10H)
(200 MHz)

^{13}C NMR ($CDCl_3$) : δ 24.96, 27.72, 28.16, 60.07, 66.35, 117.04, 124.02, 127.44, 128.18, 128.91, 131.49, 137.11, 159.46, 164.68
(50.3 MHz)

MS (m/z) : 327(M^+).

Analysis : Calculated: C, 66.02; H, 5.23; N, 4.28; S, 19.58.
($C_{18}H_{17}NOS_2$) Observed: C, 65.90; H, 5.43; N, 4.31; S, 19.73.

2.10.2f : Preparation of 2-(4-chlorophenyl)-3-styryl-5,9-dithia-2-aza-spiro(3,5)nonan-1-one 2.24f

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22** (0.164 g, 1 mmol), imine **2.23f** (0.241 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^oC to furnish the spiro azetidin-2-one **2.24f**, as a white solid (0.267 g, 69%).

MP : 154 ^{o}C.

IR ($CHCl_3$) : 1751 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.80-2.40 (m, 2H), 2.70-2.90 (m, 2H), 3.55-3.90 (m, 2H), 4.50 (d, *J* = 8.3 Hz, 1H), 6.30 (dd, *J* = 8.3 Hz, 16.1 Hz, 1H), 6.90 (d, *J* = 16.1 Hz, 1H), 7.25-7.50 (m, 9H);

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.27, 27.65, 28.23, 60.89, 65.80, 118.29, 121.38, 126.90, 128.67, 129.16, 129.31, 135.17, 136.15, 137.86, 164.41

MS (m/z) : 387 (M^+).

Analysis ($C_{20}H_{18}NOS_2Cl$) : Calculated: C, 61.92; H, 4.68; N, 3.61; S, 16.53.
Observed: C, 62.19; H, 4.83; N, 3.39; S, 16.28.

2.10.2g : Preparation of 2-(1′-phenylethyl)-3-phenyl-2-aza-5,9-dithiaspiro(3,5)nonan-1-one (mixture of 2 diastereomers, 3*R*, 1′*R* and 3*S*, 1′*R*) 2.24g

Following the general procedure, anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mol), was added to a CH_2Cl_2 solution of acid **2.22**(0.164 g, 1 mmol), imine **2.23g** (0.209 g, 1 mmol) and Et_3N (0.42 ml, 3 mmol) at 0 ^{o}C to furnish the spiro azetidin-2-one **2.25g** (as a mixture of two diastereomers) as yellow oil (0.245 g, 69%).

MP : Thick oil.

IR ($CHCl_3$) : 1751 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.50 & 1.90 (2d, *J* = 7.4 Hz and *J* = 6.9 Hz, 3H), 1.50-2.25 (m, 2H), 2.50-2.90 (m, 2H), 3.40-3.90 (m, 2H), 4.22 & 4.27 (2S, 1H), 4.35 & 5.00 (2q, *J* = 7.3 Hz, 1H), 7.00-7.50 (m, 9H).

MS (m/z) : 355 (M^+).

Analysis ($C_{20}H_{21}NOS_2$) : Calculated: C, 67.61; H, 5.92; N, 3.94; S, 18.03
Observed: C, 67.45; H, 5.86; N, 3.80; S, 17.91.

2.10.3 : Preparation of camphor derived thiols 2.27and 2.28

To a suspension of LAH (4.08 g, 108 mmol) in dry ether (100 ml), a solution of (1*S*)-(+)-10-camphorsulphonyl chloride (13.46 g, 54 mmol) in dry ether (100 ml) was added at –78 ^{o}C under argon in small portions. The mixture was first stirred at room

temperature and then refluxed overnight. The reaction was cooled to room temperature and the excess LAH was carefully quenched with ethyl acetate and finally with dil. HCl (2%). The resulting mixture was filtered through a celite pad and washed thoroughly with ether. The filtrate was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a mixture of thiols **2.27** and **2.28** (85:25 ratio respectively, as determined by ^{1}H NMR of crude mixture) as a strongly smelling oily residue (8.20 g, 82%). The major, less polar exo-thiol **2.27** was separated by flash column chromatography (pet. ether/ethyl acetate, 98:2) as a white solid (6.20 g, 62%).

Data for the major exo-thiol **2.27**:

MP : 72 ^{o}C (Lit[26] 70 ^{o}C).

$[\alpha]^{28}_D$: -55.6 (c 10, $CHCl_3$) (Lit[26] $[\alpha]^{24}_D$ = -57.4, c 10, $CHCl_3$)

IR ($CHCl_3$) : 3400 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.80 (s, 3H), 1.05 (s, 3H), 0.95-1.80 (m, 7H), 2.15 (d, *J* = 3.9 Hz, 1H), 2.55 (dd, *J* = 12.7 Hz, 5.1 Hz, 1H), 2.75 (dd, *J* = 12.7 Hz, 9.5 Hz), 4.00 (m, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 19.80, 20.47, 23.55, 26.64, 30.21, 39.43, 45.61, 47.30, 52.81, 76.15.

2.10.4 : Preparation of ethyl glyoxylate 2.30

To a solution of diethyl-L-tartrate **2.29** (1.03 g, 5 mmol) in MeOH (20 ml), powdered $NaIO_4$ (2.14 g, 10 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 4 h. After completion of reaction (TLC), the reaction mixture was filtered and the residue was washed with methanol and the combined filtrates were concentrated under reduced pressure to get the ethyl glyoxylate **2.30**, as colourless oil (1.271 g, 95%).

IR (Neat) : 3500-3100 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.30 (t, *J* = 7.1 Hz, 3H), 3.45 (s, 3H), 3.75 (d, *J* = 11.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz), 4.85 (d, *J* = 11.0 Hz, 1H).

2.10.5 : Preparation of chiral ester 2.31

To an anhydrous dichloromethane solution (5 ml) of exo-thiol **2.27** (0.186 g, 1 mmol) and ethylglyoxylate **2.30** (0.201 g, 1.5 mmol) at 0 ^{o}C, BF_3.EtO was added and the reaction mixture was stirred at 0 ^{o}C for 30 min. After completion of reaction (TLC)**,** the reaction mixture was passed through column (silica gel 60-120, pet. ether/ dichloromethane, 50:50) and the solvent was removed under reduced pressure to get pure chiral ester **2.31** as colourless oil (0.230 g, 85%)

MP : Thick oil

$[\alpha]^{28}_{D}$: -72.6 (c 1, $CHCl_3$)

IR ($CHCl_3$) : 1755 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.92 (s, 3H), 0.90-2.10 (m, 7H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.33 (s, 3H), 2.85 (d, *J* = 14.2 Hz, 1H), 3.10 (d, *J* = 14.2 Hz, 1H), 3.65 (dd, *J* = 3.4 Hz, 7.8 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 5.30 (s, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 140.01, 20.26, 22.90, 27.09, 28.75, 33.78, 37.53, 43.05, 45.33, 46.76, 61.72, 78.59, 85.28, 167.80.

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

2.10.6 : Preparation of chiral acid 2.32

To a solution of ester **2.31** (0.270 g, 1 mmol) in anhydrous methanol (5 ml), a solution of KOH (0.066 g, 1 mmol) dissolved in dry methanol (5 ml) was added at 20 ^{o}C. The reaction mixture was further stirred at room temperature for 5 h. After completion of reaction (TLC), solvent was evaporated and the residue was diluted with water (5 ml). The aqueous layer was carefully acidified with 10% HCl at 0 ^{o}C and extracted with dichloromethane (3 x 5 ml). The organic layer was washed with brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded the pure acid **2.32**, as colourless oil (0.220 g, 91%).

MP : Thick oil.

IR ($CHCl_3$) : 3500-3300 cm^{-1}, 1730cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.95 (s, 3H), 0.80-2.10 (m, 7H), 1.30 (s, 3H), 2.85 (d, *J* =

14.2 Hz, 1H), 3.10 (d, *J* = 14.2 Hz, 1H), 3.65 (dd, *J* = 3.4 Hz, 7.8 Hz, 1H), 5.35 (s, 1H).

MS (m/z) : 242(M^+).

Analysis ($C_{12}H_{18}O_3S$) : Calculated: C, 59.48; H, 7.49; S, 13.20.
Observed: C, 59.33; H, 7.62; S, 13.43.

2.10.7 : General procedure for the synthesis of spiro azetidin-2-ones 2.34a-c & 2.35a-c.

An anhydrous dichloromethane solution of triphosgene (0.148 g, 0.5 mmol) was slowly added at 0 ^oC to a CH_2Cl_2 solution (15 ml) of acid **2.32** (0.242 g, 1 mmol), imine (**2.33a-c**, 1 mmol) and triethylamine (0.42 ml, 3 mmol). After completion of addition, the reaction mixture was allowed to attain room temperature and then stirred at this temperature for 12h. The reaction mixture was then diluted with CH_2Cl_2 and washed successively with water (3 x 10 ml), saturated $NaHCO_3$ solution (3 x 10 ml) and brine (10 ml). The organic layer was dried over anhydrous sodium sulphate and solvent removed under reduced pressure to get the crude product, which was flash chromatographed to yield diastereomeric mixture of spiro azetidin-2-ones **2.34a-c** and **2.35a-c**. The diastereomeric ratio was determined from the ^1H NMR of crude reaction mixture.

2.10.7a : Preparation of Spiro azetidin-2-ones 2.34a & 2.35a.

Following the general procedure, an anhydrous CH_2Cl_2 solution of triphosgene (0.148 g, 0.5 mmol) was added at 0 ^oC to a CH_2Cl_2 solution of acid **2.32** (0.242 g, 1 mmol), imine **2.33a** (0.211 g, 1 mmol) and triethylamine (0.42 ml, 3 mmol) to get a diastereomeric mixture of spiro azetidin-2-ones **2.34a** and **2.35a** (0.175 g, 40%). (The ratio was almost 50:50 as determined from the ^1H NMR of crude reaction product). The diastereomers **2.34a** and **2.35a** were separated by flash chromatography and crystallization. The data for the individual diastereomers is as follows.

Data for the Spiro azetidin-2-one 2.34a

MP : 173-174 ^{o}C (white solid).

$[\alpha]^{28}_{D}$: +16.4 (c 0.5, $CHCl_3$).

IR ($CHCl_3$) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.83 (s, 3H), 1.15 (s, 3H), 0.95-1.70 (m. 7H), 2.60 (d, *J* = 13.7 Hz, 1H), 3.10 (dd, *J* = 3.2 Hz, 8.5 Hz, 1H), 3.30 (d, *J* = 13.7 Hz, 1H), 3.70 (s, 3H), 4.93 (s, 1H), 6.80 (d, *J* = 9.3 Hz, 2H), 7.15-7.50 (m. 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 19.96, 20.51, 26.61, 27.04, 29.69, 30.95, 36.10, 44.47, 47.06, 55.42, 71.48, 80.69, 92.35, 114.39, 118.96, 127.94, 128.39, 128.64, 130.84, 133.64, 156.41, 164.26.

MS (m/z) : 435 (M^+).

Analysis ($C_{26}H_{29}NO_3S$) : Calculated: C, 71.69; H, 6.71; N, 3.21; S, 7.35.
Observed: C, 71.45; H, 6.64, N, 3.14; S, 7.21.

Data for the spiro azetidin-2-one 2.35a

MP : 146-148 ^{o}C (white solid).

$[\alpha]^{28}_{D}$: -49.7 (c 0.75, $CHCl_3$).

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.90 (s, 3H), 1.15 (s, 3H), 0.80-1.75 (m, 7H), 2.75 (d, *J* = 14.2 Hz, 1H), 3.75 (s, 3H), 3.71 (merged doublet, 1H), 4.45 (dd, *J* = 3.9 Hz, 6.8 Hz, 1H), 4.91 (s, 1H), 6.80 (d, J = 8.5 Hz, 2H), 7.15-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.31, 22.97, 26.49, 27.18, 33.64, 37.71, 42.67, 45.41, 46.98, 55.46, 68.19, 82.27, 88.51, 114.44, 118.81, 127.93, 128.15, 128.33, 131.02, 132.82, 156.40, 163.85.

MS (m/z) : 435 (M^+).

Analysis ($C_{26}H_{29}NO_3S$) : Calculated: C, 71.69; H, 6.71; N, 3.21; S, 7.35.
Observed: C, 71.83; H, 6.53, N, 3.36; S, 7.50.

2.10.7b : Preparation of spiro azetidin-2-ones 2.34b & 2.35b.

Following the general procedure, an anhydrous CH_2Cl_2 solution of triphosgene (0.148 g, 0.5 mmol) was added at 0 ^oC to a CH_2Cl_2 solution of acid **2.32** (0.242 g, 1 mmol), imine **2.33b** (0.237 g, 1 mmol) and triethylamine (0.42 ml, 3 mmol) to get a diastereomeric mixture of spiro azetidin-2-ones **2.34b** and **2.35b** (0.188 g, 41%). (The ratio was almost 50:50 as determined from the ^1H NMR of crude reaction product). One of the diastereomer could be separated by crystallization and the data for the separated diastereomer is as follows.

MP : 174-176 ^oC (white solid).

$[\alpha]^{28}_D$: +15.6 (c 0.5, $CHCl_3$)

IR ($CHCl_3$) : 1743 cm^{-1}

^1H NMR ($CDCl_3$) (200 MHz) : δ 0.85 (s, 3H), 1.20 (s, 3H), 0.80-2.05 (m, 7H), 2.60 (d, *J* = 14.0 Hz, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 3.65-3.80 (m, 1H), 3.75 (s, 3H), 4.50 (d, *J* = 8.8 Hz, 1H), 6.35 (dd, *J* = 8.8 Hz, 16.1 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 16.1 Hz, 1H), 7.15-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.02, 20.51, 26.73, 26.89, 31.04, 36.53, 44.65, 47.24, 47.58, 55.51, 70.19, 81.24, 92.23, 114.45, 118.93, 124.03, 126.81, 128.46, 128.79, 131.39, 136.64, 156.50, 164.13.

MS (m/z) : 461 (M^+).

Analysis ($C_{28}H_{31}NO_3S$) : Calculated: C, 72.85; H, 6.77; N, 3.03, S, 6.94.
Observed: C, 72.98; H, 6.94; N, 3.18, S, 7.05.

2.10.7c : Preparation of spiro azetidin-2-ones 2.34c & 2.35c

Following the general procedure, an anhydrous CH_2Cl_2 solution of triphosgene (0.148 g, 0.5 mmol) was added at 0 ^oC to a CH_2Cl_2 solution of acid **2.32** (0.242 g, 1 mmol), imine **2.33b** (0.241 g, 1 mmol) and triethylamine (0.42 ml, 3 mmol) to get a diastereomeric mixture of spiro azetidin-2-ones **2.34c** and **2.35c** (0.176 g, 38%). (The ratio was almost 50:50 as determined from the ^1H NMR of the crude reaction product).

The diastereomers could not be separated by column chromatography or crystallization. Data for the mixture **2.34c** & **2.35c** is as follows

MP : Pale yellow oil.

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

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 0.89 & 0.93 (2s, total 3H,), 1.22 & 1.27 (2s, total 1H), 1.00-1.95 (m, total 7H), 2.55 & 3.35 (2d, J = 13.7 Hz, total 1H), 2.75 & 3.75 (2d, J = 14.1 Hz, total 1H), 3.70-3.85 & 4.40-4.55 (m, total 1H), 4.5 (two doublets merged together, total 1H, C4 –H of two diastereomers), 6.20-6.40 (m, total 1H), 6.75-6.95 (m, total 1H), 7.15-7.50 (m, total 7H).

MS (m/z) : 465 (M^+).

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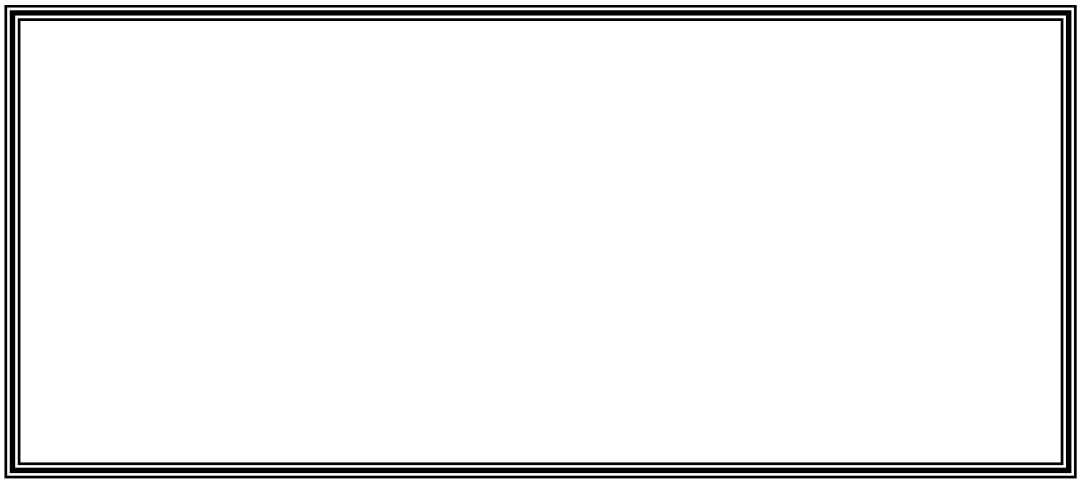

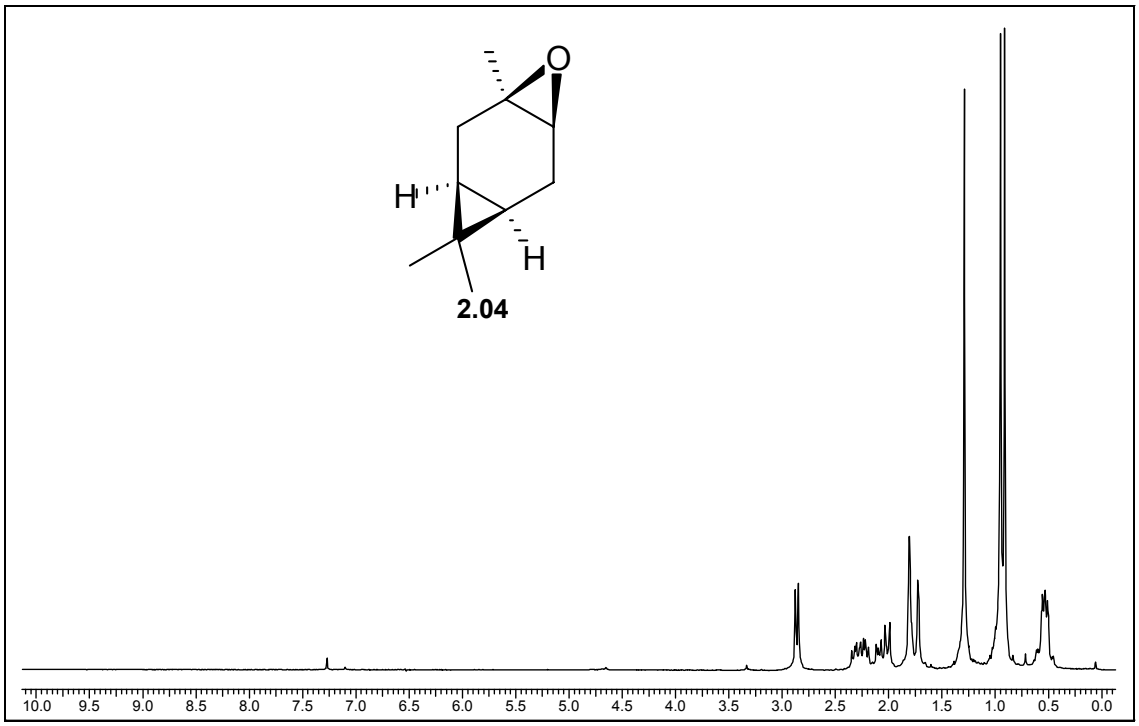
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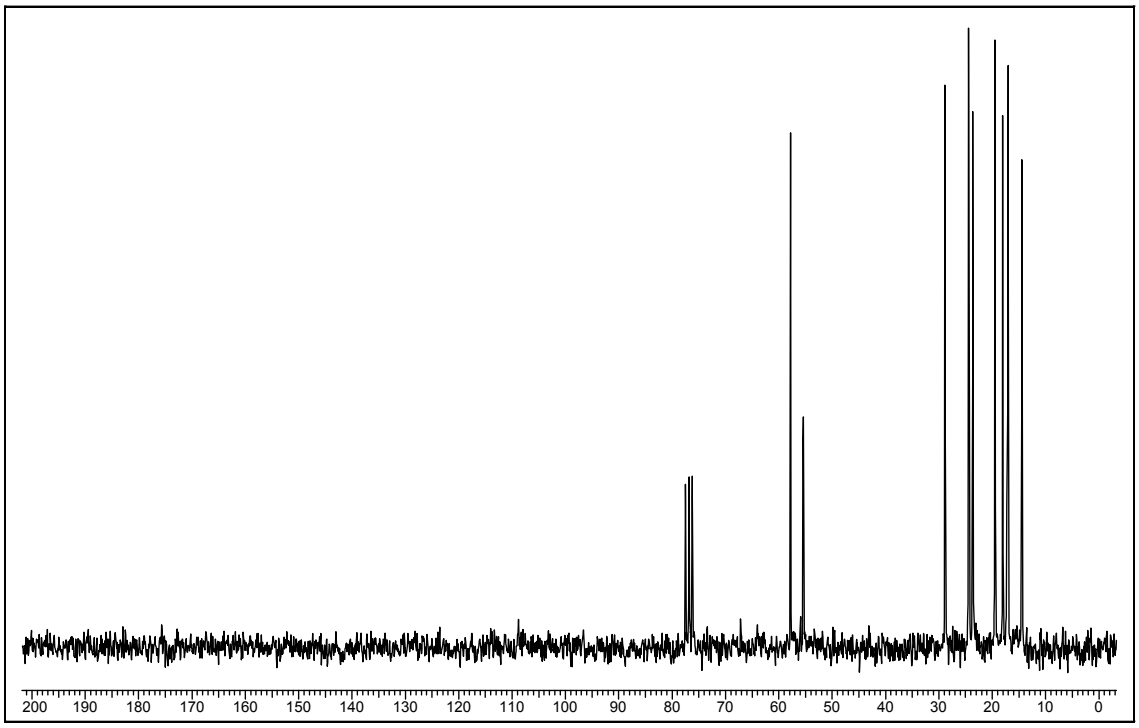
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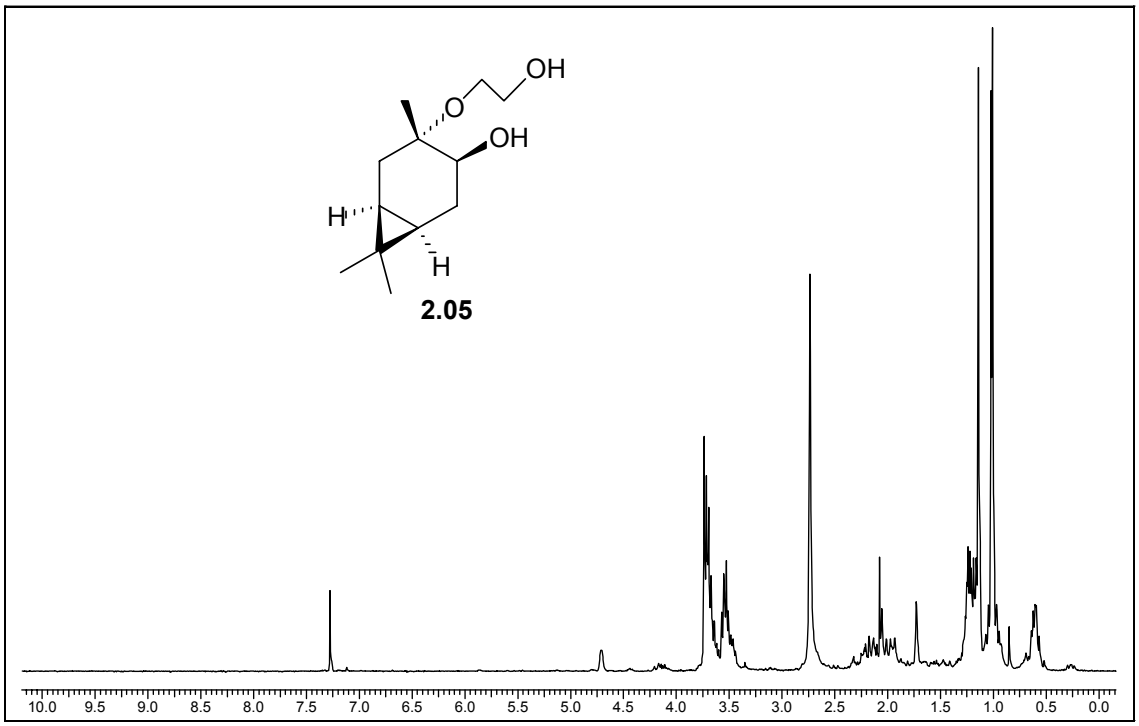
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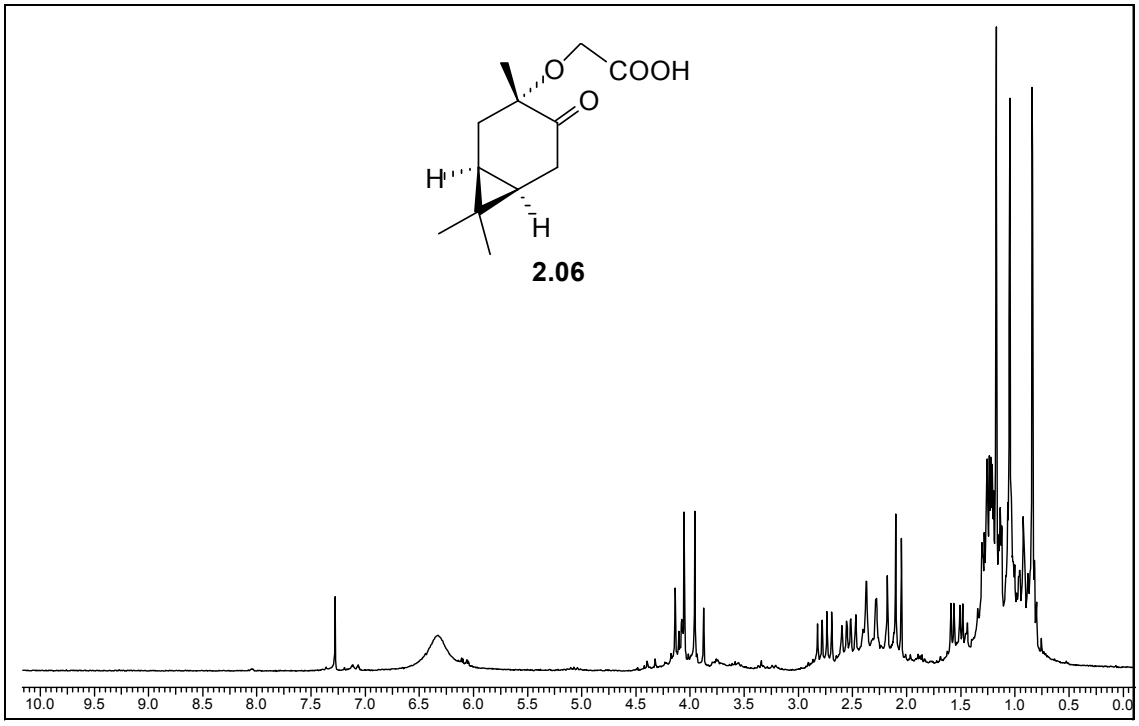
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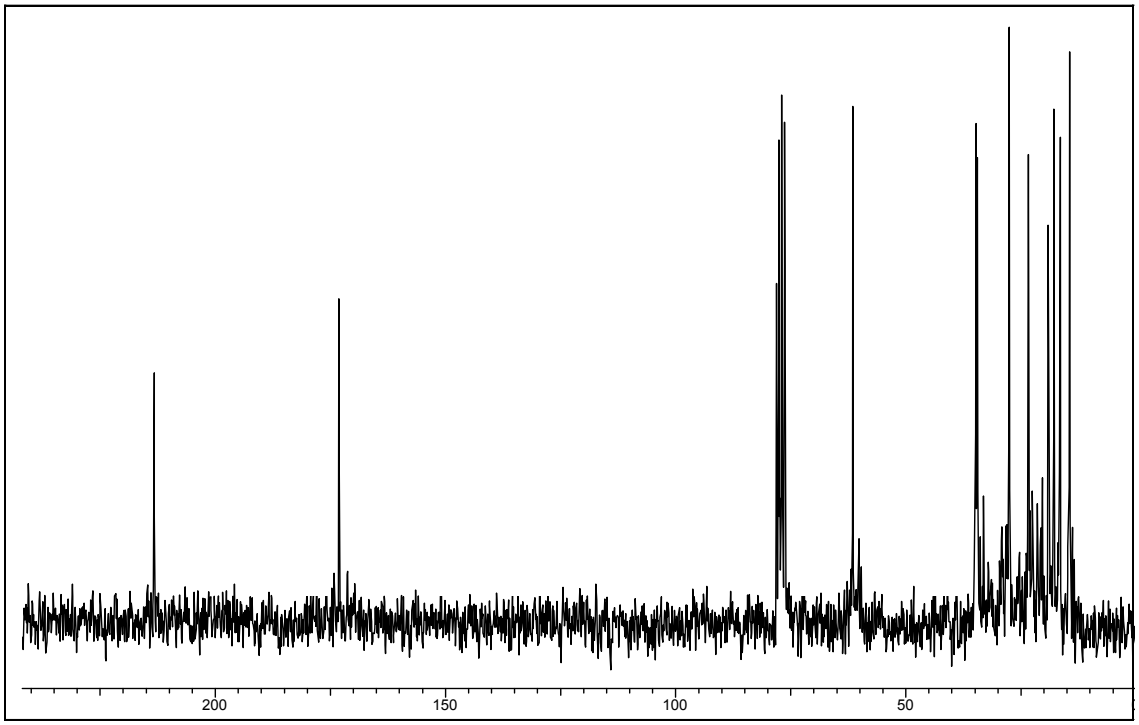
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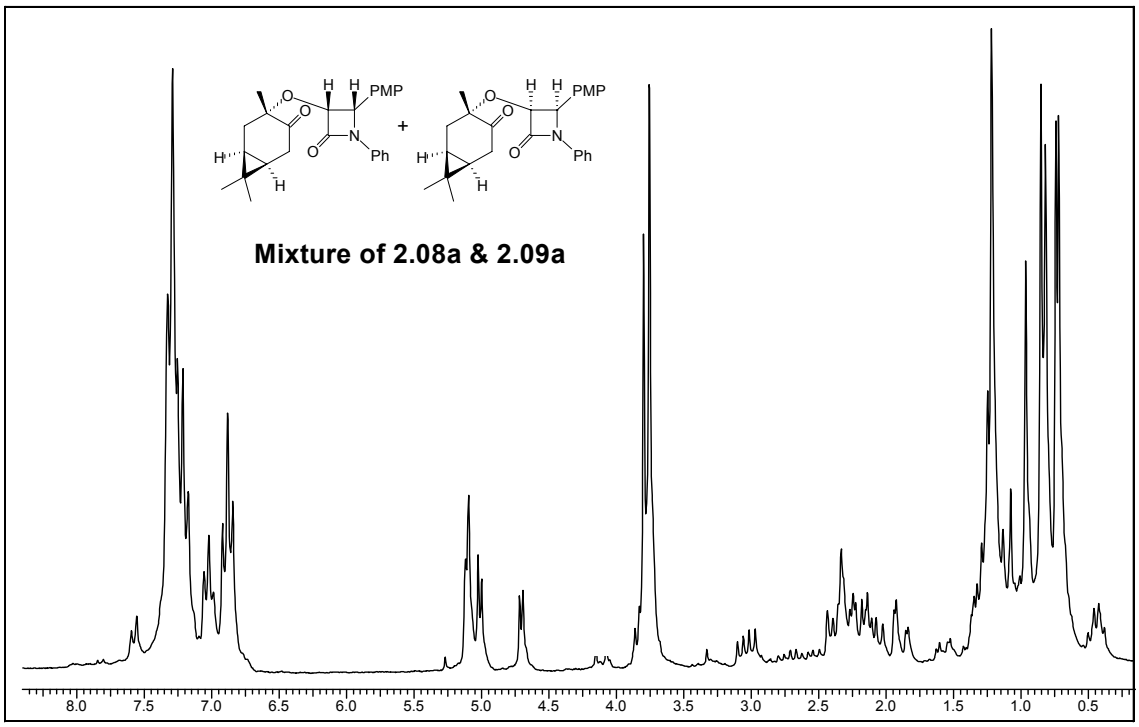
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Mixture of 2.08a & 2.09a
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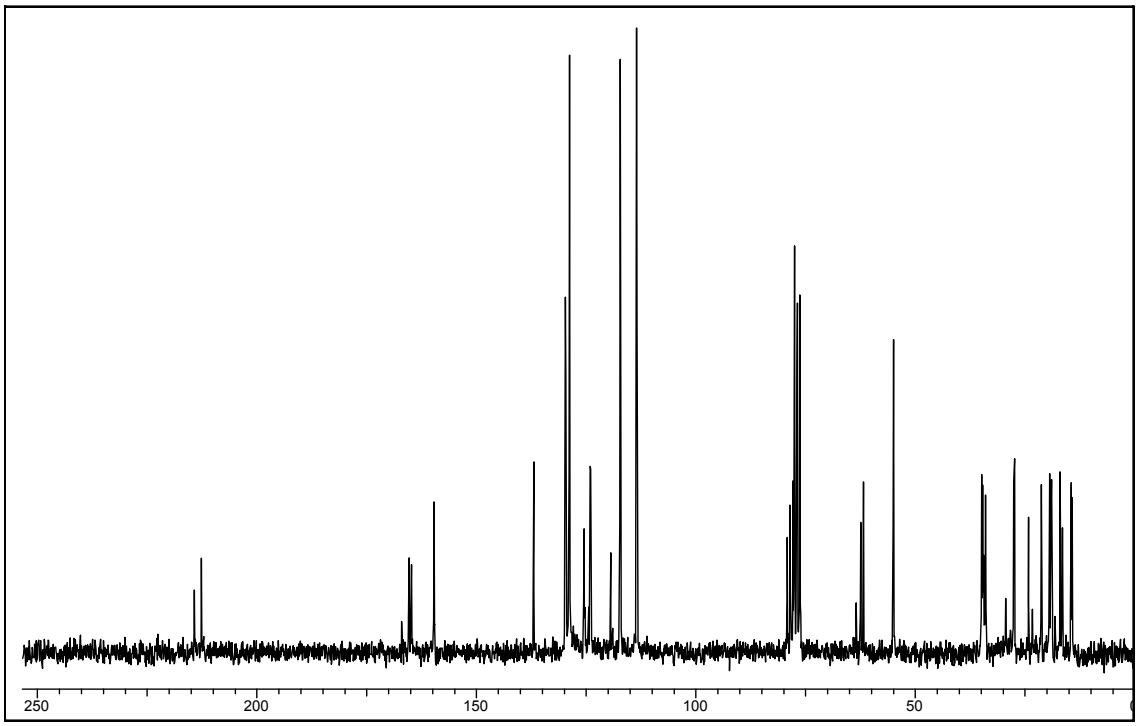
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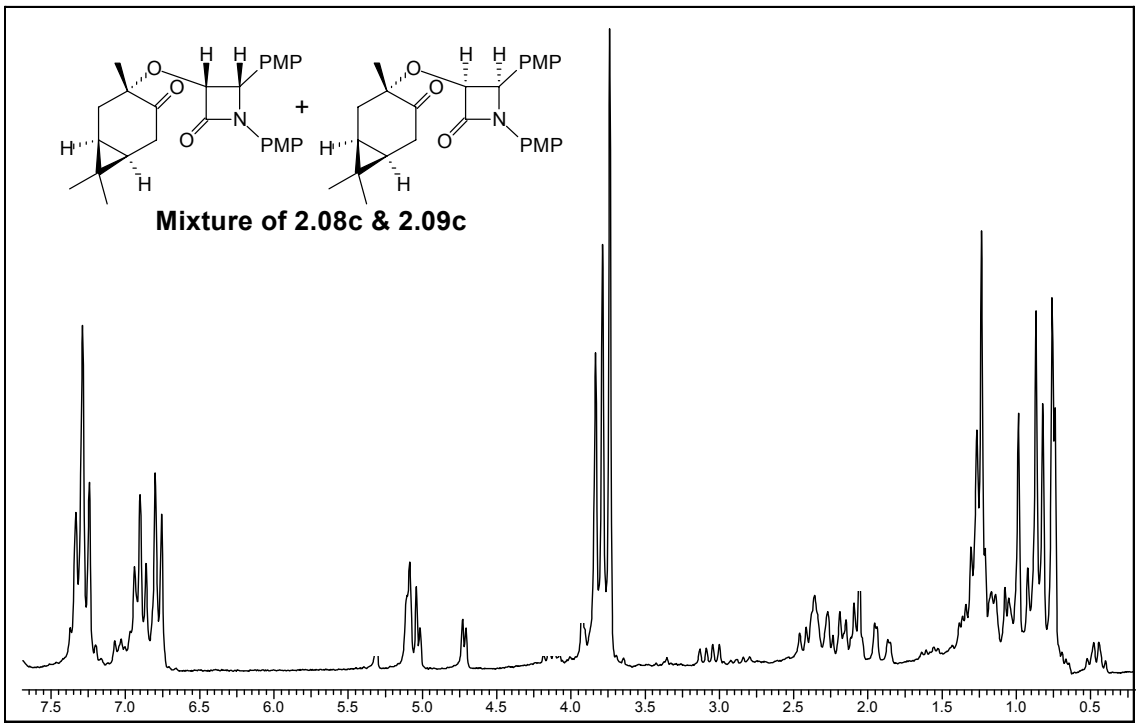
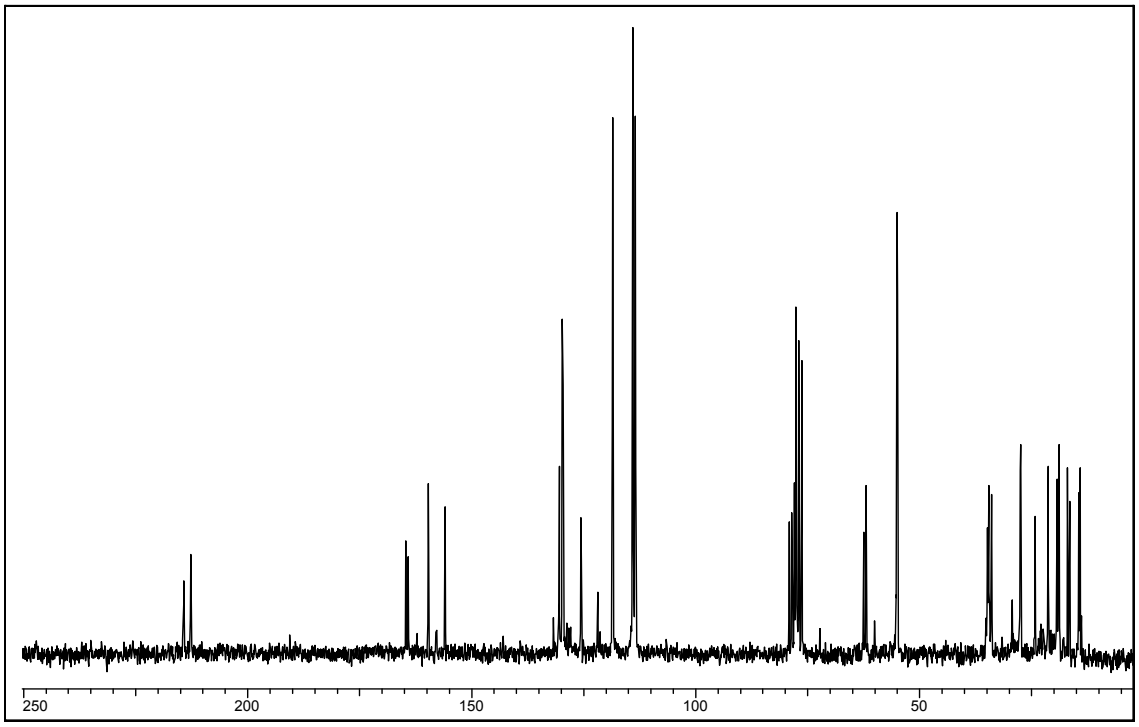
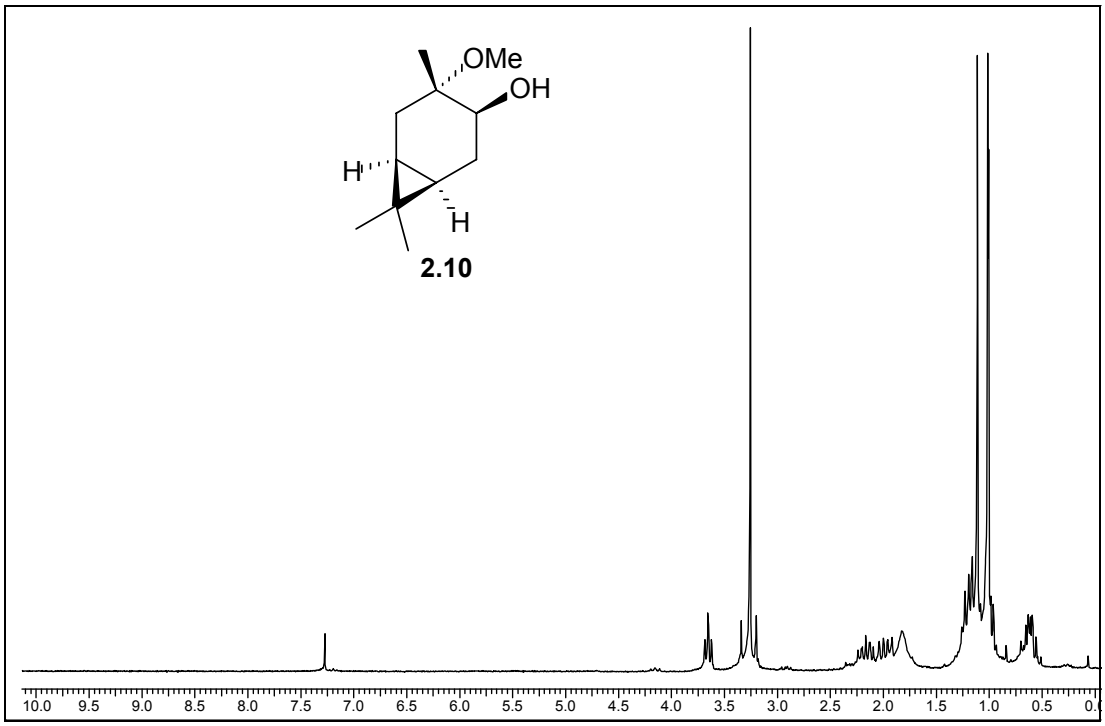


Mixture of 2.08c & 2.09c

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H
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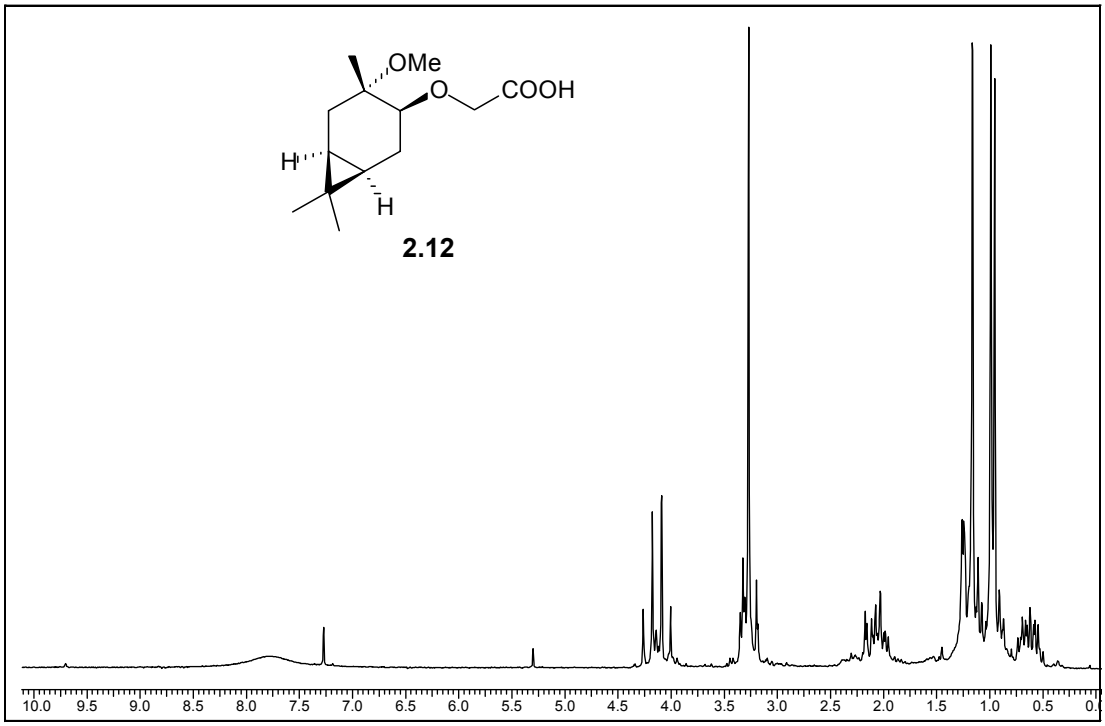
2.10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COOH
H
H
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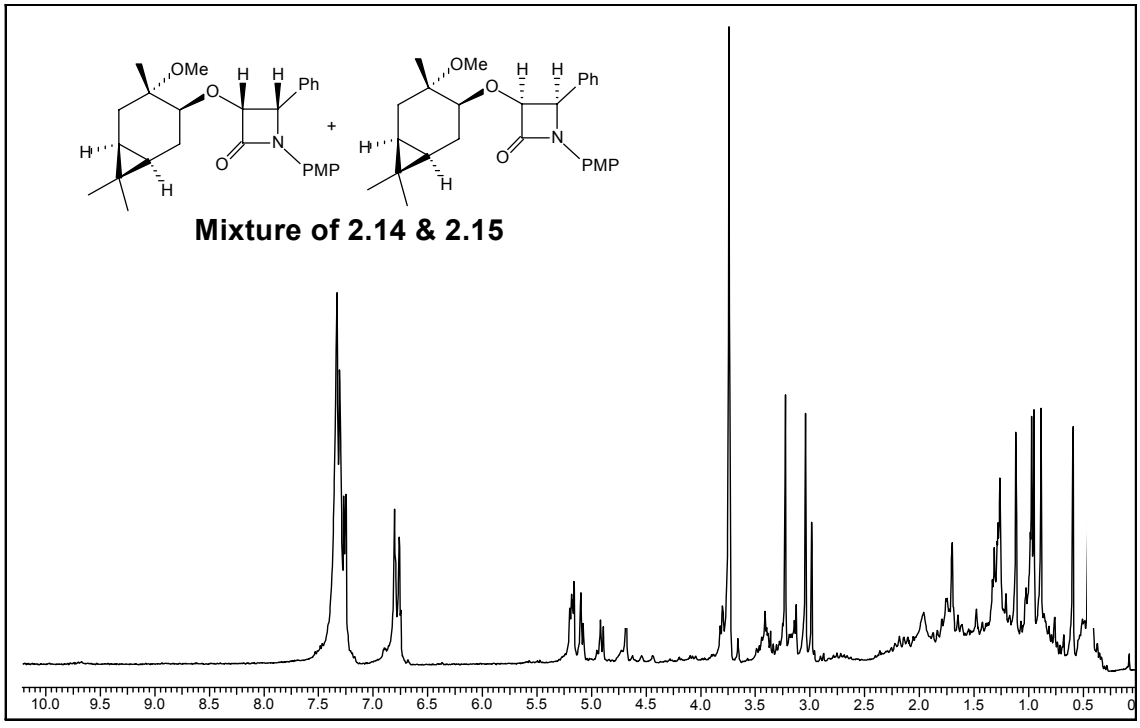
2.12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H
Ph
O
N
PMP
O
H
H
+
OMe
H
H
Ph
O
N
PMP
O
H
H
Mixture of 2.14 & 2.15
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9.5
9.0
8.5
8.0
7.5
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6.5
6.0
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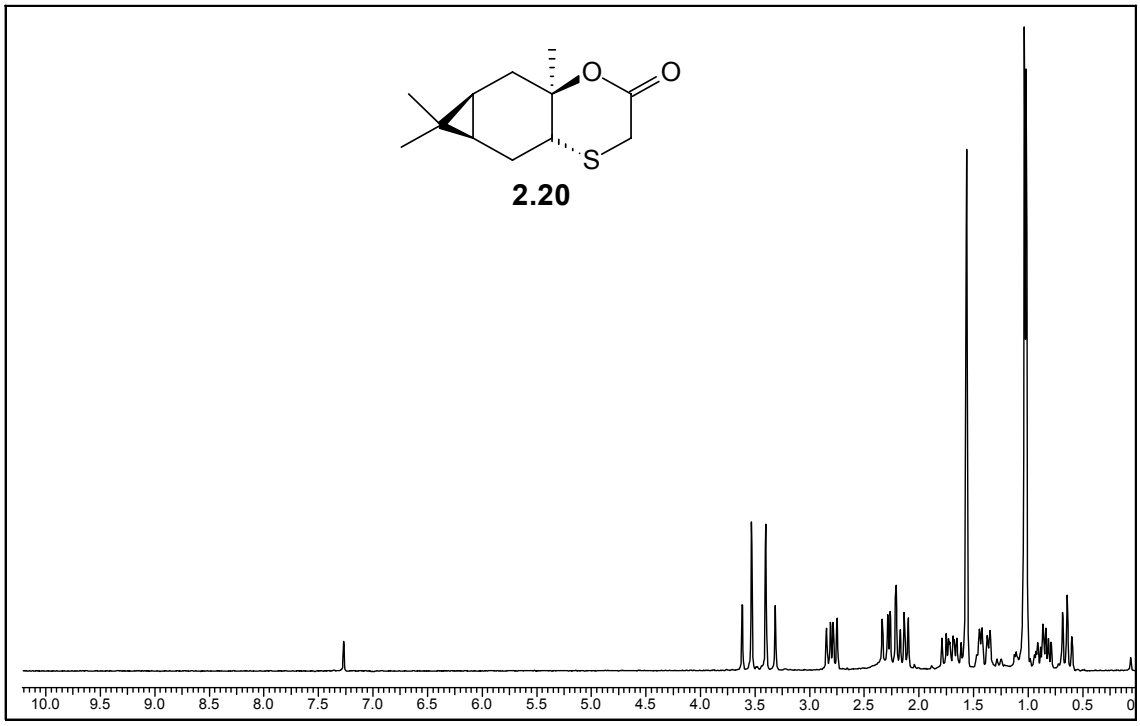

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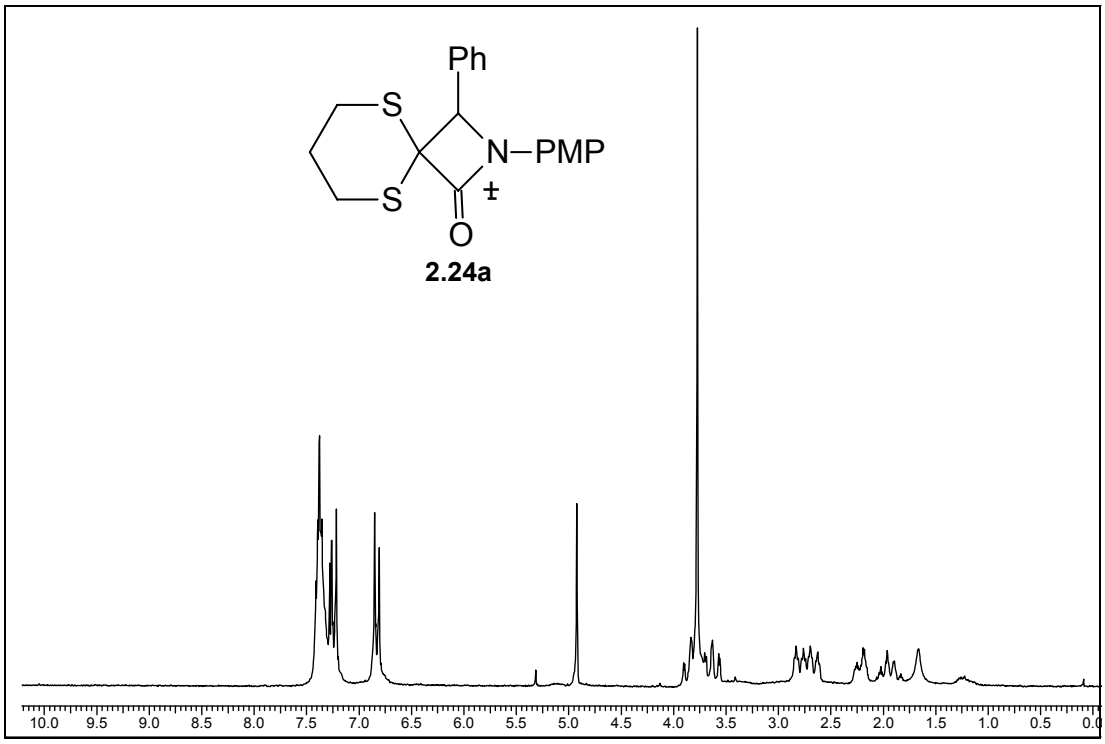
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S
O
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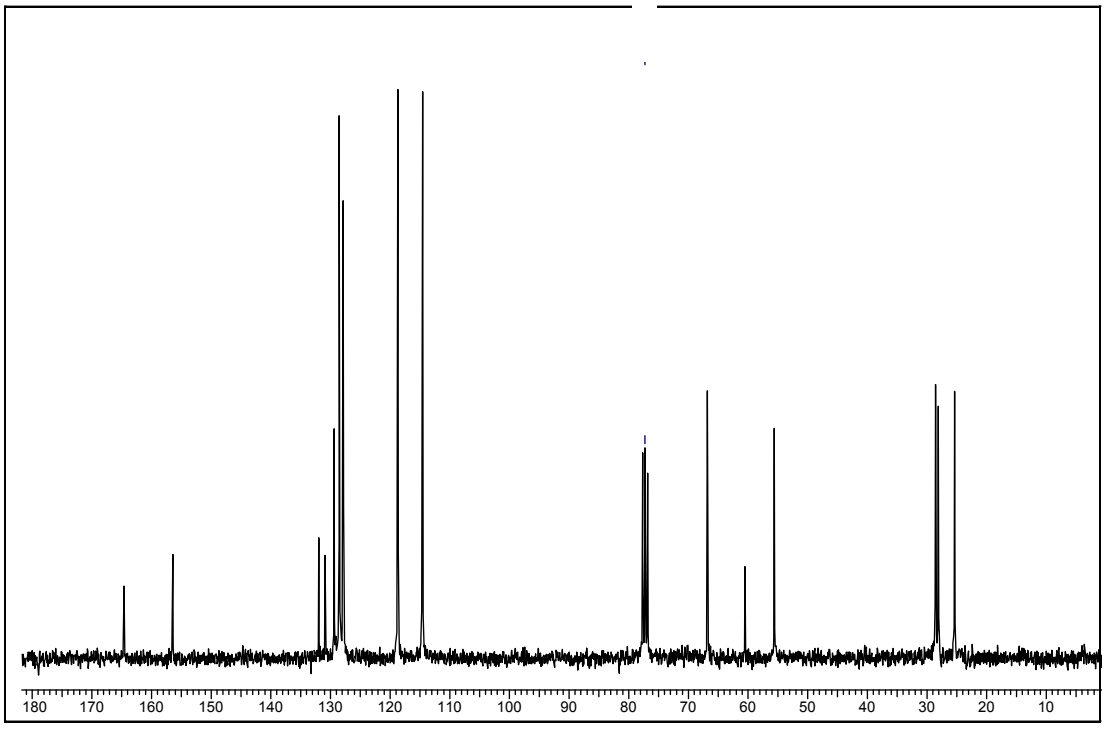
2.24a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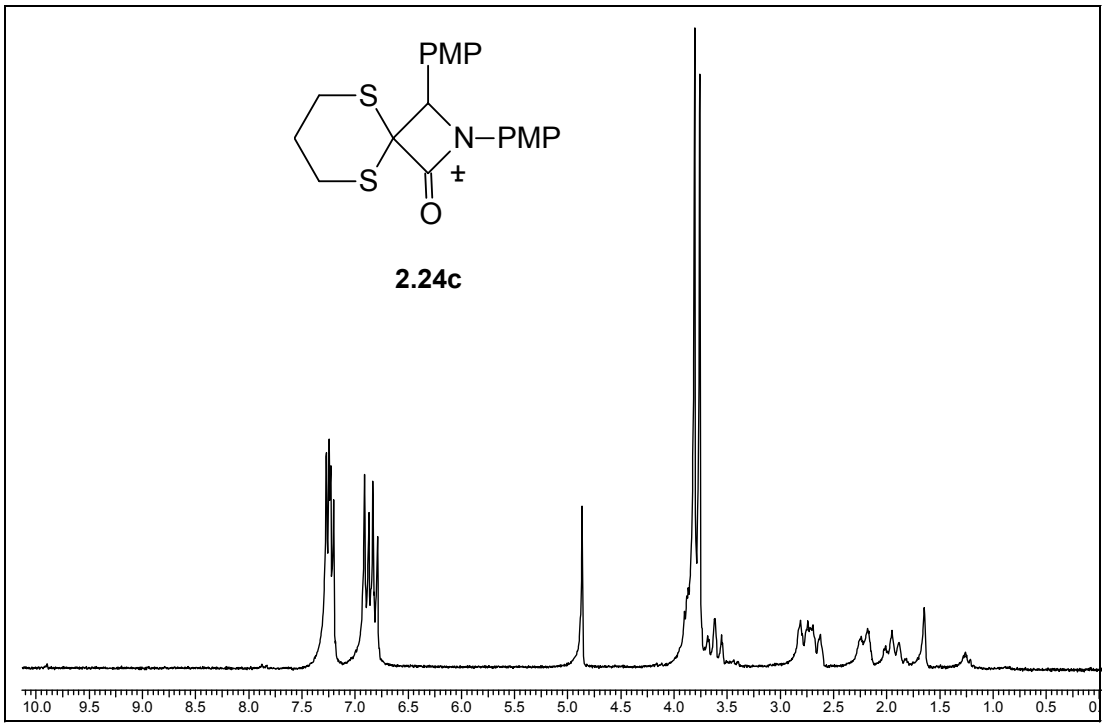
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N–PMP
S
±
O
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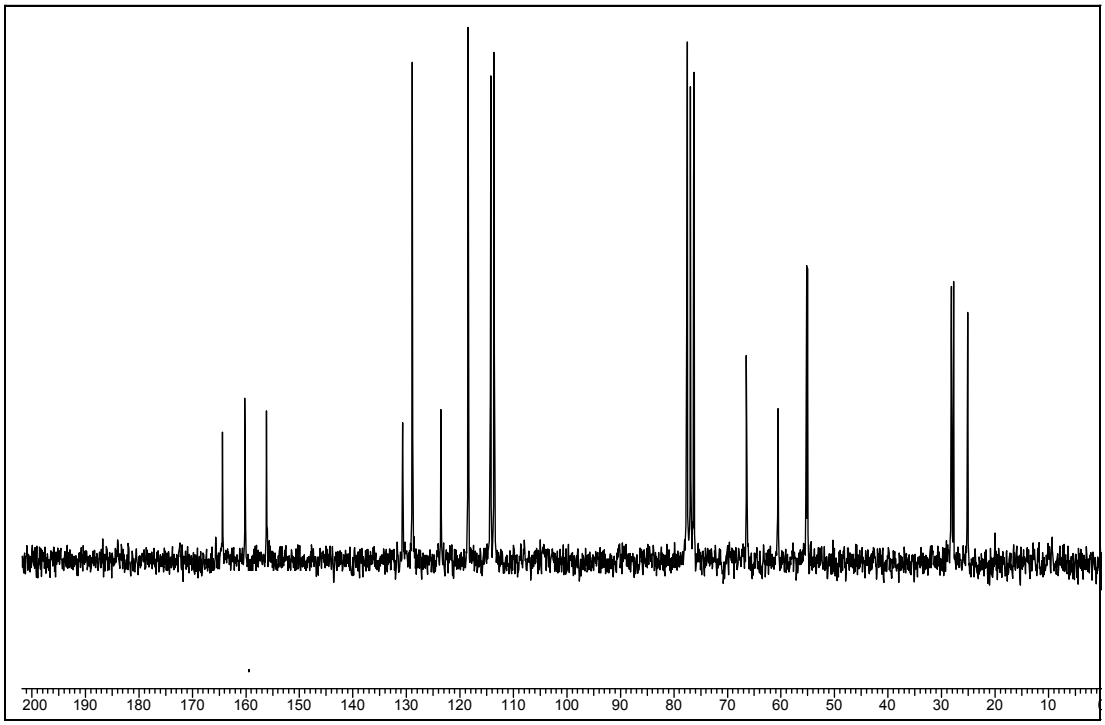
2.24c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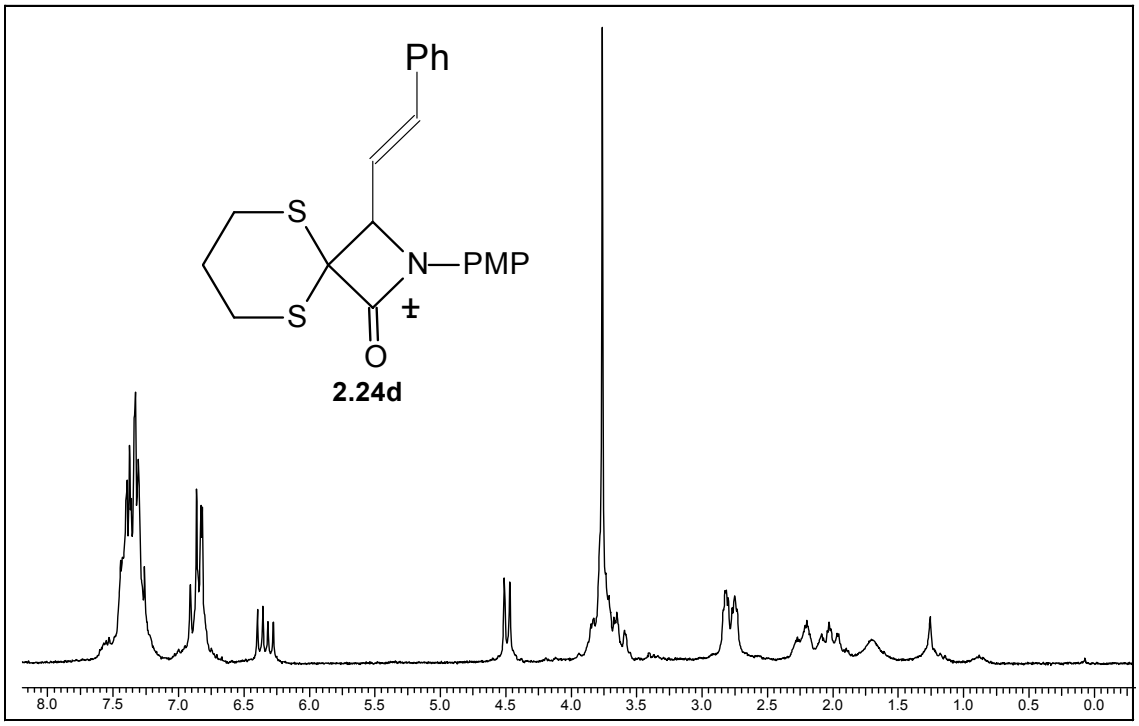
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N—PMP
S
O
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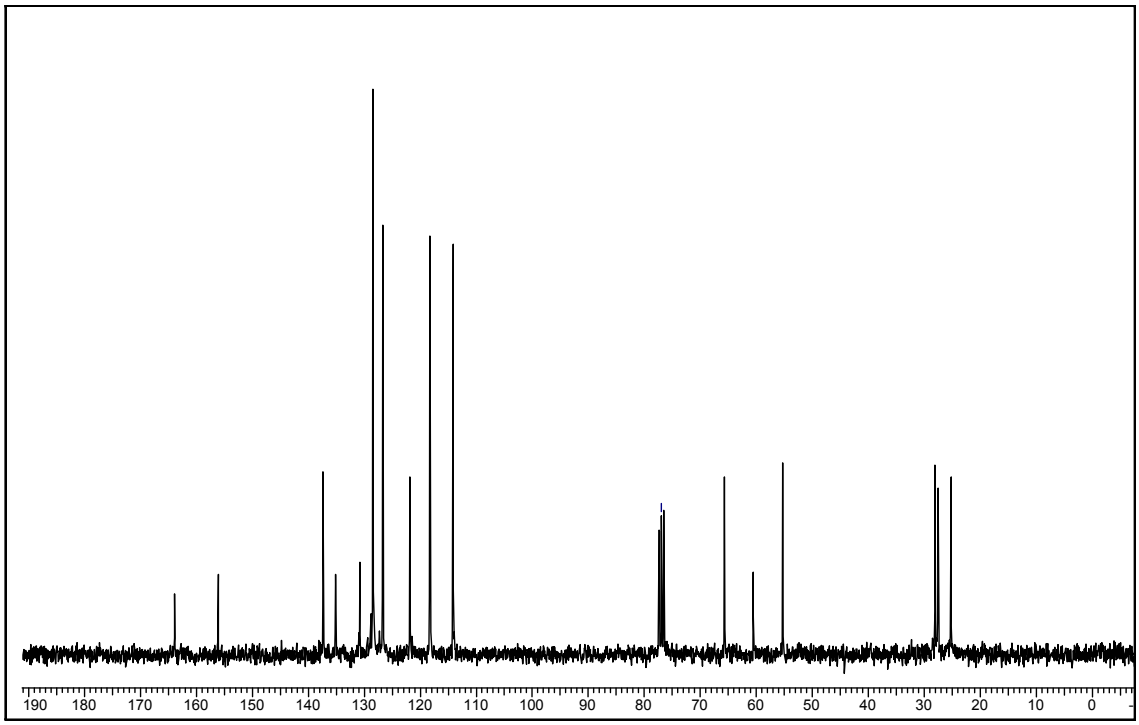
2.24d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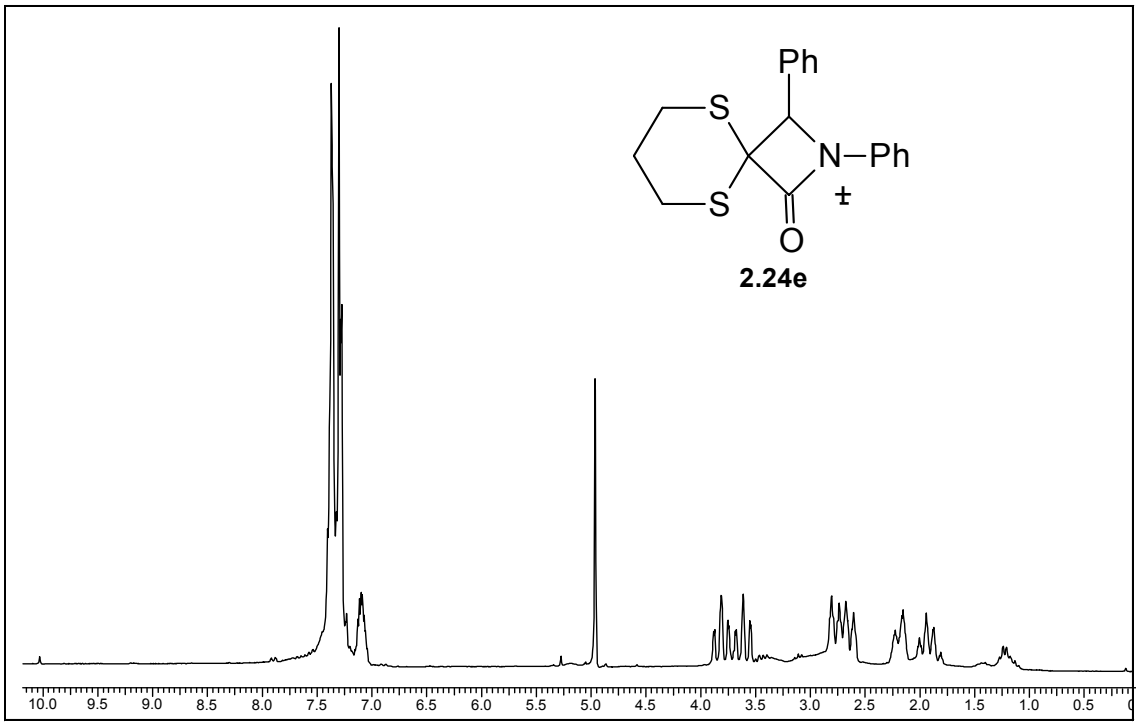
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S
N–Ph
±
S
O
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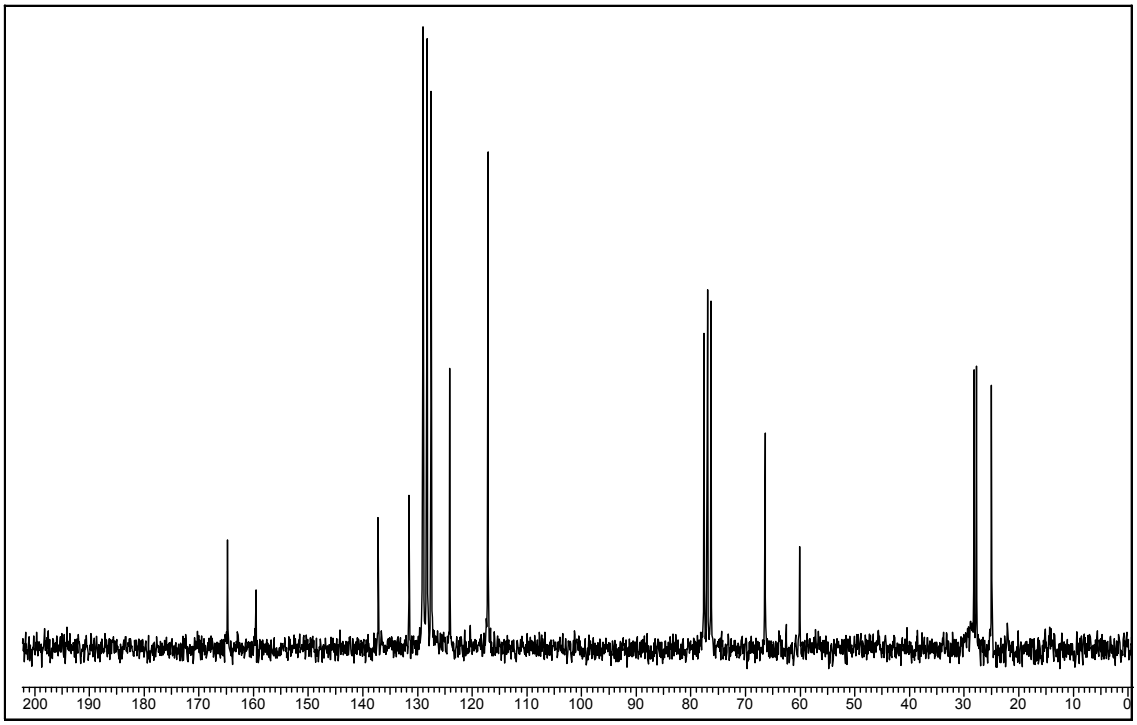
2.24e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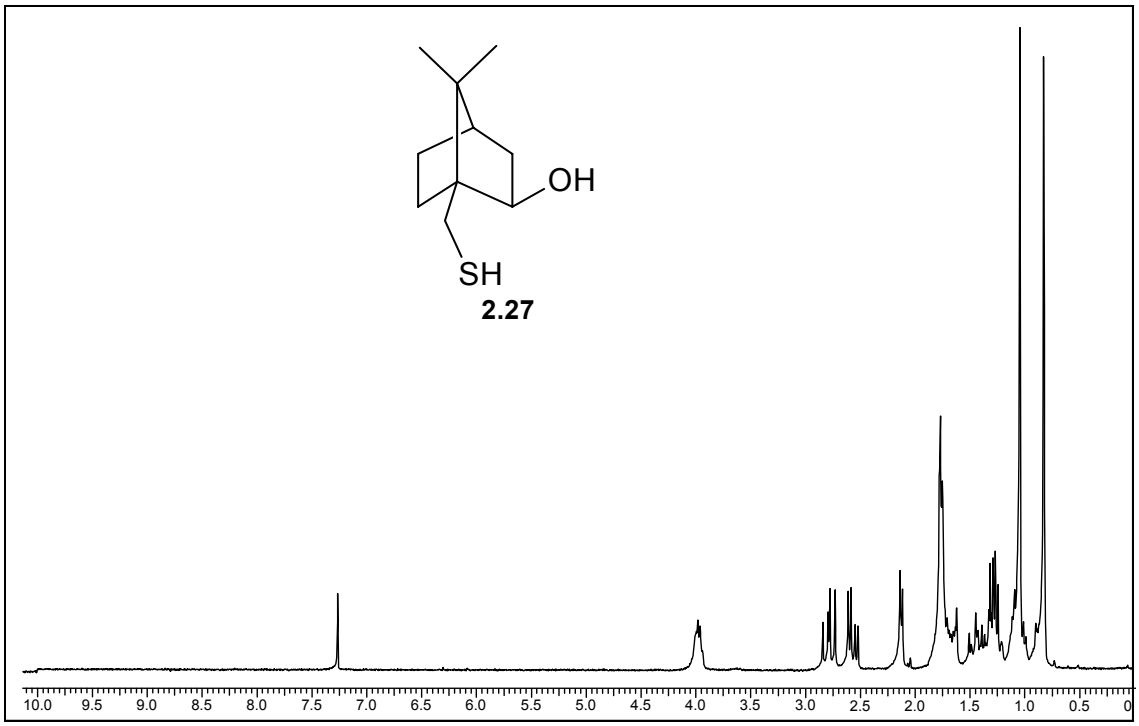
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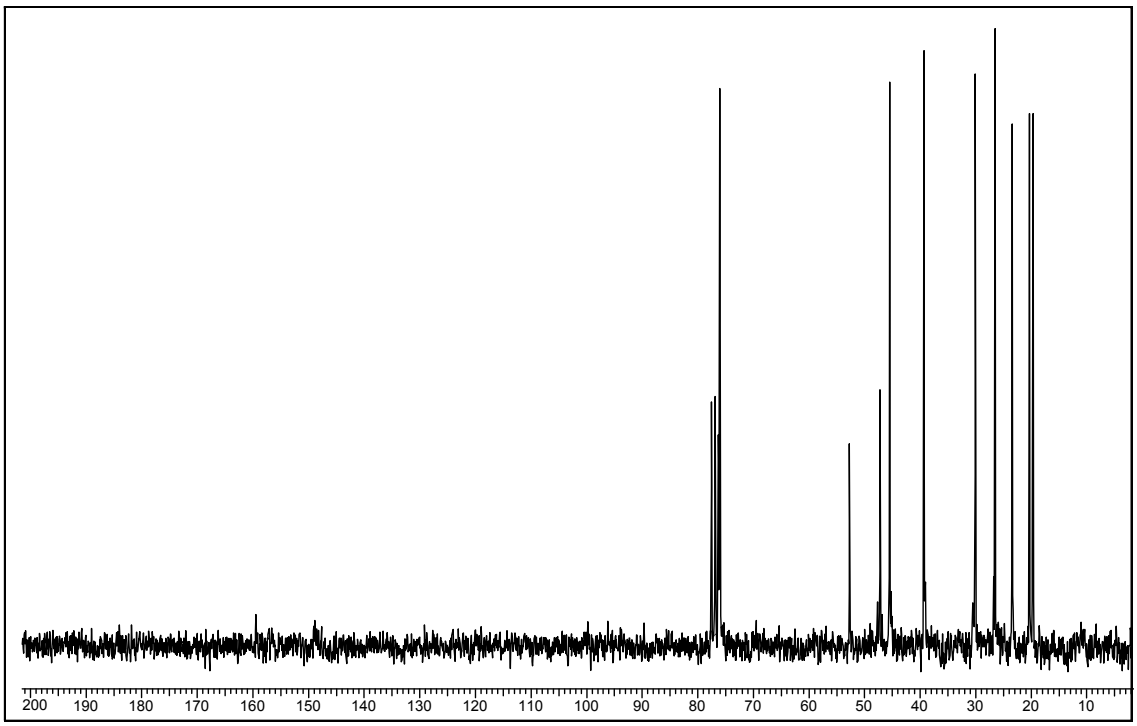
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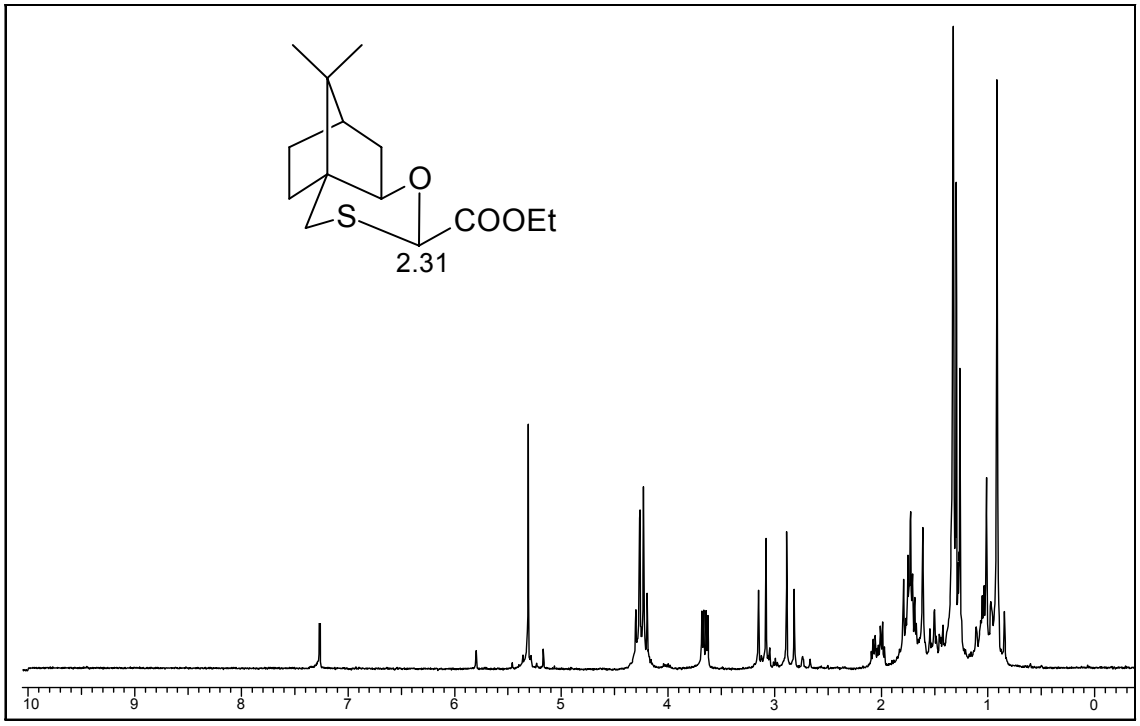
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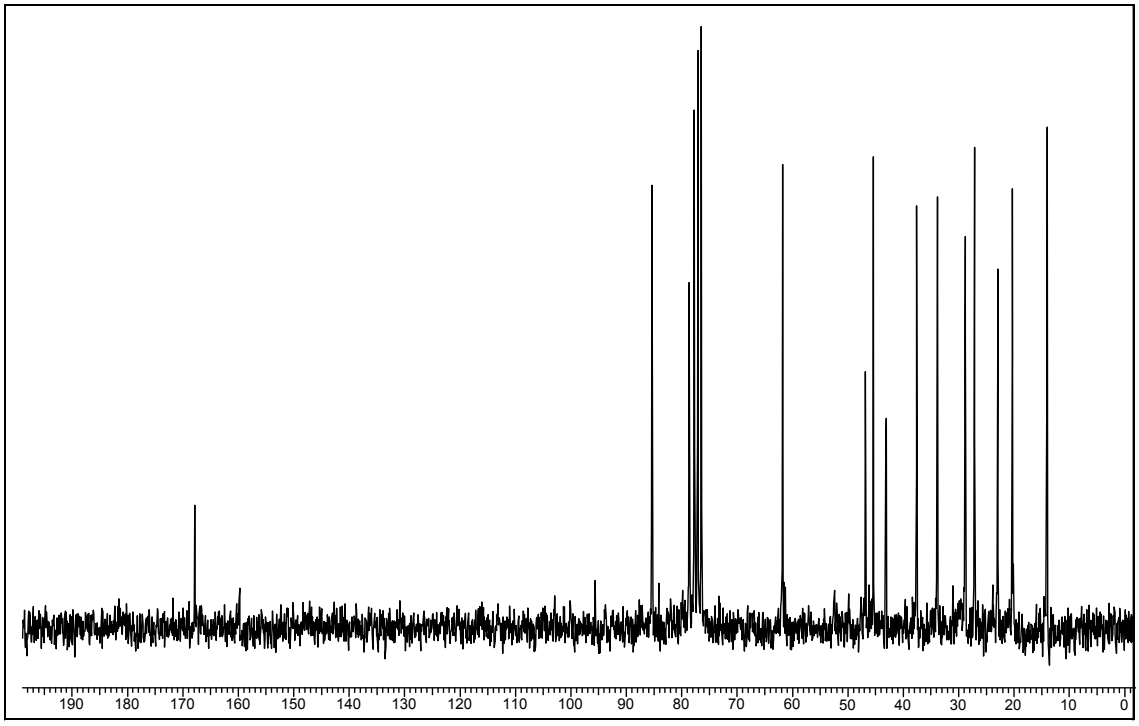
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20
10
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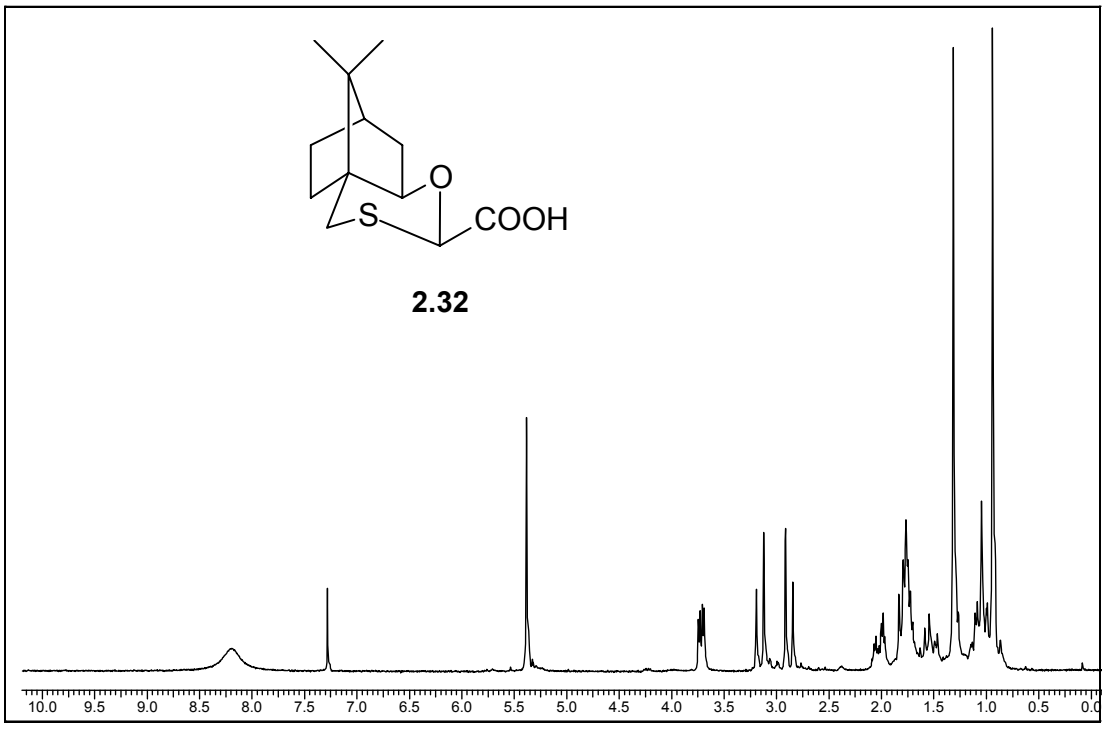

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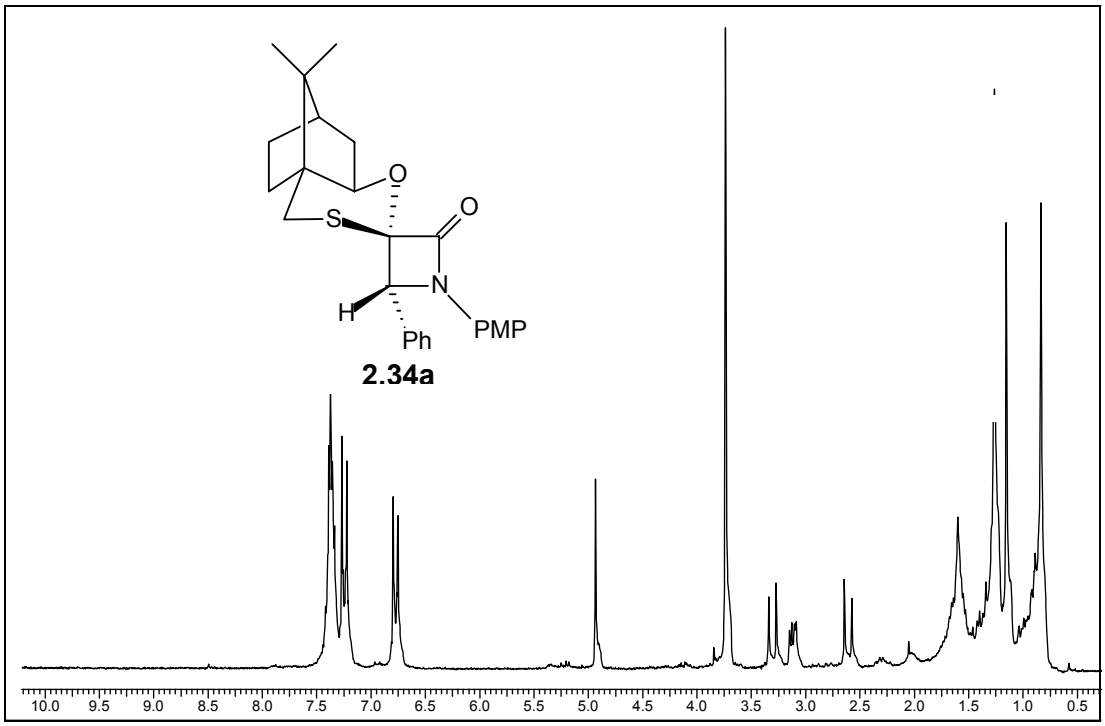
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H
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PMP
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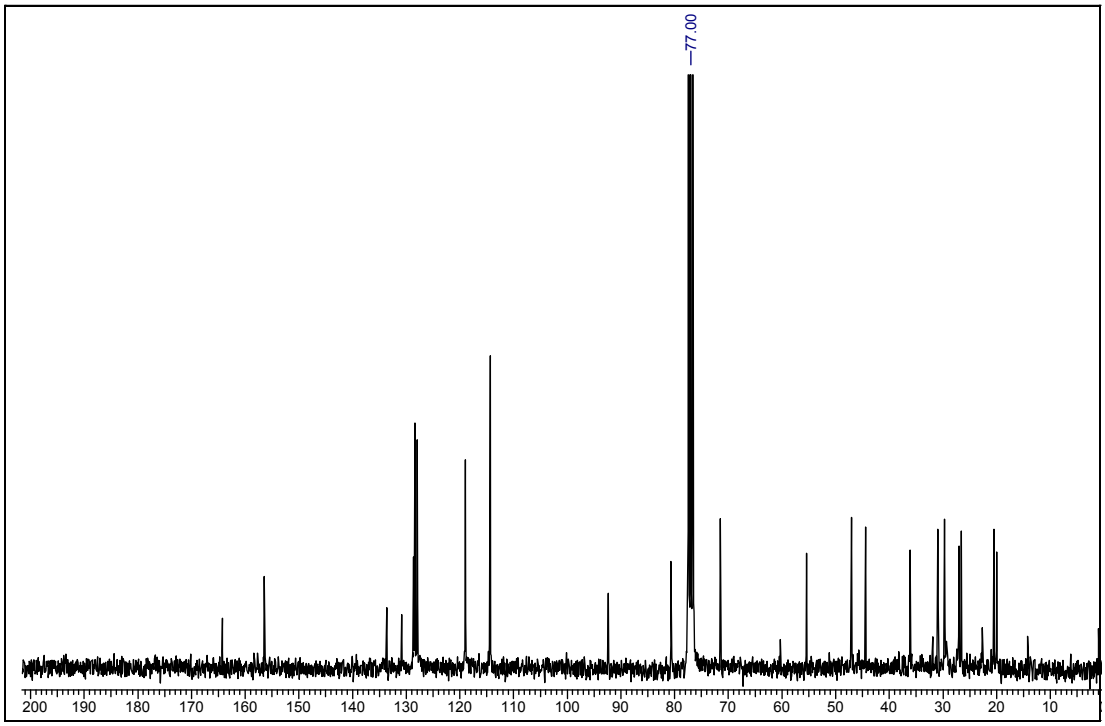
2.34a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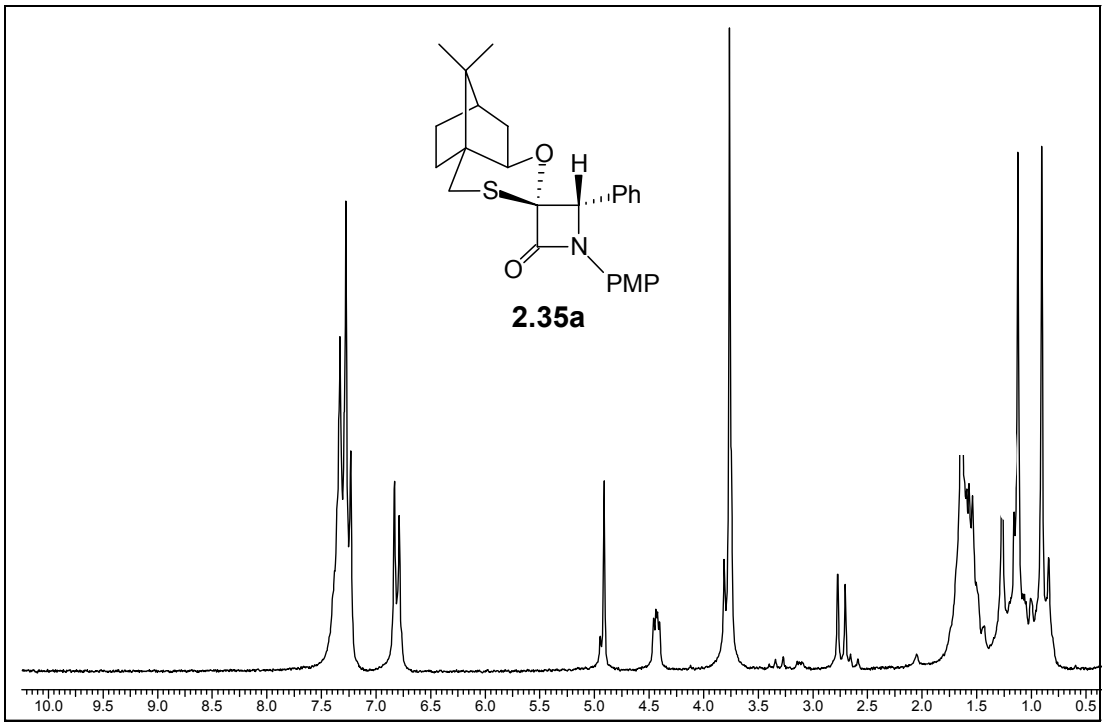
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S
Ph
N
O
PMP
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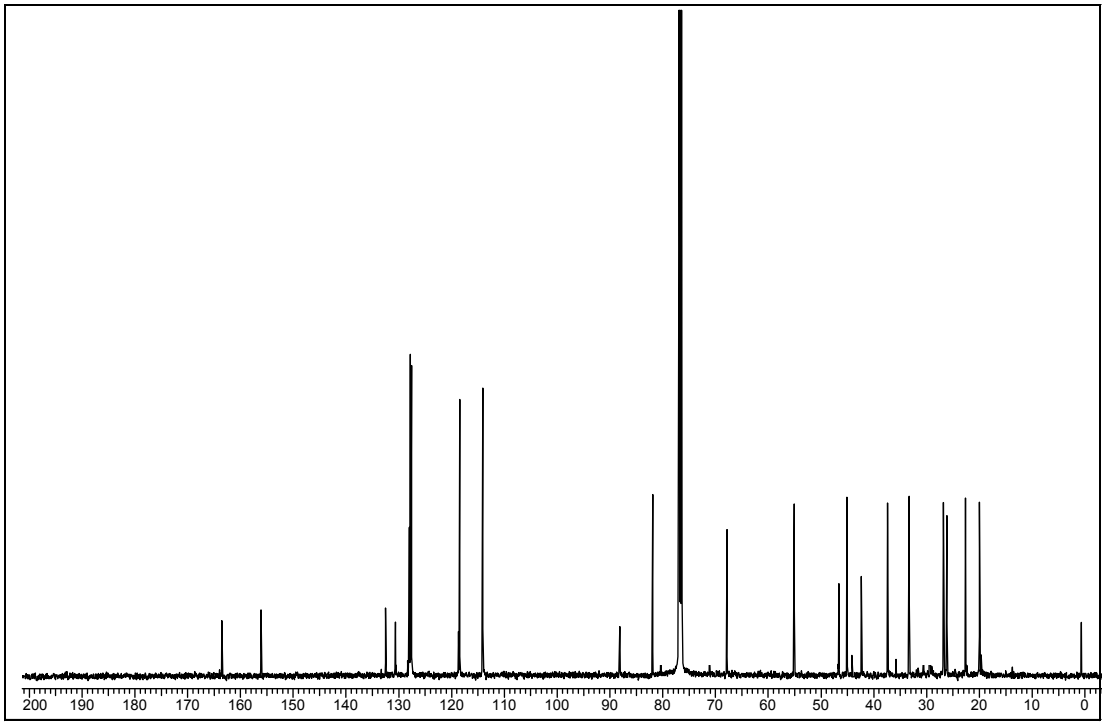
2.35a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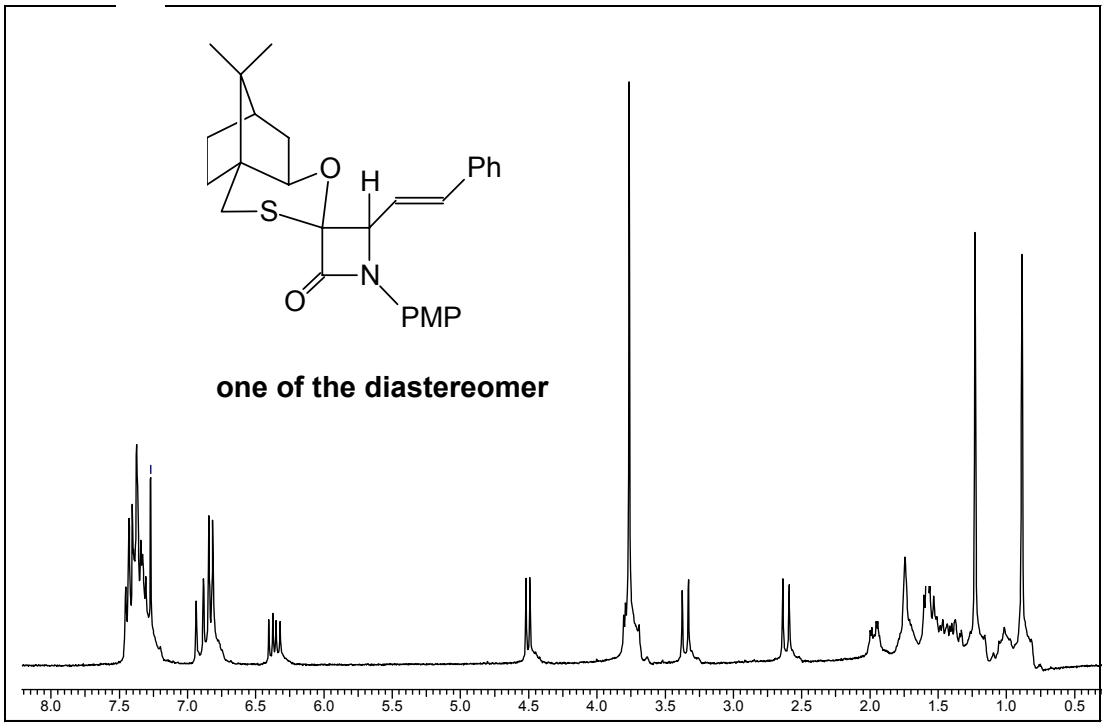
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H
Ph
S
N
O
PMP
one of the diastereomer
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7.5
7.0
6.5
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5.0
4.5
4.0
3.5
3.0
2.5
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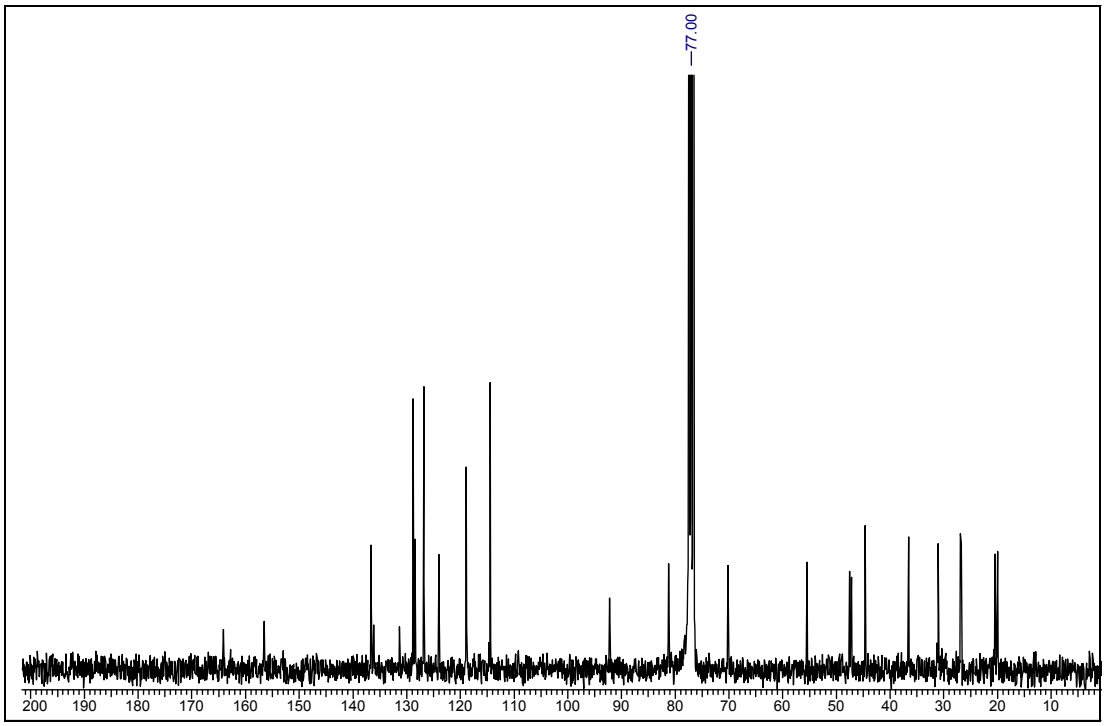
1.0
0.5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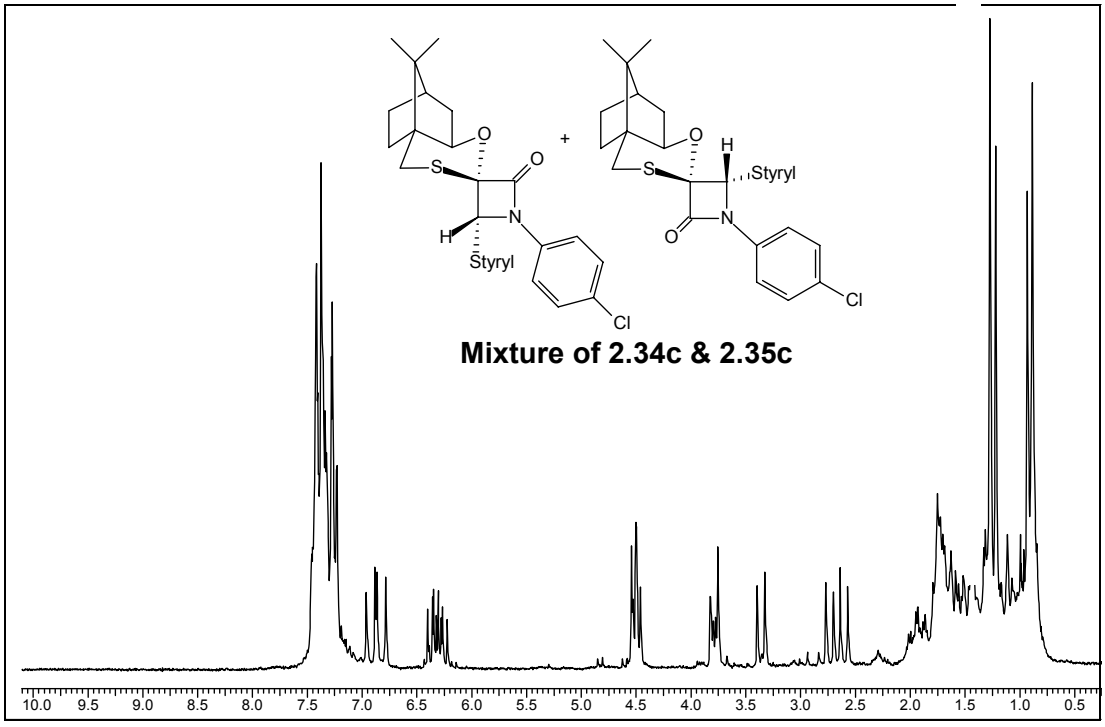


Mixture of 2.34c & 2.35c

CHAPTER 3

SECTION A

4-FORMYL AZETIDIN-2-ONE, SYNTHON FOR THE SYNTHESIS OF 4-AMINOPIPERIDIN-2-ONES

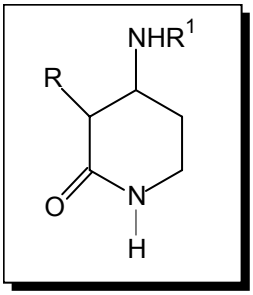
CHAPTER 3

SECTION B

STUDIES TOWARDS SYNTHESIS OF BLASTIDIC ACID

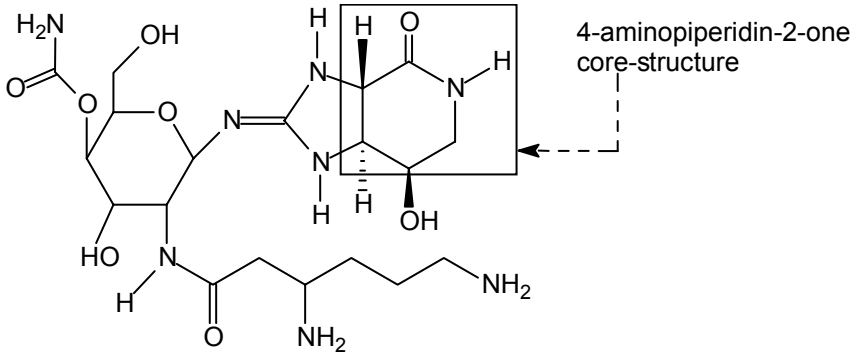
3.1: Introduction

4-Aminopiperidin-2-ones are versatile building blocks. They can serve as conformationally restrained β-amino acid equivalents in peptidomimetics. Conformationally locked peptide surrogates have been used extensively in the design and development of enzyme inhibitors or neuroreceptor ligands.[1] They can also be utilized as monomer for more rigid peptide nucleic acids (PNA), pseudopeptide mimic of natural nucleic acids.[2]

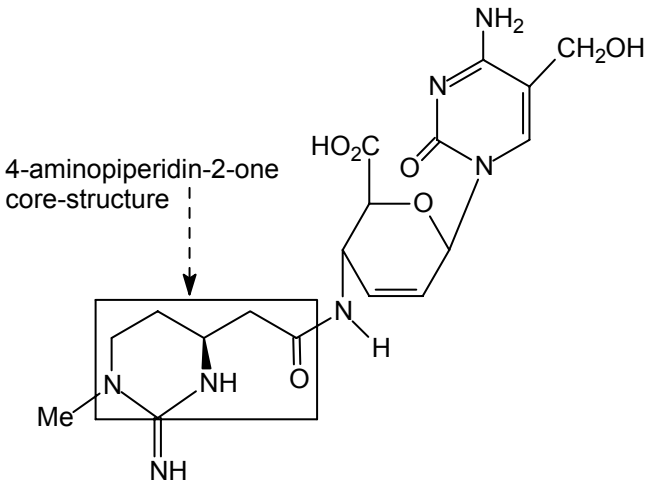


4-aminopiperidin-2-one

Apart from their potential use in peptidomimetics, 4-aminopiperidin-2-one motif also forms a part structure of important molecules like streptothricin F, a potent antibiotic,[3] 5′-hydroxymethyl cytomycin, new nucleoside antibiotic from Streptomyces sp. HKI-0052[4] and Blastidic acid (it will be discussed in Section B).

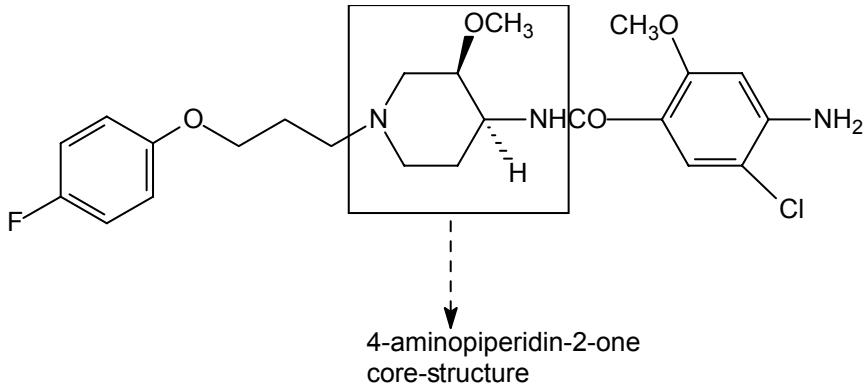


Streptothricin F



5′Hydroxymethyl cytomycin

Cisapride[5], an important drug that is used for gastro-esophagal reflux disease has a 4-aminopiperidine as a core structure, which can be obtained by reduction of 4-aminopiperidin-2-one



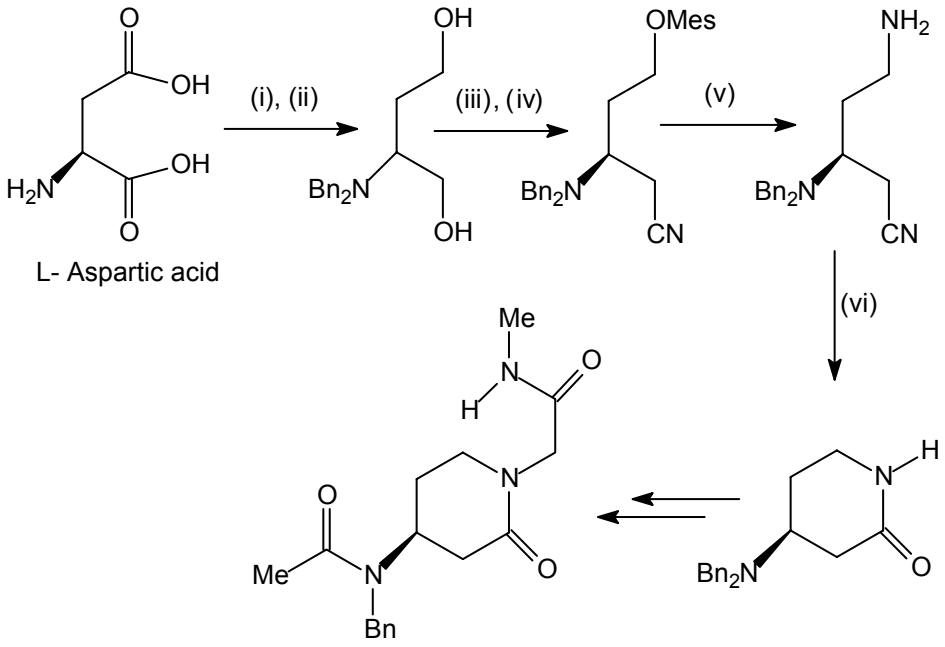
(3′*R*, 4′*S*)- Cisapride

Although, 4-aminopiperidin-2-ones are very important intermediate for number of biologically important compounds, there are very few synthetic methods available for their synthesis.

Gmeiner et al.[6] have developed a stereoselective synthesis of 4-aminopiperidin-2-one derivatives **A**, starting from L-aspartic acid and have also studied their conformational characteristics as bioactive β-turn mimetics (Scheme 3.01). Conformational analysis of the 4-aminopiperidin-2-one derivative **B** in dilute solution by IR and NMR spectroscopy at room temperature clearly indicated that it predominantly adopts a reverse turn structure stabilized by CO –NH hydrogen bond in an 11 membered

ring. Reverse turn templates assume importance because of the presence of β- or γ- turn conformations[7] in a large number of small peptides having regulatory roles in organisms.

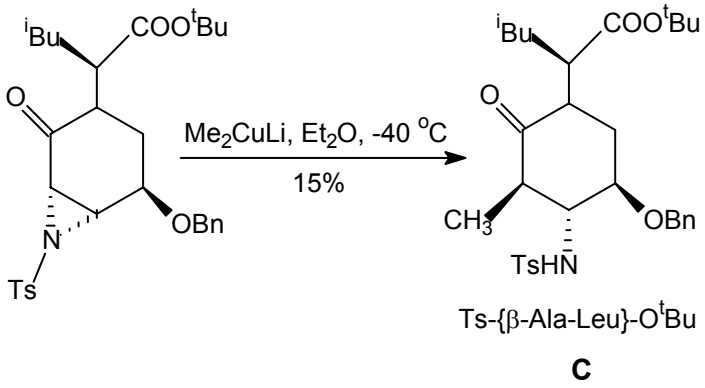
Scheme 3.01



Reagents and conditions: (i) excess $C_6H_5CH_2Br$, H_2O, K_2CO_3. (ii) LAH redn. (iii) MesCl (2.5 eq), Et_3N, -25 ^oC, 25 min. (iv) LiCN (1.2 eq), THF / DMF, rt, 3 h. (v) NH_3 / MeOH, - 30 ^oC to rt, 4 d. (vi) HCl (MeOH-H_2O, 99:1), 60 ^oC, 12 h.

Diez et al.[8] have synthesized 4-aminopiperidin-2-one **C**, a conformationally restricted β-alanine derivative, by opening of aziridine ring of 3,4 –aziridinolactams by dimethyl lithium cuprate (Scheme 3.02).

Scheme 3.02



3.2: Present work

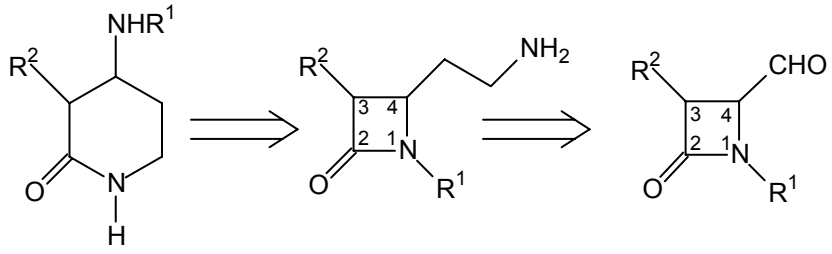
The azetidin-2-one skeleton has attracted significant interest among the synthetic and medicinal chemists over the years mainly because it is the core structure of natural and synthetic β-lactam antibiotic. However, recently the use of azetidin-2-ones as synthetic intermediate has found considerable interest. With plethora of methods available for the synthesis of azetidin-2-ones, applications of azetidin-2-ones as efficient chiral synthons for other classes of molecules has been a subject of many investigations.[9] In fact the development of a methodology based on the azetidin-2-one nucleus has reached such a level of importance as to merit its own name, "the β-lactam synthon method".[10] Of late, a significant degree of interest is focused on the synthesis and reactivity of 4-formylazetidin-2-ones, due to their potential use as building blocks in the synthesis of biologically active compounds like α and β-amino acids, polyhydroxy amino acids, polycyclic β-lactams, alkaloids and complex natural products.[11]

We were interested to utilize 4-formylazetidin-2-one as a chiral synthon for the synthesis of 4-aminopiperidin-2-one. This section describes our efforts toward synthesis of racemic as well as optically pure 4-aminopiperidin-2-ones starting from appropriate 4-formylazetidin-2-ones.

3.3 : Results and Discussion

Our strategy was to install an ethylamine side chain at C-4 position of the azetidin-2-one, followed by intramolecular nucleophilic ring opening by the amino group of C-4 side chain, to afford the required 4-aminopiperidin-2-one (Scheme 3.03).

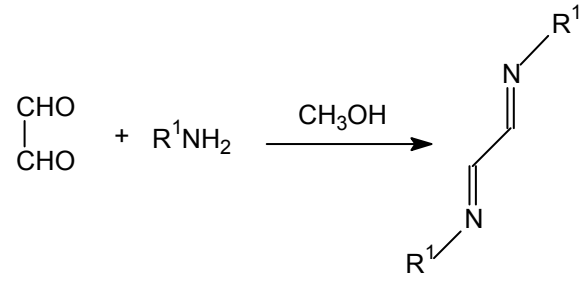
Scheme 3.03



3.3.1 : Synthesis of racemic 4-aminopiperidin-2-ones 3.11a,b

Initially we proposed to achieve the synthesis of racemic 4-aminopiperidin-2-one **3.11a** starting from racemic 4-formylazetidin-2-one **3.05a**. The 4-formylazetidin-2-one **3.05a** was prepared from diimine **3.03a** following a reported procedure.[12] The diimine **3.03a** was prepared from glyoxal **3.01** (40% aqueous solution) and *p*-anisidine **3.02a** by following a reported procedure[13] (Scheme 3.04).

Scheme 3.04

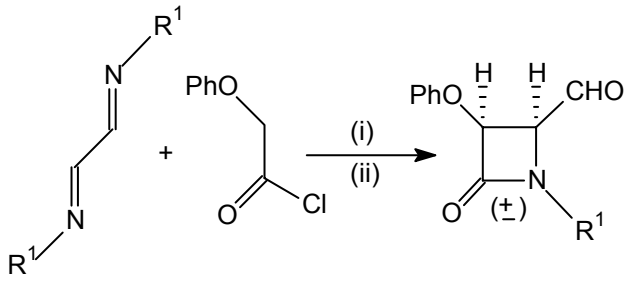


3.01 **3.02a,b** **3.03a,b**

3.03a: R^1 = *p*-OMe-C_6H_4
3.03b: R^1 = *p*-CH_3-C_6H_4

The desired *cis*-4-formyl-azetidin-2-one **3.05a** was prepared by treating the diimine **3.03a** with phenoxyacetyl chloride **3.04** in the presence of triethylamine, by following a reported procedure[12] (Scheme 3.05).

Scheme 3.05



3.03a,b **3.04** **3.05a,b**

3.05a, R^1 = PMP
3.05b, R^1 = *p*-$CH_3C_6H_4$

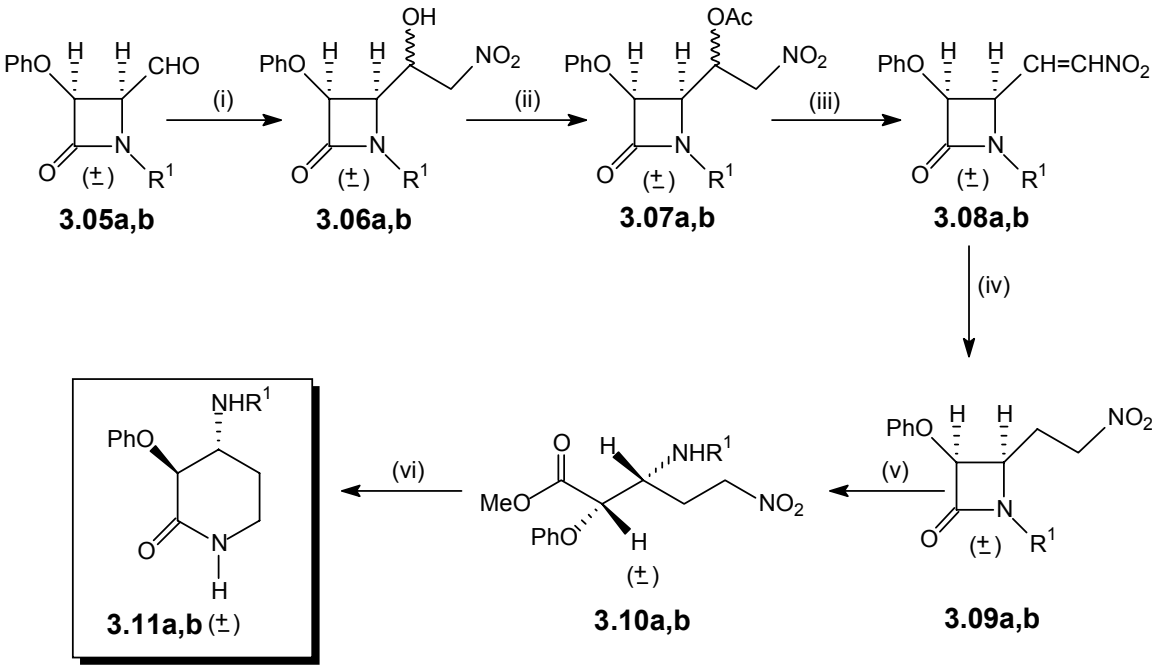
Reagents and conditions: (i) Toluene, rt, 1h. (ii) 5% HCl, rt, 2 h.

The IR spectrum of **3.05a** showed peaks at 1747 cm^{-1} and 1726 cm^{-1} corresponding to the β-lactam and aldehyde carbonyl respectively.

The ^{1}H NMR spectrum showed a singlet at 3.75 ppm corresponding to -OMe protons of PMP group. The C-3 and C-4 β-lactam protons appeared as a doublet at 5.05 ppm (J = 5.3 Hz) and as a doublet of doublet at 4.75 ppm with J = 5.3 Hz, 3.4 Hz respectively. The J value of 5.3 Hz indicated the *cis* stereochemistry of the C-3 and C-4 β-lactam protons. The aromatic protons of the PMP group appeared as doublets at 6.80 ppm and 7.10 ppm with J = 8.8 Hz. The remaining aromatic protons appeared as multiplets between 7.20 to 7.45 ppm. The aldehydic proton appeared as doublet at 9.80 ppm (J = 3.4 Hz).

Transformation of the racemic *cis*-4-formylazetidin-2-one **3.05a** to the requisite 4-aminopiperidin-2-one **3.11a** was carried out by the synthetic sequence described in Scheme 3.06.

Scheme 3.06



3.11a R^1 = PMP
3.11b R^1 = *p*-$CH_3C_6H_4$

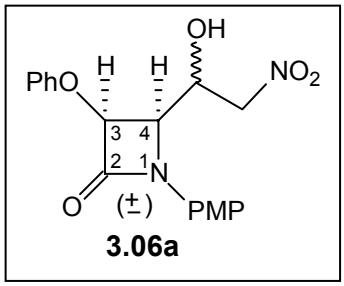
Reagents and conditions: (i) CH_3NO_2, Et_3N, rt, 4 h. (ii) Ac_2O, Conc. H_2SO4, 0 ^oC, 1 h (iii) $NaHCO_3$, benzene, reflux, 5 h. (iv) Bu_3SnH, DCM: MeOH (10:1), rt, 24 h (v) methanolic HCl (20%), rt, 24 h (vi) 10% Pd/C, $HCOONH_4$, MeOH, rt, 3-20 h.

The 4-formylazetidin-2-one **3.05a** was reacted with nitro methane in the presence of catalytic amount of triethylamine at room temperature for 4 h. After completion of the reaction (TLC), the excess nitromethane was removed under reduced

pressure to furnish a diastereomeric mixture (80:20) of nitro alcohol **3.06a**. The structure of major isomer was confirmed by spectral and analytical data.

The IR spectra of **3.06a** showed band at 3500-3100 cm^{-1} corresponding to the -OH, a band at 1755 cm^{-1} corresponding to the β-lactam carbonyl and peaks at 1560 cm^{1}, 1380 cm^{-1} corresponding to nitro group.

The ^{1}H NMR spectrum of **3.06a** showed a singlet at 3.80 ppm corresponding to the –OMe protons. The C-4 proton and the methylene protons of the C-4 side chain appeared as multiplets between 4.50 ppm to 4.65 ppm. The methine proton of the C-4 side chain appeared as multiplets between 4.85 ppm to 5.05 ppm. The C-3 proton of the β-lactam ring appeared as doublet at 5.45 ppm (J = 5.4 Hz). The –OH proton appeared as a broad singlet at 2.00 ppm. Two aromatic protons of PMP group appeared as a doublet at 6.90 ppm (J = 8.7 Hz). The remaining aromatic protons appeared as multiplets between 7.00 ppm to 7.60 ppm.

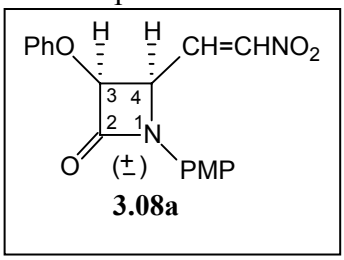


3.06a

The ^{13}C NMR showed a peak at 163.13 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbons appeared at 157.11 ppm and 156.85 ppm. The remaining aromatic carbons appeared at 129.68, 123.07, 120.09, 115.86 and 114.36 ppm respectively. The C-3 and C-4 carbons of the β-lactam appeared at 79.51 ppm and 68.67 ppm. The –OMe carbon appeared at 55.29 ppm. The methylene and methine carbon of the C-4 side chain appeared at 77.53 ppm and 58.41 ppm respectively.

The dehydration of the diastereomeric mixture of nitro alcohol **3.06a** under acidic ($CuSO_4$, SiO_2) as well as basic (DBU) condition did not give the expected nitro olefin **3.08a**. Therefore, the hydroxy group of **3.06a** was acetylated with acetic anhydride in the presence of catalytic Conc. sulphuric acid at 0 ºC to get the diastereomeric nitro acetate **3.07a** and the corresponding acetate was refluxed in benzene in the presence of sodium bicarbonate to get nitro alkene **3.08a**. (Scheme 3.06)

The IR spectrum of nitro alkene **3.08a**, showed a sharp peak at 1758 cm^{-1} corresponding to the β-lactam carbonyl. The peaks at 1531 and 1357 cm^{-1} corresponded to the nitro group.

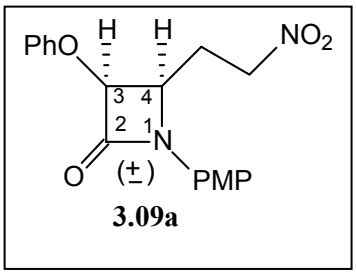


3.08a

The ^{1}H NMR spectrum of **3.08a** showed a singlet at 3.80 ppm corresponding to the –OMe protons of the PMP group. The C-4 β-lactam proton appeared as a multiplet between 5.00 to 5.10 and the C-3 β-lactam proton appeared as doublet at 5.55 ppm (J = 4.9 Hz). Two aromatic protons of the *p*-anisyl group, appeared as a doublet at 6.9 ppm (J = 9.3 Hz). The remaining aromatic as well as the olefinic protons appeared as multiplets between 6.95 ppm to 7.40 ppm.

The ^{13}C NMR spectrum of **3.08a** showed a peak at 161.04 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbons appeared at 159.50, 157.00 and 156.59 ppm, while the remaining aromatic carbons appeared at 129.65, 122.88, 118.36, 115.39 and 114.61 ppm. The olefinic carbons appeared at 142.88 and 134.61 ppm. The C-3 β-lactam carbon appeared at 81.57 ppm and the signal due to C-4 carbon merged with the peak corresponding to –OMe carbon of the PMP group at 55.32 ppm. The compound **3.08a** also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 340.

The double bond of the nitro alkene **3.08a** was reduced using tributyltin hydride[14]. In a typical procedure, to a solution of nitroalkene **3.08a** in anhydrous CH_2Cl_2: MeOH (10:1)**,** tributyltin hydride was added at room temperature and stirred for 24 h. After completion of reaction, the solvent was removed to get crude product, which was subsequently purified by column chromatography to afford pure nitroalkane **3.09a** as a white solid (Scheme 3.06). The structure of **3.09a** was confirmed by spectral and analytical techniques



3.09a

The IR spectrum of **3.09a** showed a sharp peak at 1753 cm^{-1} corresponding to the β-lactam carbonyl and peaks at 1551 and 1396 cm^{-1} characteristic of the nitro group.

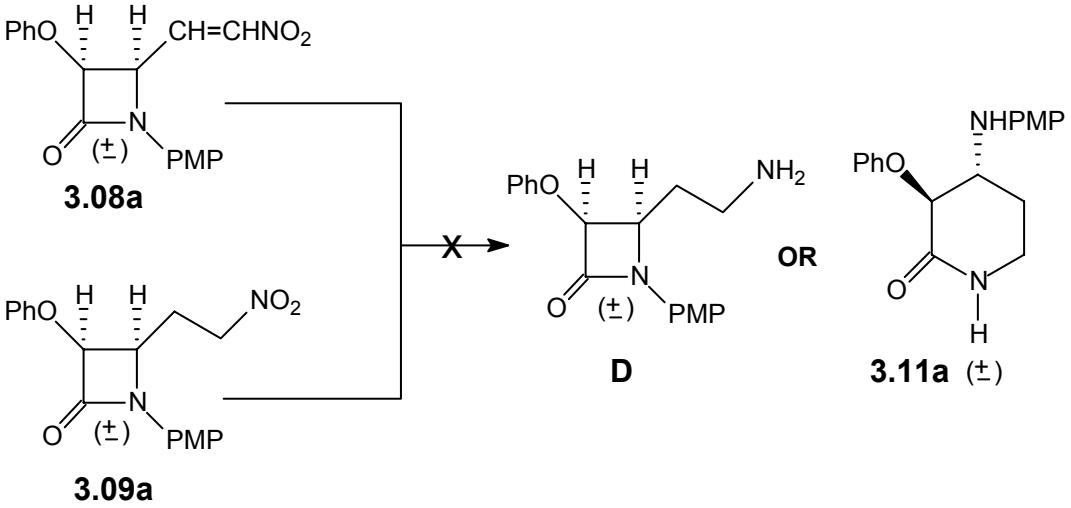
The ^{1}H NMR spectrum of **3.09a** showed multiplets between 2.50 ppm and 3.00 ppm corresponding to the protons of the $–CH_2$ group attached to the C-4 carbon. The

methoxy protons of the PMP group appeared as singlet at 3.80 ppm. The C-4 proton and the protons of the methylene group bearing the nitro group appeared as multiplets between 4.50 ppm to 4.65 ppm. The C-3 proton appeared as doublet at 5.45 ppm (J = 4.9 Hz). The aromatic protons of the PMP group appeared as doublets at 6.90 ppm and 7.15 ppm (J = 8.8 Hz). The remaining aromatic protons appeared as multiplets between 7.25 ppm to 7.50 ppm. The ^{1}H NMR data matched with that of the reported value.[14]

The ^{13}C NMR spectrum of **3.09a** showed a peak at 162.07 ppm corresponding to the β-lactam carbonyl. The aromatic quaternary carbons appeared at 159.50, 157.00, 156.78 ppm while the remaining aromatic carbons appeared in the region between 129.57 ppm and 114.61 ppm. The methylene carbons of the C-4 side nitroethyl side chain appeared at 24.96 ppm and 71.35 ppm. The C-3 and C-4 carbons of the β-lactam ring appeared at 55.29 ppm and 79.69 ppm respectively. The –OMe carbon appeared at 54.26 ppm. The nitroalkane **3.09a** also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 342.

The reduction of nitroalkane **3.09a** or the nitroalkene **3.08a** with catalytic hydrogenation using Pd/C and Raney Ni catalysts gave complex mixture instead of either amino β-lactam **D** or 4-aminopiperidin-2-one **3.11a** (a product by intramolecular nucleophilic ring opening by the amino group of the C-4 side chain of amino β-lactam **3.12a**) (Scheme 3.07).

Scheme 3.07



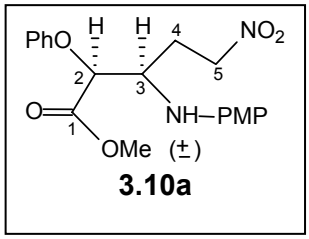
Hence, we decided to cleave the N-C2 bond of the β-lactam ring of the nitro alkane **3.09a**, followed by reductive cyclization of the C-4 nitro ethyl side chain of the

β-lactam. The β-lactam ring of the nitro alkane **3.09** was cleaved by stirring with methanolic HCl (20%) at room temperature for 24 h to get the nitro ester **3.10a** (Scheme 3.06). The structure of nitro ester **3.10a** was confirmed from spectral and analytical techniques.

The IR spectrum of **3.10a** showed peaks at 1755 cm^{-1}, 3380 cm^{-1}, 1552 cm^{-1} and 1380 cm^{-1} corresponding to the carbonyl, amino and nitro group respectively.

The ^{1}H NMR of **3.10a** showed multiplets between 2.25 ppm to 2.55 ppm for the C-4 methylene protons. The –OMe protons of the *p*-anisyl and the methyl ester group appeared as singlets at 3.75 ppm and 3.50 ppm respectively. The C-3 methine proton appeared as multiplets between 4.10 to 4.25 ppm. The C-5 methylene protons and the NH proton appeared as multiplets between 4.50 to 4.70 ppm. The C-2 methine proton appeared as doublet at 4.75 ppm (J = 2.50 Hz). The aromatic protons of the *p*-anisyl group appeared as doublets at 6.65 ppm and 6.80 ppm (J = 8.8 Hz). The remaining aromatic protons appeared as multiplets between 7.00 to 7.40 ppm.

The ^{13}C NMR spectrum showed a peak at 169.78 ppm corresponding to the carbonyl carbon. The aromatic quaternary carbons appeared at 157.43, 153.24 ppm and 140.37 ppm, while the remaining aromatic carbons appeared at 129.64, 122.29, 116.04, 115.26 and 115.04 ppm. The C-2 and C-3 methine carbons appeared at 77.62 ppm and 55.68 ppm respectively. The C-4 and C-5 methylene carbons appeared at 30.17 ppm and 72.44 ppm. The –OMe carbon of the ester and the PMP group appeared at 52.08 ppm and 54.80 ppm respectively. The ester **3.10a** also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 374.



3.10a

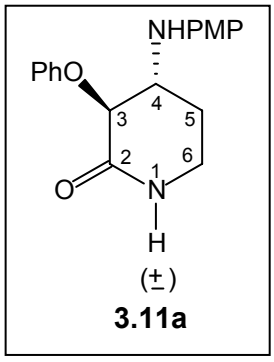
In the next step, the reduction of nitro group of the ester **3.10a** was successfully achieved by transfer hydrogenation[15] using ammonium formate and Pd/C (10%) in methanol as a solvent, at room temperature. The lactamization also occurred directly during the transfer hydrogenation of nitro ester to get *N*-substituted-4-aminopiperidin-2-one **3.11a** (Scheme 3.06). In a typical procedure for reductive cyclization, to a solution of ester **3.10a** in anhydrous methanol, Pd/C (10%) and ammonium formate were added and the reaction mixture was stirred at room temperature under argon. After completion of reaction (TLC), the catalyst was filtered through celite bed. The solvent was removed

under reduced pressure and the residue was dissolved in dichloromethane, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product, which was purified by column chromatography to afford pure 4-aminopiperidin-2-one **3.11a**. The structure of **3.11a** was confirmed by spectral and analytical techniques.

The IR spectrum of **3.11a** showed a peak at 1666 cm^{-1} and 3400-3200cm^{-1} corresponding to the carbonyl and -NH group.

The ^1H NMR spectra of **3.11a** showed multiplets in region 1.80-2.10 ppm and in the region 2.40-2.60 ppm corresponding to the C-5 methylene protons. The –OMe protons of the PMP group appeared as singlet at 3.75 ppm. The C-4 methine proton, C-6 methylene protons and the –NH proton of the amine appeared as multiplets between 3.50 to 3.90 ppm. The C-3 methine proton appeared as doublet at 4.75 ppm (J = 5.8 Hz). The aromatic protons along with the amide proton, appeared as multiplets between 6.60 ppm to 7.40 ppm.

The ^{13}C NMR spectrum of **3.11a** showed a peak at 162.69 ppm corresponding to the amide carbonyl carbon. The C-5 and C-6 methylene carbons appeared at 23.90 ppm and 46.32 ppm respectively. The aromatic quaternary carbons appeared at 158.17, 152.95 and 139.68 ppm. The remaining aromatic carbons appeared at 129. 32, 122.12, 116.34, 115.97 and 114.72 ppm. The C-3 and C-4 methine carbons appeared at 77.53 ppm and 52.13 ppm. The –OMe carbon appeared at 55.51 ppm. The 4-aminopiperidin-2- one **3.11a** gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 312.



3.11a

Similarly, the racemic 4-aminopiperidin-2-one **3.11b** was also synthesized following the same synthetic sequence as shown Scheme 3.06. The starting 4-formylazetidin-2-one **3.05b** was prepared by the reaction of bisimine **3.03b** with phenoxyacetyl chloride **3.04** (Scheme 3.05). Thus we could successfully achieve the synthesis of racemic 4-aminopiperidin-2-ones **3.11a,b** in good overall yield (35%) starting from 4-formylazetidin-2-ones **3.05a,b** (Scheme 3.06, Table 1).

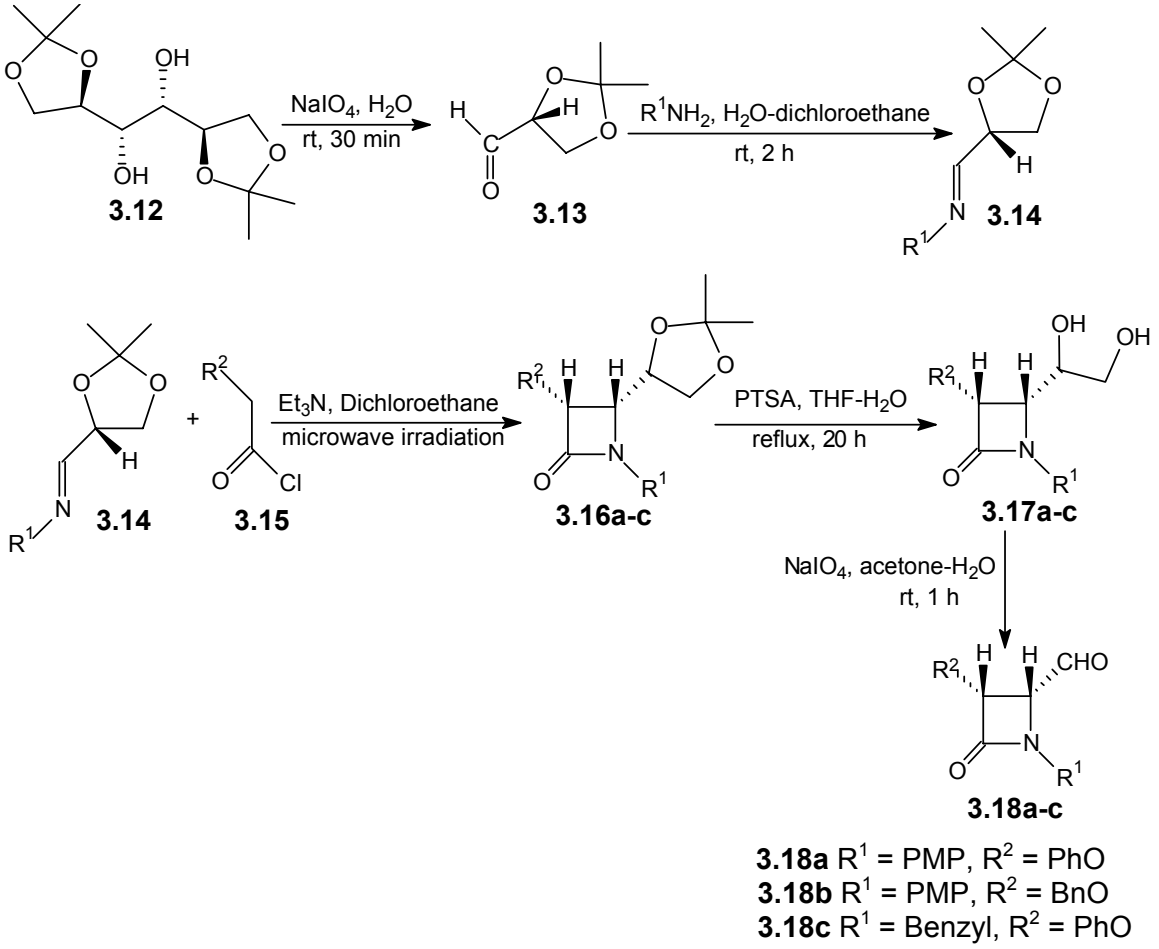
Table 1: *Synthesis of nitro alkenes* (**3.08a,b**), *nitro alkanes* (**3.09a,b**), *nitro esters* (**3.10a,b**) *and 4-aminopiperidin-2-ones* (**3.11a,b**).

Compound No	R^1	M. P. (^oC)	Yield (%)
3.08a	PMP	120-121	71
3.08b	*p*-CH_3-C_6H_4	110-111	70
3.09a	PMP	115-116	80
3.09b	*p*-CH_3-C_6H_4	Thick oil	75
3.10a	PMP	Thick oil	90
3.10b	*p*-CH_3-C_6H_4	Thick oil	88
3.11a	PMP	Thick oil	70
3.11b	*p*-CH_3-C_6H_4	Thick oil	78

3.3.2 : Synthesis of optically pure 4-aminopiperidin-2-ones

Having optimized the reaction conditions for the synthesis of racemic 4-aminopiperidin-2-ones **3.11a,b** (Scheme 3.06), we were interested in the asymmetric synthesis of enantiopure 4-aminopiperidin-2-ones, starting from optically pure 4-formylazetidin-2-ones **3.18a-c**. The enantiopure β-lactams **3.16a-c** were obtained by the reaction of schiff base **3.14** (derived from D-glyceraldehyde acetonide **3.13**) with acid chloride **3.15** following a reported procedure.[16] The acetonide group of the β-lactams **3.16a-c** was cleaved by PTSA[17] to get the diols **3.17a-c**, which were oxidized by $NaIO_4$ to get the required enantiopure 4-formylazetidin-2-ones **3.18a-c**[18] (Scheme 3.08).

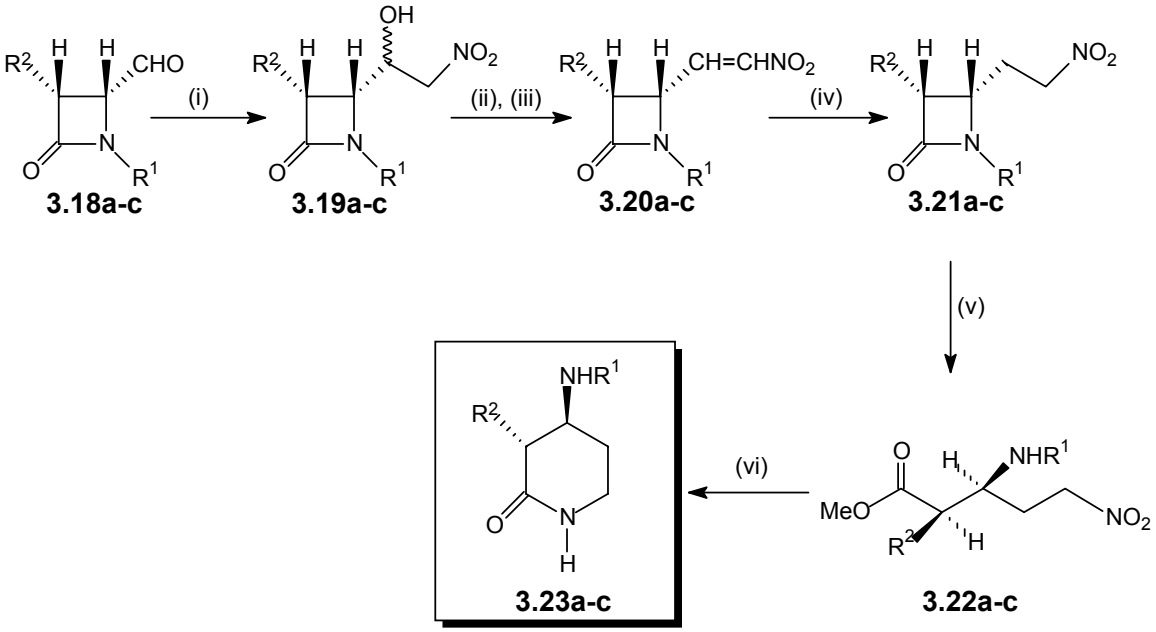
Scheme 3.08



3.18a R^1 = PMP, R^2 = PhO
3.18b R^1 = PMP, R^2 = BnO
3.18c R^1 = Benzyl, R^2 = PhO

By following the synthetic sequence optimized for the synthesis of racemic 4-aminopiperidin-2-ones, we achieved the asymmetric synthesis of enantiopure 4-aminopiperidin-2-ones **3.23a-c** starting from the enantiopure 4-formylazetidin-2-ones **3.18a-c**, in good overall yields (Scheme 3.09, Table 2).

Scheme 3.09



Reagents and conditions: (i) CH_3NO_2, Et_3N, rt, 4 h. (ii) Ac_2O, Conc. H_2SO4, 0 ^oC, 1 h (iii) $NaHCO_3$, benzene, reflux, 5 h. (iv) Bu_3SnH, DCM: MeOH (10:1), rt, 24 h (v) methanolic HCl (20%), rt, 12-24 h (vi) 10% Pd/C, $HCOONH_4$, MeOH, rt, 3-16 h.

Table 2: *Synthesis of nitro alkenes* (**3.20a-c**), *nitro alkanes* (**3.21a-c**), *nitro esters* (**3.22a-c**) *and 4-aminopiperidin-2-ones* (**3.23a-c**).

Compound No.	R^1	R^2	M. P. (^oC)	$[\alpha]_D^{28}$	Yield[a] (%)
3.20a	PMP	PhO	116-118	+102.8 (c 1.05, $CHCl_3$)	70
3.20b	PMP	BnO	137-138	+99.2 (c 1, $CHCl_3$)	75
3.20c	Bn	PhO	95-97	+53.8 (c, 0.5, $CHCl_3$)	72
3.21a	PMP	PhO	108-110	121.9 (c 1.05, $CHCl_3$)	85
3.21b	PMP	BnO	Thick oil	+98.6 (c 0.9, $CHCl_3$)	73
3.21c	Bn	PhO	Thick oil	+120.6 (c 0.9, $CHCl_3$)	65
3.22a	PMP	PhO	98-100	-60.6 (c 1.1, $CHCl_3$)	82
3.22b	PMP	BnO	Thick oil	-11.9 (c 1, $CHCl_3$)	91
3.22c	Bn	PhO	Thick oil	-11.6 (c 1.1, $CHCl_3$)	91
3.23a	PMP	PhO	73-75	+68.2 (c 1.1, $CHCl_3$)	80
3.23b	PMP	BnO	140-141	+43.1 (c 1.03, $CHCl_3$)	66
3.23c	Bn	PhO	130-132	+25.0 (c 1.1, $CHCl_3$)	62

[a] Isolated yields.

3.4 : Summary

We have successfully used 4-formylazetidin-2-one as an efficient building block for the synthesis of 4-aminopiperidin-2-ones *via* methanolysis of the β-lactam ring followed by reductive cyclization. Both racemic and enantiopure 4-aminopiperidin-2-ones (**3.11a,b** & **3.23a-c**) were synthesized in good overall yields starting from 4-formyl-azetidin-2-ones (**3.05a,b** & **3.18a-c**).

3.5 : Introduction

Blastidic acid is a component amino acid present in the antibiotic, blasticidin S. Blasticidin S (Fig. 1) was isolated from *Streptomyces griseochromogenes* and has been extensively used as an excellent fungicide against *Pricularia oryzae*, a serious cause of rice blast disease in Japan.[19] The structural elucidation by Otake et al.[20] and confirmation by X-ray analysis[21] revealed that blasticidin S contained a guanidine β-amino acid moiety, blastidic acid and a nucleoside moiety, cytosinine. Although several synthesis of cytosinine[22] and analogs of blasticidin S[23] have been reported, there have been only two syntheses reported[24] for blastidic acid, that too very recently.

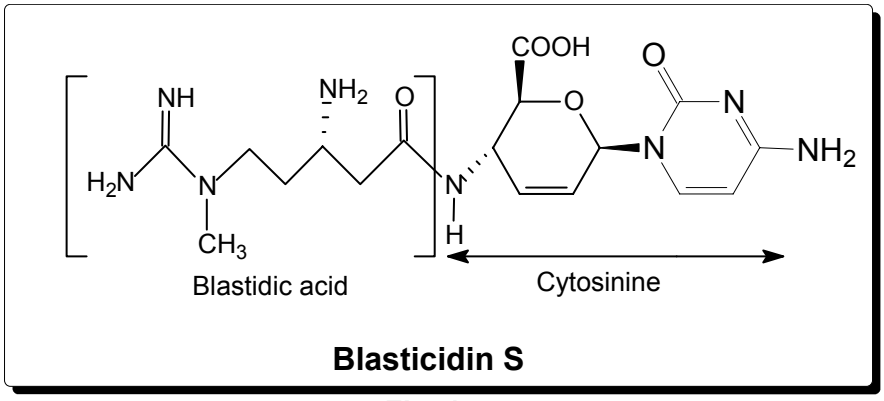
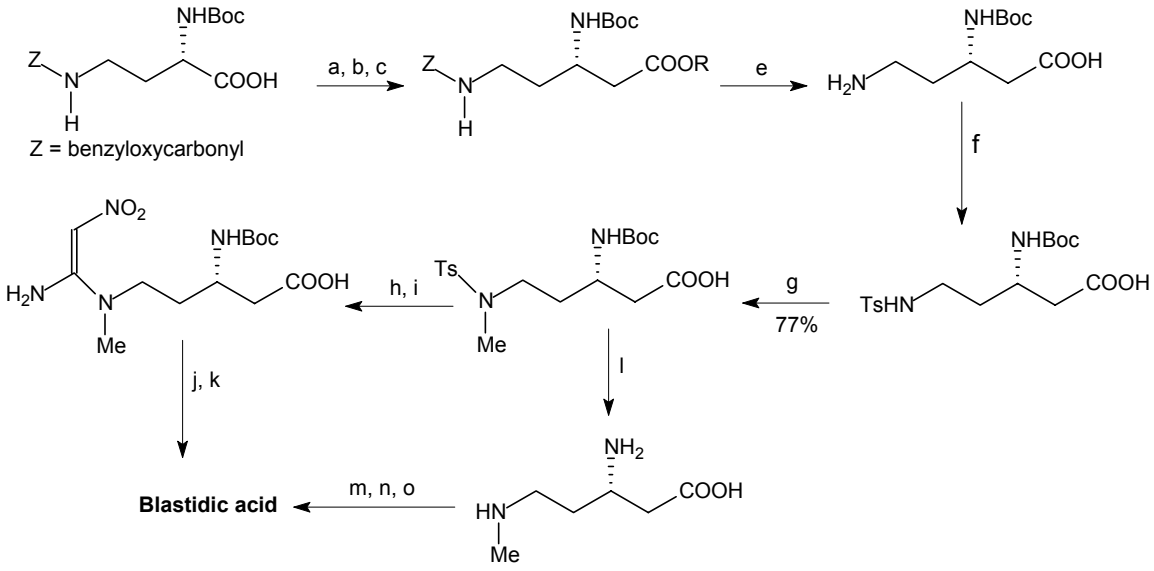


Fig. 1

The first synthesis of blastidic acid was reported by Nomoto and Shimoyama[24a] starting from L-α,γ-diaminobutyric acid. They achieved the synthesis through extension of the carbon chain of the starting amino acid, followed by *N*-methylation and amidination of an ω-amino group as illustrated in scheme 3.10.

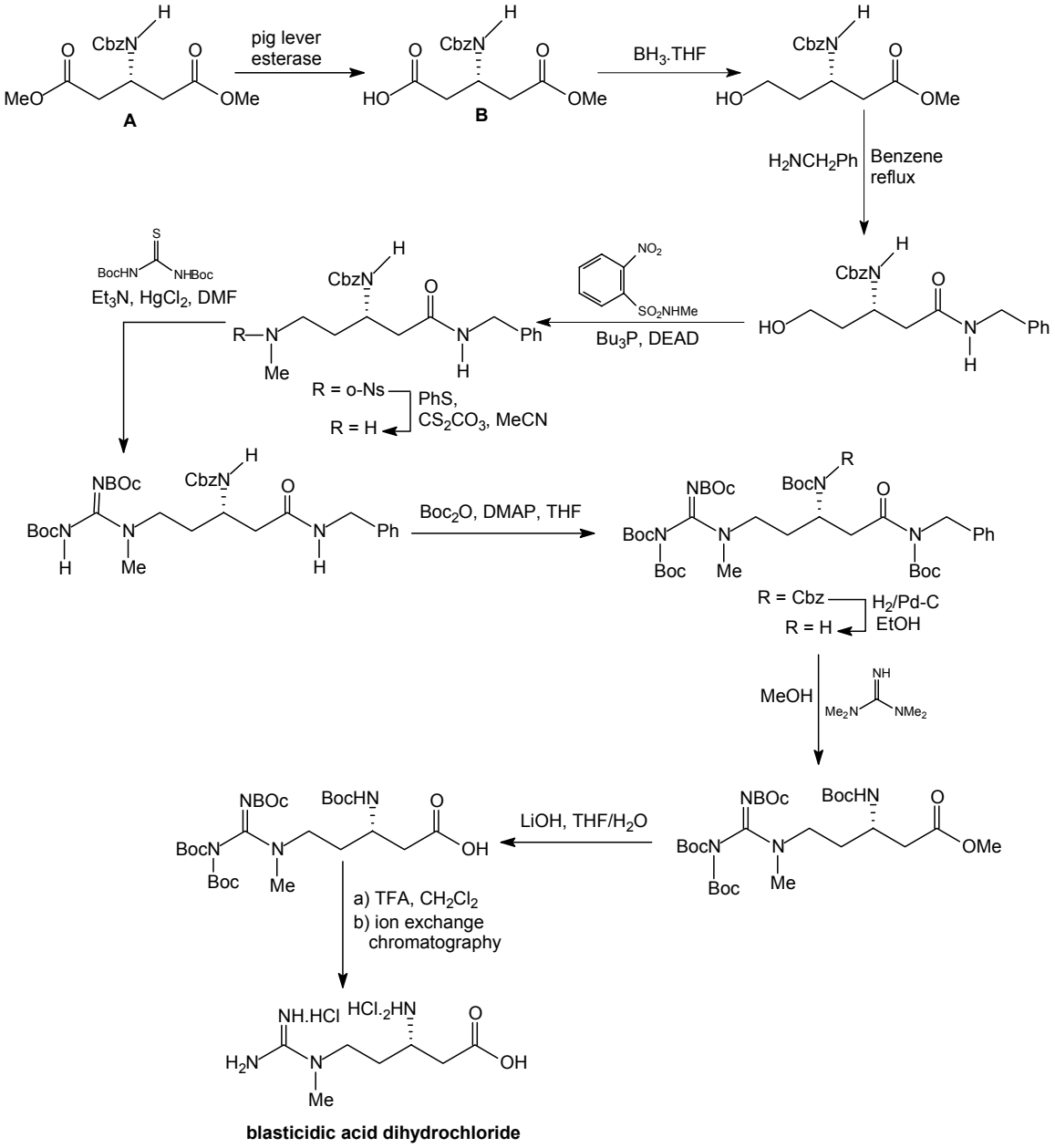
Scheme 3.10



Reagents and conditions: (a) $ClCO_2Et$, *N*-methylmorpholine, AcOEt, -15 ^oC. (b) CH_2N_2, AcOEt-Et_2O, -15 ^oC. (c) $C_6H_5C0_2Ag$, MeOH, 0 ^oC. (d) 2 M NaOH. (e) H_2/5%PdC, MeOH. (f) TsCl, 1 M NaOH. (g) MeI, 2 M NaOH-dioxane. (h) Na, liq NH_3, -70 ^oC. (i) 25% HBr, 110 ^oC. (m) $CuCO_3.Cu(OH)_2$, H_2O. (n) o-isomethylurea, 1 M NaOH. (o) H_2S, 6 M HCl.

The second synthesis was reported by Ichikawa et al.[24b] starting from (3*S*)-3-[(benzyloxycarbonyl) amino]-glutarate **B**, which was prepared from *meso* diester **A** by enantioselective hydrolysis with pig lever esterase. The synthesis of Boc protected blastidic acid was achieved in 9 steps *via* Mitsunobu reaction as illustrated in Scheme 3.11

Scheme 3.11



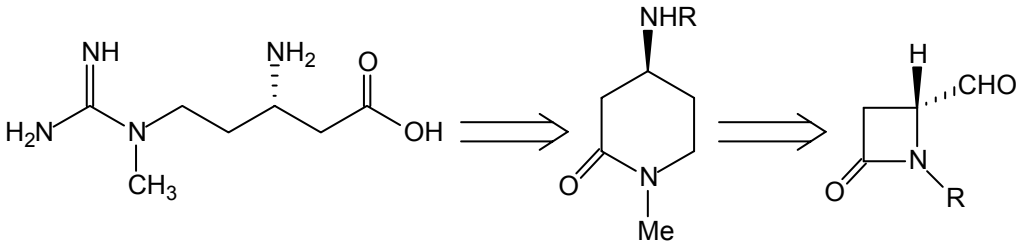
3.5 : Present work

This section describes our efforts made towards the synthesis of blastidic acid, using 4-formylazetidin-2-one as a synthon.

3.6 : Results and Discussion

Our strategy was to synthesize 3-unsubstituted-4-aminopiperidin-2-one **C** using our earlier optimized protocol (Section A) and then to transform the 4-aminopiperidin-2-one to blastidic acid (Scheme 3.12).

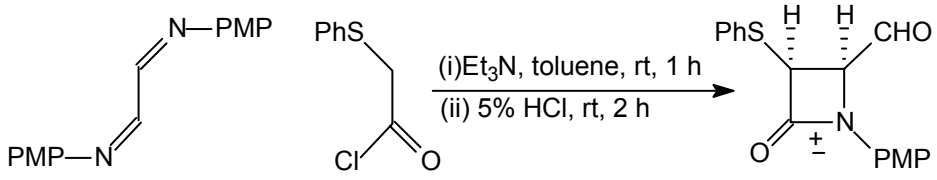
Scheme 3.12



C

Initially, we chose the racemic 3-phenylthio-4-formyl-azetidin-2-one **3.25** as the synthon, so that the PhS- group could be removed at a later stage to get the 3-unsubstituted-4-aminopiperidin-2-one. The β-lactam **3.25** was synthesized from phenylthioacetyl chloride **3.24** and bisimine **3.03a** following a reported procedure[12] (Scheme 3.13)

Scheme 3.13

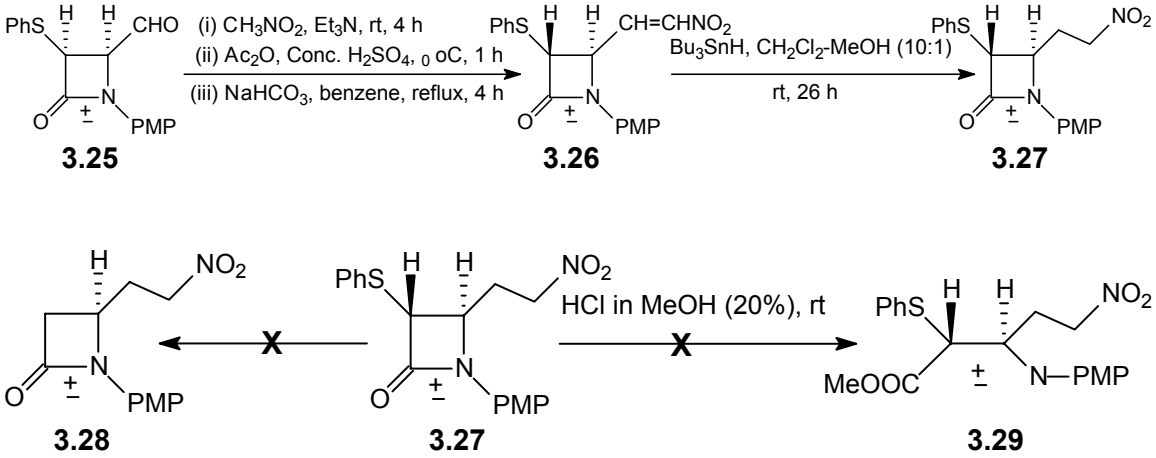


3.03a **3.24** **3.25**

The *cis* 4-formyl-azetidin-2-one **3.25** was converted to the nitro alkene **3.26** by following our earlier standardized procedure (see chapter 3, section A). We observed a *cis*-*trans* isomerisation of *cis* 4-formyl-azetidin-2-one **3.25** during the reaction with nitromethane in the presence of triethylamine and a mixture of *trans* and *cis* alkene (85:15 ratio, determined from the ^{1}H NMR of the crude reaction mixture) was obtained. This was confirmed by stirring *cis* 4-formyl-azetidin-2-one **3.25** in dichloromethane in the presence of triethylamine wherein a mixture of *trans* and *cis* (80:20) 4-formyl-azetidin-2-ones were obtained. The major *trans* alkene **3.26** was separated by flash chromatography and it was reduced with tributyltin hydride to get the nitro alkane **3.27**.

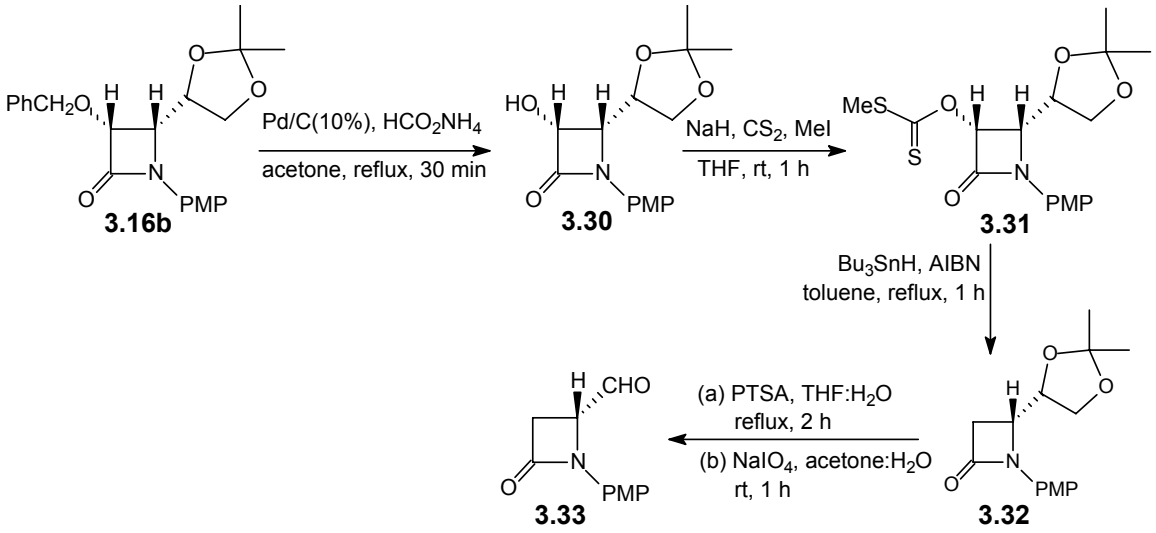
At this stage, all our attempts to remove the thiophenol group (using Raney Ni or Bu_3SnH) in **3.27** or to cleave the β-lactam ring of **3.27** were unsuccessful (Scheme 3.14).

Scheme 3.14



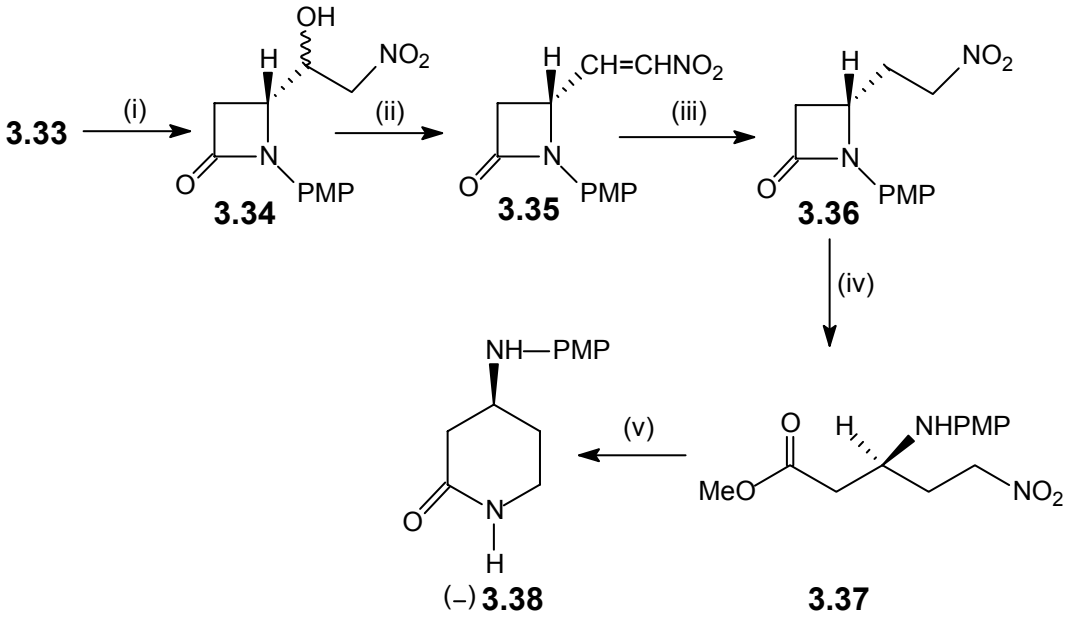
Hence we planned an alternative synthetic route towards the synthesis of blastidic acid starting from enantiopure azetidin-2-one **3.16b**, as described in Scheme 3.15. The required enantiopure β-lactam **3.16b** was prepared by the reaction of schiff base **3.14** (derived from D-glyceraldehyde acetonide **3.13** and *p*-anisidine) with benzyloxyacetyl chloride, following a reported procedure[16] (Scheme 3.08). The β-lactam **3.16b** was debenzylated[25] using Pd/C (10%) and ammonium formate in acetone to get the 3-hydroxy-β-lactam **3.30**, which was converted to the 3-unsubstituted-4-formylazetidin-2-one by following a reported procedure[26] (Scheme 3.15). The 3-hydroxy azetidin-2-one **3.30** on treatment with NaH and CS_2 followed by quenching with CH_3I, afforded the S-methyl xanthate **3.31**,[26] which was subjected to Barton's condition (Bu_3SnH and AIBN) under refluxing toluene to get the 3-unsubstituted-β-lactam **3.32**.[26] The acetonide group of **3.32** was hydrolyzed (PTSA, THF-H_2O) to the diol, which was oxidized using $NaIO_4$ to get the 3-unsubstituted-4-formyl-azetidin-2-one **3.33**[26] (Scheme 3.15)

Scheme 3.15



The 4-formyl-azetidin-2-one **3.33** was treated with nitromethane in the presence of catalytic amount of triethylamine to get the diastereomeric nitro alcohol **3.34**, which was subsequently acylated and the diastereomeric mixture of acetates was refluxed in benzene in presence of sodium bicarbonate to get the nitro alkene **3.35** (Scheme 3.16). The structure of **3.35** was confirmed by spectral and analytical data.

Scheme 3.16



Reagents and conditions: (i) CH_3NO_2, Et_3N, rt, 4 h (ii) a) Ac_2O, Con. H_2SO_4, 0 ^oC, 1h. b) $NaHCO_3$, benzene, reflux, 5 h. (iii) Bu_3SnH, DCM:MeOH (10:1), rt, 3 h. (iv) methanolic HCl (20%), rt, 24 h. (v) Pd/C (10%), HCO_2NH_4, MeOH, rt, 2 h.

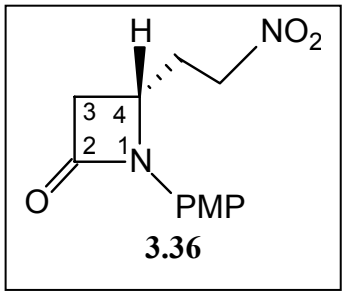
The IR spectrum of nitroalkene **3.35**, showed a sharp peak at 1745 cm^{-1} corresponding to the β-lactam carbonyl. The peaks at 1531 cm^{-1} and 1357 cm^{-1} corresponded to the nitro group.

The ^{1}H NMR spectrum of **3.35** showed two doublet of doublet at 3.00 ppm (J = 3 Hz, 15.1 Hz) and at 3.50 ppm (J = 5.8 Hz, 15.1 Hz) corresponding to the C-3 methylene proton. The –OMe protons appeared as sharp singlet at 3.80 ppm. The C-4 β-lactam proton appeared as multiplet between 4.65 to 4.85 ppm.
The aromatic protons appeared as doublets at 6.90 ppm and 7.25 ppm with J = 9.3 Hz. The olefinic protons appeared as a doublet at 7.20 ppm with J = 13.2 Hz and doublet of doublet at 7.38 ppm with J = 13.2 Hz & 6.3 Hz.

The ^{13}C spectrum of **3.35** showed a peak at 161.84 ppm corresponding to the β-lactam carbonyl carbon. The aromatic quaternary carbons appeared at 156.36 ppm and 130.37 ppm, while the remaining aromatic carbons appeared at 117.77 ppm and 114.42 ppm. The olefinic carbons appeared at 141.15 ppm and 138.61 ppm. The C-3 and C-4 β-lactam carbons appeared at 43.59 ppm and 47.59 ppm respectively. The methoxy carbon appeared at 55.28 ppm. This compound also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 248.

The double bond of the nitro alkene **3.35** was reduced using Bu_3SnH[12] in DCM-MeOH as solvent to get the nitroalkane **3.36**. Its structure was assigned by spectral and analytical data.

The IR spectrum of **3.36** showed a sharp peak at 1743 cm^{-1} corresponding to the β-lactam carbonyl carbon. Peaks at 1554 cm^{-1} and 1388 cm^{-1} corresponded to the nitro group.



3.36

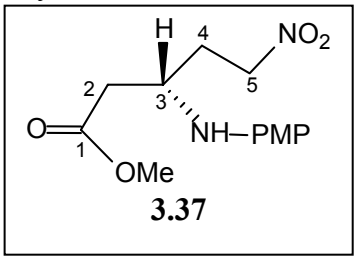
The ^{1}H NMR spectrum of **3.36** showed multiplets between 2.10 ppm to 2.35 ppm and between 2.75 ppm to 2.95 ppm corresponding to the protons of the methylene group attached to the C-4 carbon. The other methylene protons of the C-4 side chain appeared as multiplets between 4.40 ppm to 4.55 ppm. The C-3 methylene protons appeared as two doublet of doublets at 2.75 ppm (J = 2.1 Hz, 14.9

Hz) and 3.25 ppm (J = 5.1 Hz, 14.9 Hz) respectively. The C-4 proton appeared as multiplets between 4.10 ppm to 4.25 ppm. The OMe protons appeared as singlet at 3.80 ppm. The aromatic protons of the PMP group appeared as two doublets at 6.90 ppm and 7.25 ppm (J = 8.8 Hz).

The ^{13}C NMR spectrum of **3.36** showed a peak at 162.08 corresponding to the β-lactam carbonyl carbon. The aromatic quaternary carbons appeared at 156.07 ppm and 130.08 ppm while the remaining aromatic carbons appeared at 118.24 ppm and 114.31 ppm. The C-3 methylene carbon appeared at 41.49 ppm and the C-4 carbon appeared at 47.92 ppm. The methylene carbons of the C-4 side chain appeared at 71.26 ppm and 29.25 ppm. The –OMe carbon appeared at 55.13 ppm. This compound also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 250.

The β-lactam ring of the nitroalkane **3.36** was cleaved by stirring with methanolic HCl (20%) at room temperature for 24 h to get the β-amino-nitroester **3.37**. The structure of nitroester **3.37** was confirmed from spectral and analytical techniques.

The IR spectrum of **3.37** showed bands at 3365 cm^{-1}, 1730 cm^{-1}, 1550 cm^{-1}, 1380 cm^{-1} corresponding to amino, carbonyl and nitro group respectively.

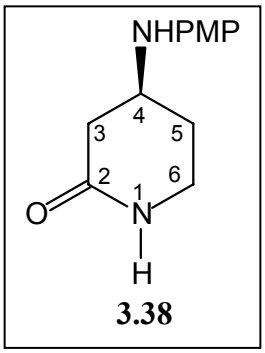


3.37

The ^{1}H NMR spectrum of **3.37** showed multiplets between 2.10 ppm to 2.60 ppm corresponding to the C-4 and C-2 methylene protons. The OMe protons of the ester and the PMP group appeared as sharp singlets at 3.70 ppm and 3.80 ppm respectively. The C-3 proton and the –NH proton appeared as multiplets between 3.75 ppm to 3.90 ppm. The C-5 methylene protons appeared as multiplets between 4.50 ppm to 4.65 ppm. The aromatic protons appeared as doublets at 6.65 ppm and 6.80 ppm with J = 9.3 Hz.

The reductive cyclization of the nitro ester **3.37** to the 3-unsubstituted-4-aminopiperidin-2-one **3.38** was achieved by transfer hydrogenation[13] using ammonium formate and Pd/C (10%) in methanol at room temperature (2 h). The structure of **3.38** was confirmed by spectral and analytical techniques.

The IR spectrum of **3.38** showed bands at 3336 cm^{-1} and 1633 cm^{-1} corresponding to the –NH and the carbonyl group.



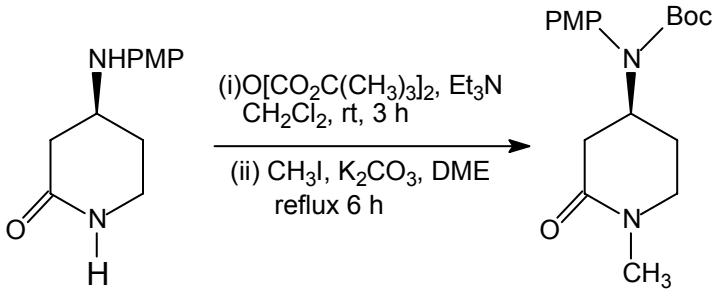
3.38

The ^{1}H NMR spectrum of **3.38** showed multiplets between 1.90 ppm to 3.00 ppm corresponding to the C-3 and C-5 methylene protons. The C-6, C-4 and the amine –NH protons appeared as multiplets between 3.50 to 4.00 ppm. The methoxy protons of the PMP group appeared as singlet at 3.75 ppm. The amide –NH proton appeared as a broad singlet at 5.50 ppm . The aromatic protons appeared as doublets at 6.65 ppm and 6.85 ppm with J = 8.8 Hz.

The ^{13}C NMR spectrum of **3.38** showed a peak at 163.12 ppm corresponding to the amide carbonyl carbon. The aromatic quaternary carbons appeared at 153.68 ppm and 138.53 ppm. The remaining aromatic carbons appeared at 116.48 ppm and 115.08 ppm. The methylene carbons appeared at 27.89, 37.34 and 46.23 ppm. The C-4 methine carbon appeared at 48.44 ppm and the OMe carbon of the PMP group appeared at 55.72 ppm. The compound also gave satisfactory elemental analysis and the mass spectrum showed a molecular ion peak at (m/z) 220.

The amino group of 4-aminopiperidin-2-one **3.38** was protected with Boc using di-*tert*-butyl dicarbonate and the Boc protected piperidin-2-one was refluxed in 1,2 dimethoxyethane (DME) with anhydrous K_2CO_3 and CH_3I to get the *N*-methylated 4-aminopiperidin-2-one **3.39**, which is a key intermediate for blastidic acid.

Scheme 3.17



3.38 **3.39**

3.7 : Summary

We have successfully transformed 4-formylazetidin-2-one (**3.33**) to 4-aminopiperidin-2-one (**3.38**). The 4-amino group was protected with Boc and the amide nitrogen was alkylated with methyl iodide. This compound **3.39** is the key intermediate for blastidic acid.

Section A

3.8 : Experimental

3.8.1a : Preparation of *N*, *N*′-bis(*p*-anisyl)ethylenediimine 3.03a

Glyoxal **3.01** (40% aqueous solution, 10 ml, 69 mmol) was added dropwise to a hot solution of amine **3.02a** (16.96 g, 138 mmol) in 80 ml of methanol. A yellow solid precipitated and isopropyl alcohol was added and methanol distilled until solution occurred. Cooling to room temperature gave the diimine, **3.03a** as yellow needles (11 g, 60 %), m. p 156-158 ^{o}C (Lit[11] 153-154 ^{o}C).

3.8.1b : Preparation of *N*, *N*′-bis(*p*-tolyl)ethylenediimine 3.03b

Glyoxal **3.01** (40% aqueous solution, 10 ml, 69 mmol) was added dropwise to a cooled (0 ^{o}C) solution of amine **3.02a** (14.80 g, 138 mmol) in 35 ml of isopropanol. A yellow solid precipitated, which was filtered off and recrystallized from isopropanol to get bisimine **3.03b** as yellow needles (4 g, 25 %), m. p. 160-162 ^{o}C (Lit[11] 164-165 ^{o}C).

3.8.2 : General procedure for the preparation of 4-formylazetidin-2-ones 3.05a & 3.05b

To a stirred suspension of diimine (**3.03**, 15 mmol) and triethylamine (2.50 ml, 18 mmol) in anhydrous toluene, was added an anhydrous toluene solution of phenoxyacetyl chloride (**3.04**, 16.5 mmol, 2.30 ml) dropwise at room temperature under argon. The resulting mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), 5% aqueous HCl (35 ml) was added and the heterogeneous mixture was stirred at room temperature for 2 h. The organic layer was then diluted with toluene, washed with 5% aqueous HCl, water, brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the crude product, which was purified by crystallization from methanol.

3.8.2a : Preparation of 1-(4-methoxyphenyl)-3-phenoxy-4-formylazetidin-2-one 3.05a

Following the general procedure, treatment of phenoxyacetyl chloride **3.04** (2.30 ml, 16.5 mmol) with diimine **3.03a** (4.0 g, 15 mmol) and triethylamine (2.50 ml, 18 mmol) gave the 4-formylazetidin-2-one **3.05b** as a white solid (3.10 g, 70%).

MP : 106-108 ^{o}C (Lit[12] 109-110 ^{0}C)

IR ($CHCl_3$) : 1747 cm^{-1}, 1726 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 4.75 (dd, *J* = 5.3 Hz, 3.4 Hz), 5.05 (d, *J* = 5.3 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.20-7.45 (m, 5H), 9.80 (d, *J* = 3.4 Hz).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.32, 63.08, 81.50, 114.58, 115.61, 118.18, 122.96, 129.61, 130.27, 156.81, 157.03, 161.26, 197.02.

3.8.2b : Preparation of 1-(4-methylphenyl)-3-phenoxy-4-formylazetidin-2-one 3.05b

Following the general procedure, treatment of phenoxyacetyl chloride **3.04** (2.30 ml, 16.5 mmol) with diimine **3.03b** (3.540 g, 15 mmol) and triethylamine (2.50 ml, 18 mmol) gave the 4-formylazetidin-2-one **3.05b** as a white solid (3.02 g, 72%).

MP : 92-93 ^{o}C.

IR ($CHCl_3$) : 1764 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.30 (s, 3H), 4.75 (dd, *J* = 5.3 Hz, 3.4 Hz, 1H), 5.50 (d, *J* = 5.3 Hz, 1H), 7.00-7.40 (m, 9H), 9.75 (d, *J* = 3.4 Hz, 1H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.76, 62.85, 81.30, 115.52, 116.62, 122.95, 129.64, 129.78, 134.38, 135.04, 156.73, 161.51, 197.09.

3.8.3 : Preparation of 1-(4-methoxyphenyl)-4-(1-hydroxy-2-nitroethyl)-3-phenoxy-azetidin-2-one 3.06a

To a solution of 4-formylazetidin-2-one **3.05a** (1.780 g, 6 mmol), in nitromethane (20 ml), was added triethylamine (0.1 ml, 1 mmol) at room temperature and the reaction mixture was stirred for 4 h. The excess nitromethane was removed under reduced

pressure to afford a diastereomeric mixture (80:20) of nitro alcohols **3.06a**, as thick oil (1.90 g, 90%).

IR ($CHCl_3$) : 3500-3100 cm^{-1}, 1755 cm^{-1}, 1560 cm^{-1}, 1380 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 2.00 (bs, 1H) 3.80 (s, 3H), 4.50-4.65 (m, 3H), 4.85-5.05 (m, 1H), 5.45 (d, *J* = 5.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.00-7.60 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.29, 58.41, 68.67, 77.53, 79.51, 114.36, 115.86, 120.09, 123.07, 129.68, 156.85, 157.11, 163.13.

3.8.4 : Preparation of 1-(4-methoxyphenyl)-4-(1-acetoxy-2-nitroethyl)-3-phenoxy-azetidin-2-one 3.07a

The diastereomeric mixture of nitro alcohols **3.06a** (1.750 g, 4.9 mmol) was dissolved in acetic anhydride (20 ml) and cooled to 0 ^oC. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^oC for 1 h. After completion of reaction (TLC), water (2 ml) was added at 0 ^oC and stirred for 30 min. It was extracted with ethyl acetate (2 x 15 ml) and the organic layer was washed with saturated $NaHCO_3$ (3 x 10 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diastereomeric mixture (80:20) of nitro acetate **3.07a** as a white solid (1.800 g, 92%).

MP : 112-114 ^oC.

IR ($CHCl_3$) : 1755 cm^{-1}, 1562 cm^{-1}, 1377 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.85 (s, 3H), 3.80 (s, 3H), 4.75-5.00 (m, 3H), 5.50 (d, *J* = 4.9 Hz, 1H), 5.95-6.10 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.10 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 20.00, 55.25, 55.88, 68.78, 74.73, 79.40, 114.28, 115.57, 119.76, 122.88, 129.61, 156.85, 157.03, 162.44, 169.02.

MS (m/z) : 400 (M^+).

3.8.5 : Preparation of 1-(4-methoxyphenyl)-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.08a

To a solution of nitro acetate **3.07a** (1.602 g, 4 mmol) in benzene (20 ml) was added sodium bicarbonate (2.700 g, 32 mmol) and the mixture was refluxed for 5 h. After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitro alkene, which was further purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate- 75:25) to get pure nitro alkene **3.08a** as a white solid (1.160 g, 86%).

MP : 120-121 ^{o}C (Lit[14]120-123 ^{o}C).

IR ($CHCl_3$) : 1758 cm^{-1}, 1531 cm^{-1}, 1357 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.80 (s, 3H), 5.00-5.10 (m, 1H), 5.55 (d, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.95-7.40 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.32, 81.57, 114.61, 115.39, 118.36, 122.88, 129.65, 134.61, 142.88, 156.59, 157.10, 159.50, 161.04.

MS (m/z) : 340 (M^{+}).

Analysis ($C_{18}H_{16}N_2O_5$) : Calculated: C, 63.52; H, 4.74; N, 8.23
Observed: C, 63.76; H, 4.65; N, 8.44.

3.8.6: Preparation of 1-(4-methoxyphenyl)-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.09a

To a solution of nitro alkene **3.08a** (1.20 g, 3.5 mmol) in anhydrous dichloromethane (15 ml) and methanol (1.5 ml), tributyltin hydride (1.1 ml, 4.2 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to get pure nitro alkane **3.09a** as a white solid (0.960 g, 80%).

MP : 115 -116^{o}C (Lit[14] 112-114 ^{o}C).

IR ($CHCl_3$) : 1753 cm^{-1}, 1551 cm^{-1}, 1396 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.50-3.00 (m, 2H), 3.80 (s, 3H), 4.50-4.65 (m, 3H), 5.54 (d, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz,

2H), 7.25-7.80 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 24.96, 54.26, 55.29, 71.35, 79.69, 114.61, 115.57, 118.58, 122.63, 129.57, 156.78, 157.00, 159.50, 162.07.

MS (m/z) : 342 (M^+).

Analysis ($C_{18}H_{18}N_2O_5$) : Calculated: C, 63.15; H, 5.29; N, 8.18
Observed: C, 63.08; H, 4.53; N, 8.30.

3.8.7 : Preparation of methyl-3-[(4-methoxyphenyl)amino]-5-nitro-2-phenoxypentanoate 3.10a

A solution of nitro alkane **3.09a** (0.900 g, 2.6 mmol) in methanolic HCl (20%, 10 ml) was stirred at room temperature for 24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with saturated bicarbonate solution (10 ml), brine (10 ml), and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude nitro ester, which was purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate-80:20) to afford the pure nitro ester **3.10a**, as a pale yellow oil (0.880 g, 90%).

MP : Oil.

IR ($CHCl_3$) : 1755cm^{-1}, 3380cm^{-1}, 1552cm^{-1}, 1380cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.25-2.55 (m, 2H), 3.50 (s, 3H), 3.75 (s, 3H), 4.10-4.25 (m, 1H), 4.50-4.70 (m, 3H), 4.75 (d, J = 2.5 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 7.00-7.40 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 30.17, 52.08, 54.80, 55.68, 72.44, 77.62, 115.04, 115.26, 116.04, 122.29, 129.64, 140.37, 153.24, 157.43, 169.78.

MS (m/z) : 374 (M^+).

Analysis ($C_{19}H_{22}N_2O_6$) : Calculated: C, 60.95; H, 5.92; N, 7.48
Observed: C, 60.70; H, 5.71; N, 7.25.

3.8.8 : Preparation of 4-[(4-methoxyphenyl)amino]-3-phenoxy-piperidin-2-one 3.11a

To a solution of nitro ester **5a** (0.600 g, 1.6 mmol) in anhydrous methanol (10 ml), 10% Pd/C (100 mg) was added followed by ammonium formate (0.500 g, 8 mmol) and the reaction mixture was stirred at room temperature under argon for 3 h. After completion of reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with water (5 ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent gave crude product as a brown solid, which was purified by column chromatography (silica gel 60-120, pet. ether/ ethyl acetate-60:40) to afford pure 4-aminopiperidin-2-one **3.11a** as a pale yellow oil (0.350 g, 70%).

MP : Oil.

IR ($CHCl_3$) : 3400-3200 cm^{-1}, 1666 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.80-2.10 (m, 1H), 2.40-2.60 (m. 1H), 3.50-3.90 (m, 4H), 3.75 (s, 3H), 4.75 (d, J = 5.9 Hz, 1H), 6.60-7.40 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 23.90, 46.32, 52.13, 55.51, 77.53, 114.72, 115.97, 116.34, 122.50, 129.32, 139.68, 152.95, 158.17, 162.69.

MS (m/z) : 312 (M^+).

Analysis ($C_{18}H_{20}N_2O_3$) : Calculated: C, 69.19; H, 6.45; N, 8.97
Observed: C, 69.39; H, 6.60; N, 8.82.

3.8.9 : Preparation of 1-(4-methylphenyl)-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.08b

To a solution of 4-formylazetidin-2-one **3.05b** (1.60 g, 5.7 mmol), in nitromethane (20 ml), was added triethylamine (0.1 ml, 1 mmol) at room temperature and the reaction mixture was stirred for 4 h. The excess nitromethane was removed under reduced pressure to afford a viscous oil of diastereomeric mixture of nitro alcohols **3.06b**. This mixture was dissolved in acetic anhydride (20 ml) and cooled to 0 ^oC. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^oC for 1 h. After completion of reaction (TLC), 2 ml water was added at 0 ^oC and stirred for 30 min. It was extracted with ethyl acetate (2 x 15 ml) and the organic layer was washed with

saturated $NaHCO_3$ (3 x 10 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diastereomeric mixture of nitro acetates, which was refluxed with benzene (20 ml) in the presence of $NaHCO_3$ (4.0 g) for 5 h. After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitro alkene (**3.08b**), which was further purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate- 75:25) to get pure nitro alkene (**3a**) as a white solid (1.28 g, 70%).

MP : 110-111 ^{o}C.

IR ($CHCl_3$) : 1762 cm^{-1}, 1515 cm^{-1}, 1357 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.40 (s, 3H), 5.05-5.15 (m, 1H), 5.60 (d, *J* = 4.8 Hz, 1H), 6.95-7.50 (m, 11H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 20.80, 55.31, 81.63, 115.52, 116.96, 123.02, 129.75, 129.97, 133.79, 134.56, 135.22, 142.94, 156.73, 161.36.

MS (m/z) : 324 (M^+).

Analysis ($C_{18}H_{16}N_2O_4$) : Calculated: C, 66.66; H, 4.98; N, 8.64.
Observed: C, 66.52; H, 4.87; N, 8.70.

3.8.10 : Preparation of 1-(4-methylphenyl)-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.09b

To a solution of nitro alkene **3.08b** (1.20 g, 3.7 mmol) in anhydrous dichloromethane (15 ml) and methanol (1.5 ml), tributyltin hydride (1.2 ml, 4.4 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to get pure nitro alkane (**3.09a)** as colourless oil (0.960 g, 75%).

MP : Oil

IR ($CHCl_3$) : 1755 cm^{-1}, 1554 cm^{-1}, 1390 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.40 (s, 3H), 2.50-2.65 (m, 1H), 2.75-2.95 (m, 1H), 4.50-4.65 (m, 3H), 5.45 (d, *J* = 4.9 Hz, 1H), 7.00-7.50 (m, 9H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 20.72, 25.06, 54.52, 71.45, 79.79, 115.74, 117.18, 122.76,

129.67, 129.89, 133.94, 134.71, 157.17, 162.46.

MS (m/z) : 326 (M^+)

Analysis ($C_{18}H_{18}N_2O_4$) : Calculated: C, 66.25; H, 5.56; N, 8.59
Observed: C, 66.24; H, 5.43; N, 8.80.

3.8.11 : Preparation of methyl-3-[(4-methylphenyl)amino]-5-nitro-2-phenoxypentanoate 3.10b

A solution of nitro alkane **3.09b** (0.820 g, 2.5 mmol) in methanolic HCl (20%, 10 ml) was stirred at room temperature for 24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with saturated bicarbonate solution (10 ml), brine (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude nitro ester, which was purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate-80:20) to afford the pure nitro ester **3.10b**, as pale yellow oil (0.790 g, 88%).

MP : Oil.

IR ($CHCl_3$) : 1755 cm^{-1}, 1552 cm^{-1}, 1380 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : 2.25 (s, 3H), 2.30-2.55 (m, 2H), 3.50 (s, 3H), 4.15-4.35 (m, 1H), 4.50-4.70 (m, 2H), 4.75 (d, J = 2.4 Hz, 1H), 6.60 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 7.00-7.50 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 19.95, 29.77, 51.82, 53.36, 72.00, 76.08, 113.98, 114.79, 121.92, 127.80, 129.31, 129.49, 143.68, 156.99, 169.37.

MS (m/z) : 358 (M^+).

Analysis ($C_{19}H_{22}N_2O_5$) : Calculated: C, 63.68; H, 6.19; N, 7.82
Observed: C, 63.50; H, 5.95; N, 7.77.

3.8.12 : Preparation of 4-[(4-methylphenyl)amino]-3-phenoxy-piperidin-2-one 3.11b

To a solution of nitro ester **3.10b** (0.710 g, 2 mmol) in anhydrous methanol (10 ml), 10% Pd/C (100 mg) was added followed by ammonium formate (0.630 g, 10 mmol) and the reaction mixture was stirred at room temperature under argon for 20 h. After

completion of reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with water (5 ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent gave crude product as a brown solid, which was purified by column chromatography (silica gel 60-120, pet. ether/ ethyl acetate-60:40) to afford pure 4-aminopiperidin-2-one **3.11a** as a pale yellow oil (0.450 g, 78%).

MP : Thick oil.

IR ($CHCl_3$) : 3348 cm^{-1}, 1665 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.90-2.10 (m, 1H), 2.25 (s, 3H), 2.45-2.55 (m, 1H), 3.55-4.05 (m, 4H), 4.75 (d, J = 5.4 Hz, 1H), 6.55 (d, J = 8.3 Hz, 2H), 6.90-7.50 (m, 8H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 20.25, 23.96, 46.27, 51.64, 77.62, 114.35, 116.59, 122.21, 128.09, 129.45, 129.78, 143.49, 158.31, 162.61.

MS (m/z) : 296 (M^+).

Analysis ($C_{18}H_{20}N_2O_2$) : Calculated: C, 72.95; H, 6.81; N, 9.46
Observed: C, 73.12; H, 6.65; N, 9.55.

3.8.13 : General procedure for the preparation of azetidin-2-ones 3.16a-c

Preparation of Schiff base **3.14**

$NaIO_4$ (2.140 g, 10 mmol) was dissolved in H_2O (20 ml) and cooled to 0 ^oC. To the cooled solution, 1,2,5,6-Di-*O*-isopropylidine-D-mannitol **3.12** (2.620 g, 10 mmol) was added in portions with stirring. After completion of addition, the reaction mixture was stirred at room temperature for 30 min and was filtered to provide an aqueous solution of D-glyceraldehyde acetonide **3.13**. To the cooled (0-5 ^oC) filtrate, was added a solution of amine (20 mmol) in 1,2-dichloroethane (20 ml). The reaction mixture was stirred at room temperature for 2 h after which the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloroethane (2 x 20 ml). The combined organic layer containing the Schiff base **3.14** was dried over anhydrous sodium sulphate. The Schiff base solution in dichloroethane was used as such for the next reaction

Preparation of azetidin-2-ones **3.16a-c** *from Schiff base* **3.14**:

To the dichloroethane solution of Schiff base **3.14**, in a 500 ml conical flask was added sequentially, triethylamine (6.7 ml, 48 mmol) and acid chloride (**3.15**, 24 mmol). The flask was capped with a glass funnel and placed in a microwave oven (BPL model, 800 Watts). The mixture was irradiated at 70% power for 5 min. The reaction mixture was then diluted with dichloroethane (30 ml) and the organic layer was washed with water (3 x 15 ml), saturated sodium bicarbonate solution (3 x 15 ml), saturated brine solution (15 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the crude product, which was purified by column chromatography (silica gel 60-120, pet.ether/ethyl acetate 88:12) to get pure azetidin-2-ones **3.16a-c**.

3.8.13a : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-3-phenoxy-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin2-one 3.16a

Following the general procedure, imine **3.14** prepared from D-glyceraldehyde acetonide **3.13** and *p*-anisidine (2.460 g, 20 mmol) was treated with triethylamine (6.7 ml, 48 mmol) and phenoxyacetyl chloride (3.4 ml, 24 mmol) under microwave condition to get azetidin-2-one **3.16a** as a white solid (4.72 g, 64%).

MP : 141-143 ^{o}C (Lit[17] 145-146 ^{o}C).

$[\alpha]^{28}_{D}$: +182.1 (c 0.55, MeOH) (Lit[17] +185.4, c 0.5, MeOH)

IR ($CHCl_3$) : 1745 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.35 (s, 3H), 1.55 (s, 3H), 3.75-3.85 (m, 1H), 3.75 (s, 3H), 4.30-4.45 (m, 2H), 4.50-4.65 (m, 1H), 5.35 (d, *J* = 5.3 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.00-7.40 (m, 5H), 7.75 (d, *J* = 8.8 Hz, 2H).

3.8.13b : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-3-benzyloxy-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin2-one 3.16b

Following the general procedure, imine **3.14** prepared from D-glyceraldehyde acetonide **3.13** and *p*-anisidine (2.460 g, 20 mmol) was treated with triethylamine (6.7

ml, 48 mmol) and benzyloxyacetyl chloride (3.8 ml, 24 mmol) under microwave condition to get azetidin-2-one **3.16b** as a white solid (4.70 g, 62%).

MP : 117-118 ^{o}C (Lit[16,17] 120 ^{o}C).

$[\alpha]^{28}_{D}$: + 108.2 (c 0.5, MeOH) (Lit[17] +109.2, c 0.54, MeOH).

IR ($CHCl_3$) : 1735 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : 1.35 (s, 3H), 1.54 (s, 3H), 3.73-3.89 (m, 1H), 3.75 (s, 3H), 4.10-4.50 (m, 3H), 4.70-4.80 (m, 2H), 5.00 (d, *J* = 11.8 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 2H), 7.30-7.45 (m, 5H), 7.70 (d, J = 9.2 Hz, 2H).

3.8.13c : Preparation of (3*R*,4*S*)-1-benzyl-3-phenoxy-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin2-one 3.16c

Following the general procedure, imine **3.14** prepared from D-glyceraldehyde acetonide **3.13** and benzylamine (2.6 ml, 20 mmol) was treated with triethylamine (6.7 ml, 48 mmol) and phenoxyacetyl chloride (3.3 ml, 24 mmol) under microwave condition to get azetidin-2-one **3.16b** as a white solid (4.20 g, 60%).

MP : 123-125 ^{o}C

$[\alpha]^{28}_{D}$: +79.8 (c 1.05, $CHCl_3$).

IR ($CHCl_3$) : 1757 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.35 (s, 3H), 1.45 (s, 3H), 3.60-3.80 (m, 2H), 4.10-4.20 (m, 1H), 4.30 (d, *J* = 14.1 Hz, 1H), 4.40-4.55 (m, 1H), 4.90 (d, *J* = 14.1 Hz, 1H), 5.15 (d, *J* = 4.9 Hz, 1H), 7.00-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : 24.92, 26.51, 45.18, 59.29, 66.61, 76.86, 79.84, 109.54, 115.50, 122.33, 127.59, 128.47, 128.66, 129.43, 135.42, 17.18, 165.49.

3.8.14 : General procedure for preparation of 4-formylazetidin-2-ones 3.18a-c

A mixture of azetidin-2-one (**3.16a-c**, 10 mmol) and *p*-toluenesulphonic acid monohydrate (0.570 g, 3 mmol) in THF (40 ml) and water (15 ml) was refluxed for 24 h. After completion of reaction (TLC) the reaction mixture was neutralized with sodium bicarbonate and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 ml) and the organic layer was washed with saturated brine

solution (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the diol **3.17a-c**, which was dissolved in acetone (50 ml) and water (25 ml) and cooled to 0 ^{o}C. To the cooled diol solution, $NaIO_4$ (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was taken in dichloromethane (30 ml) and the organic layer was washed with water (2 x 10 ml), saturated sodium bicarbonate solution (2 x 10 ml), saturated brine solution (15 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the 4-formylazetidin-2-ones **3.18a-c**.

3.8.14a : Preparation of (3*R*,4*R*)-1-(4-methoxyphenyl)-3-phenoxy-4-formylazetidin-2-one 3.18a

Following the general procedure, treatment of azetidin-2-one **3.16a** (3.70 g, 10 mmol) with PTSA (0.570 g, 3 mmol) followed by oxidation of the diol **3.17a** using $NaIO_4$ (2.60 g, 12 mmol) gave the 4-formylazetidin-2-one **3.18a** as a white solid (2.70 g, 90%).

MP : 135-137 ^{o}C (Lit[18] 138-139 ^{o}C).

$[\alpha]^{28}_{D}$: +171.0 (c 1, CH_2Cl_2) (Lit[18] $[\alpha]_D$ = +173.5, c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1747 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.80 (s, 3H), 4.75 (dd, *J* =5.3 Hz, 3.4 Hz, 1H), 5.05 (d, *J* = 5.3 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H) 7.25-7.40 (m, 5H), 9.80 (d, *J* = 3.4 Hz, 1H).

3.8.14b : Preparation of (3*R*,4*R*)-1-(4-methoxyphenyl)-3-benzyloxy-4-formylazetidin-2-one 3.18b

Following the general procedure, treatment of azetidin-2-one **3.16b** (3.83 g, 10 mmol) with PTSA (0.570 g, 3 mmol) followed by oxidation of the diol **3.17b** using $NaIO_4$ (2.60 g, 12 mmol) gave the 4-formylazetidin-2-one **3.18b** as a white solid (2.645 g, 85%).

MP : 152-153 ^{o}C (Lit[18] 154-155 ^{o}C).

$[\alpha]^{28}_{D}$: +176.3 (c 1, CH_2Cl_2) (Lit[18] $[\alpha]_D$ = +178.5, c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1753 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 3.8 (s, 3H), 4.50 (dd, *J* = 5.4 Hz, 3.9 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.85 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 5.4 Hz, 1H), 6.80-7.50 (m, 9H), 9.75 (d, *J* = 3.9 Hz, 1H).

3.8.14c : Preparation of (3*R*,4*R*)-1-benzyl-3-phenoxy-4-formylazetidin-2-one 3.18c

Following the general procedure, treatment of azetidin-2-one **3.16c** (3.50g, 10 mmol) with PTSA (0.570 g, 3 mmol) followed by oxidation of the diol **3.17c** using $NaIO_4$ (2.60 g, 12 mmol) gave the 4-formylazetidin-2-one **3.18c** as colourless oil (2.36 g, 85%).

MP : Oil.

$[\alpha]^{28}_D$: +53.2 (c 1, CH_2Cl_2) (Lit[18] $[\alpha]_D$ = +57.6, c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1762 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 4.25 (dd, *J* = 2.5 Hz, 4.9 Hz, 1H), 4.50 (d, *J* = 14.6 Hz, 1H), 4.75 (d, *J* = 14.6 Hz, 1H), 5.50 (d, *J* = 4.9 Hz, 1H), 7.00-7.50 (m, 10H), 9.50 (d, *J* = 2.5 Hz, 1H).

3.8.15 : General procedure for the preparation of nitro alkenes 3.20a-c

To a solution of 4-formylazetidin-2-one (**3.18a-c**, 6 mmol), in nitromethane (20 ml), was added triethylamine (0.1 ml, 1 mmol) at room temperature and the reaction mixture was stirred for 4 h. The excess nitromethane was removed under reduced pressure to afford a viscous oil of diastereomeric mixture of nitro alcohols **3.19a-c**. This mixture was dissolved in acetic anhydride (20 ml) and cooled to 0 ^oC. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^oC for 1 h. After completion of reaction (TLC), 2 ml water was added at 0 ^oC and stirred for 30 min. It was extracted with ethyl acetate (2 x 15 ml) and the organic layer was washed with saturated $NaHCO_3$ (3 x 10 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diastereomeric mixture of nitro acetates, which was refluxed with benzene (20 ml) in the presence of $NaHCO_3$ (4.0 g, 48 mmol) for 5 h. After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitro alkene which

was further purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate- 75:25) to get pure nitro alkenes **3.20a-c**

3.8.15a : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.20a

Following the general procedure, treatment of 4-formylazetidin-2-one **3.18a** (1.780 g, 6 mmol) with nitromethane and triethylamine, followed by acetylation and elimination gave the nitro alkene **3.20a** (1.424 g, 70%).

MP : 116-118 ^{o}C

$[\alpha]^{28}_{D}$: +102.8 (c 1.05, $CHCl_3$).

IR ($CHCl_3$) : 1764 cm^{-1}, 1533 cm^{-1}, 1357 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 5.10 (m, 1H), 5.60 (d, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.95-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.35, 81.59, 114.68, 115.41, 118.39, 122.95, 129.71, 134.67, 142.91, 156.62, 157.02, 159.40, 161.07.

MS (m/z) : 340 (M^+).

Analysis ($C_{18}H_{16}N_2O_5$) : Calculated: C, 63.52; H, 4.74; N, 8.23
Observed: C, 63.45; H, 4.85; N, 8.01.

3.8.15b : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-4-(2-nitrovinyl)-3-benzyloxy-azetidin-2-one 3.20b

Following the general procedure, treatment of 4-formylazetidin-2-one **3.18b** (1.87 g, 6 mmol) with nitromethane and triethylamine, followed by acetylation and elimination gave the nitro alkene **3.20b** (1.590 g, 75%).

MP : 137-138 ^{o}C

$[\alpha]^{28}_{D}$: +99.2 (c 1, $CHCl_3$)

IR ($CHCl_3$) : 1758 cm^{-1}, 1531 cm^{-1}, 1357 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.8 (s, 3H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.65-4.75 (m, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 5.05 (d, *J* = 5.4 Hz, 1H), 6.9 (d, *J* =8.8 Hz, 2H), 7.00-7.50 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.42, 55.79, 74.21, 83.36, 114.64, 118.35, 128.06, 128.24, 128.72, 129.78, 135.56, 135.89, 142.28, 156.91, 162.50.

MS (m/z) : 354 (M^+).

Analysis ($C_{19}H_{18}N_2O_5$) : Calculated: C, 64.38; H, 5.12; N, 7.90
Observed: C, 64.18; H, 4.96; N, 8.10.

3.8.15c : Preparation of (3*R*,4*S*)-1-benzyl-4-(2-nitrovinyl)-3-phenoxy-azetidin-2-one 3.20c

Following the general procedure, treatment of 4-formylazetidin-2-one **3.18c** (1.684 g, 6 mmol) with nitromethane and triethylamine, followed by acetylation and elimination gave the nitro alkene **3.20c** as a white solid (1.395 g, 72%).

MP : 95-97 ^oC

$[\alpha]^{28}_D$: +53.8 (c 0.5, $CHCl_3$).

IR ($CHCl_3$) : 1766 cm^{-1}, 1531 cm^{-1}, 1355 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 4.30 (d, *J* = 14.7 Hz, 1H), 4.45 (dd, *J* = 4.8 Hz, 8.0 Hz, 1H), 4.70 (d, *J* = 14.7 Hz, 1H), 5.50 (d, *J* = 4.8 Hz, 1H), 6.90-7.50 (m, 12H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 45.18, 55.10, 82.19, 115.28, 122.74, 128.47, 129.02, 129.57, 133.91, 134.68, 142.48, 156.52, 164.16.

MS (m/z) : 324 (M^+).

Analysis ($C_{18}H_{16}N_2O_4$) : Calculated: C, 66.65; H, 4.97; N, 8.64
Observed: C, 66.42; H, 4.73; N, 8.75.

3.8.16 : General procedure for the preparation of nitro alkanes 3.21a-c

To a solution of nitro alkenes (**3.20a-c**, 3.5 mmol) in anhydrous dichloromethane (15 ml) and methanol (1.50 ml), tributyltin hydride (1.1 ml, 4.2 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to get the pure nitro alkanes (**3.21a-c**).

3.8.16a : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.21a

Following the general procedure, nitro alkene **3.20a** (1.130 g, 3.5 mmol) was stirred with tributyltin hydride (1.1 ml, 4.2 mmol) at room temperature for 24 h to get the nitro alkane **3.21a** as a white solid (0.960 g, 85%).

MP : 108-110 ^{o}C

$[\alpha]^{28}_{D}$: +121.9 (c 1.05, $CHCl_3$).

IR ($CHCl_3$) : 1755 cm^{-1}, 1554 cm^{-1}, 1379 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.45-2.60 (m, 1H), 2.75-2.90 (m, 1H), 3.80 (s, 3H), 4.40-4.60 (m, 3H), 5.45 (d, *J* = 4.9 Hz, 1H), 6.9 (d, *J* = 8.8 Hz, 2H), 7.05-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.96, 54.26, 55.29, 71.35, 79.35, 79.69, 114.61, 115.57, 118.58, 122.63, 129.57, 156.78, 157.00, 159.50, 162.07.

MS (m/z) : 342 (M^+).

Analysis ($C_{18}H_{18}N_2O_5$) : Calculated: C, 63.15; H, 5.29; N, 8.18
Observed: C, 63.22; H, 5.44; N, 8.27.

3.8.16b : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-4-(2-nitroethyl)-3-benzyloxy-azetidin-2-one 3.21b

Following the general procedure, nitro alkene **3.20b** (1.240g, 3.5 mmol) was treated with tributyltin hydride (1.1 ml, 4.2 mmol) at room temperature for 24 h to get the nitro alkane **3.21b**, as thick colourless oil (1.030 g, 73%).

MP : Thick oil.

$[\alpha]^{28}_{D}$: +98.6 (c 0.9, $CHCl_3$).

IR ($CHCl_3$) : 1758 cm^{-1}, 1554 cm^{-1}, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.35-2.55 (m, 1H), 2.60-2.80 (m, 1H), 3.80 (s, 3H), 4.30-4.40 (m, 1H), 4.45-4.60 (m, 2H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 5.4 Hz, 1H), 5.05 (d, *J* = 11.7 Hz, 1H), 6.90 (d, *J* = 9.3 Hz, 2H), 7.25-7.50 (m, 7H).

^{13}C NMR ($CDCl_3$) : δ 25.06, 54.14, 55.35, 71.49, 73.25, 80.53, 114.64, 118.50,

(50.3 MHz) 127.87, 128.87, 128.50, 129.93, 136.66, 156.69, 163.86.

MS (m/z) : 356 (M^+).

Analysis : Calculated: C, 64.02; H, 5.66; N, 7.86

($C_{19}H_{20}N_2O_5$) Observed: C, 64.16; H, 5.52; N, 7.65.

3.8.16c : Preparation of (3*R*,4*S*)-1-benzyl-4-(2-nitroethyl)-3-phenoxy-azetidin-2-one 3.21c

Following the general procedure, nitro alkene **3.20c** (1.130g, 3.5 mmol) was treated with tributyltin hydride (1.1 ml, 4.2 mmol) at room temperature for 24 h to get the nitro alkane **3.21c**, as thick colourless oil (0.750 g, 65%).

MP : Thick oil.

$[\alpha]^{28}_D$: +120.6 (c 0.9, $CHCl_3$).

IR ($CHCl_3$) : 1758 cm^{-1}, 1554 cm^{-1}, 1384 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.30-2.40 (m, 2H), 3.85-3.95 (m, 1H), 4.30-4.40 (m, 3H), 4.60 (d, *J* = 15.2 Hz, 1H), 5.25 (d, *J* = 4.9 Hz, 1H), 6.95-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.98, 44.91, 54.87, 71.60, 80.60, 115.52, 122.58, 128.20, 129.05, 129.67, 134.86, 157.06, 165.44.

MS (m/z) : 326 (M^+).

Analysis : Calculated: C, 66.23; H, 5.56; N, 8.58

($C_{18}H_{18}N_2O_4$) Observed: C, 66.35; H, 5.44; N, 8.70.

3.8.17 : General procedure for the preparation of nitro esters 3.22a-c

A solution of nitro alkanes (**3.21a-c**, 3 mmol) in methanolic HCl (20%, 10 ml) was stirred at room temperature for 12 to 24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with saturated bicarbonate solution (10 ml), brine (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude nitro ester, which was purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate 80:20) to afford the pure nitro ester **3.22a-c**.

3.8.17a : Preparation of methyl(2*R*,3*S*)-3-[(4-methoxyphenyl)amino]-5-nitro-2-phenoxypentanoate 3.22a

Following the general procedure, nitro alkane **3.21a** (1.020 g, 3 mmol) was stirred in methanolic HCl (20%) for 24 h (TLC) to get the nitro ester **3.22a** as a pale yellow solid (0.910 g, 82%).

MP : 98-100 ^{o}C.

$[\alpha]^{28}_{D}$: -60.6 (c 1.1, $CHCl_3$).

IR ($CHCl_3$) : 3382 cm^{-1}, 1751 cm^{-1}, 1552 cm^{-1}, 1377 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.25-2.55 (m, 2H), 3.50 (s, 3H), 3.76 (s, 3H), 4.16-4.23 (m, 1H), 4.50-4.70 (m, 3H), 4.75 (d, *J* = 2.4 Hz, 1H), 6.65-7.35 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 29.99, 52.04, 54.50, 55.46, 72.26, 76.84, 114.75, 114.97, 115.82, 122.10, 129.53, 140.19, 152.87, 157.21, 169.67.

MS (m/z) : 374 (M^{+}).

Analysis ($C_{19}H_{22}N_2O_6$) : Calculated: C, 60.95; H, 5.92; N, 7.48
Observed: C, 60.75; H, 6.08; N, 7.31.

3.8.17b : Preparation of methyl(2*R*,3*S*)-3-[(4-methoxyphenyl)amino]-5-nitro-2-benzyloxypentanoate 3.22b

Following the general procedure, nitro alkane **3.21b** (1.060 g, 3 mmol) was stirred in methanolic HCl (20%) for 12 h (TLC) to get the nitro ester **3.22b** as a pale yellow oil (1.100 g, 91%).

MP : Thick oil.

$[\alpha]^{28}_{D}$: -11.9 (c 1, $CHCl_3$).

IR (Neat) : 3373 cm^{-1}, 1747 cm^{-1}, 1550 cm^{-1}, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.15-2.35 (m, 2H), 3.50 (s, 3H), 3.75 (s, 3H), 3.80-4.55 (m, 6H), 4.90 (d, *J* = 11.7 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.25-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 29.91, 51.64, 54.61, 55.53, 72.37, 72.74, 77.70, 114.82, 115.67, 128.24, 128.42, 136.80, 140.48, 152.83, 170.73.

MS (m/z) : 388 (M^+).

Analysis : Calculated: C, 61.83; H, 6.23; N, 7.21
($C_{20}H_{24}N_2O_6$) Observed: C, 61.62; H, 6.40; N, 7.38.

3.8.17c : Preparation of methyl(2*R*,3*S*)-3-benzylamino-5-nitro-2-phenoxypentanoate 3.22c

Following the general procedure, nitro alkane **3.21c** (0.970 g, 3 mmol) was stirred in methanolic HCl (20%) for 24 h (TLC) to get the nitro ester **3.22c** as a pale yellow oil (0.975 g, 91%).

MP : Thick oil.

$[\alpha]^{28}_D$: -11.6 (c 1.1, $CHCl_3$).

IR (Neat) : 3348 cm^{-1}, 1753 cm^{-1}, 1550 cm^{-1}, 1379 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.10-2.50 (m, 3H), 3.25-3.40 (m, 1H), 3.70-4.00 (m, 2H), 3.81 (s, 3H), 4.50-4.65 (m, 2H), 4.75 (d, *J* = 3.4 Hz, 1H), 6.80-7.50 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 29.33, 51.01, 52.23, 56.27, 72.55, 77.08, 114.97, 122.03, 127.14, 128.13, 128.31, 129.56, 139.67, 157.35, 170.40.

MS (m/z) : 358 (M^+).

Analysis : Calculated: C, 63.66; H, 6.19; N, 7.82
($C_{19}H_{22}N_2O_5$) Observed: C, 63.52; H, 6.05; N, 7.66.

3.8.18 : General procedure for preparation of 4-aminopiperidin-2-ones 3.23a-c

To a solution of nitro esters (**3.22a-c**, 1.6 mmol) in anhydrous methanol (10 ml), 10% Pd/C (0.100 g) was added, followed by ammonium formate (0.500 g, 8 mmol), and the reaction mixture was stirred at room temperature under argon for 2-16 h. After completion of reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with water (5ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent gave crude product which was purified by column chromatography (silica gel 60-120, pet. ether/ ethyl acetate-60:40) to afford pure 4-aminopiperidin-2-ones **3.23a-c**.

3.8.18a : Preparation of (3*R*,4*S*)-4-[(4-methoxyphenyl)amino]-3-phenoxy-piperidin-2-one 3.23a

Following the general procedure, nitro ester **3.22a** (0.598 g, 1.6 mmol) was treated with 10% Pd/C (0.100 g) and ammonium formate (0.500 g, 8 mmol) at room temperature for 3 h to get the 4-aminopiperidin-2-one **3.23a** as a white solid (0.394 g, 80%).

MP : 73-75 ^{o}C.

$[\alpha]^{28}_{D}$: +68.2 (c 1.1, $CHCl_3$).

IR ($CHCl_3$) : 3336 cm^{-1}, 1654 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.85-2.00 (m, 1H), 2.30-2.55 (m, 1H), 3.60-3.90 (m, 4H), 3.75 (s, 3H), 4.75 (d, *J* = 5.8 Hz, 1H), 6.60-7.40 (m, 10H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.28, 46.77, 52.58, 55.93, 78.17, 115.18, 116.43, 116.80, 122.42, 129.74, 140.18, 153.41, 158.59, 163.22.

MS (m/z) : 312 (M^+).

Analysis ($C_{18}H_{20}N_2O_3$) : Calculated: C, 69.19; H, 6.45; N, 8.97
Observed: C, 69.39; H, 6.33; N, 8.85.

3.8.18b : Preparation of (3*R*,4*S*)-4-[(4-methoxyphenyl)amino]-3-benzyloxy-piperidin-2-one 3.23b

Following the general procedure, nitro ester **3.22b** (0.622 g, 1.6 mmol) was treated with 10% Pd/C (0.100 g) and ammonium formate (0.500 g, 8 mmol) at room temperature for 6 h to get the 4-aminopiperidin-2-one **3.23b** as a white solid (0.345 g, 66%).

MP : 140-141 ^{o}C

$[\alpha]^{28}_{D}$: +43.1(c 1.03, $CHCl_3$)

IR ($CHCl_3$) : 3352 cm^{-1}, 1633 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.75-2.00 (m, 1H), 2.35-2.55 (m, 1H), 3.50-3.80 (m, 4H), 3.75 (s, 3H), 4.00 (d, *J* = 5.3 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 5.00 (d, *J* = 11.7 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2 H), 6.75

(d, J = 8.3 Hz, 2H), 7.20 –7.50 (m, 6H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.40, 45.61, 53.22, 55.75, 73.54, 76.78, 115.01, 116.18, 128.09, 128.50, 137.50, 139.67, 153.46, 163.45

MS (m/z) : 326 (M^+)

Analysis ($C_{19}H_{22}N_2O_3$) : Calculated: C, 69.90; H, 6.79; N, 8.58
Observed: C, 69.73; H, 6.74; N, 8.70.

3.8.18c : Preparation of (3*R*,4*S*)-4-benzylamino-3-phenoxy-piperidin-2-one 3.23c

Following the general procedure, the nitro ester **3.22c** (0.574 g, 1.6 mmol) was treated with 10% Pd/C (0.100 g) and ammonium formate (0.500 g, 8 mmol) at room temperature for 16 h to get the 4-aminopiperidin-2-one **3.23c** (0.292 g, 62%).

MP : 130-132 ^oC

$[\alpha]^{28}_D$: +25.0 (c 1.1, $CHCl_3$).

IR ($CHCl_3$) : 3330 cm^{-1}, 1662 cm^{-1}

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.70-1.90 (m, 1H), 2.20-2.35 (m, 1H), 3.10-3.20 (m, 1H), 3.35-3.90 (m, 4H), 4.60 (d, J = 7.3 Hz, 1H), 5.10 (bs, 2H), 6.80-7.35 (m, 10H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 24.33, 46.16, 51.01, 55.24, 77.67, 116.37, 122.10, 127.36, 128.02, 128.61, 129.45, 139.30, 158.71, 162.98

MS (m/z) : 296 (M^+).

Analysis ($C_{18}H_{20}N_2O_2$) : Calculated: C, 72.93; H, 6.80; N, 9.45
Observed: C, 73.10; H, 6.64; N, 9.66.

Section B

3.9 : Experimental

3.9.1 : Preparation of 1-(4-methoxyphenyl)-3-thiophenoxy-4-formylazetidin-2-one 3.25

To a stirred suspension of diimine **3.03a** (4 g, 15 mmol) and triethylamine (2.50 ml, 18 mmol) in anhydrous toluene, was added an anhydrous toluene solution of phenoxyacetyl chloride **3.24** (2.50 ml, 16.5 mmol) dropwise at room temperature under argon. The resulting mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), 5% aqueous HCl (35 ml) was added and the heterogeneous mixture was stirred at room temperature for 2 h. The organic layer was then diluted with toluene (25 ml), washed with 5% aqueous HCl (10 ml), water (3 x 10 ml), brine (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the crude product, which was purified by crystallization from methanol to get pure 4-formylazetidin-2-one **3.25** as a white solid (3.412 g, 73%)

MP : 148-150 ^{o}C (Lit[12] 153-154 ^{o}C).

IR ($CHCl_3$) : 1741 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 4.65 (dd, *J* = 5.3 Hz, 3.5 Hz, 1H), 5.00 (d, *J* = 5.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.10-7.50 (m, 7H), 9.75 (d, *J* = 3.5 Hz, 1H).

3.9.2 : Preparation of 1-(4-methoxyphenyl)-4-(2-nitrovinyl)-3-thiophenoxy-azetidin-2-one 3.26

To a solution of 4-formylazetidin-2-one **3.25b** (1.880 g, 6 mmol), in nitromethane (20 ml), was added triethylamine (0.1 ml, 1 mmol) at room temperature and the reaction mixture was stirred for 4 h. The excess nitromethane was removed under reduced pressure to afford a viscous oil of diastereomeric mixture of nitro alcohols. This mixture was dissolved in acetic anhydride (20 ml) and cooled to 0 ^{o}C. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^{o}C for 1 h. After completion of reaction (TLC), 2 ml water was added at 0 ^{o}C and stirred for 30 min. It was extracted with ethyl acetate (2 x 15 ml) and the organic layer was washed with saturated $NaHCO_3$ (3 x 10 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. The solvent was removed

under reduced pressure to afford diastereomeric mixture of nitro acetates, which was refluxed with benzene (20 ml) in the presence of $NaHCO_3$ (4.0 g, 48 mmol) for 5 h. After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitro alkene, which was further purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate, 80:20) to get pure nitro alkene **3.26** as pale yellow oil (1.250 g, 67%).

MP : Oil.

IR (Neat) : 1758 cm^{-1}, 1512 cm^{-1}, 1352 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.75 (s, 3H), 4.35 (d, *J* = 2.5 Hz, 1H), 4.45 (dd, *J* = 2.5 Hz, 6.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.10-7.70 (m, 9H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 55.28, 56.31, 59.36, 114.53, 118.32, 128.76, 129.31, 129.60, 130.48, 133.06, 136.69, 141.55, 156.80, 166.95.

MS (m/z) : 356 (M^+).

Analysis ($C_{18}H_{16}N_2O_4S$) : Calculated: C, 60.66; H, 4.52; N, 7.86; S, 8.98
Observed: C, 60.62; H, 4.60; N, 7.66; S, 8.77

3.9.3 : Preparation of 1-(4-methoxyphenyl)-4-(2-nitroethyl)-3-thiophenoxy-azetidin-2-one 3.27

To a solution of nitro alkene **3.26** (1.250 g, 3.5 mmol) in anhydrous dichloromethane (15 ml) and methanol (1.5 ml), tributyltin hydride (1.1 ml, 4.2 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel 230-400 mesh, pet. ether/ethyl acetate, 80:20) to get pure nitro alkane **3.27** as pale yellow oil (0.914 gm, 73%).

MP : Oil.

IR (Neat) : 1753 cm^{-1}, 1556 cm^{-1}, 1379cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.00-2.25 (m, 1H), 2.75-2.95 (m, 1H), 3.75 (s, 3H), 3.90-4.00 (m, 1H), 4.10 (d, *J* = 2.0 Hz, 1H), 4.15-4.50 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.15-7.60 (m, 7H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 28.70, 55.35, 56.78, 57.44, 70.86, 114.60, 119.12, 128.76,

129.34, 131.14, 133.57, 156.80, 161.73.

MS (m/z) : 358 (M^+).

Analysis ($C_{18}H_{18}N_2O_4S$) : Calculated: C, 60.32; H, 5.07; N, 7.82; S, 8.93
Observed: C, 60.47; H, 5.01; N, 7.87; S, 8.87

3.9.4 : Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-3-hydroxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin2-one 3.30

A mixture of azetidin-2-one **3.16b** (3.830 g, 10 mmol), ammonium formate (3.160, 50 mmol) and 10% Pd/C (0.600 g) in anhydrous acetone (30 ml) was refluxed for 30 min. After completion of reaction (TLC), the catalyst was filtered through a celite bed and washed with acetone. The solvent was removed under reduced pressure to afford the 3-hydroxy β-lactam **3.30** as a white solid (2.776 g, 95%).

MP : 196-198 ^oC (Lit[16] 200 ^oC).

IR ($CHCl_3$) : 3330 cm^{-1}, 1737 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.35 (s, 3H), 1.50 (s, 3H), 3.75 (s, 3H), 3.80-3.95 (m, 1H), 4.20-4.35 (m, 2H), 4.40-4.55 (m, 1H), 5.05 (d, *J* = 5.5 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H).

3.9.5 : Preparation of *S*-methyl xanthate 3.31

To a cooled (0 ^oC) suspension of NaH (50% dispersion in oil, 0.345 g, 7.2 mmol) in anhydrous THF (5 ml), a solution of 3-hydroxy β-lactam **3.30** (1.750 g, 6 mmol) in anhydrous THF (15 ml) was slowly added. After completion of addition, the reaction mixture was stirred at room temperature for 30 min. Then it was cooled to 0 ^oC and CS_2 (1.10 ml, 18 mmol) was added and the reaction mixture was stirred for 1.5 h at 0 ^oC. The MeI (1.50 ml, 24 mmol) was added at 0 ^oC and the reaction mixture was stirred at room temperature for 30 min. After completion of reaction (TLC), saturated NH_4Cl (5 ml) was added and the solvent was removed under reduced pressure. The residue was taken in dichloromethane (25 ml) and the organic layer was washed with water (10 ml), saturated brine solution (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (silica gel, 230-400 mesh, pet.ether/ethyl acetate 85:15), to afford the pure *S*-methyl xanthate ester **3.31** as a white solid (1.783 g, 78%).

MP : 108-110 °C (Lit[26] 110-112 °C).

$[\alpha]^{28}_D$: +60.4 (c 1, CH_2Cl_2) (Lit[26] $[\alpha]^{30}_D$ = +62.7 c 1, CH_2Cl_2).

IR ($CHCl_3$) : 1757 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.4 (s, 3H), 1.55 (s, 3H), 2.65 (s, 3H), 3.60-3.70 (m, 1H), 3.75 (s, 3H), 4.05-4.20 (m, 1H), 4.35-4.45 (m, 2H), 6.90 (m, 3H), 7.70 (d, *J* = 9.3 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 19.47, 24.77, 26.27, 55.20, 61.45, 66.41, 76.34, 78.87, 109.94, 113.83, 119.60, 130.48, 156.62, 160.77, 214.47.

3.9.6 : Preparation of (4*R*)-1-(4-methoxyphenyl)-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin2-one 3.32

To a solution of *S*-methyl xanthate **3.31** (1.512 g, 4 mmol) in anhydrous toluene (50 ml) were added Bu_3SnH (1.30 ml, 4.8 mmol) and AIBN (30 mg). The contents were refluxed under argon for 1 h. After completion of reaction (TLC), the reaction mixture was cooled and filtered. The solvent from the filtrate was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (silica gel, 230-400 mesh, pet. ether/ethyl acetate, 80:20) to furnish the pure 3-unsubstituted β-lactam **3.32** as a white solid (0.935 g, 86%).

MP : 109-110 °C (Lit[26] 110-112 °C).

$[\alpha]^{28}_D$: +71.2 (c 0.5, CH_2Cl_2) (Lit[26] $[\alpha]^{30}_D$ = +74.9 c 0.5, CH_2Cl_2).

IR ($CHCl_3$) : 1743 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 1.4 (s, 3H), 1.55 (s, 3H), 2.75 (dd, *J* = 2.4 Hz, 15.2 Hz, 1H), 3.15 (dd, *J* = 5.4 Hz, 15.2 Hz, 1H), 3.70-3.80 (m, 1H), 3.75 (s, 3H), 4.00-4.20 (m, 2H), 4.35-4.50 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.5 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 25.02, 26.68, 38.48, 53.44, 5.46, 65.68, 77.18, 110.63, 114.16, 118.98, 131.44, 156.21, 163.64.

3.9.7 : Preparation of (4*R*)-1-(4-methoxyphenyl)-4-formyl-azetidin-2-one 3.33

A mixture of β-lactam **3.32** (1.665 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.342 g, 1.8 mmol) in THF (20 ml) and water (8 ml) was refluxed for 2 h.

After completion of reaction (TLC) the reaction mixture was neutralized with sodium bicarbonate and solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (25 ml) and the organic layer was washed with saturated brine solution (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the diol **3.17a-c**, which was dissolved in acetone (30 ml) and water (15 ml) and cooled to 0 ^{o}C. To the cooled diol solution, powdered $NaIO_4$ (1.540 g, 7.2 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After the completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was taken in dichloromethane (25 ml) and the organic layer was washed with water (1 x 5 ml), saturated sodium bicarbonate solution (2 x 10 ml), saturated brine solution (10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford the β-lactam **3.33** as pale yellow oil (0.980 g, 80%), which was immediately used without further purification.

IR ($CHCl_3$) : 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.10 (dd, *J* = 2.7 Hz, 15.4 Hz, 1H), 3.40 (dd, *J* = 5.8 Hz, 15.4 Hz, 1H), 3.75 (s, 3H), 4.35-4.45 (m, 1H), 6.85 (d, *J* = 9.3 Hz, 2H), 7.25 (d, *J* = 9.3 Hz, 2H), 9.75 (d, *J* = 4.4 Hz, 1H).

3.9.8 : Preparation of (4*R*)-1-(4-methoxyphenyl)-4-(2-nitrovinyl)-azetidin-2-one 3.35

To a solution of 4-formyl azetidin-2-one **3.33** (1.230 g, 6 mmol), in nitromethane (20 ml), was added triethylamine (0.1 ml, 1 mmol) at room temperature and the reaction mixture was stirred for 4 h. The excess nitromethane was removed under reduced pressure to afford a viscous oil of diastereomeric mixture of nitro alcohols **3.34**. This mixture was dissolved in acetic anhydride (20 ml) and cooled to 0 ^{o}C. A drop of Conc. H_2SO_4 was added to the reaction mixture and stirred at 0 ^{o}C for 1 h. After completion of reaction (TLC), 2 ml water was added at 0 ^{o}C and stirred for 30 min. It was extracted with ethyl acetate (2 x 15 ml) and the organic layer was washed with saturated $NaHCO_3$ (3 x 10 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diastereomeric mixture of nitro acetates, which was refluxed with benzene (20 ml) in the presence of $NaHCO_3$ (4.0 g, 48 mmol) for 5 h.

After completion of reaction (TLC), solid was removed by filtration and the solvent from the filtrate was removed under reduced pressure to afford the crude nitro alkene, which was further purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate, 80:20) to get pure nitro alkene **3.35** as colourless oil (1.160 g, 75%).

MP : Oil.

$[\alpha]^{28}_D$: +201.7 (c 1.15, $CHCl_3$).

IR ($CHCl_3$) : 1745 cm^{-1}, 1529 cm^{-1}, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 3.00 (dd, *J* = 3.0 Hz, 15.1 Hz, 1H), 3.50 (dd, *J* = 5.8 Hz, 15.1 Hz, 1H), 3.80 (s, 3H), 4.65-4.80 (m, 1H), 6.90 (d, *J* = 9.3 Hz, 2H), 7.20 (d, *J* = 13.2 Hz, 1H), 7.25 (d, *J* = 9.3 Hz, 2H), 7.38 (dd, *J* = 13.2 Hz, 6.3 Hz).

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 43.59, 47.59, 55.28, 114.46, 117.76, 130.37, 138.53, 141.14, 156.36, 161.84.

MS (m/z) : 248 (M^+).

Analysis ($C_{12}H_{12}N_2O_4$) : Calculated: C, 58.04; H, 4.87; N, 11.28.
Observed: C, 58.20; H, 4.68; N, 11.32.

3.9.9 : Preparation of (4*S*)-1-(4-methoxyphenyl)-4-(2-nitroethyl)-azetidin-2-one 3.36

To a solution of nitro alkene **3.36** (0.866 g, 3.5 mmol) in anhydrous CH_2Cl_2 (10 ml) and MeOH (1 ml), tributyltin hydride (1.1 ml, 4.2 mmol) was added at room temperature and stirred for 24 h. After completion of reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to get pure nitro alkane **4a** as a white solid (0.651 g, 75%).

MP : 78-80 ^oC.

$[\alpha]^{28}_D$: +66.5 (c 1.05, $CHCl_3$).

IR ($CHCl_3$) : 1743 cm^{-1}, 1554 cm^{-1}, 1388 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.10-2.35 (m, 1H), 2.75 (dd, *J* = 2.1 Hz, 14.9 Hz, 1H), 2.75-2.95 (m, 1H), 3.25 (dd, *J* = 5.1 Hz, 14.9 Hz, 1H), 3.80 (s, 3H), 4.10-4.25 (m, 1H), 4.40-4.55 (m, 2H), 6.0 (d, *J* = 8.8 Hz, 2H),

7.25 (d, *J* = 8.8 Hz, 2H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 29.25, 41.49, 47.92, 55.13, 71.27, 114.31, 118.24, 130.08, 156.07, 162.68

MS (m/z) : 250 (M^+).

Analysis ($C_{12}H_{14}N_2O_4$) : Calculated: C, 57.57; H, 5.64; N, 11.19
Observed: C, 57.45; H, 5.80; N, 11.34.

3.9.10 : Preparation of methyl(3*S*)-3-[4-(methoxyphenyl)amino]-5-nitro-pentanoate 3.37

A solution of nitro alkane **3.37** (0.752 g, 3 mmol) in methanolic HCl (20%, 10 ml) was stirred at room temperature for 24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with saturated bicarbonate solution (10 ml), brine (10 ml), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude nitro ester, which was purified by column chromatography (silica gel 60-120, pet. ether/ethyl acetate 80:20) to afford the pure nitro ester **3.37** as pale yellow oil (0.766 g, 90%).

MP : Oil.

$[\alpha]^{28}_D$: -37.9 (c 1, $CHCl_3$).

IR ($CHCl_3$) : 3365 cm^{-1}, 1730 cm^{-1}, 1550 cm^{-1}, 1380 cm^{-1}.

^{1}H NMR ($CDCl_3$) (200 MHz) : δ 2.10-2.60 (m, 4H), 3.70 (s, 3H), 3.80 (s, 3H), 4.50-4.65 (m, 2H), 6.65 (d, *J* = 9.3 Hz, 2H), 6.80 (d, *J* = 9.3 Hz, 2H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ δ 31.93, 38.15, 49.28, 57.42, 55.35, 72.55, 114.75, 115.60, 140.22, 152.65, 171.47.

MS (m/z) : 282 (M^+).

Analysis ($C_{13}H_{18}N_2O_5$) : Calculated: C, 55.29; H, 6.43; N, 9.93
Observed: C, 55.42; H, 6.25; N, 9.75.

3.9.11 : Preparation of (4*S*)-4-[(4-methoxyphenyl)amino]-piperidin-2-one 3.38

To a solution of nitro ester **3.37** (0.452g, 1.6 mmol) in anhydrous methanol (10 ml), 10% Pd/C (100 mg) was added, followed by ammonium formate (0.500 g, 8 mmol),

and the reaction mixture was stirred at room temperature under argon for 2 h. After completion of reaction (TLC), the reaction mixture was filtered through celite bed and the bed was washed with methanol. The solvent from the filtrate was removed under reduced pressure and the residue was dissolved in dichloromethane (20 ml), washed with water (5ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which was purified by column chromatography (silica gel 60-120, pet. ether/ ethyl acetate-60:40) to afford pure 4-aminopiperidin-2-ones **3.38** as a white solid (0.260 g, 73%).

MP : 144 ^oC.

$[\alpha]^{28}_D$: -9.9 (c 1.05, $CHCl_3$).

IR ($CHCl_3$) : 3336 cm^{-1}, 1633 cm^{-1}.

^1H NMR ($CDCl_3$) (200 MHz) : δ 1.90-3.00 (m, 4H), 3.50-4.00 (m, 4H), 3.75 (s, 3H), 5.5 (bs, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.85, (d, *J* = 8.8 Hz, 2H)

^{13}C NMR ($CDCl_3$) (50.3 MHz) : δ 27.89, 37.34, 46.23, 48.44, 55.72, 115.08, 116.48, 138.53, 153.68, 163.12.

MS (m/z) : 220 (M^+).

Analysis ($C_{12}H_{16}N_2O_2$) : Calculated: C, 65.42; H, 7.32; N, 12.72
Observed: C, 65.55; H, 7.43; N, 12.85.

3.9.12 : Preparation of (4*S*)-1-methyl-4-[(4-methoxyphenyl)-*N*-Boc-amino]-piperidin-2-one 3.39

To a cooled (0 ^oC) anhydrous dichloromethane solution of 4-aminopiperidin-2-one (0.100 g, 0.45 mmol) was added triethylamine (0.1 ml, 0.59 mmol) followed by di-*tert*-butyl-dicarbonate (0.118 g, 0.54 mmol). The reaction mixture was allowed to attain room temperature and was stirred for 3 h. After completion of reaction (TLC), two drops of water was added at 0 ^oC and stirred for 10 min. It was diluted with dichloromethane and the organic layer was washed with water (5 ml), brine (5 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the Boc protected compound as a thick oil, which was dissolved in 1,2 dimethoxyethane and K_2CO_3 (0.124 g, 0.9 mmol) was added and the contents were refluxed. To the refluxing mixture, CH_3I (0.3 ml, 4.5 mmol) was added and further refluxed for 6 h. K_2CO_3 was filtered and washed with dichloromethane. The solvent was removed to get the crude

product, which was subsequently flash chromatographed (silica gel 230-400 mesh, pet.ether/ethyl acetate, 55:45) to get the pure *N*-methylated compound **3.39** as pale yellow oil (0.520 g, 50%).

$[\alpha]^{28}_{D}$ **:** -15.15 (c 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$) (200 MHz) **:** δ 1.55 (s, 9H), 2.10-2.25 (m, 2H), 2.60-2.70 (m, 2H), 2.75 (s, 3H), 3.65-3.75 (m, 2H), 3.75 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$) (125.8) **:** δ 27.47, 27.61, 29.67, 34.92, 35.96, 48.31, 55.63, 85.65, 114.70, 120.16, 151.29, 154.45, 165.43.

3.10 : References

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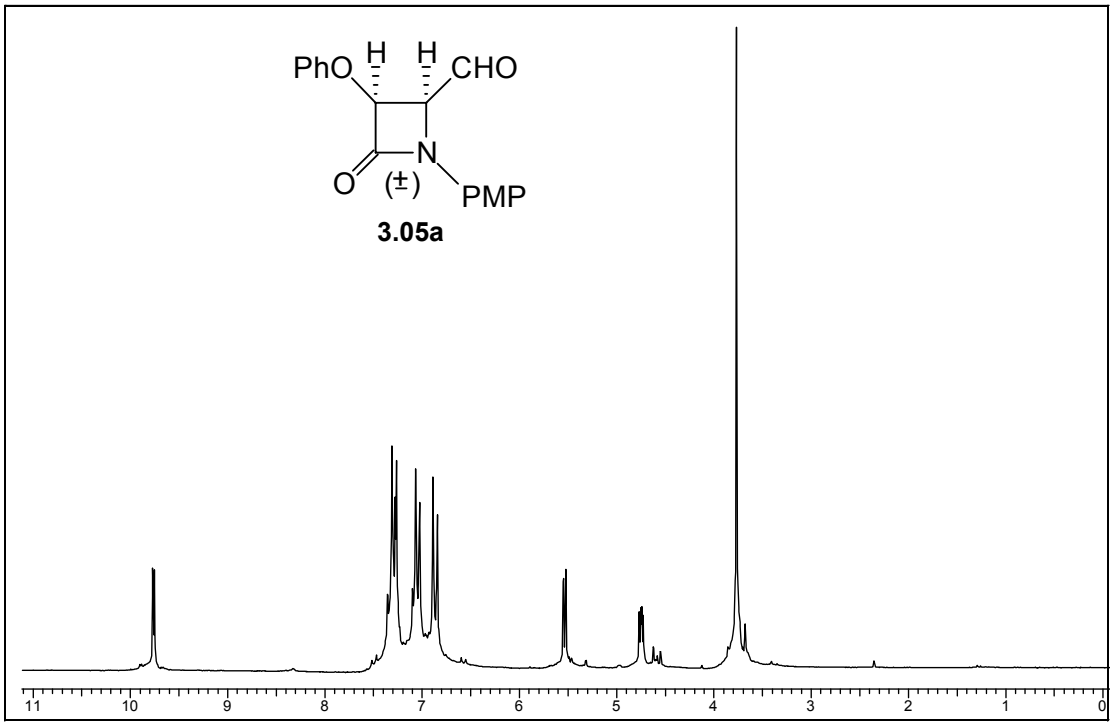

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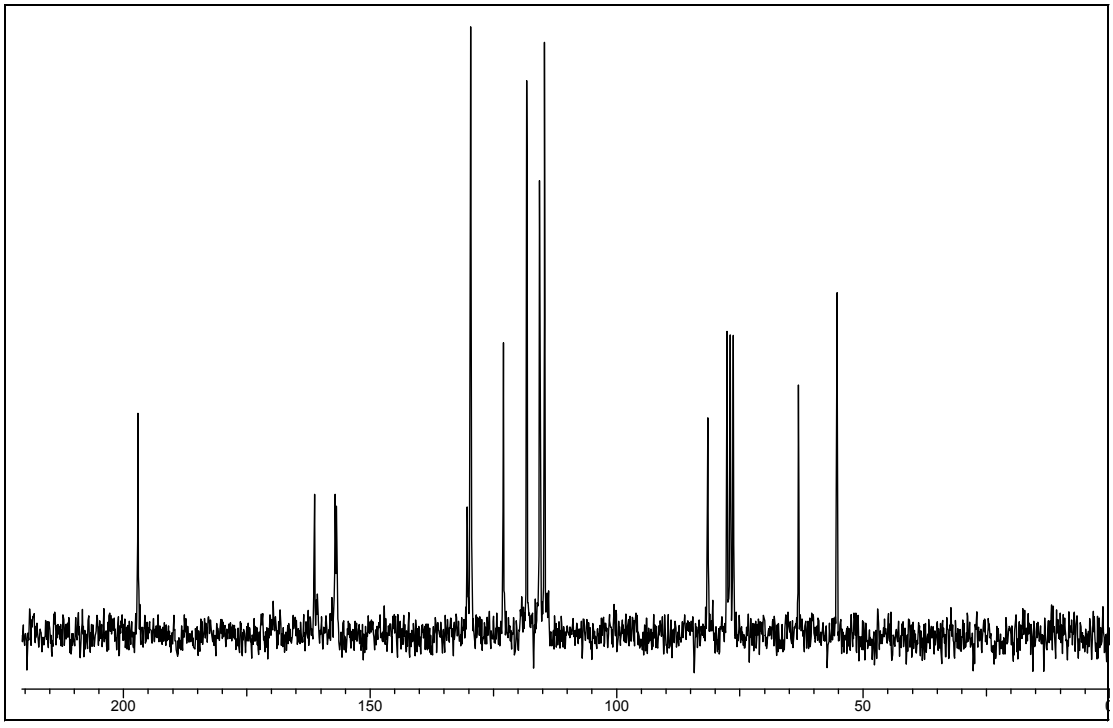

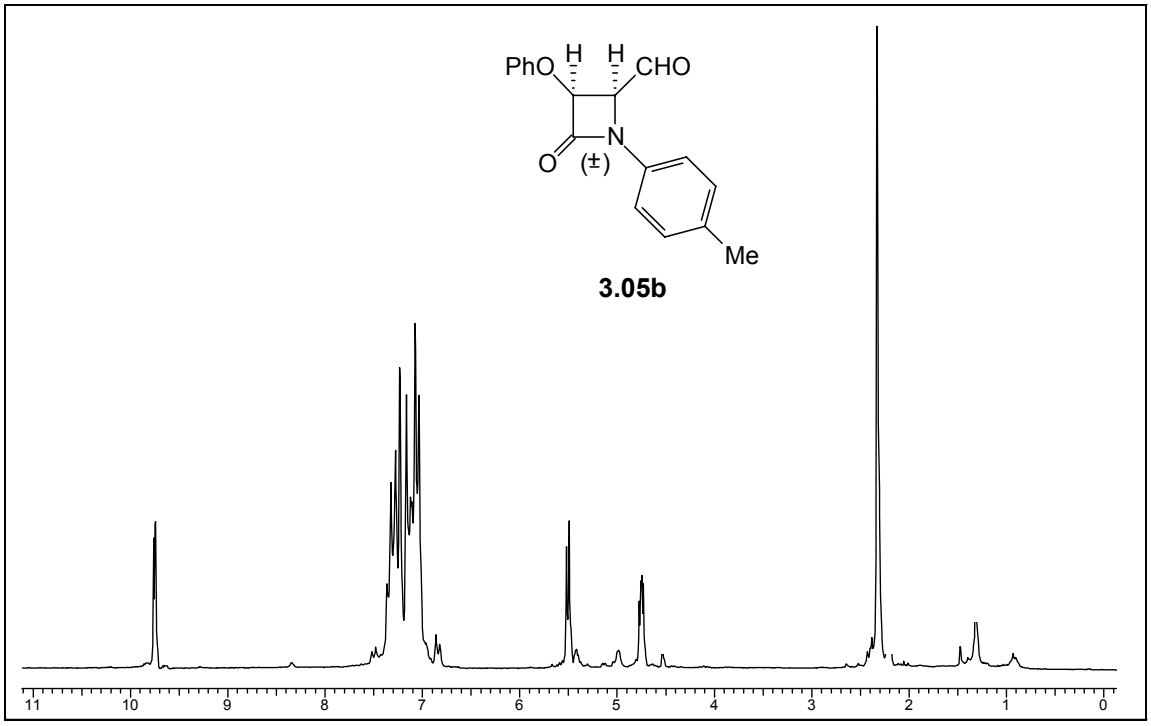
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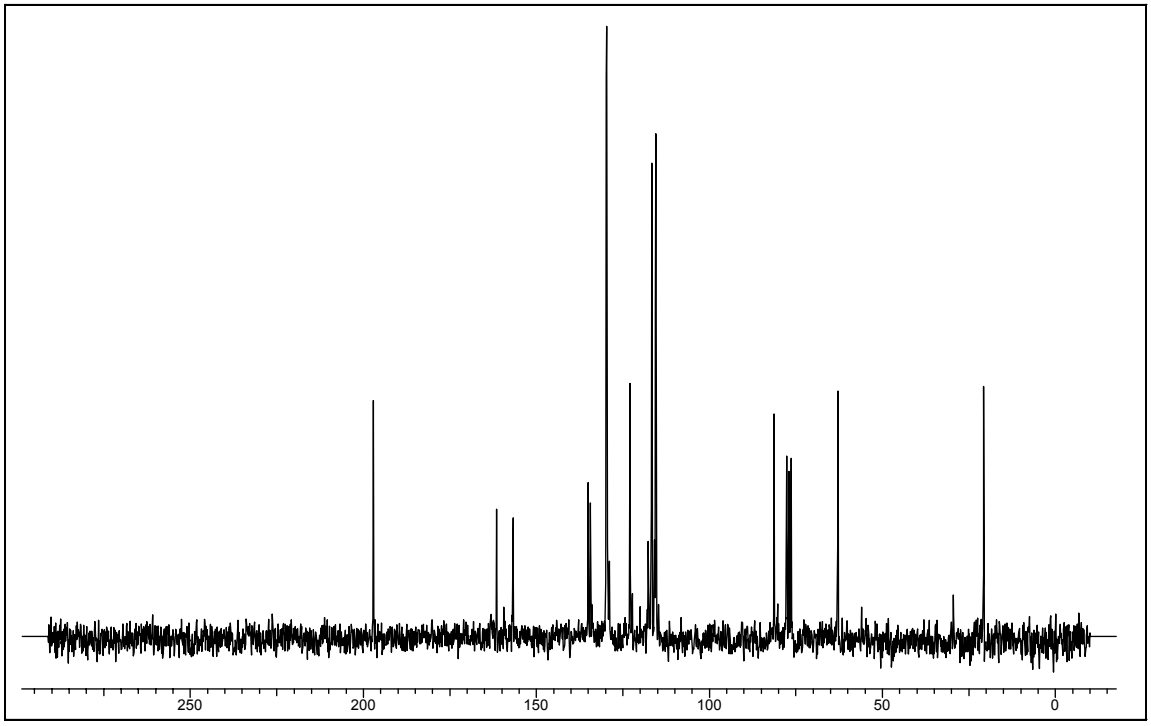
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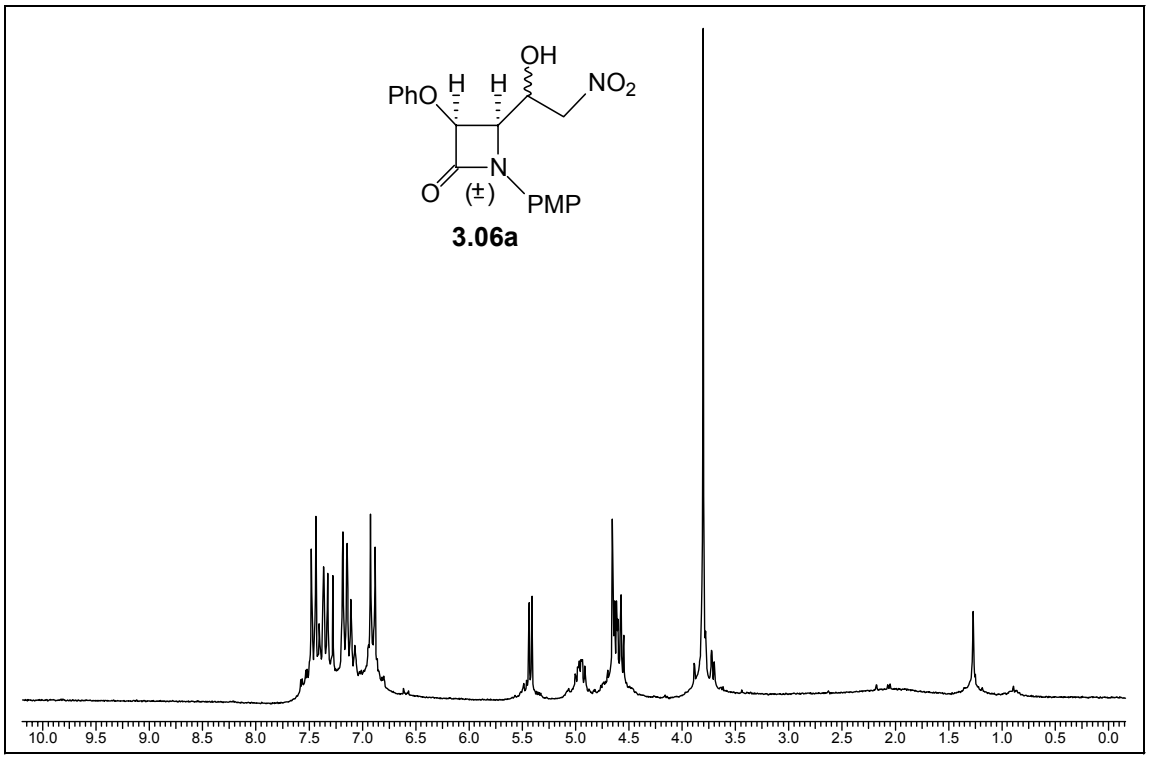
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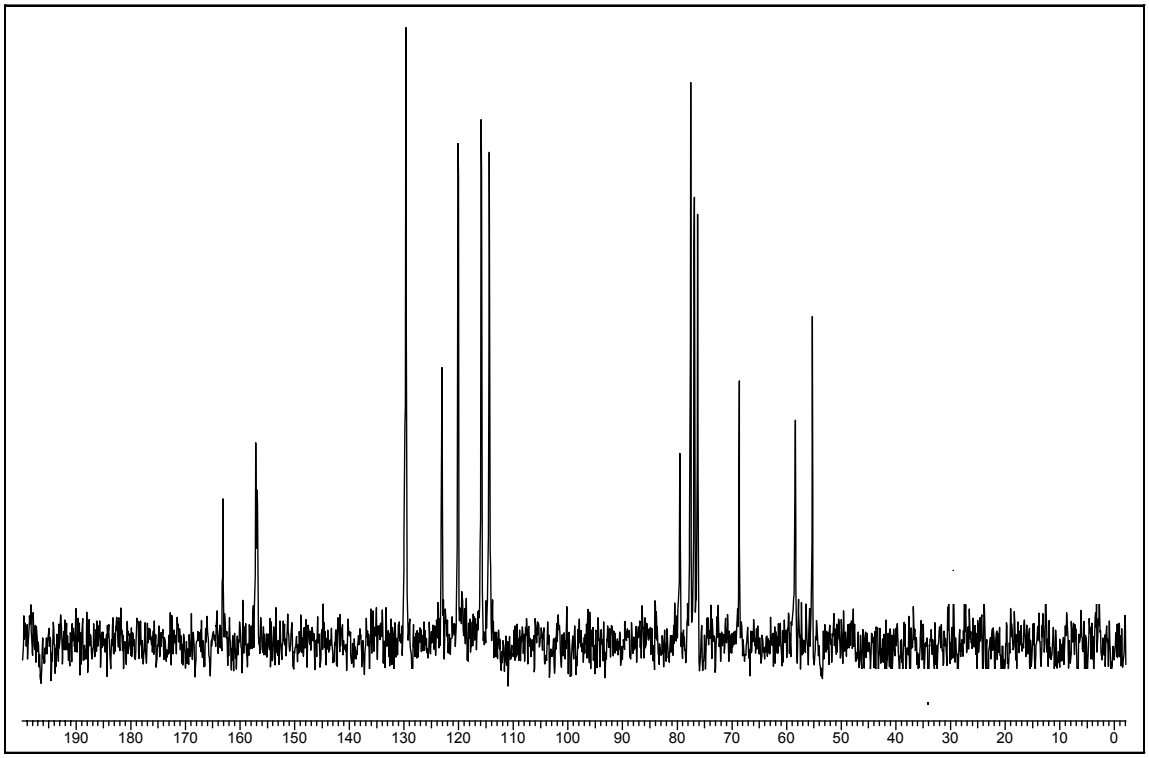
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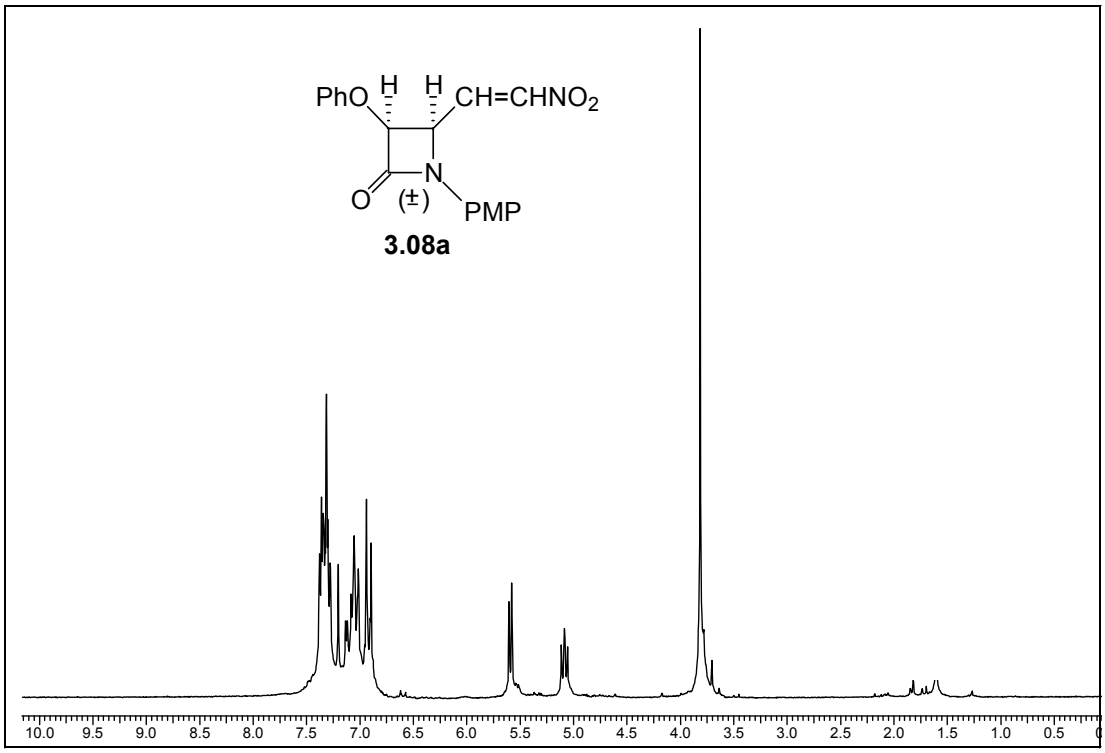
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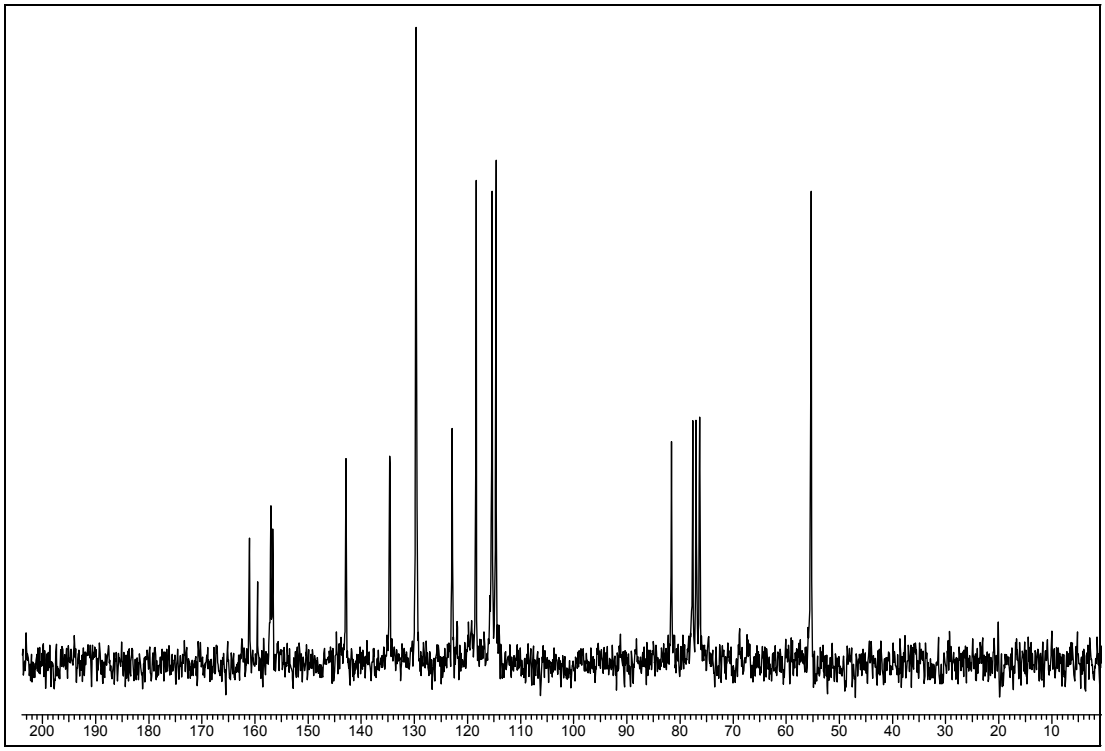
3.08a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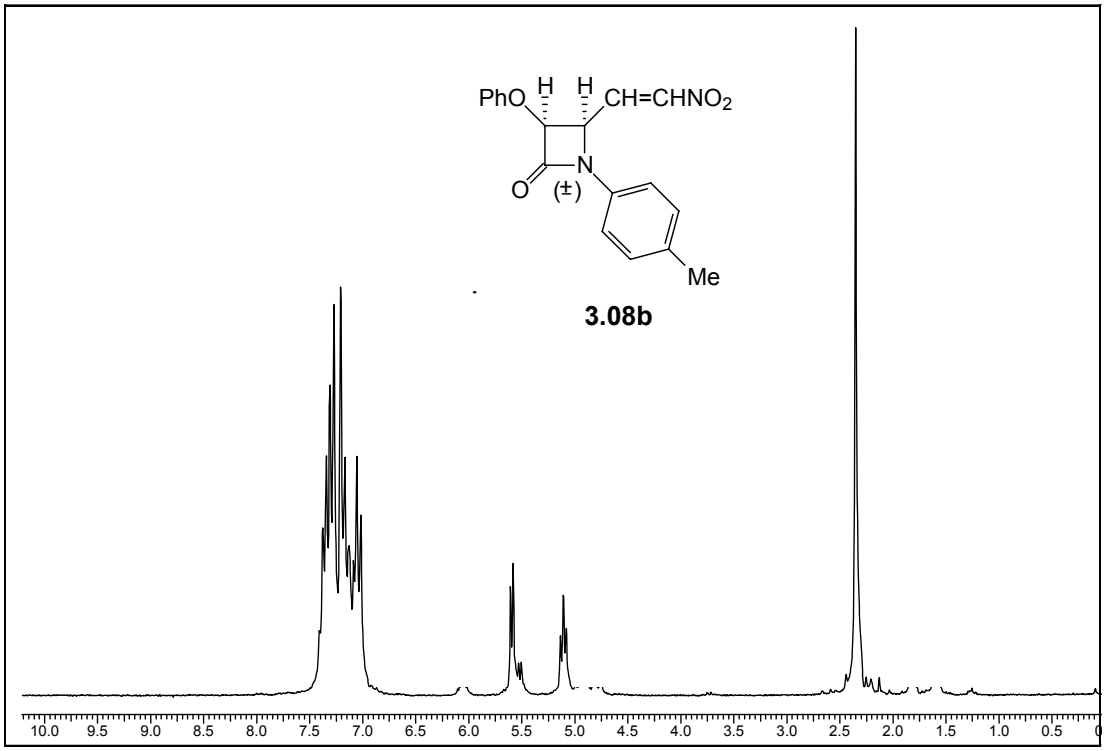
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(±)
Me
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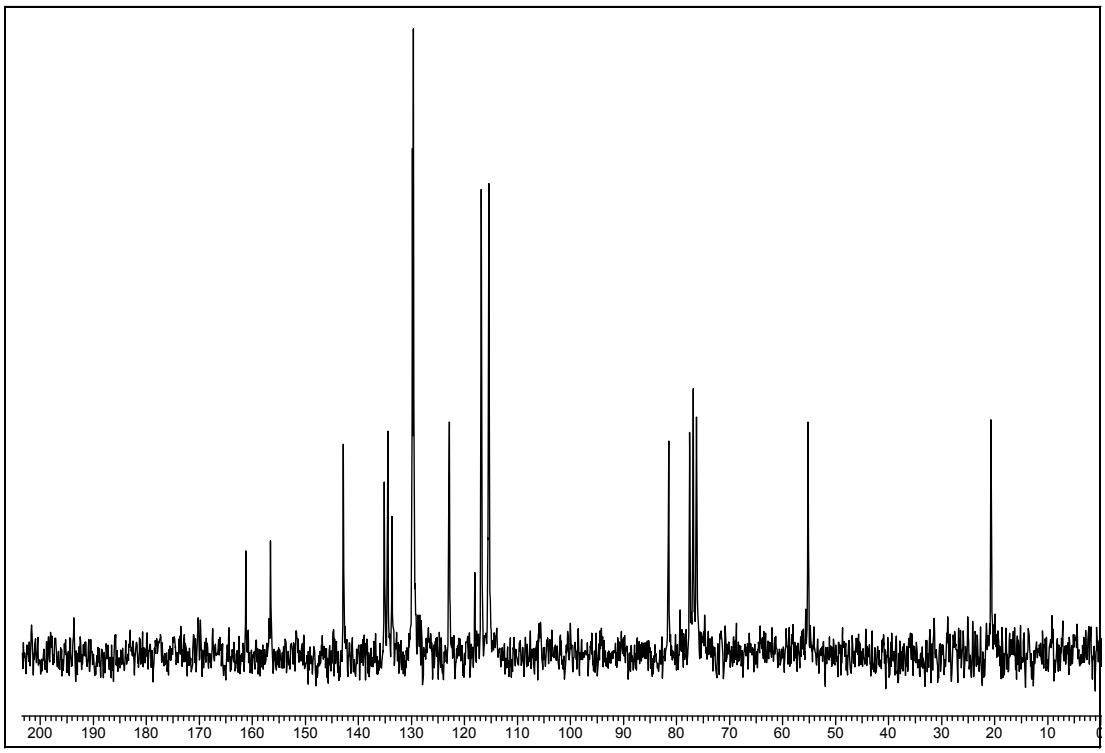
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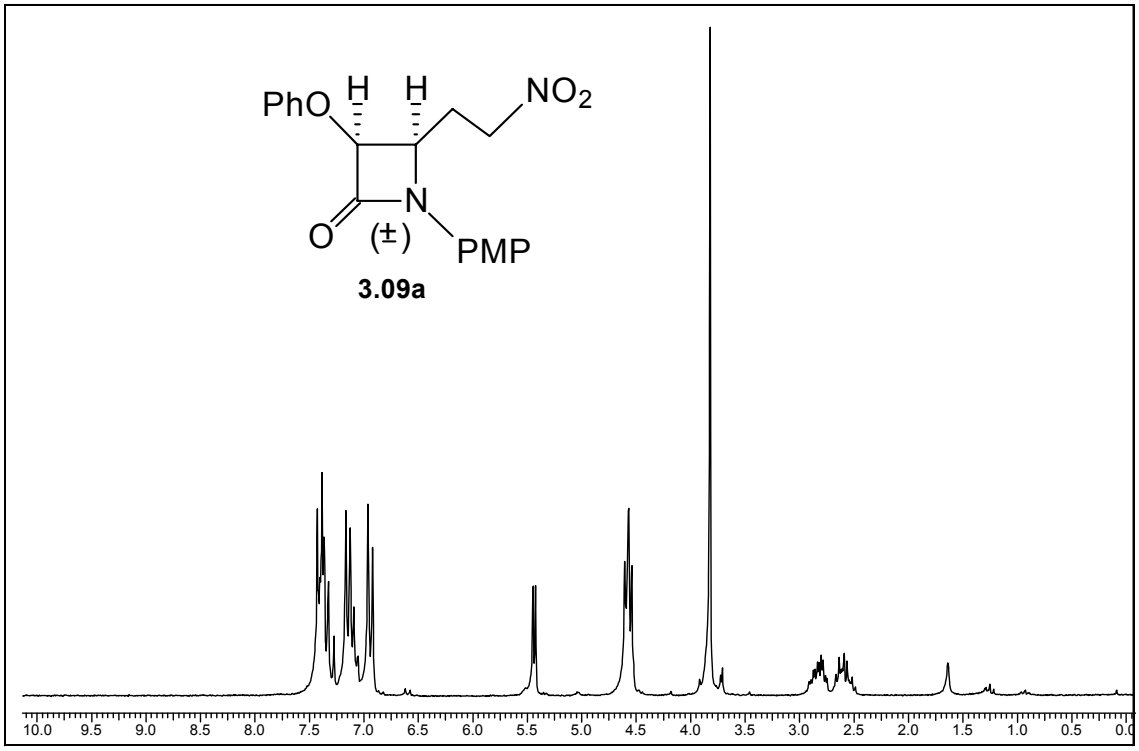
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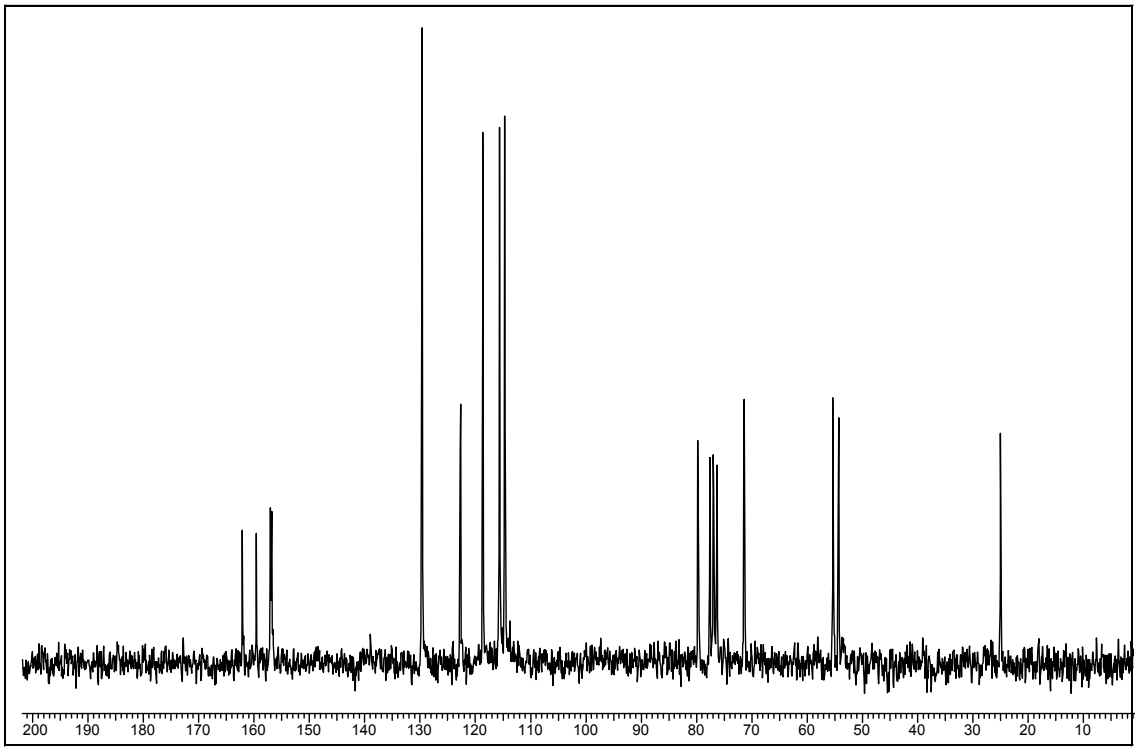
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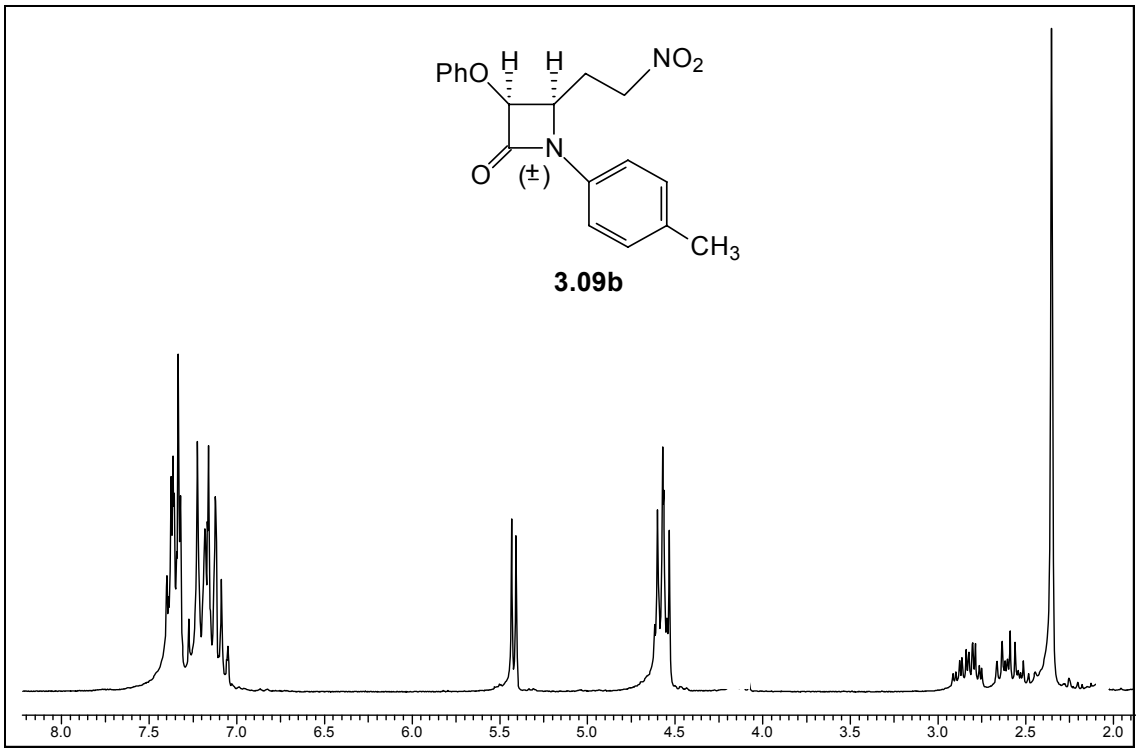
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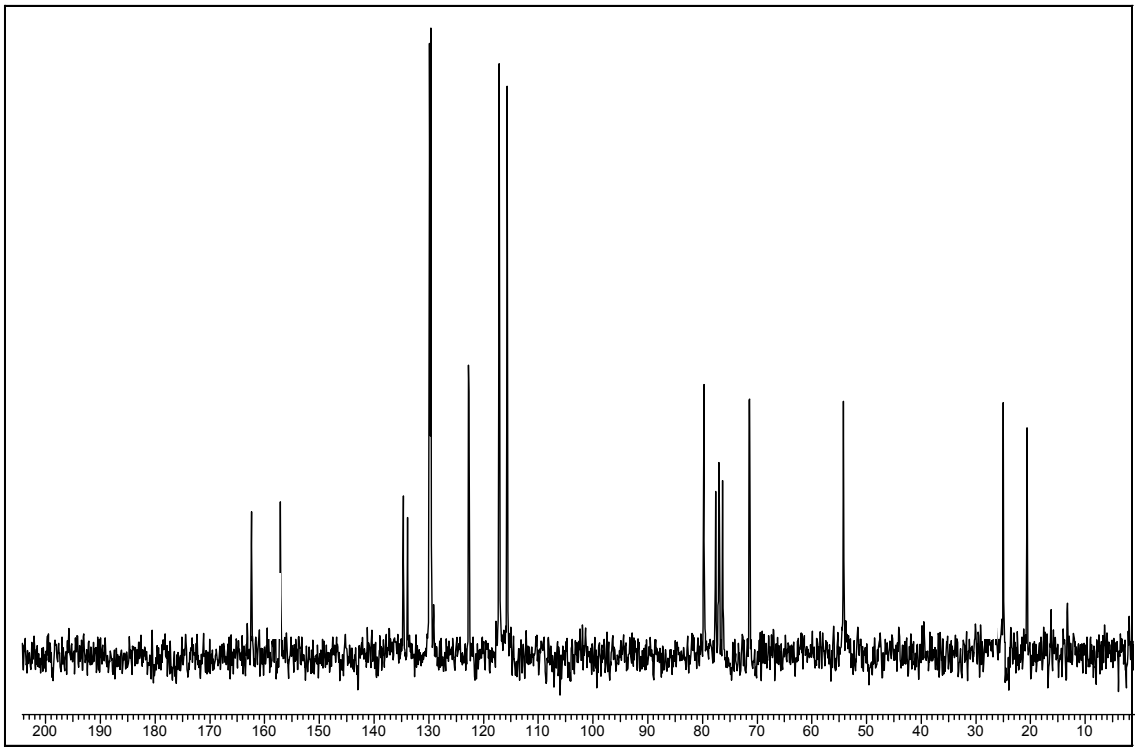
3.09b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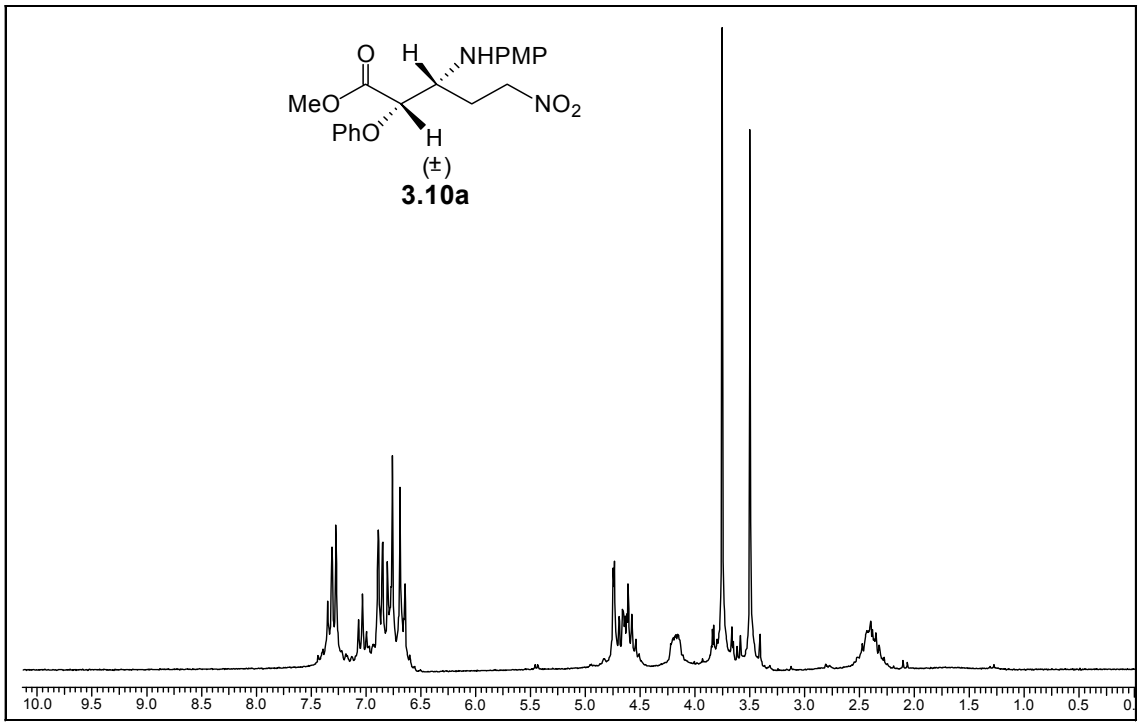
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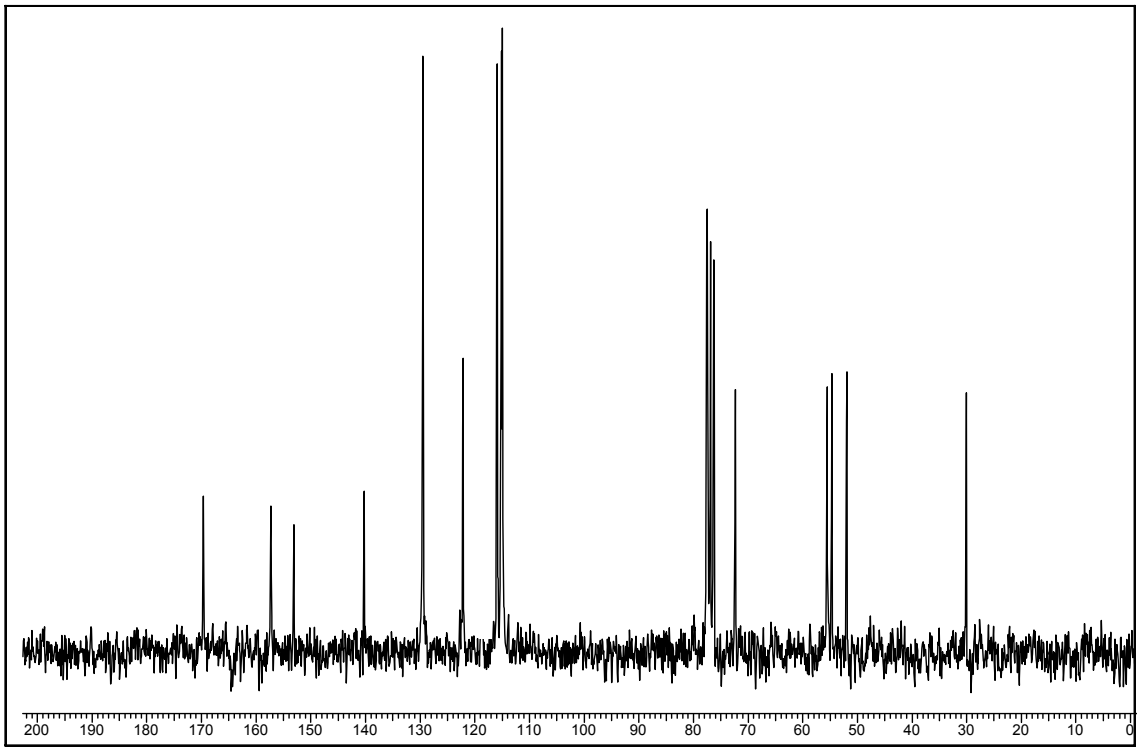
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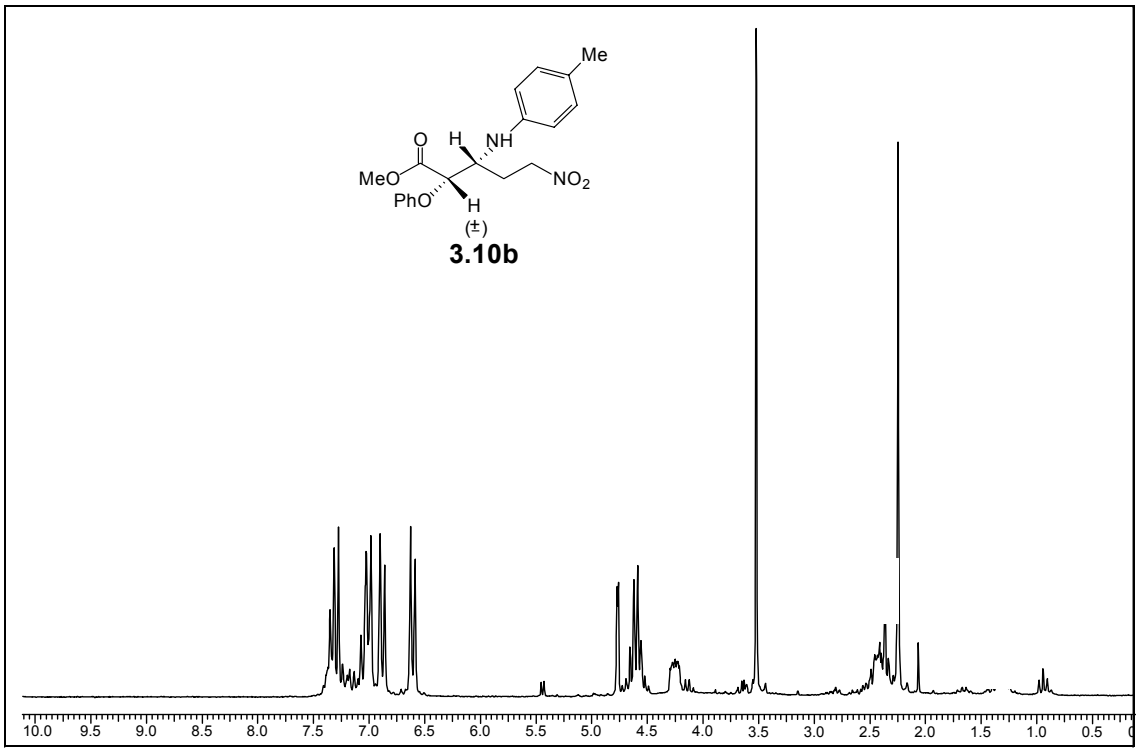
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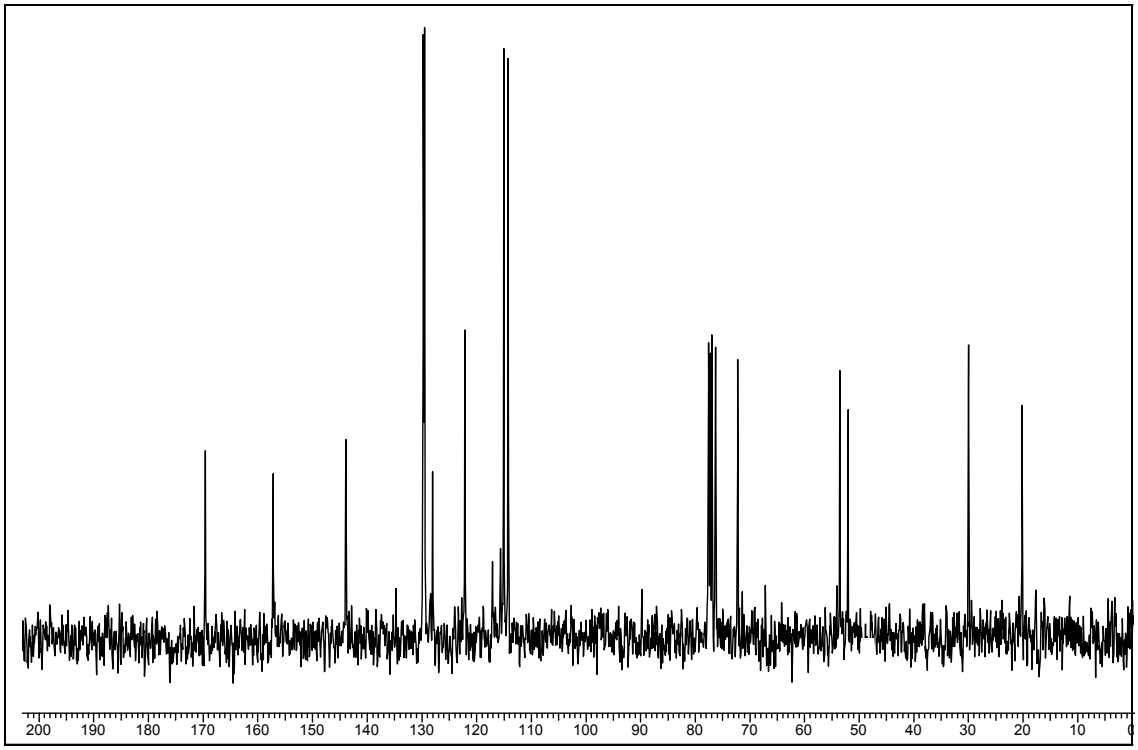
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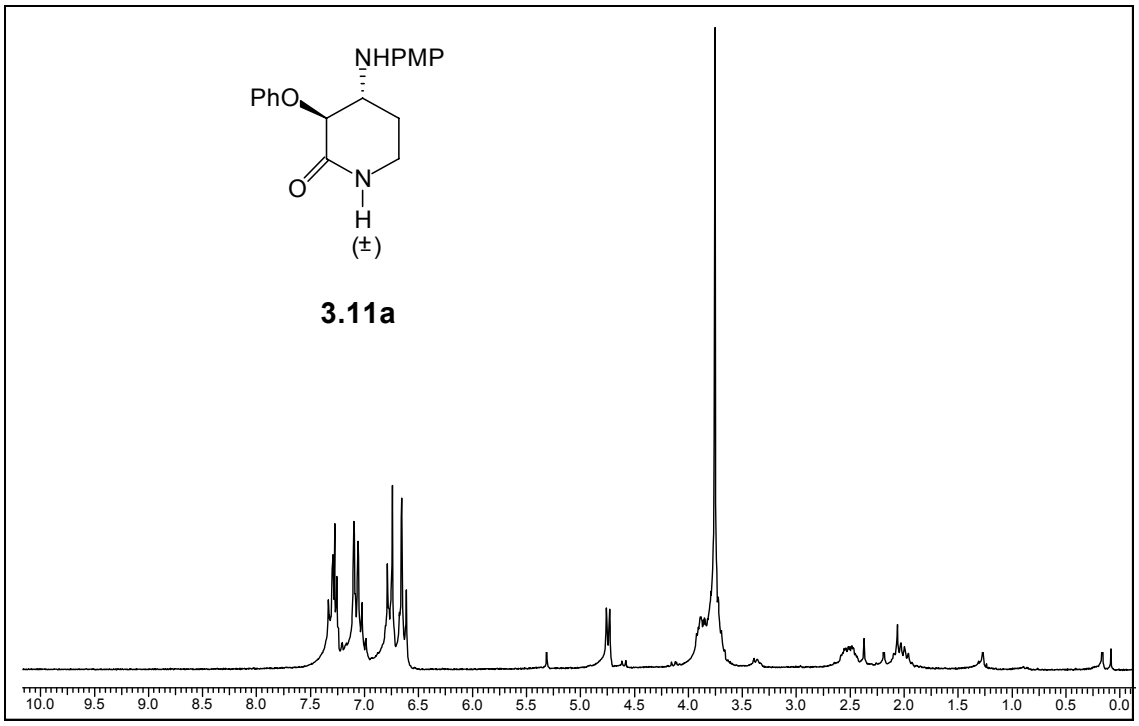
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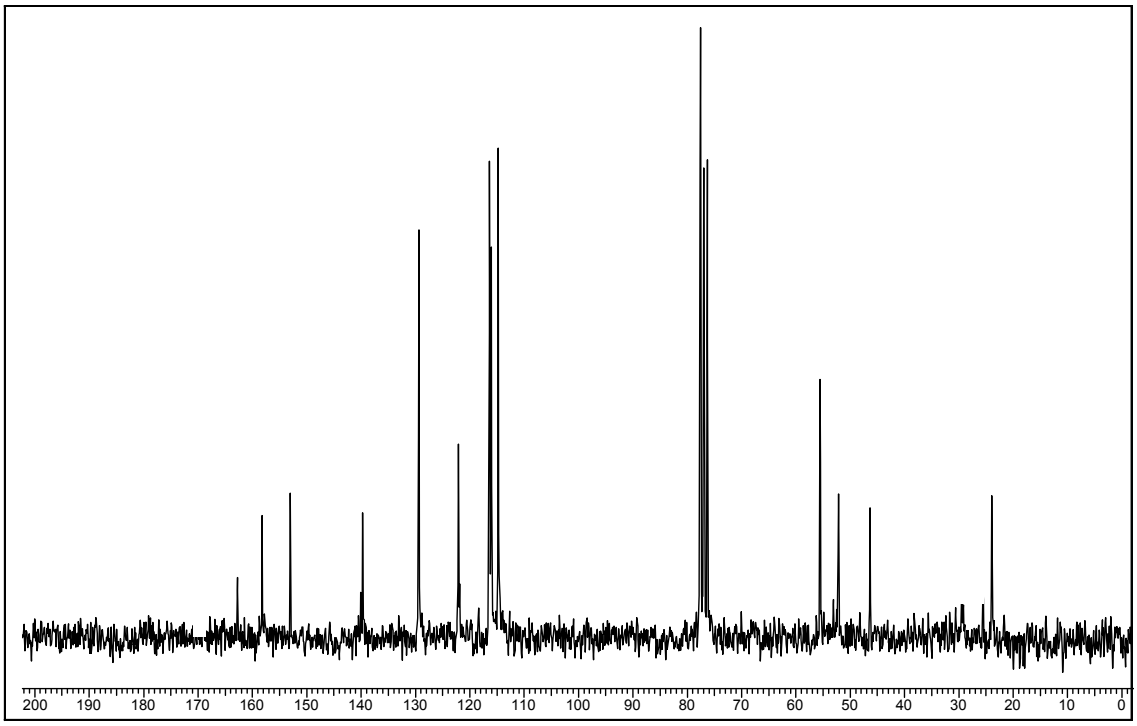
3.11a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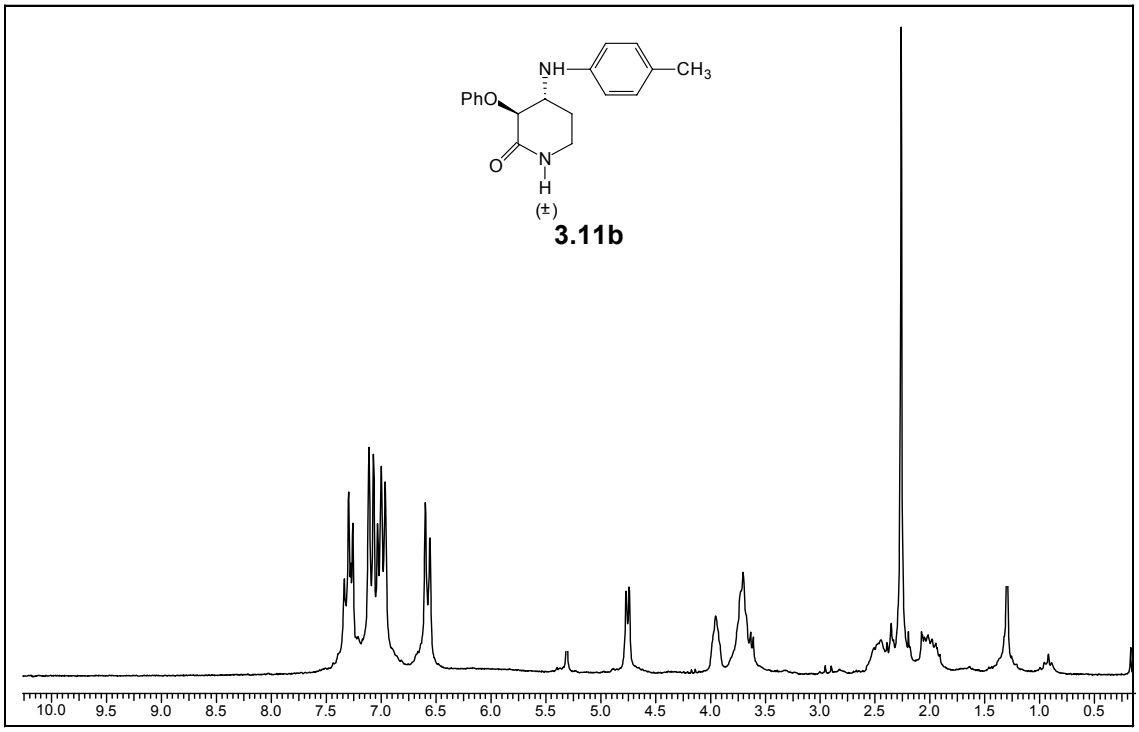
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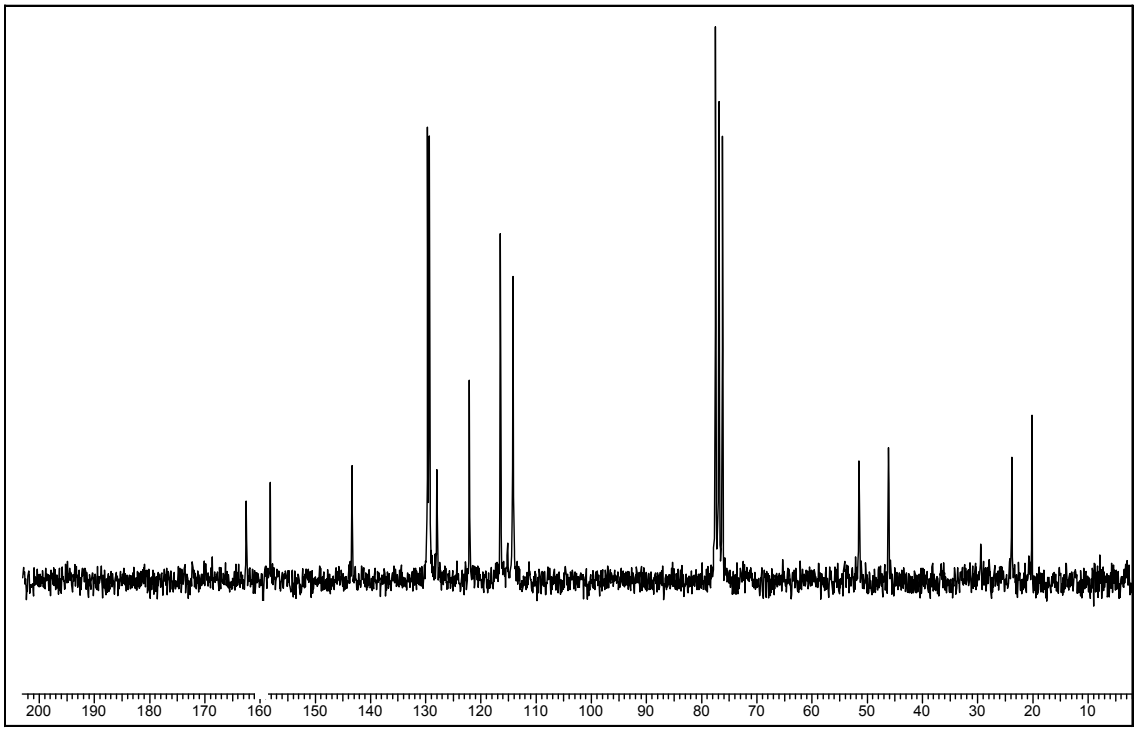
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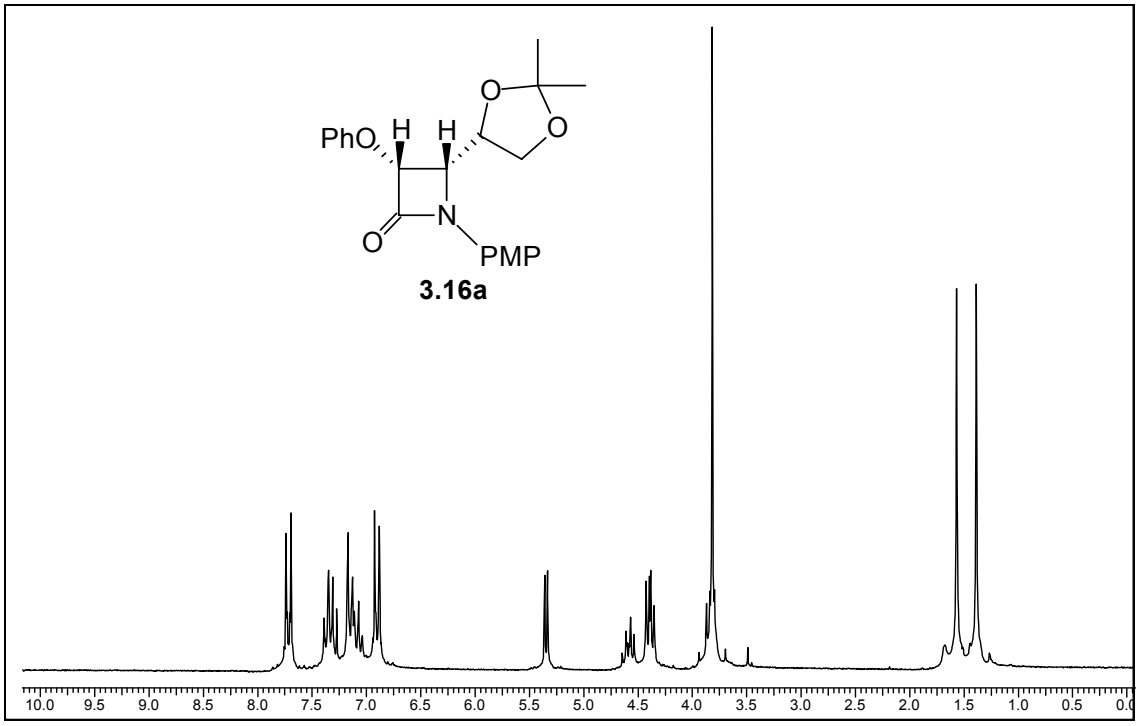
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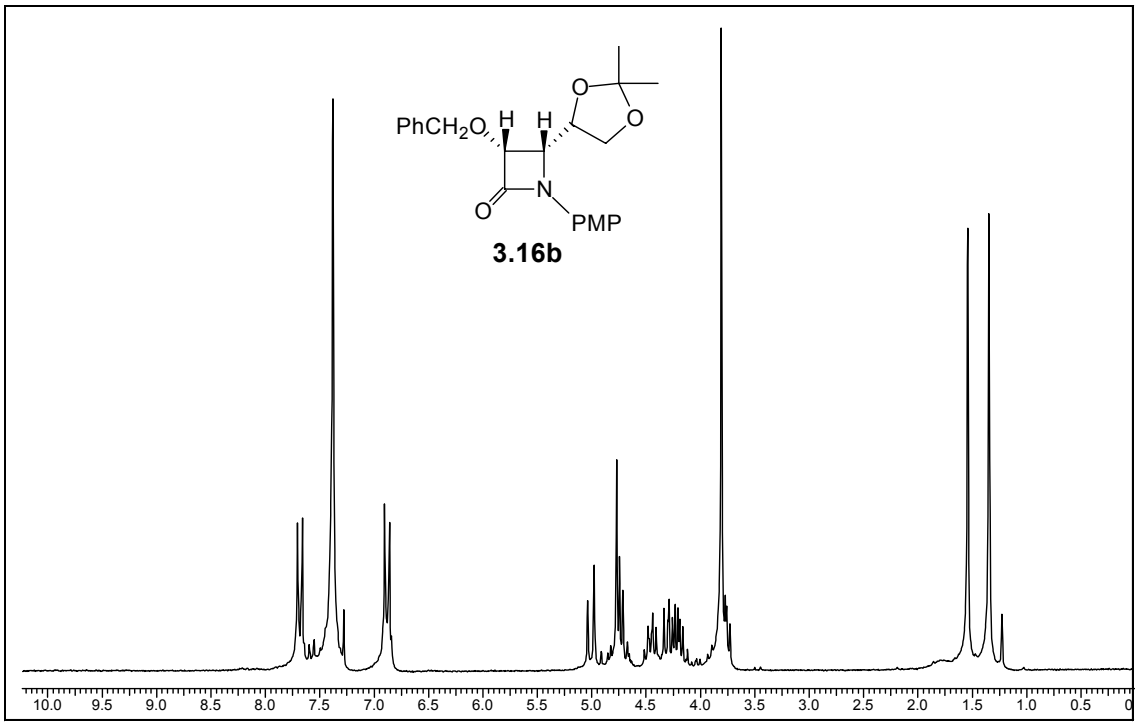
3.16a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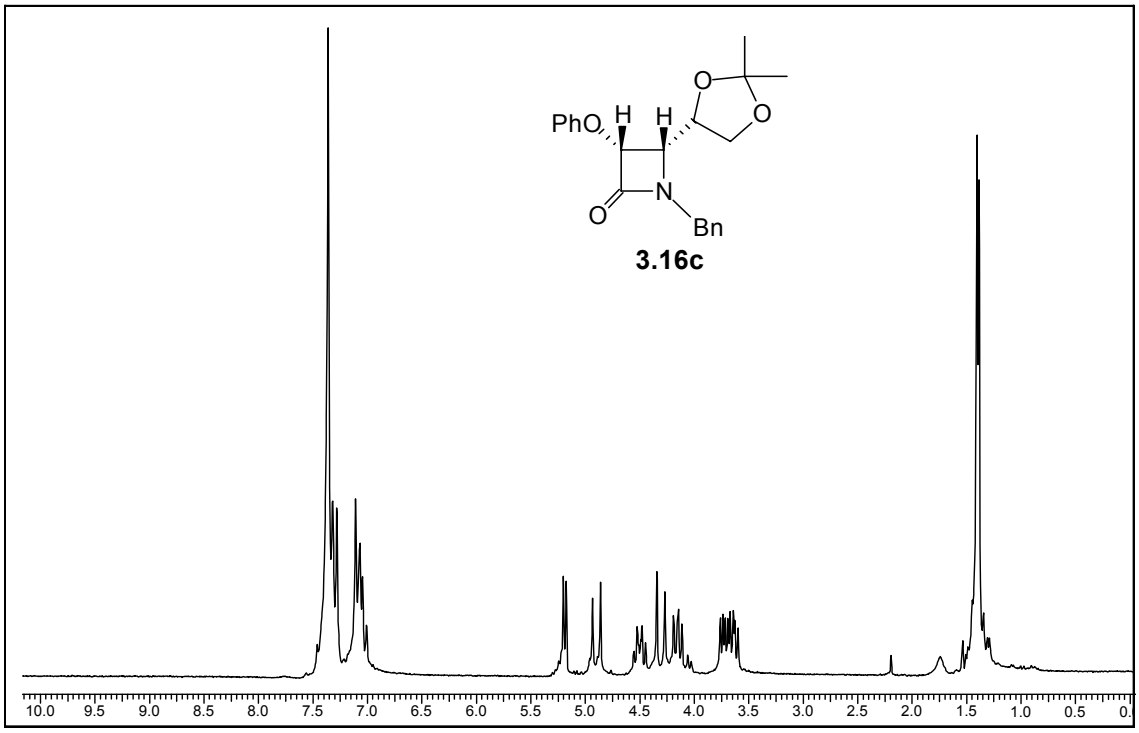
3.16b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O
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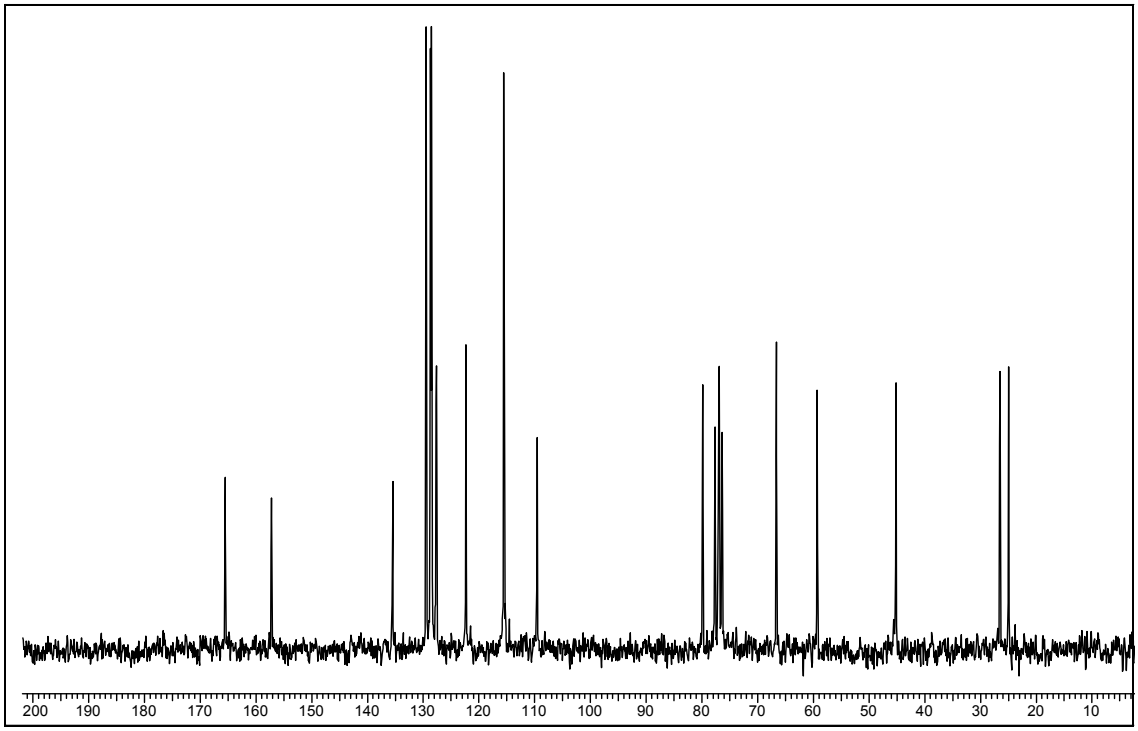
3.16c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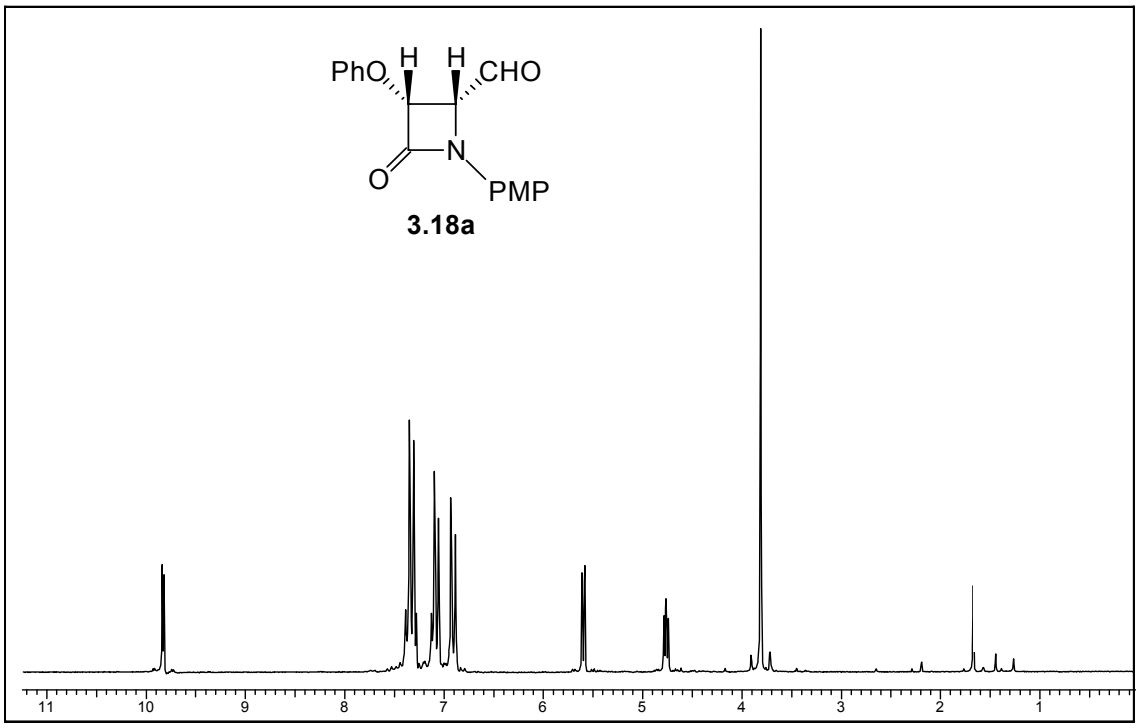
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CHO
N
O
PMP
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4
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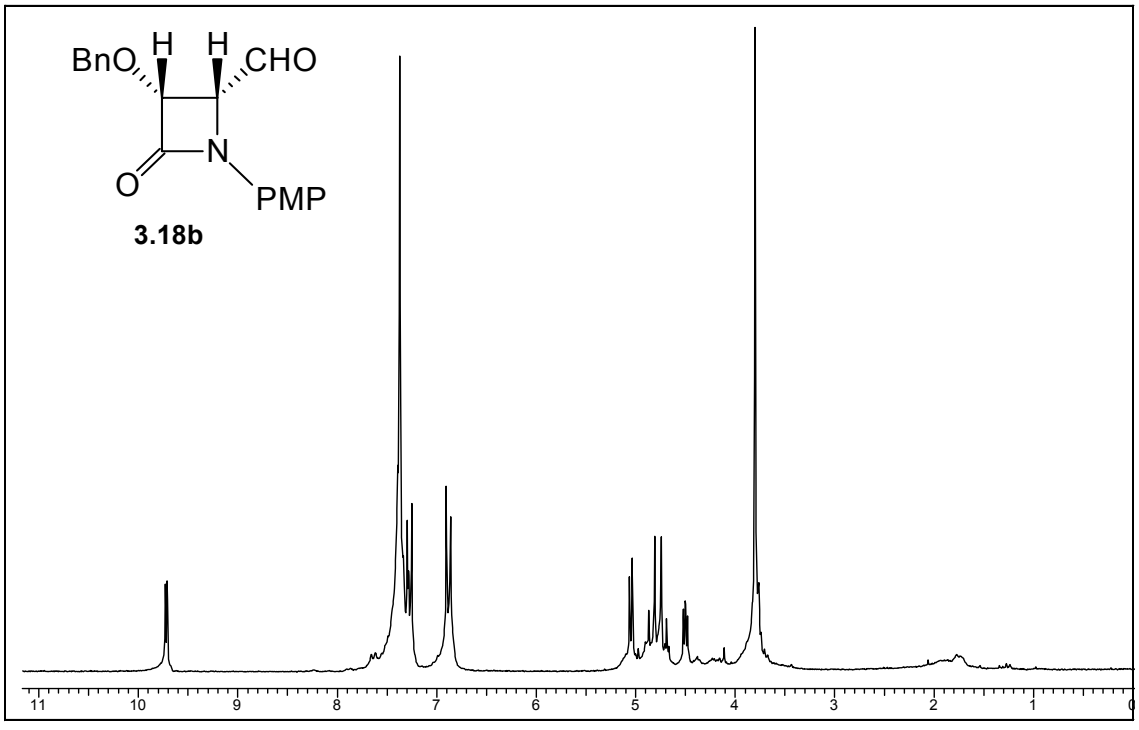
2
1

3.18a


BnO
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H
CHO
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O
PMP
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1
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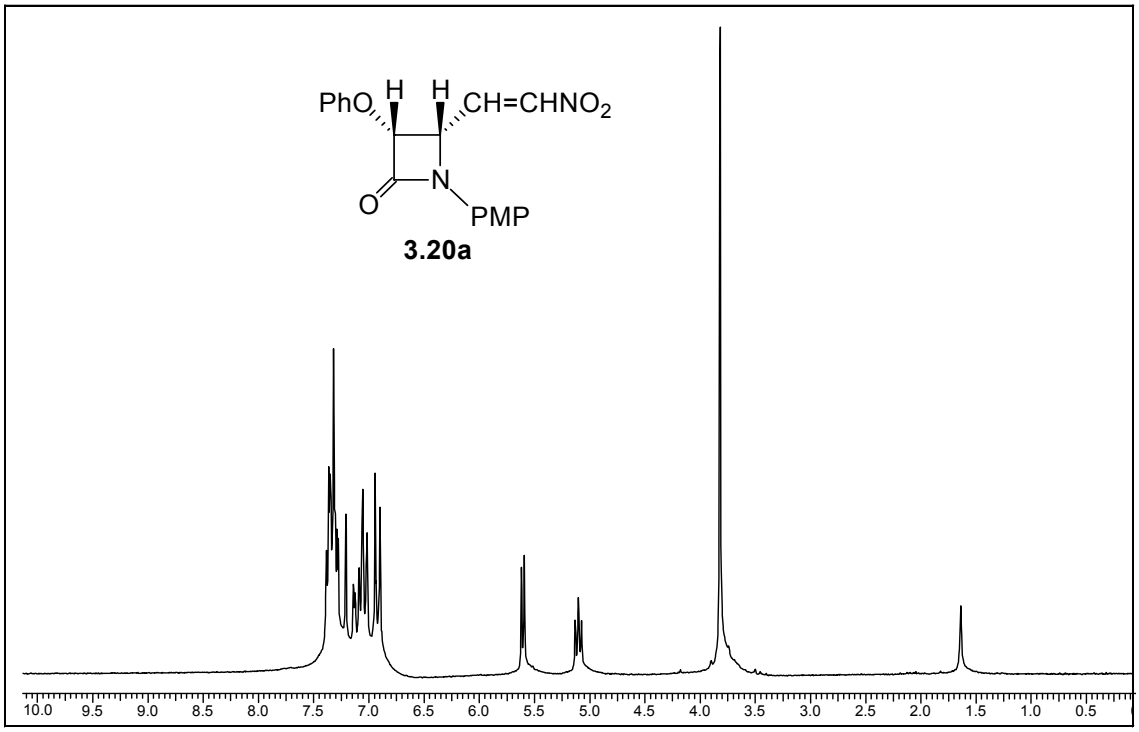
3.18b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H
H
CH=CHNO2
O
N
PMP
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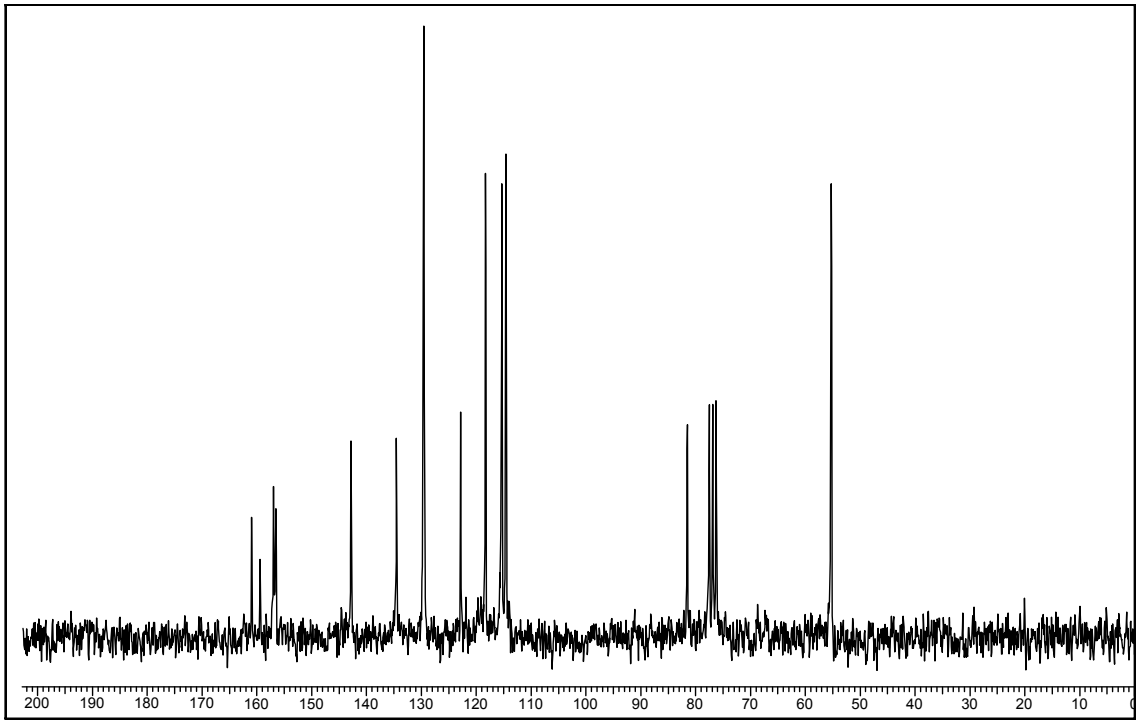
3.20a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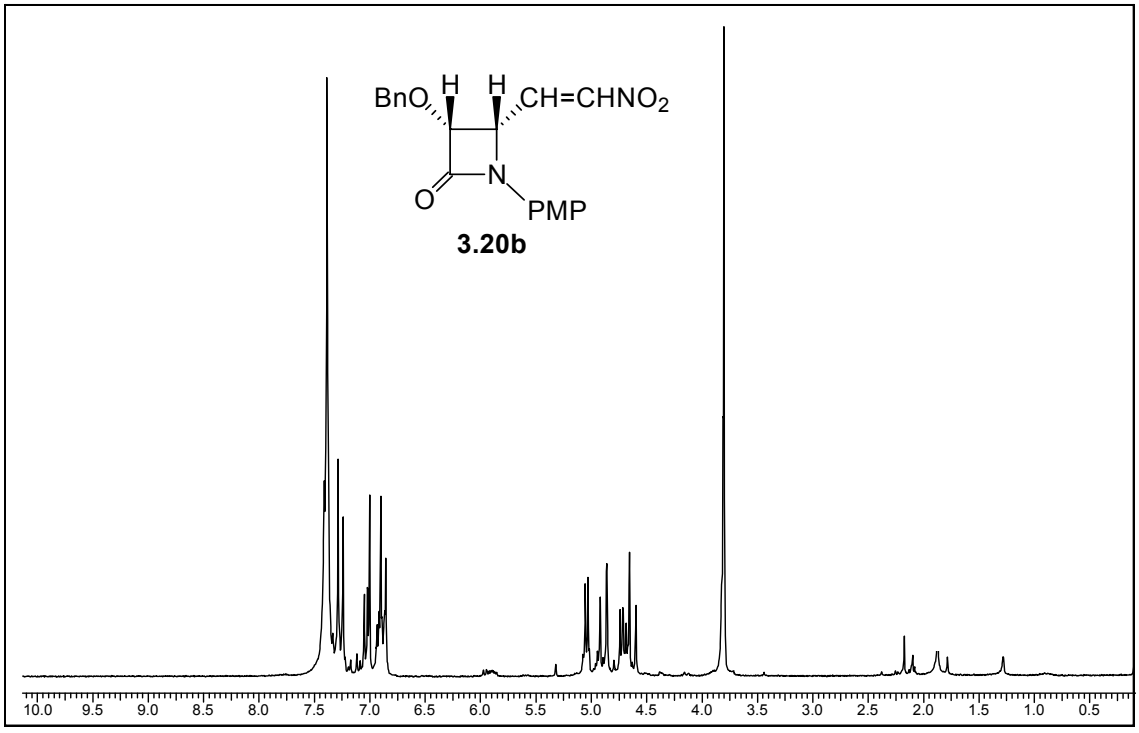
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CH=CHNO2
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N
PMP
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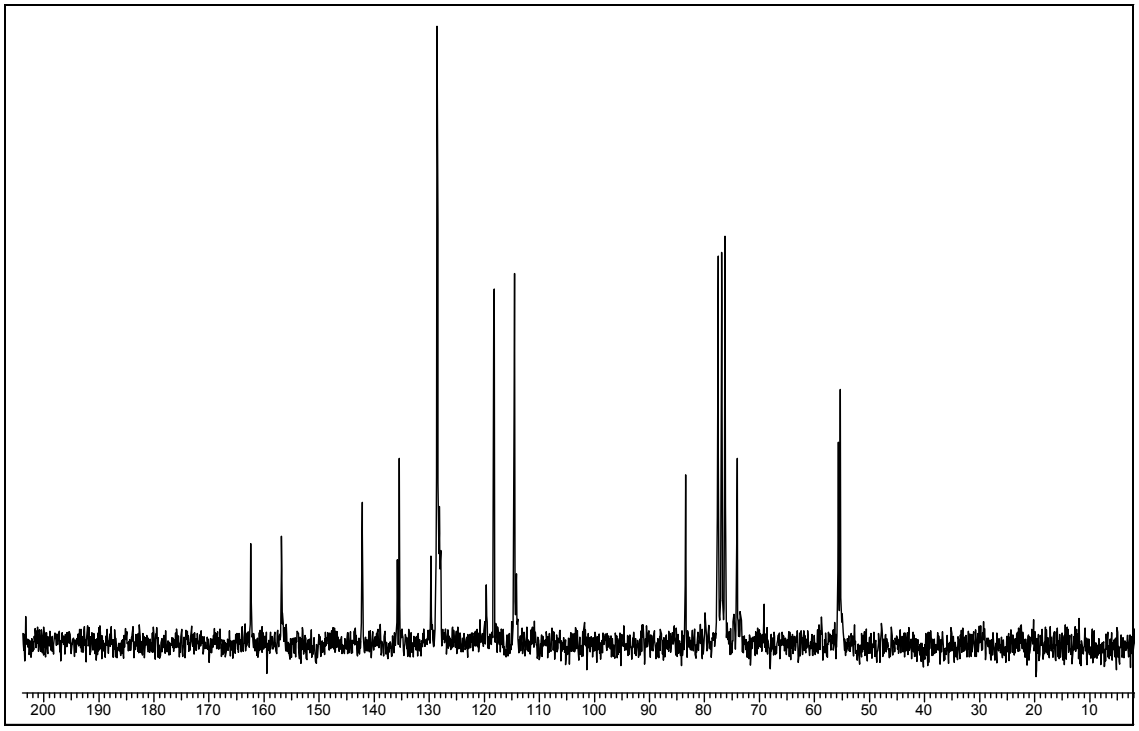
3.20b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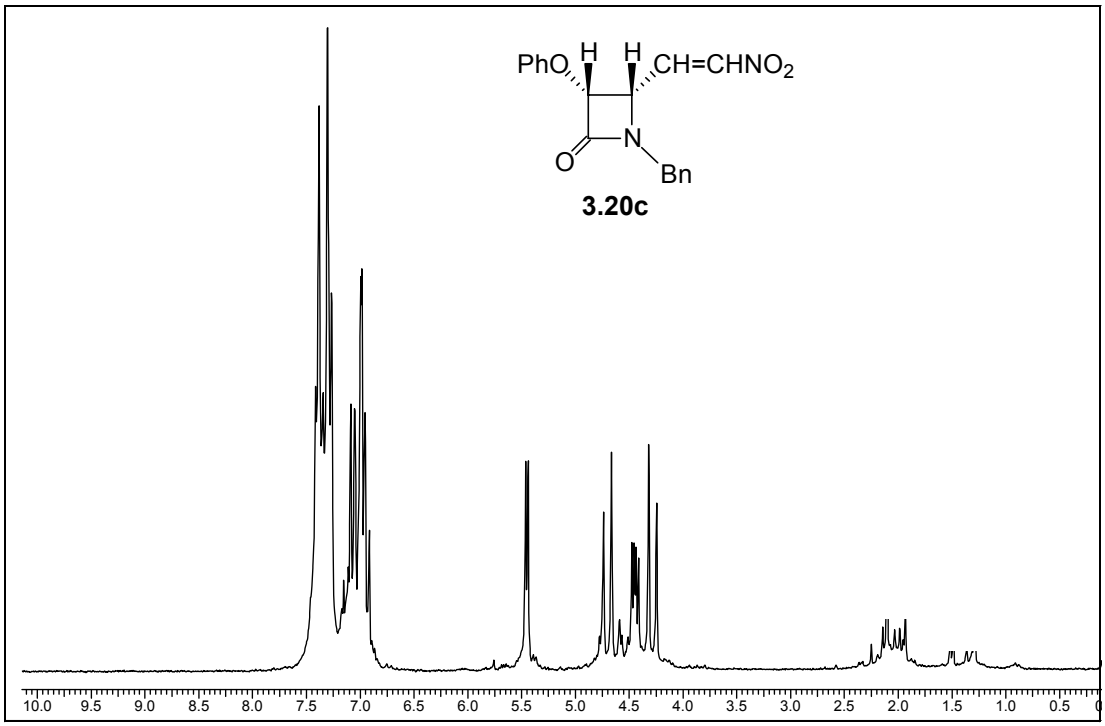
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CH=CHNO2
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Bn
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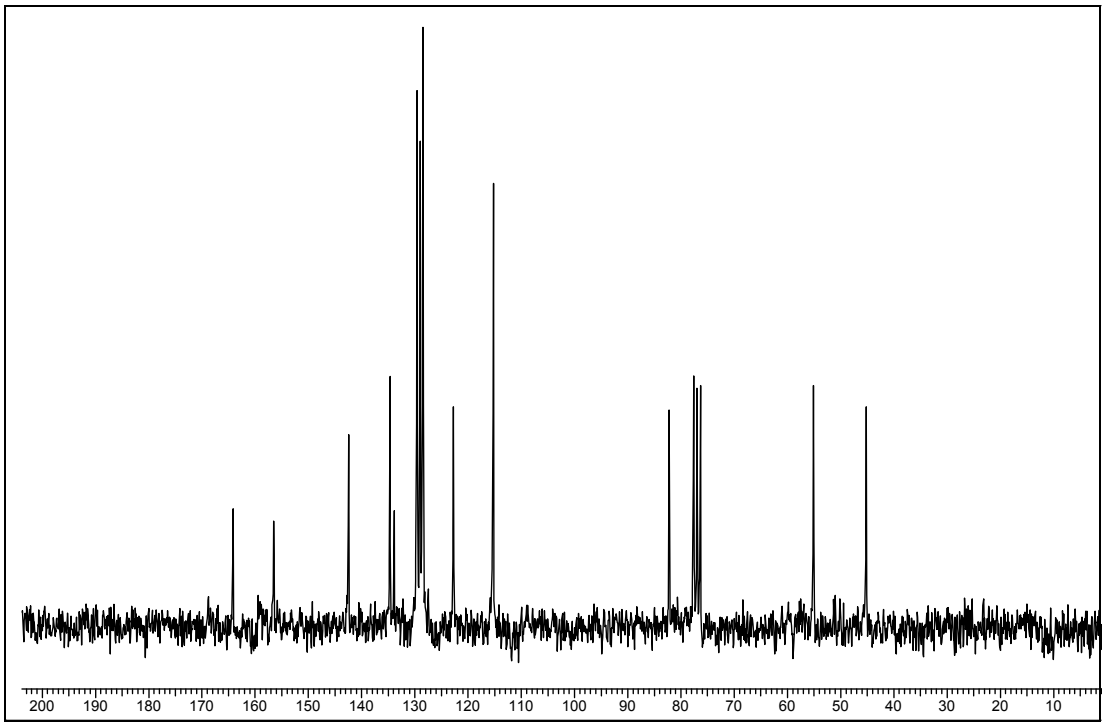
3.20c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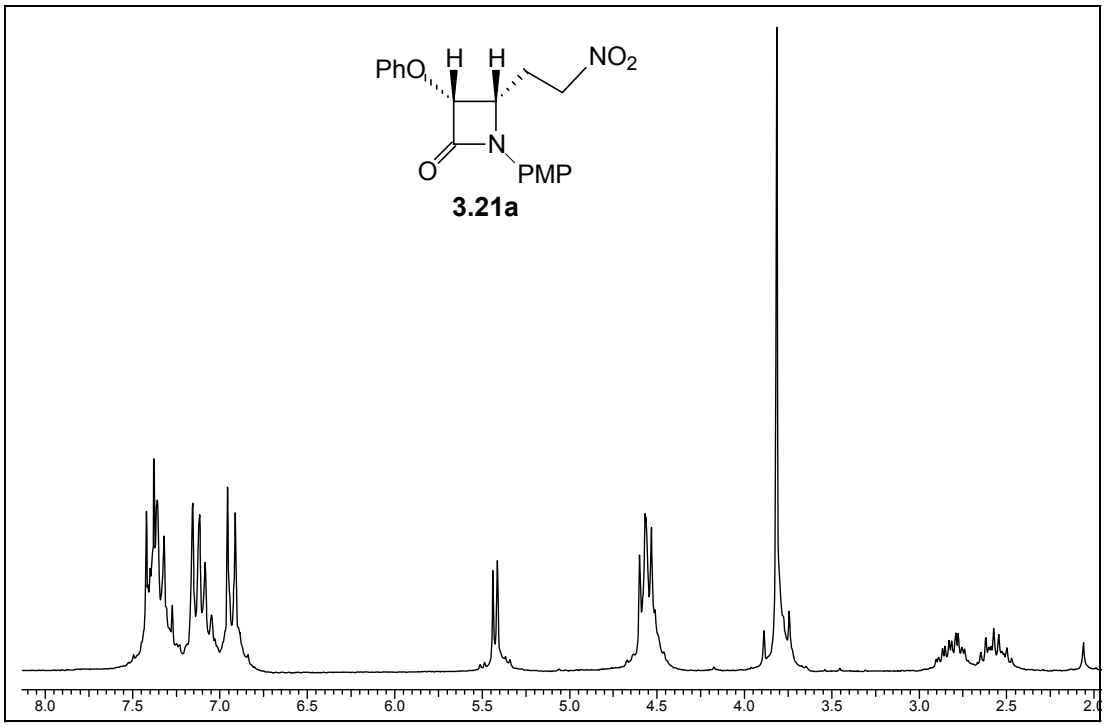
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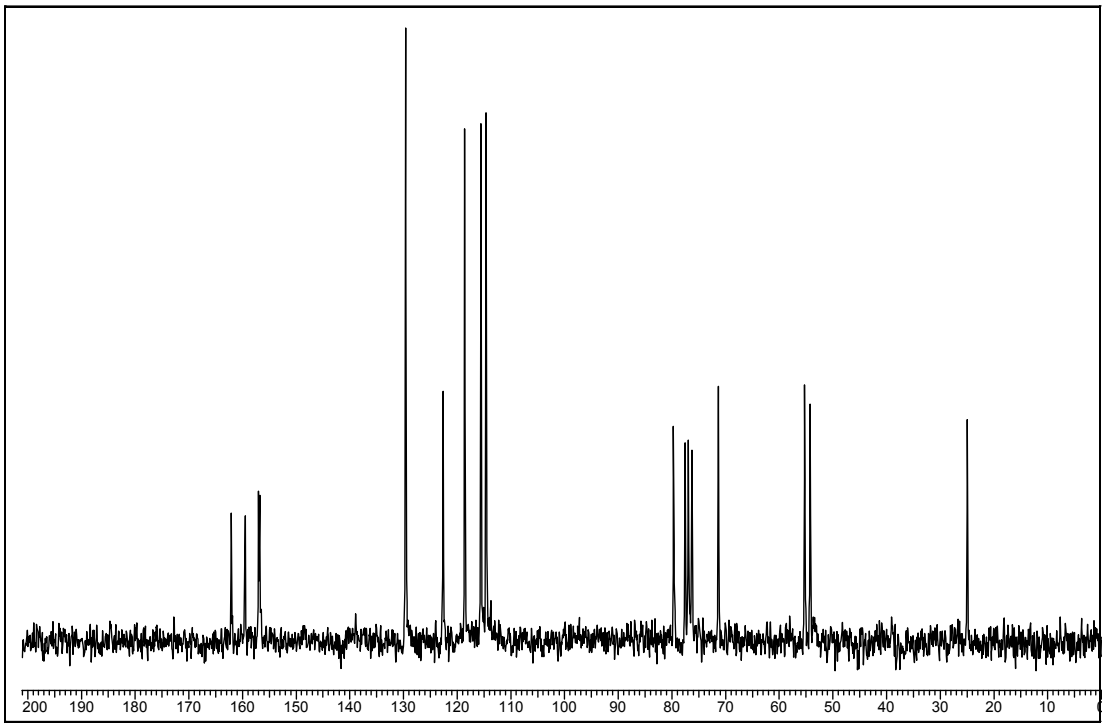
2.5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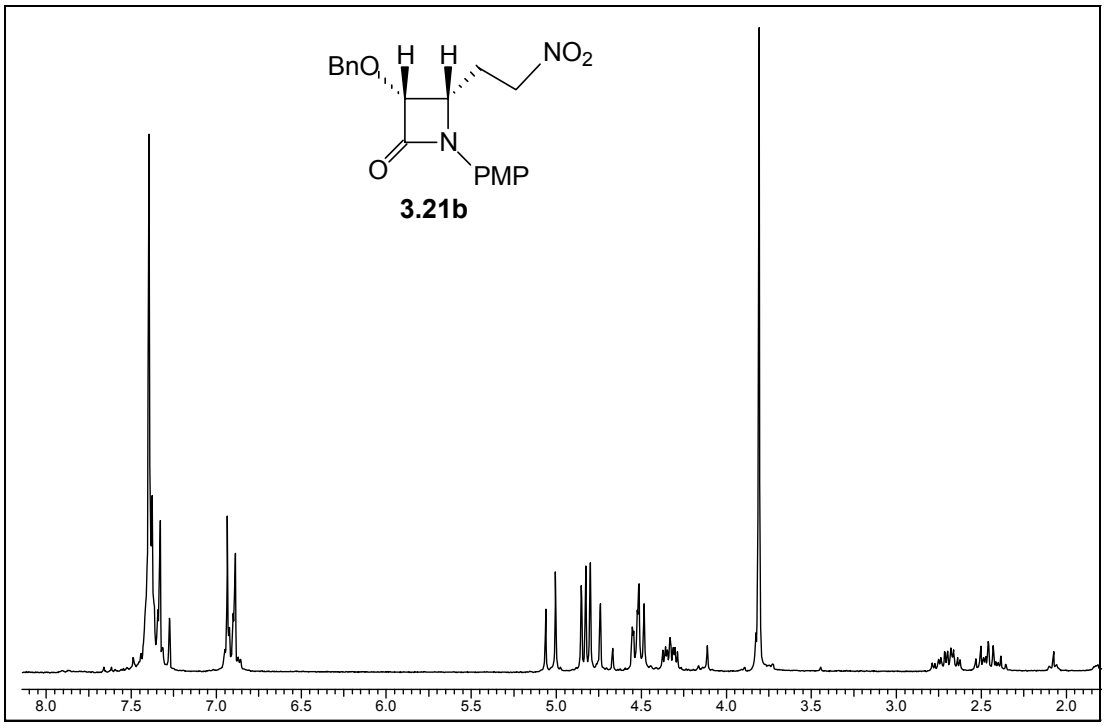
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H
H
NO2
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O
PMP
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4.0
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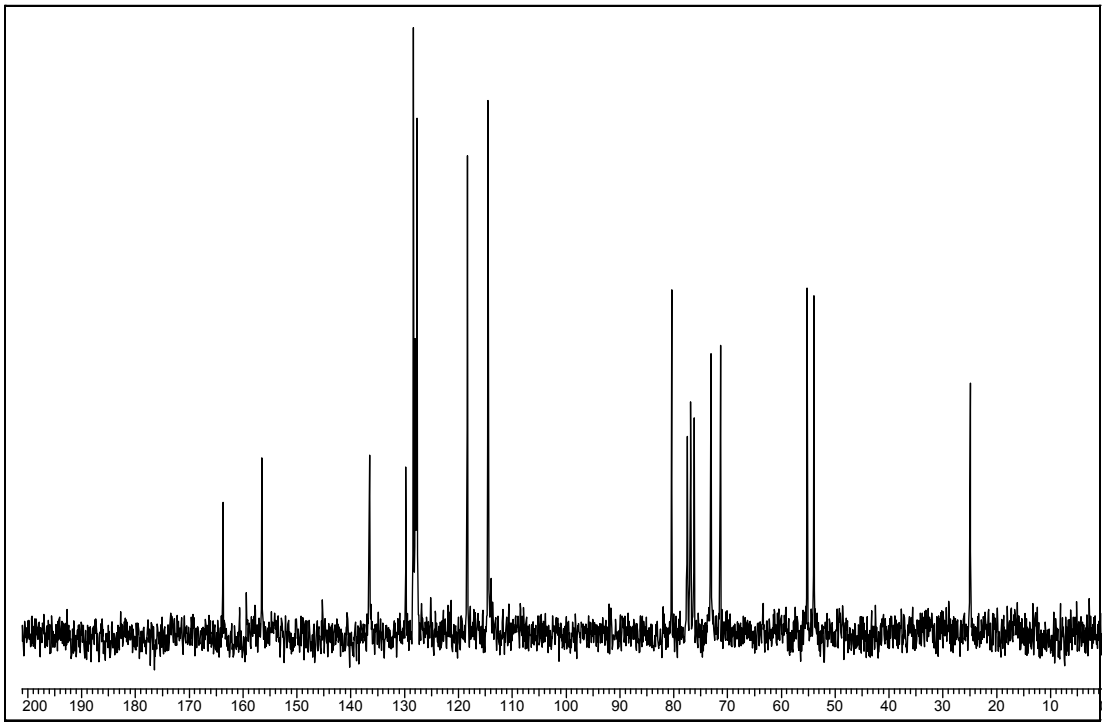
2.5
2.0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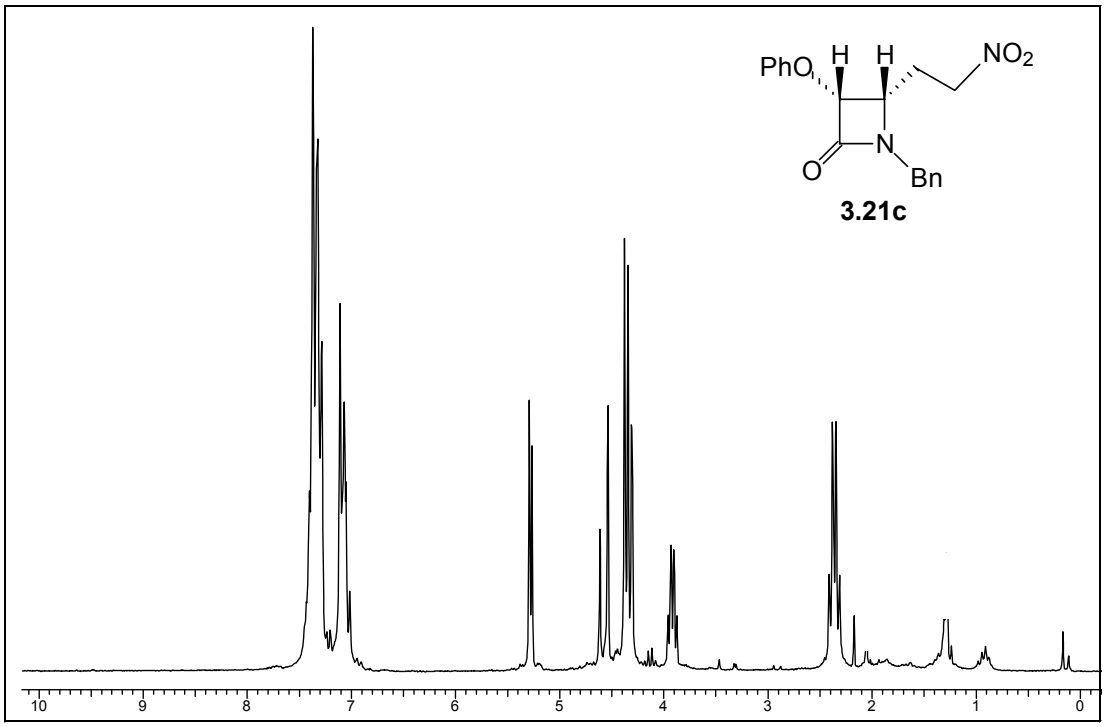
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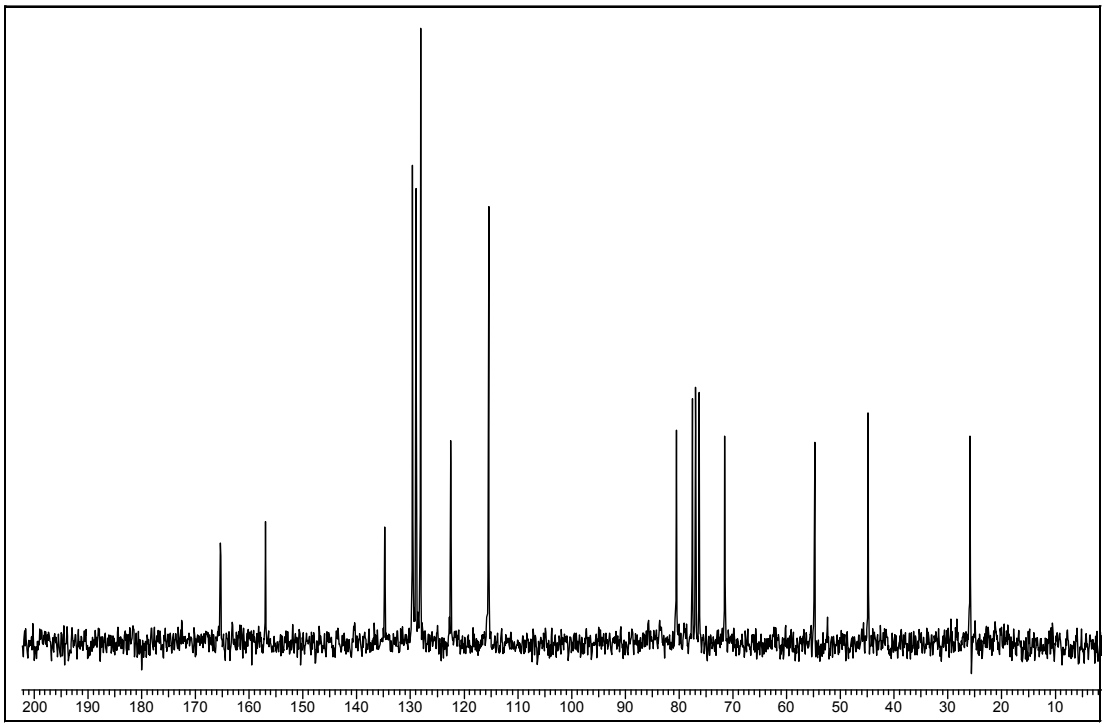
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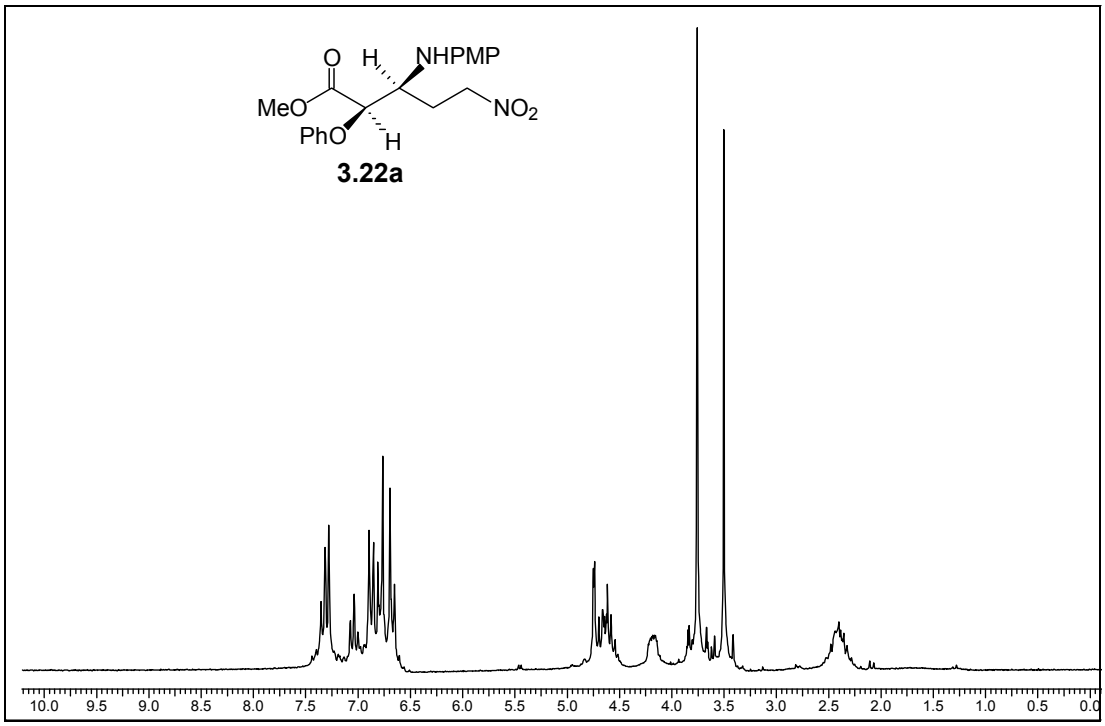
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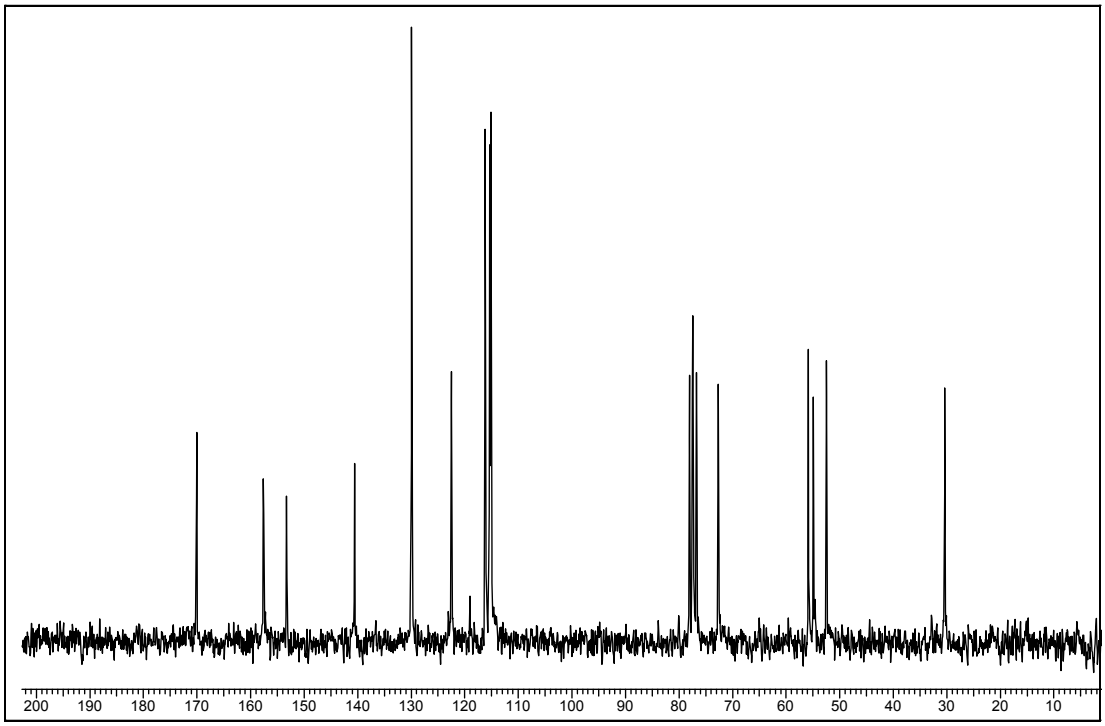
H
NHPMP
MeO
NO2
PhO
H
3.22a
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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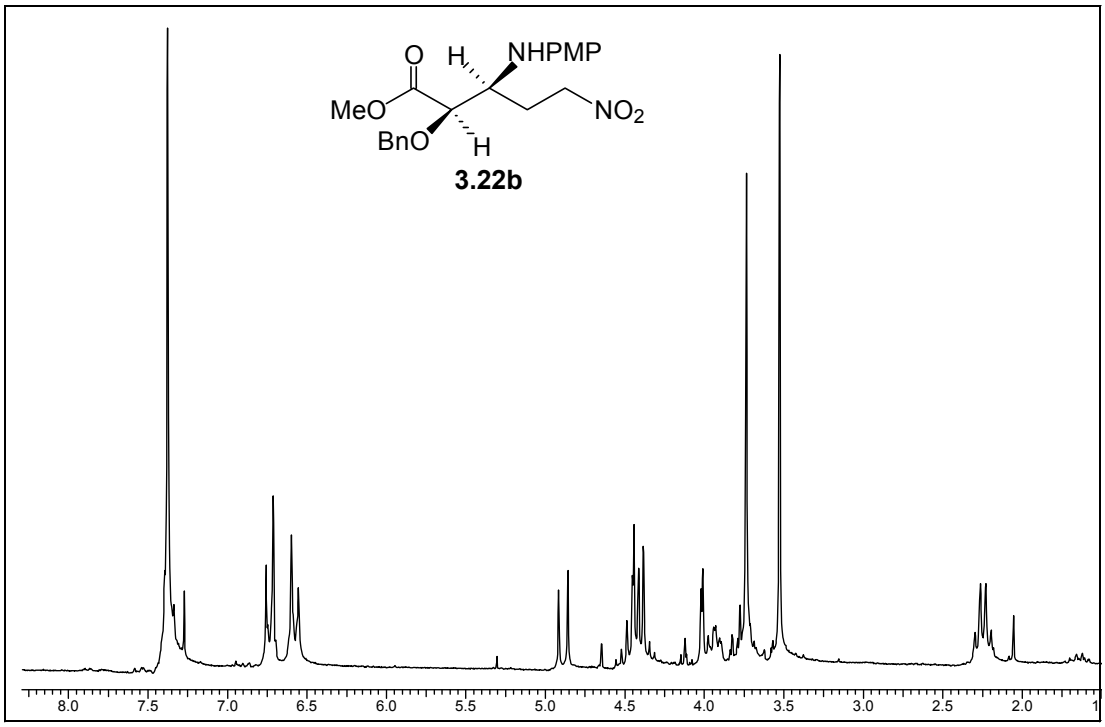
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H
NHPMP
MeO
NO2
BnO
H
3.22b
8.0
7.5
7.0
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6.0
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5.0
4.5
4.0
3.5
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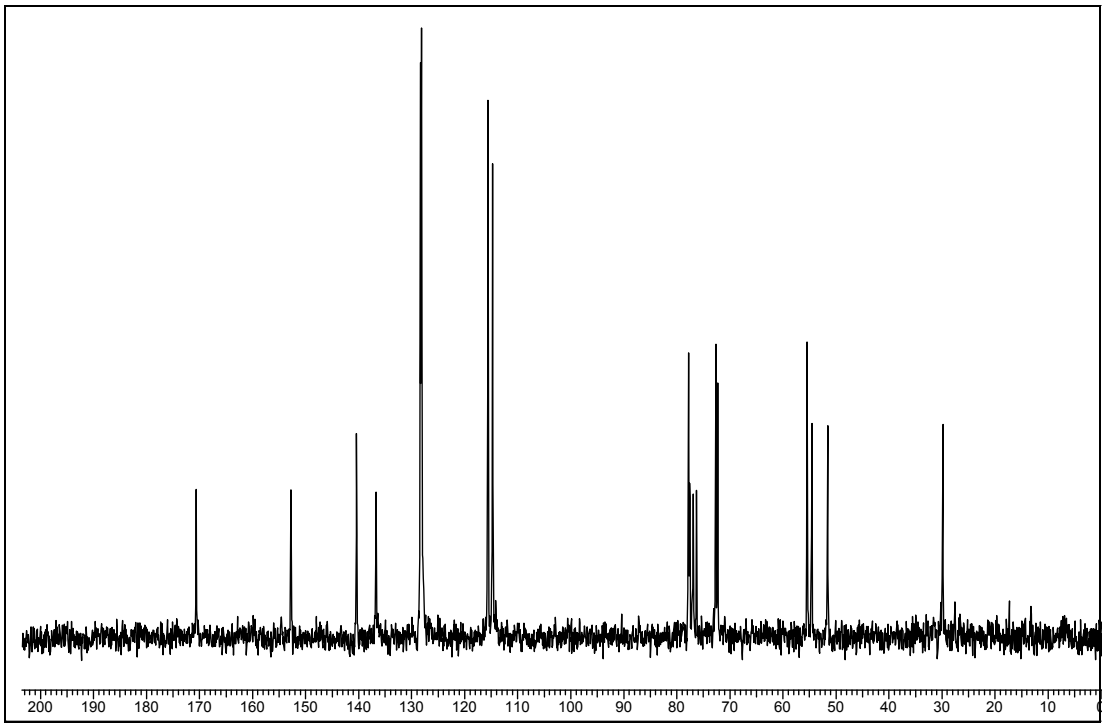
2.5
2.0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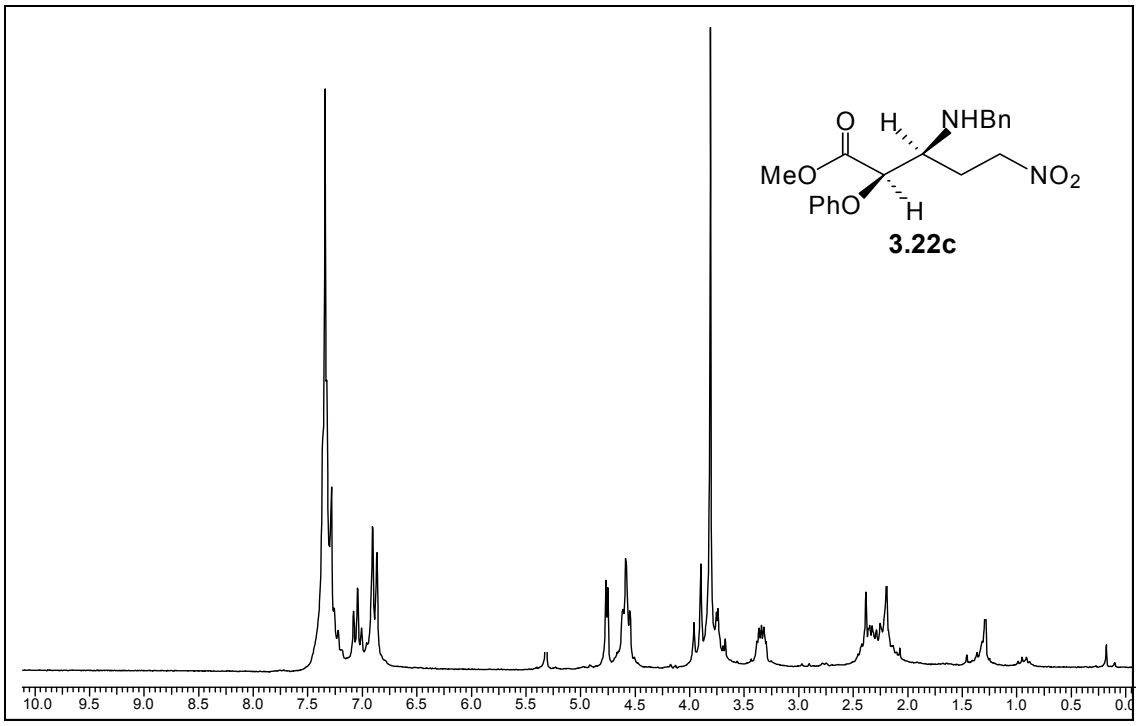
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H
NHBn
MeO
NO2
PhO
H
3.22c
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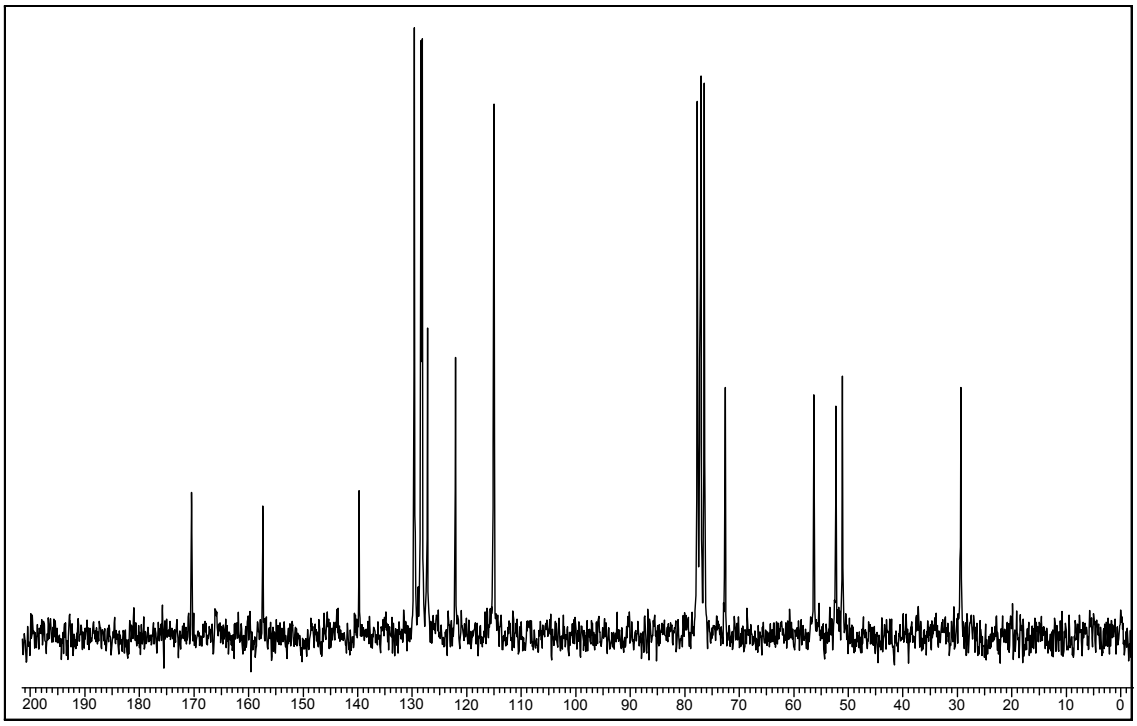
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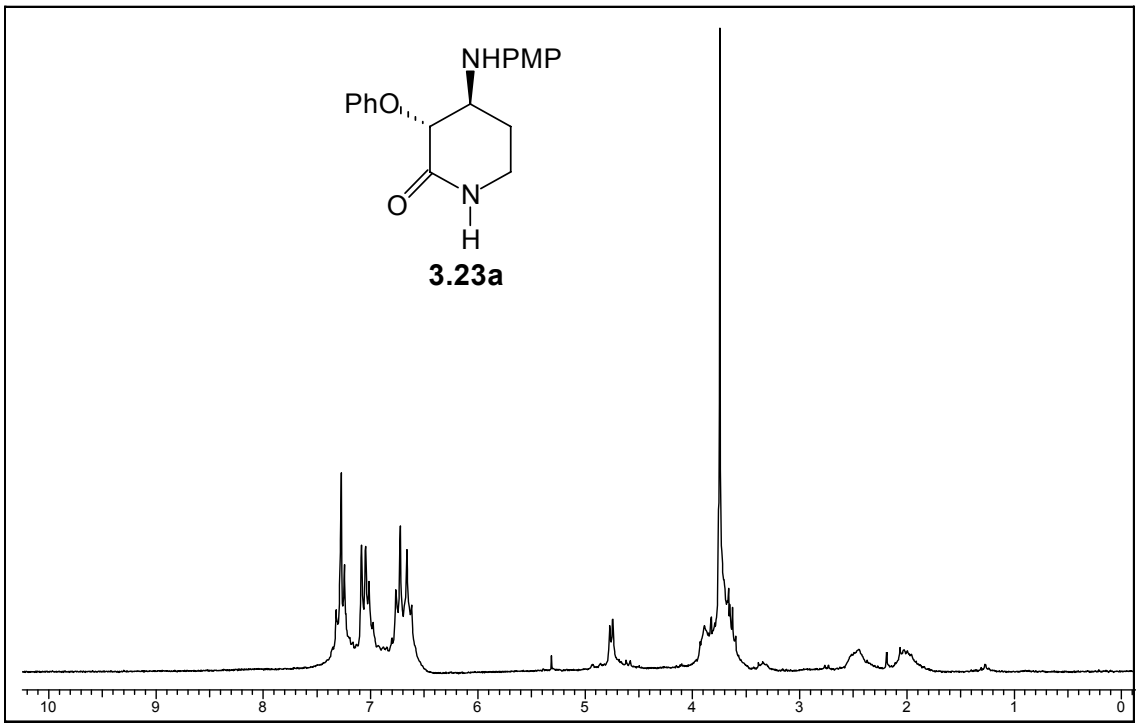
NHPMP
PhO
O
N
H
3.23a
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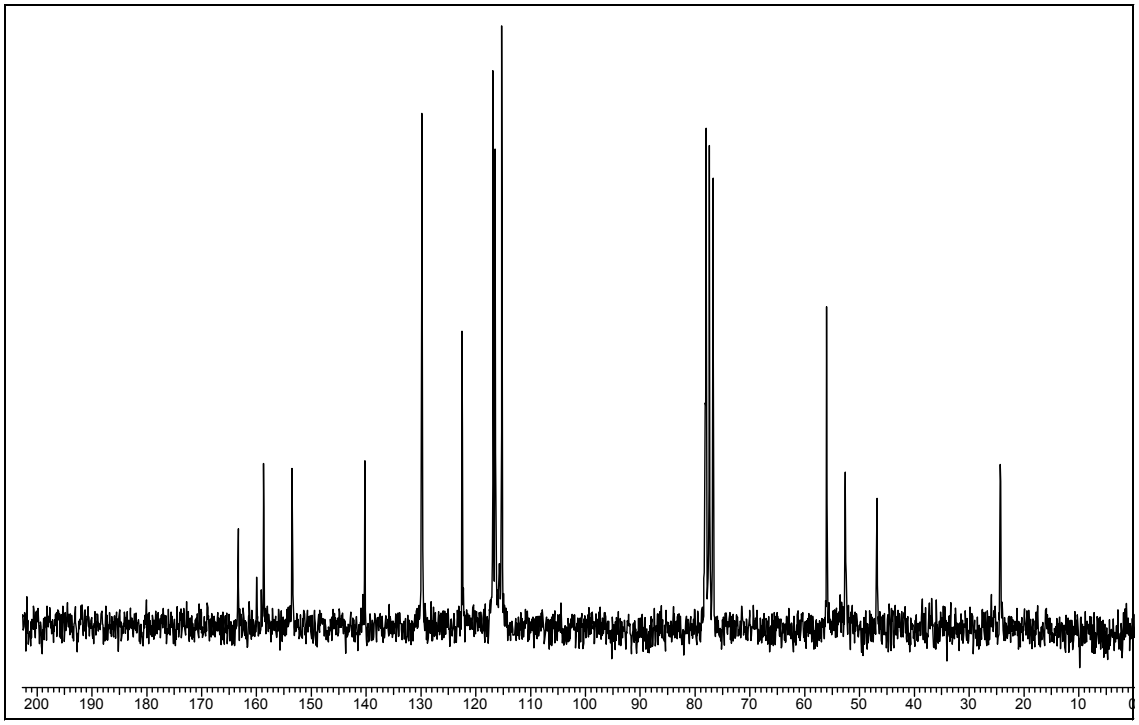
2
1
0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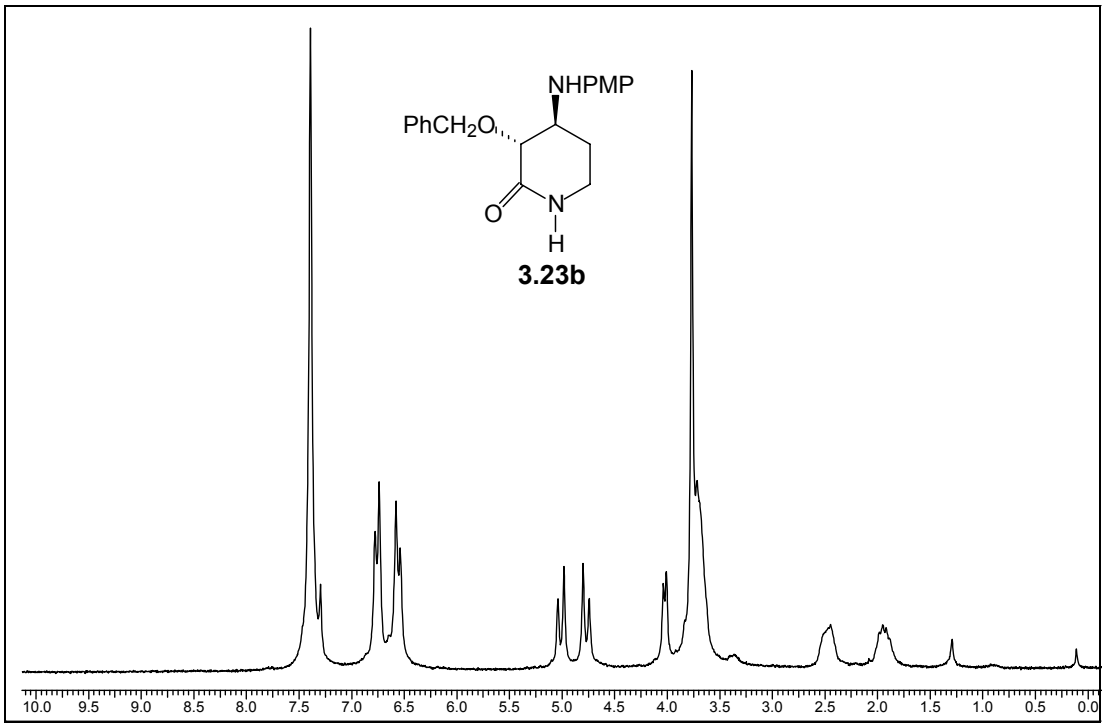
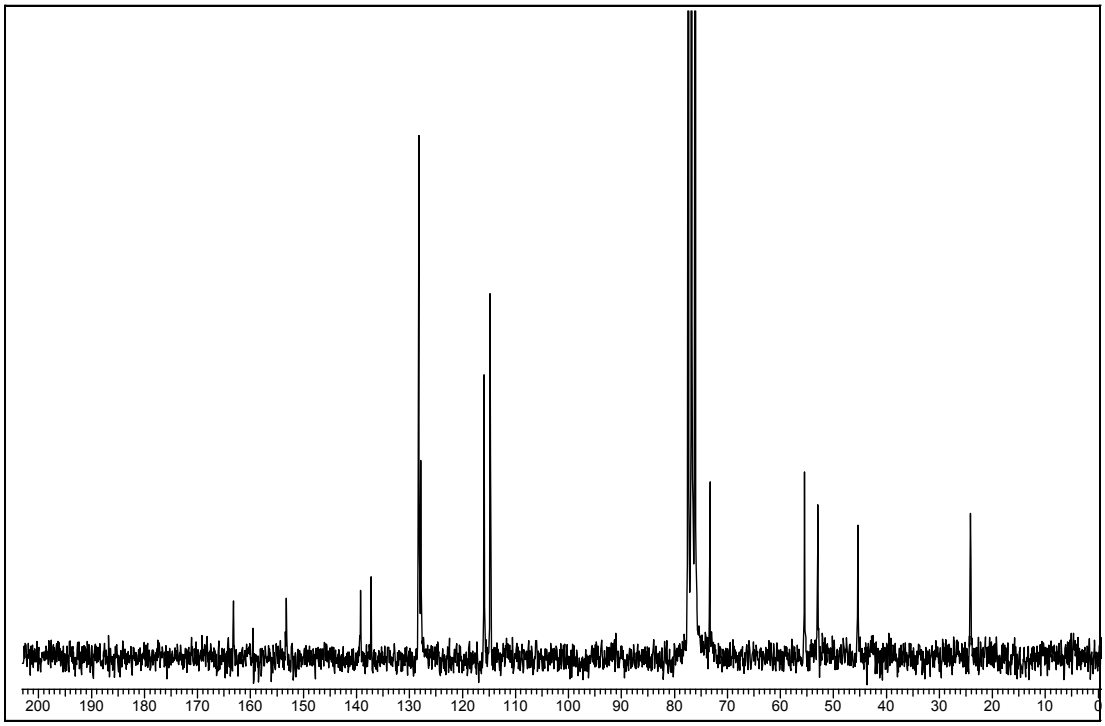

NHPMP
PhCH2O
O
N
H
3.23b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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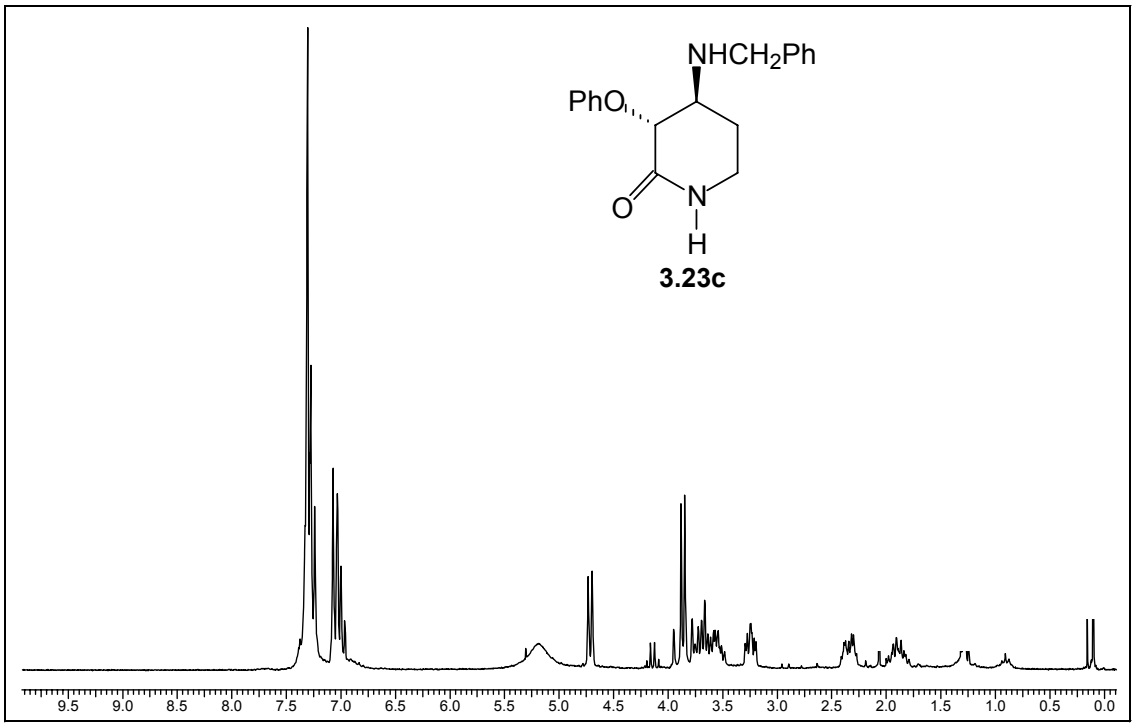
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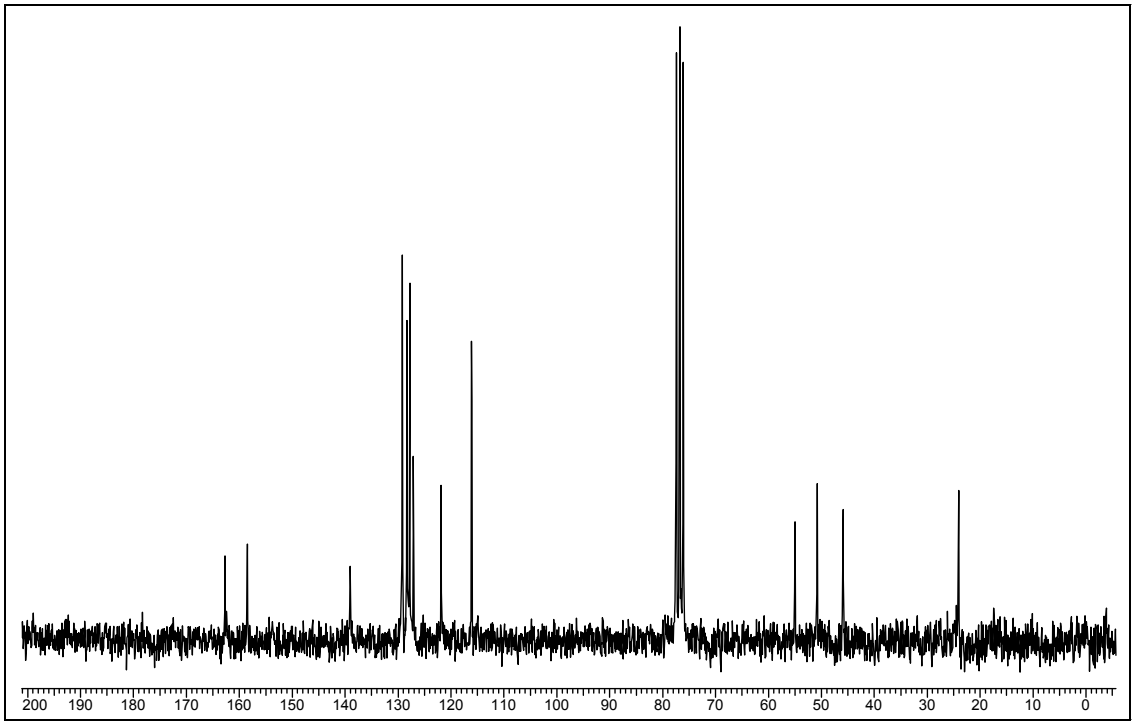
PhO
O
N
H
3.23c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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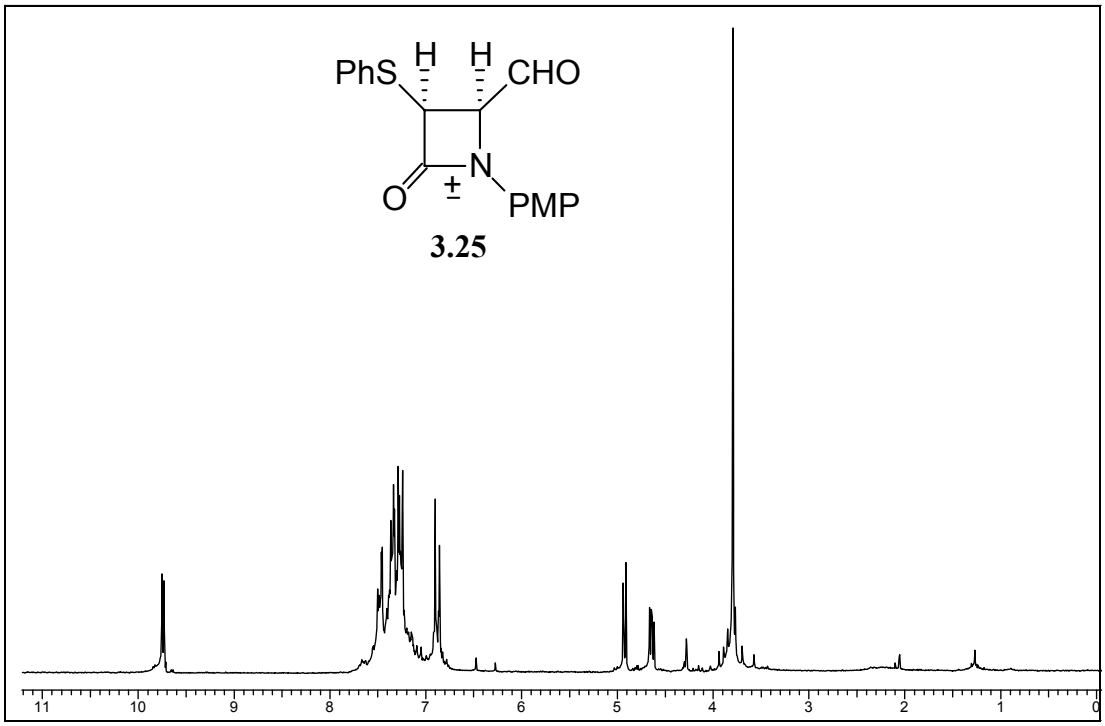

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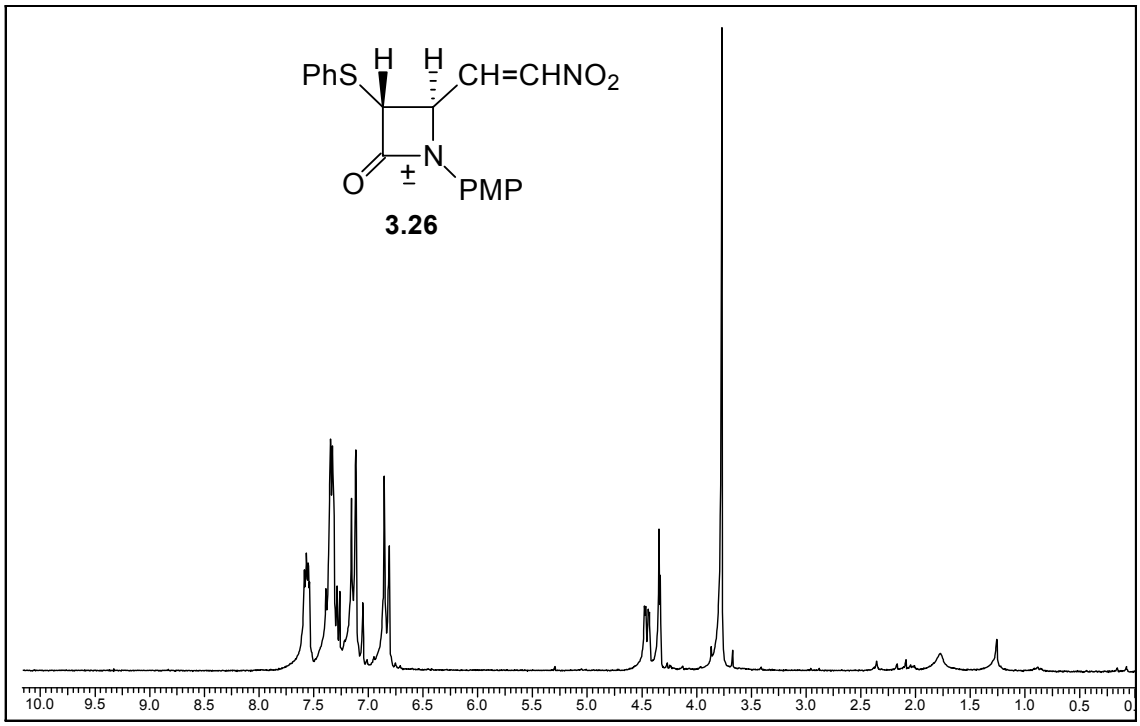
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H
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N
PMP
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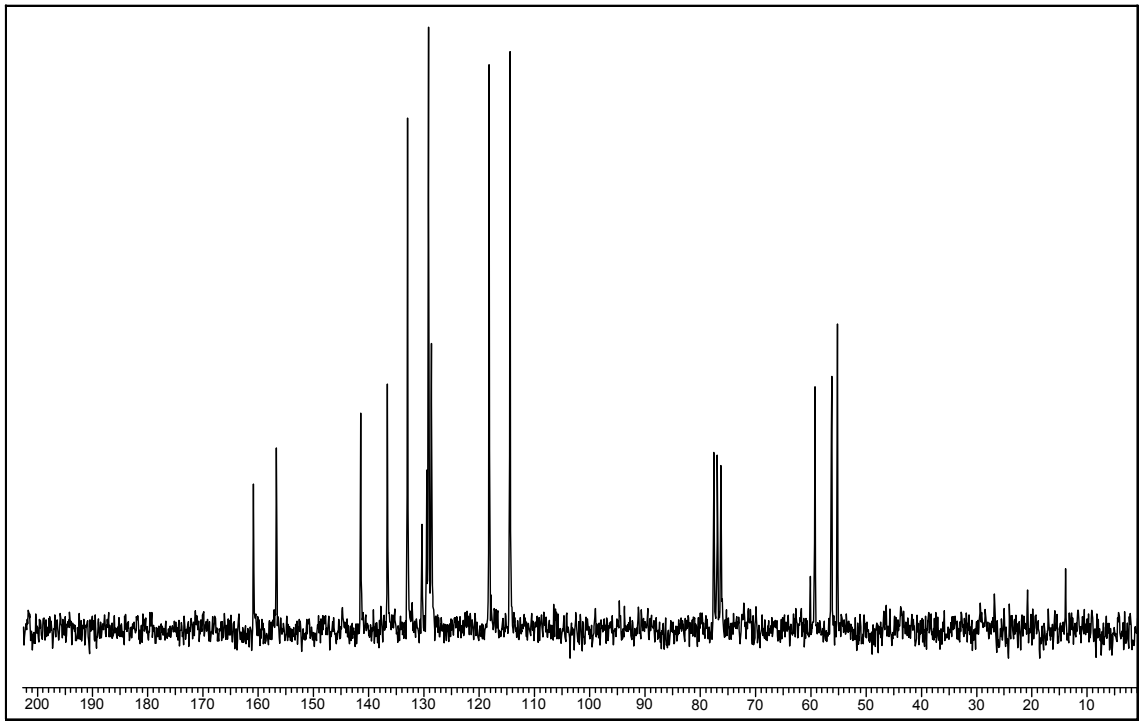
3.26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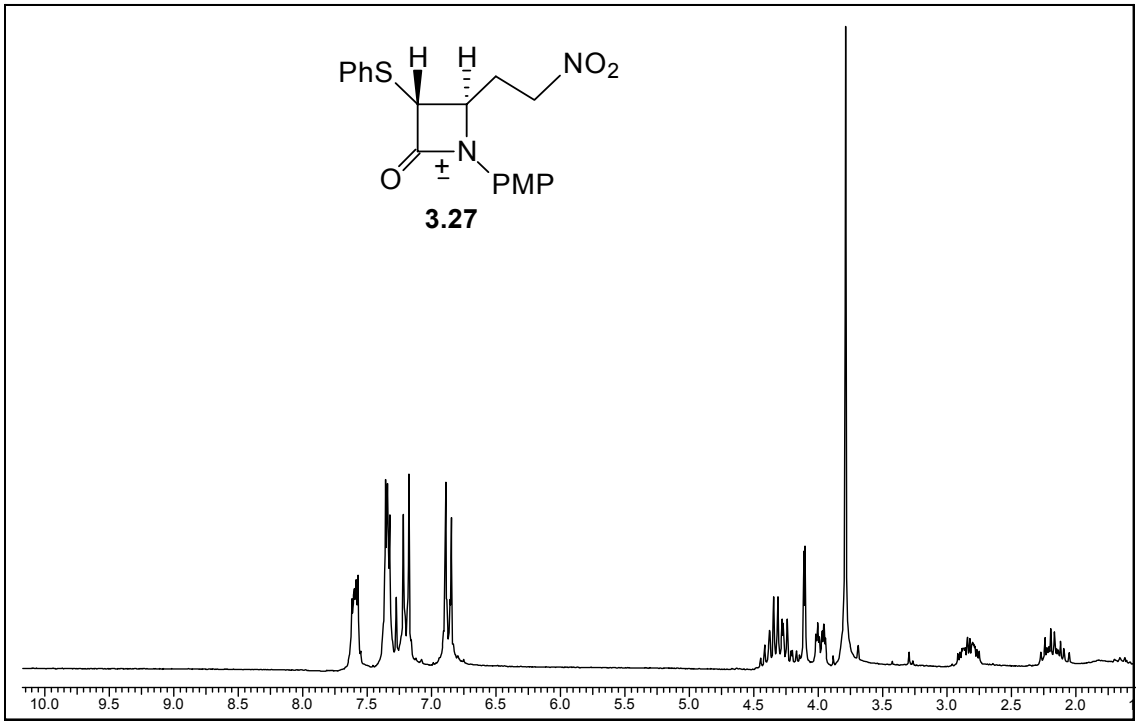
PhS
H
H
NO2
O
N
PMP
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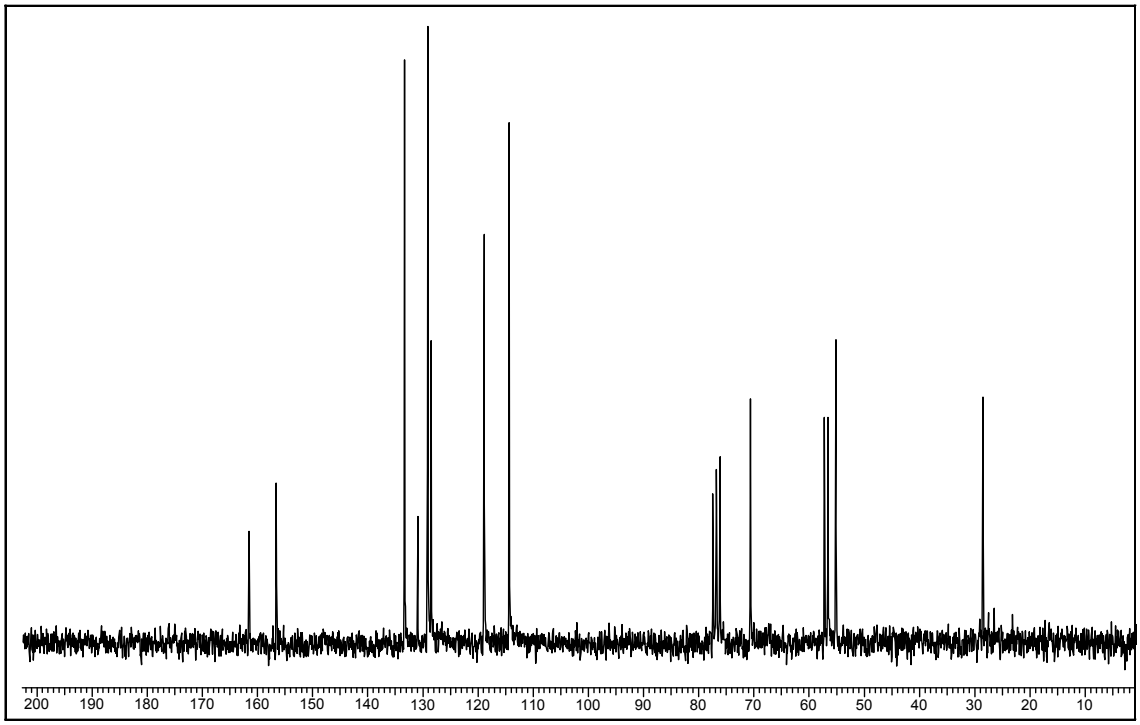
3.27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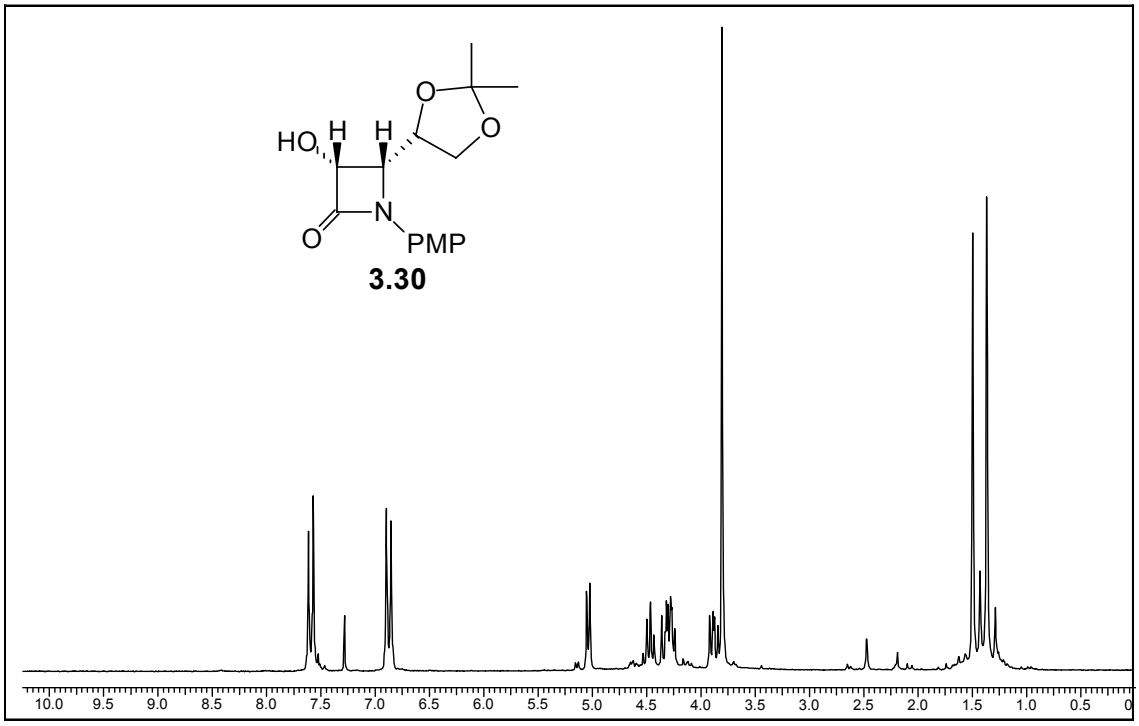
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H
H
O
O
N
O
PMP
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9.0
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8.0
7.5
7.0
6.5
6.0
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2.0
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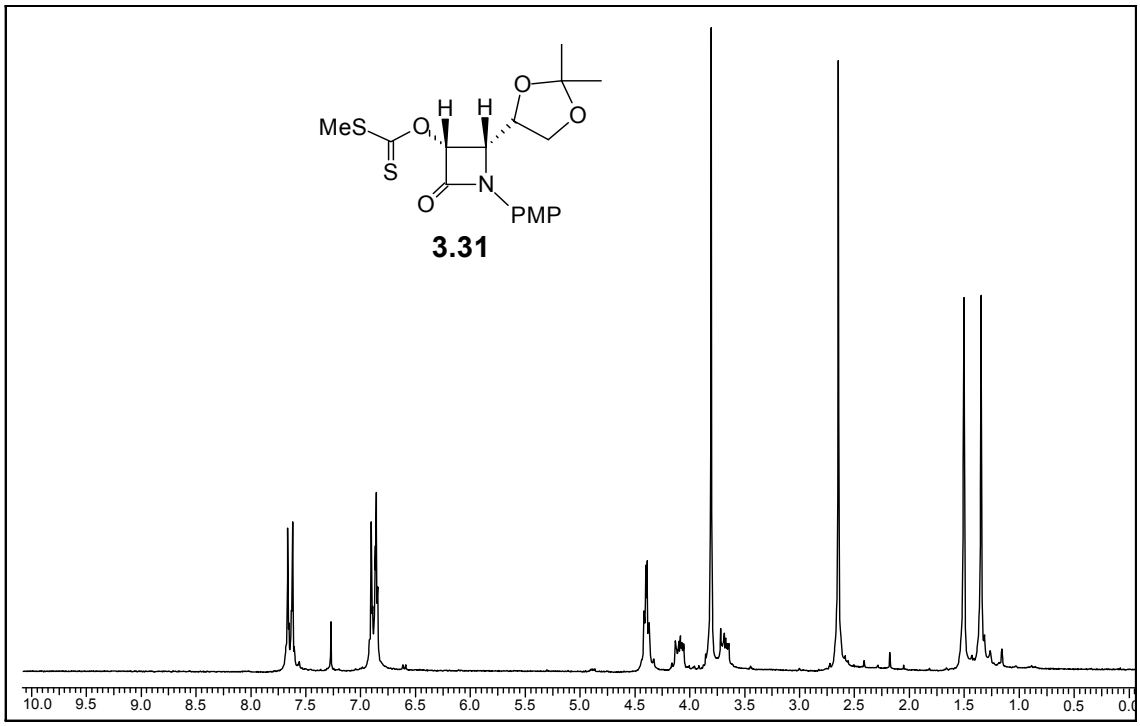
0.5

3.30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S
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H
O
O
O
N
PMP
3.31
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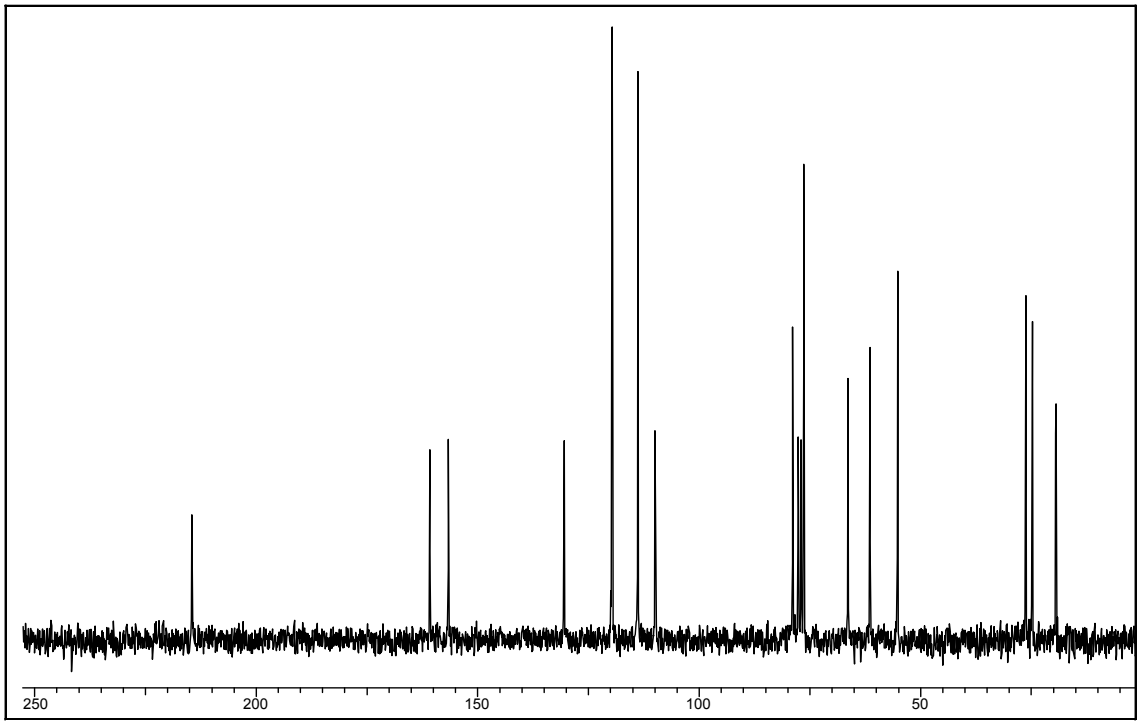
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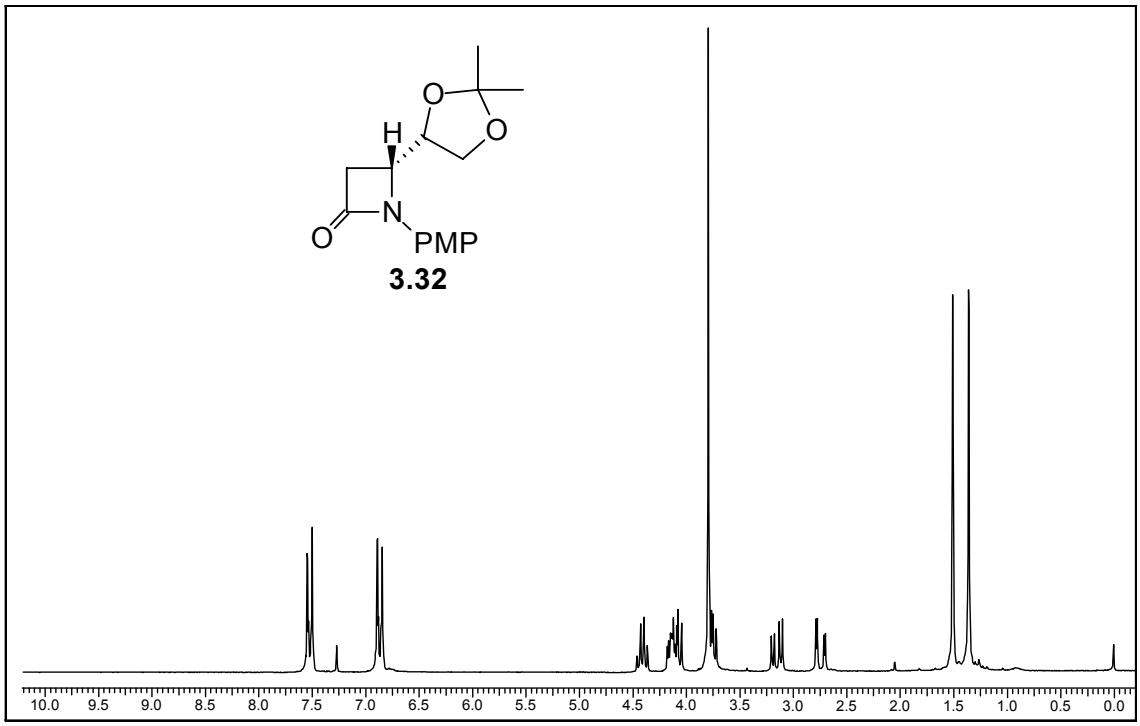
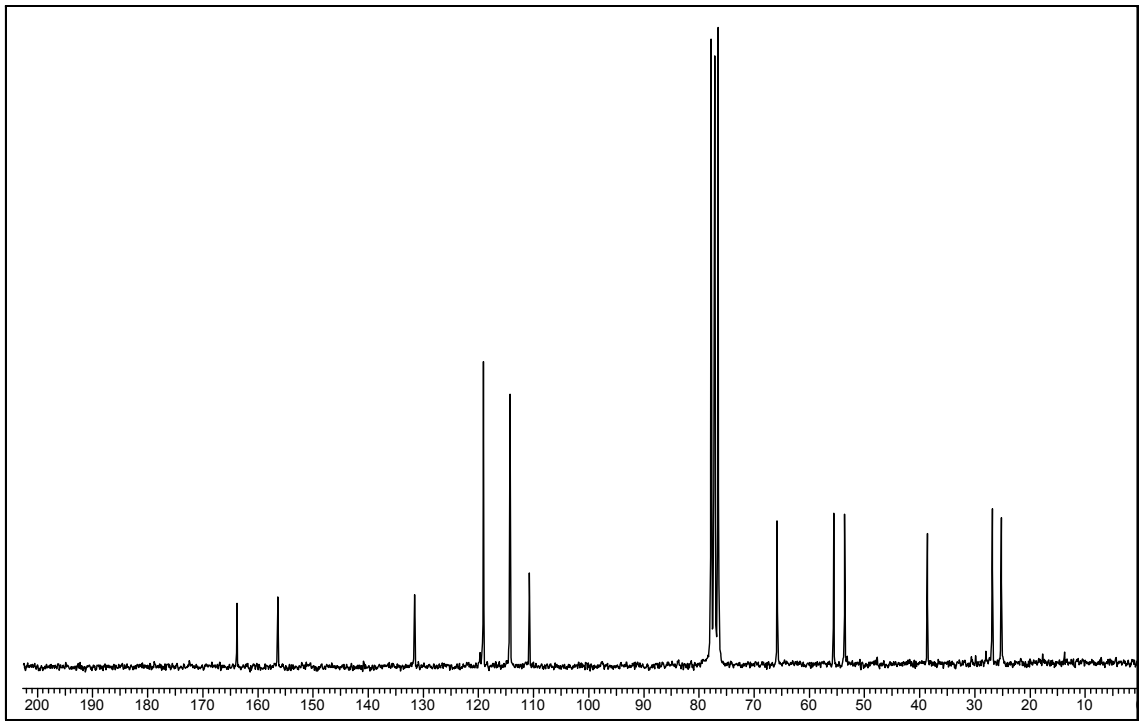

O
O
H
N
O
PMP
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

3.32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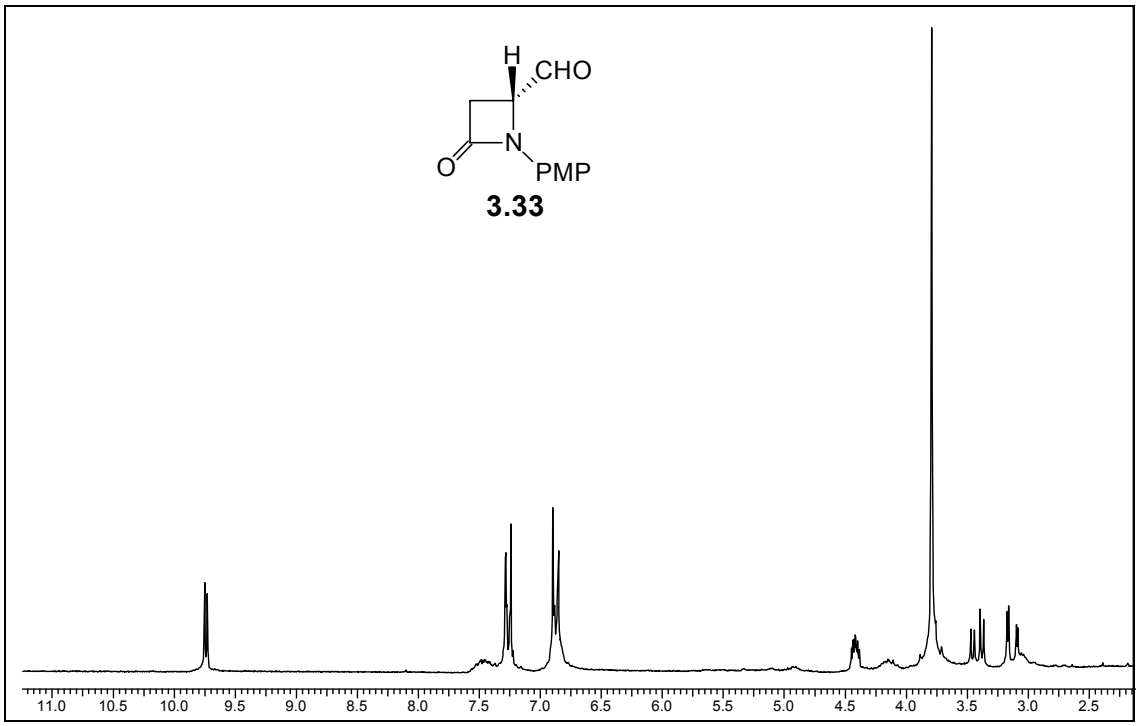
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PMP
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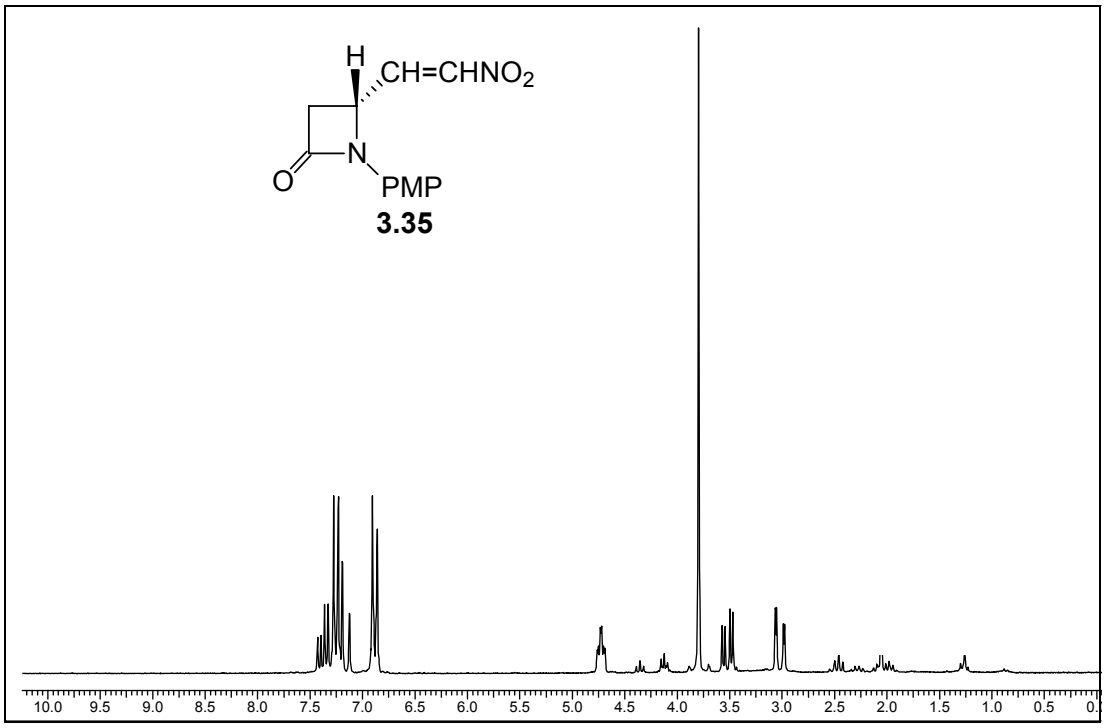
2.5


H
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O
PMP
3.35
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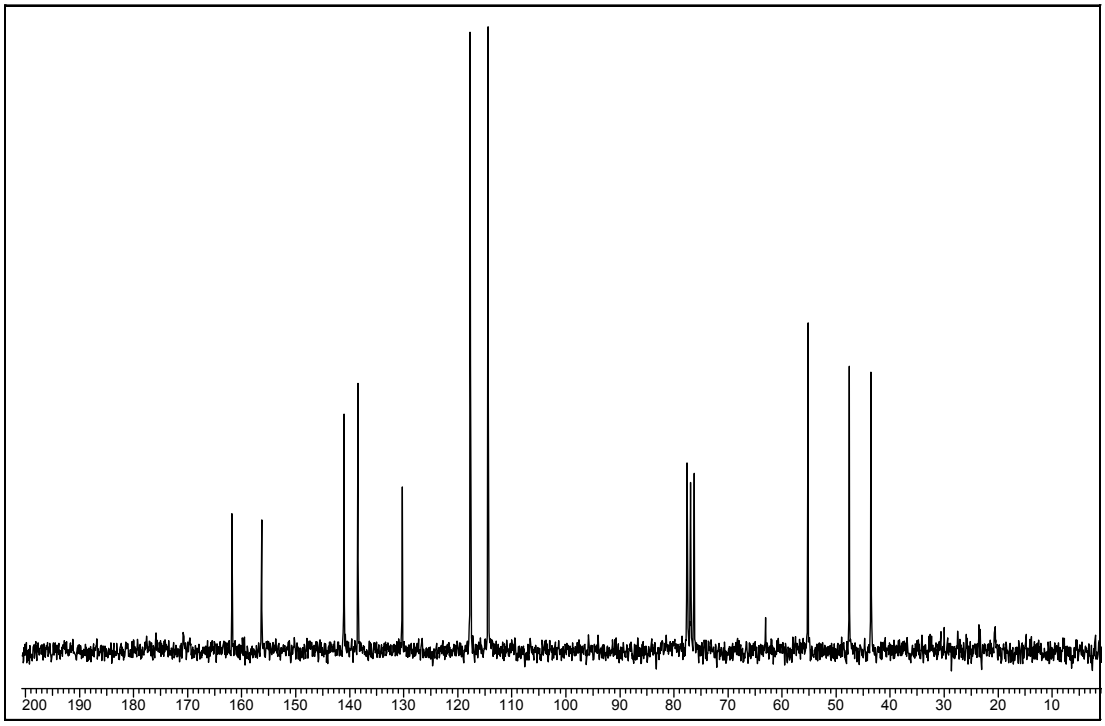
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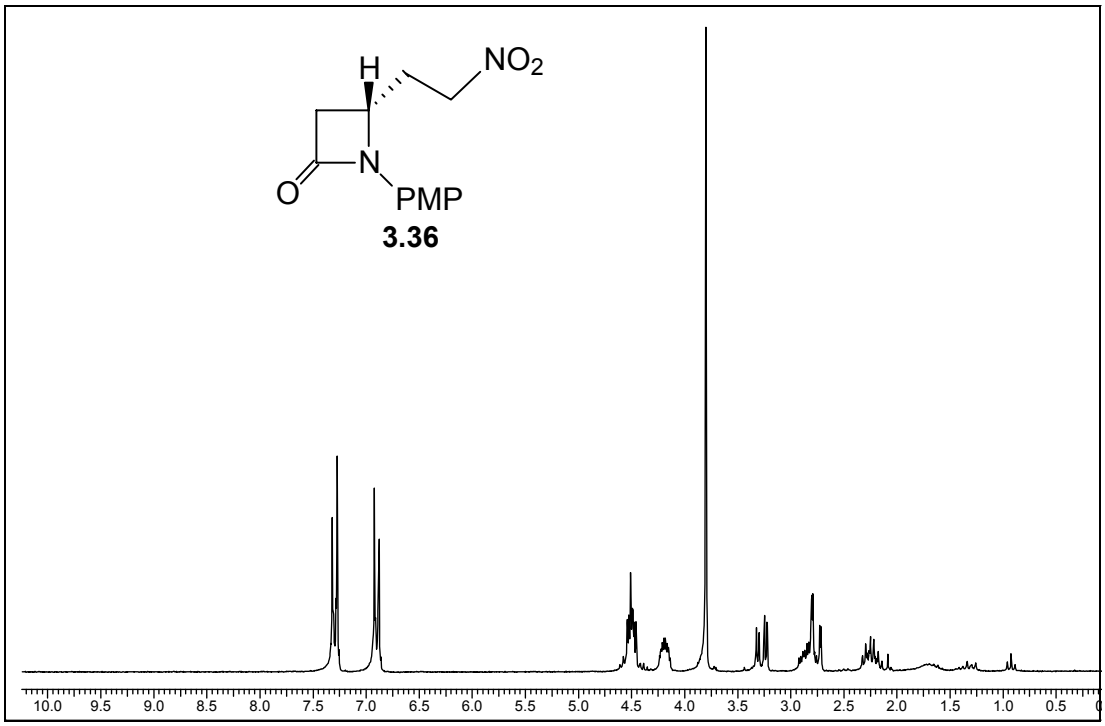
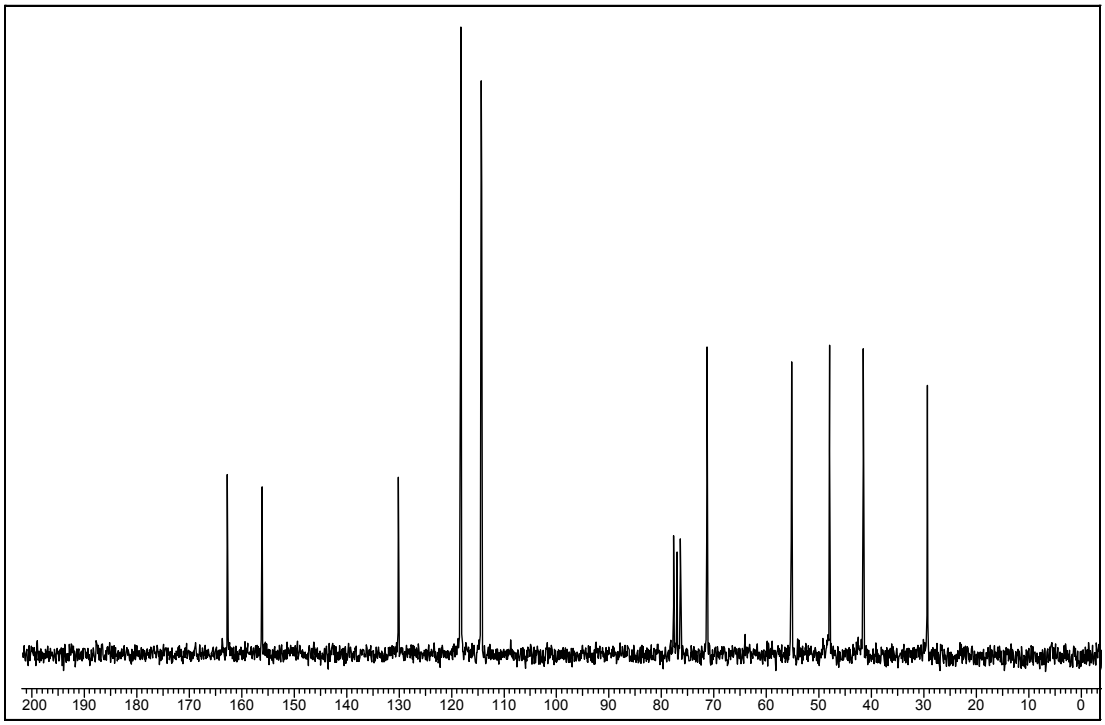

H
NO2
N
O
PMP
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

3.36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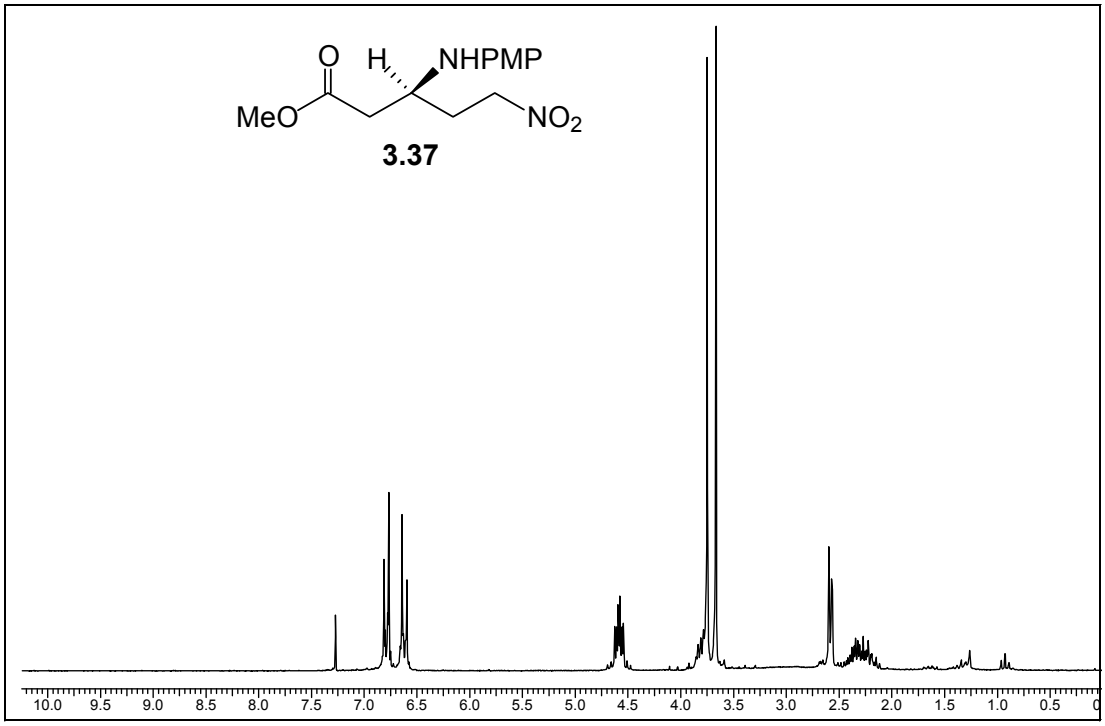
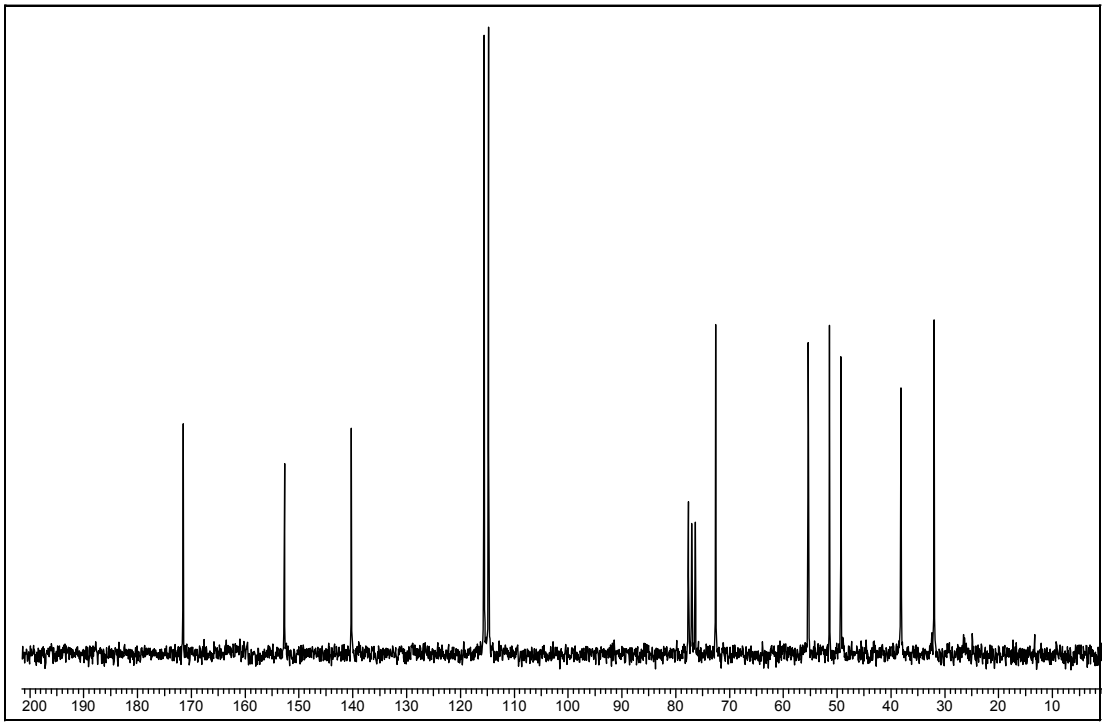

O
H
NHPMP
MeO
NO2
3.37
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5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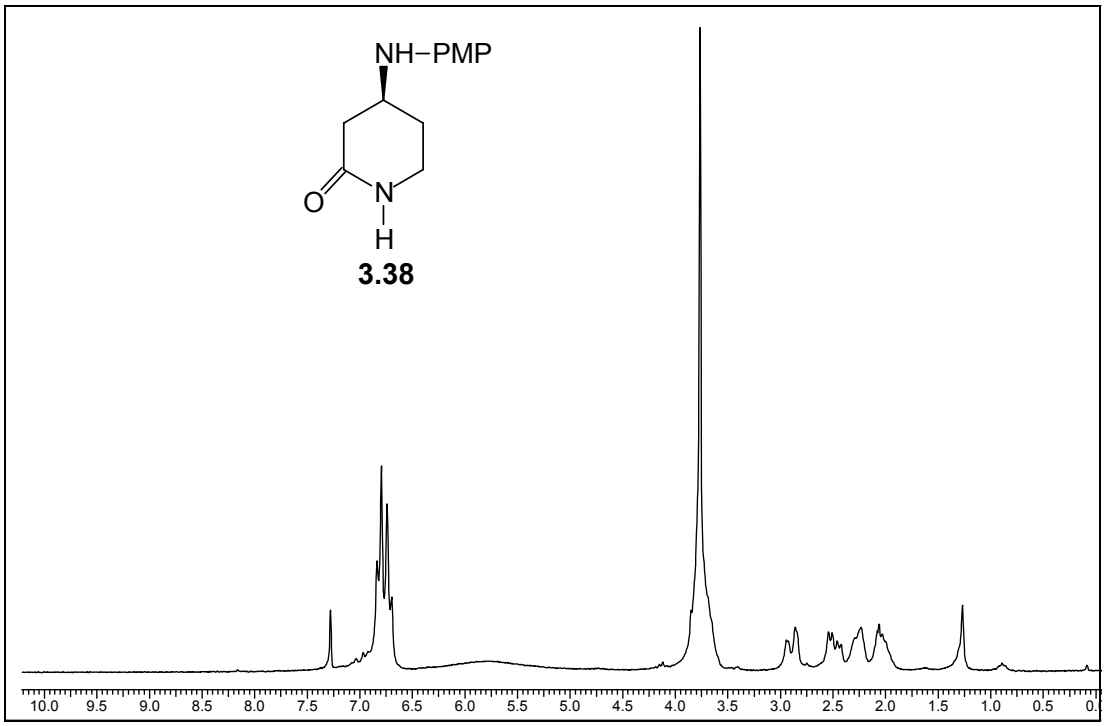
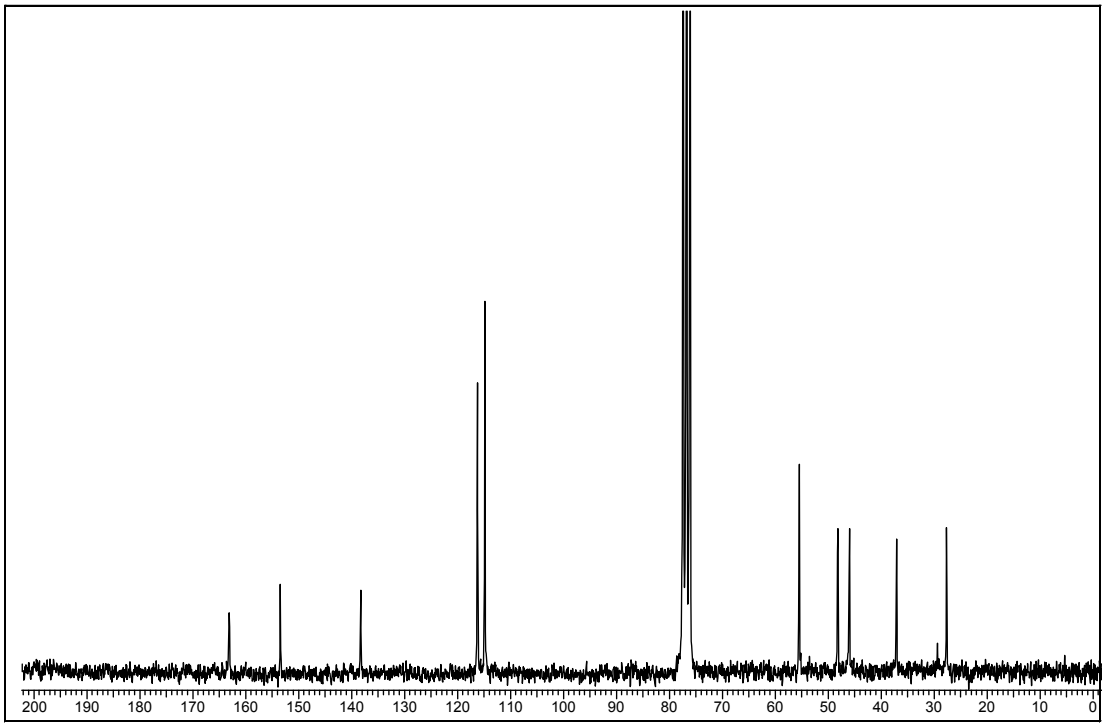

NH−PMP
O
N
H
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

3.38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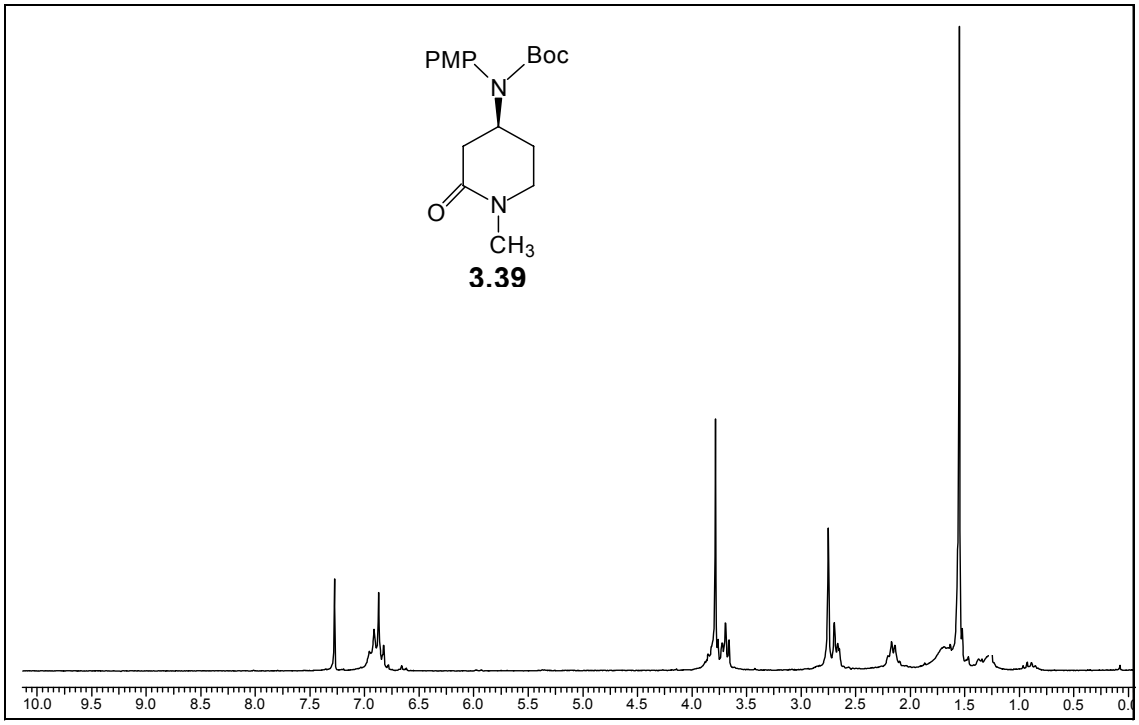
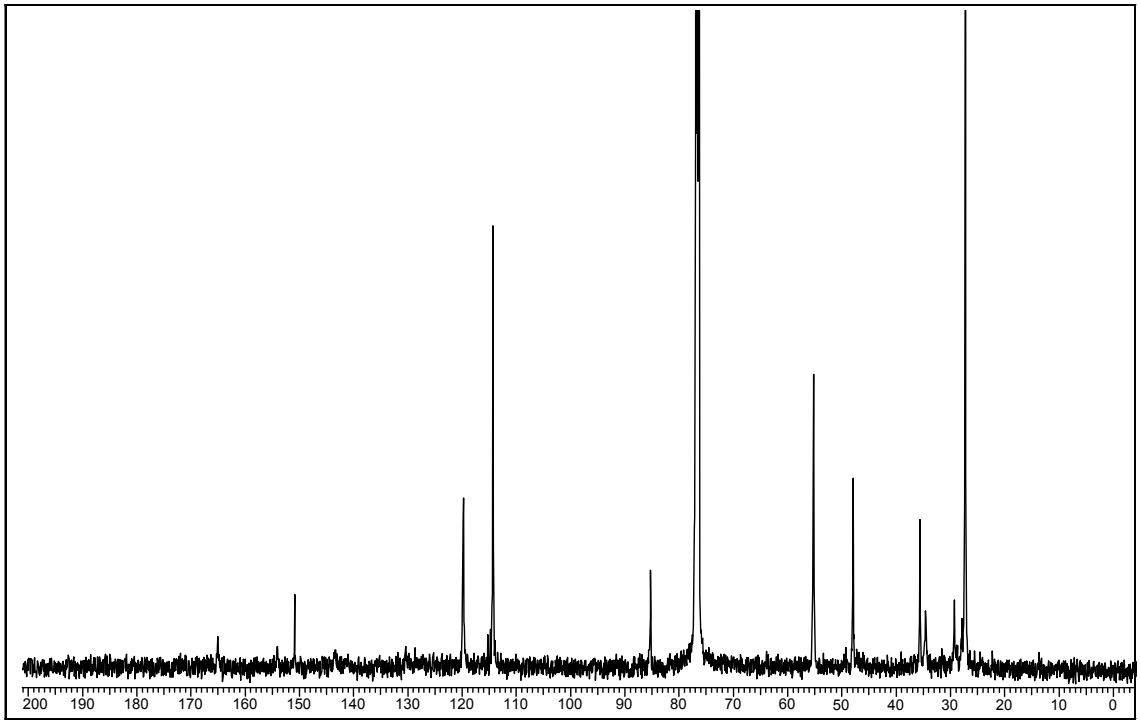

PMP
N
Boc
O
N
CH3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

3.39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List of Publications:

1. Triphosgene, an efficient acid activator for Staudinger Reaction
   D. Krishnaswamy, B. M. Bhawal and A. R. A. S. Deshmukh
   Tetrahedron Lett. **2000**, *41*, 417.

2. Triphosgene, **D. Krishnaswamy** *Synlett* (Spotlight 24), **2000**, 1860.

3. (+)-3-Carene, an Efficient Chiral Pool for the Diastereoselective Synthesis of β-lactams
   B. M. Bhawal, S. N. Joshi, **D. Krishnaswamy**, and A. R. A. S. Deshmukh.
   J. Indian Inst. Sci. **2001,** *81*, 265.

4. Triphosgene, a versatile reagent for the synthesis of azetidin-2-ones
   D. Krishnaswamy, V. V. Govande, V. K. Gumaste, B. M. Bhawal and
   A. R. A. S. Deshmukh.
   Tetrahedron **2002**, 58(11), 2215.

5. Azetidin-2-ones, synthon for biologically important compounds
   A. R. A. S. Deshmukh, B. M. Bhawal, **D. Krishnaswamy**, Vidyesh V. Govande, Bidhan A. Shinkre, and A. Jayanthi
   (Communicated).

6. Facile synthesis of enantiopure 4-aminopiperidin-2-ones from 4-formylazetidin-2-ones
   D. Krishnaswamy, V. V. Govande and A. R. A. S. Deshmukh
   (Communicated).