CHAPTER - III

SYNTHESIS OF AZETIDINONES USING (R) & (S)-2-AMINO-1-BUTANOLS

3.1 INTRODUCTION

Natural and synthetic azetidinone derivatives also called as β-lactams occupy a central place among the antibiotics.[1-9] Recent years have seen a resurgence of interest in the development of stereo and enantioselective methodologies for the synthesis of azetidinones. The utility of azetidinones as synthones for various biologically active compounds as well as their recognition as cholesterol absorption inhibitors[10-14] and enzyme inhibitors,[15-16] has given impetus to these studies.[17-21] Antibiotics belonging to the families of penicillin's, cephalosporin's, cephamycins, norcardins and monobactams have in common a β-lactam ring moiety.[7] Chiral β-lactams besides their clinical importance have also proven to be very useful synthons for the various non-β-lactam derivatives such as pyrollidones,[22] natural and synthetic α-amino acids,[23] peptides,[17] unusual amino acids,[24] α-hydroxy-β-amino acids,[25] an intermediate for taxol side chain.

3.1.1 General Methods For Synthesis Of Azetidinones

The two general methods for synthesis of azetidinones are:

a) Straudinger reaction and related methods (cyclo addition)

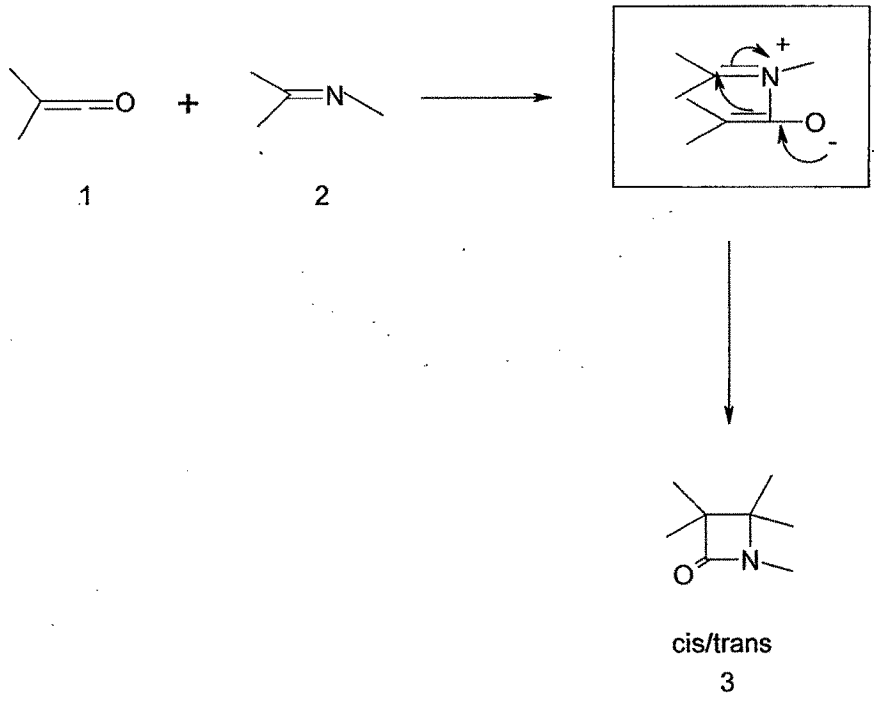
b) Cyclisation and other methods.

a) **Staudinger reaction and related methods**

Among the various methods reported for the construction of β-lactam ring, Straudinger reaction (ketene-imine cycloaddition reaction) has found wide acceptance in stereoselective synthesis of β-lactams.[26, 27] The organized transition state of cycloaddition reaction offers diverse options to design suitable partners of ketene and imine so that the product selectivity can be efficiently controlled. The presence of a chiral centre at the adjacent sites of the reacting groups can dictate the preference for a particular diastereomer.[27] Ideally there are three sites where a chirality directing group can be located: (a) the ketene (R^1), (b) the aldehyde component (R^2) of the imine and (c) the

amine component ($R^{3)}$ of the imine. The reaction is carried out thermally or photochemically using acid chlorides in the presence of triethylamine or α-diazoketene as ketene precursors.

Although commonly described as [2 + 2] cycloaddition, it is generally accepted that the reaction involves a nucleophilic attack of an imino nitrogen of the imine 2 on the sp hybridised carbon of a ketene 1 to form a zwitterionic intermediate, which then cyclises to form an azetidinone ring 3. The stereochemistry of the resulting azetidinone can be cis / trans or a mixture of both isomers (**Scheme-III.1**)

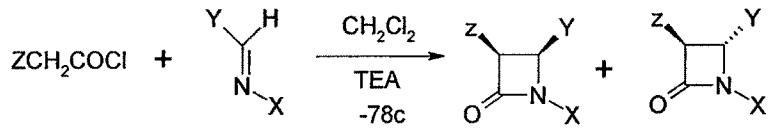


Scheme III.1

Substituents present in the imines or the acid chlorides, the nature of base and solvent, the reaction condition and even the order of addition of the reagents have been found to affect the formation of azetidinone ring.

Various chiral acid derivatives, as ketene precursors, and chiral imines have been reported to effect moderate to very high diastereoselectivity in β- lactam ring construction via asymmetric Straudinger reaction.[27-29]

Banick and Becker have reported for the first time the reaction of the polycyclic aromatic imines 5 with acid chloride 4 under normal Staudinger conditions leading to the formation of the trans azetidinone 7.[30] Authors have hinted at a possible role of bulky subsituents on the N atom of the imines in the determining the stereochemistry of the products (**Scheme III.2**).

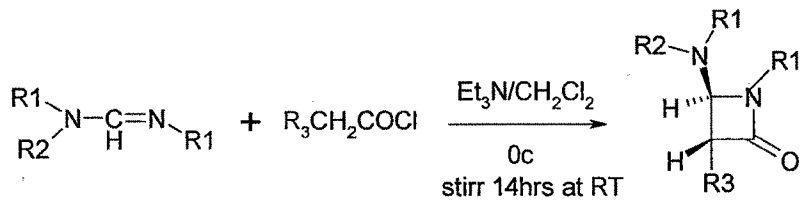


4 5 6 7

Z= OAc, OPh , Y= Ph , X=Ph, napthyl, anthracenyl.

Scheme III.2

Cycloaddition of ketenes, generated in situ from phenoxy acetyl chlorides or phthalimidoacetyl chloride and triethyl amine to the C=N bond of amidines leading to the formation of trans – 4 – acylamino– 2 – azetidinones 10 have been reported by Bhawal *et al.* (**Scheme III.3**).[31]



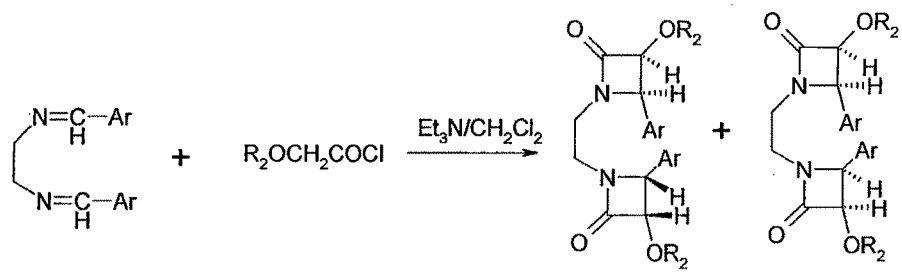
8 9 10

R_1 = Ph, 4-ClC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$; R_2=PhCO, 4-$NO_2C_6H_4CO$, Ts,

R_3 = PhO, PhthN.

Scheme III.3

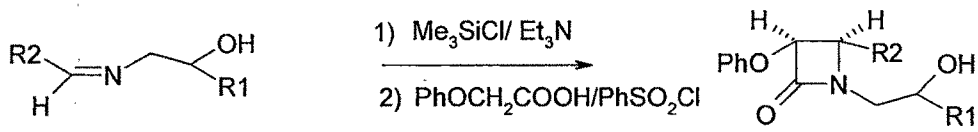
They have also reported the synthesis of bis azetidinone 13 and 14 linked with an ethylene bridge and possessing cis – stereochemistry, using the same methodology but with different ketene precursor 12 and bisimine 11 (**Scheme III.4**).[32]



11 12 13 14

Scheme III.4

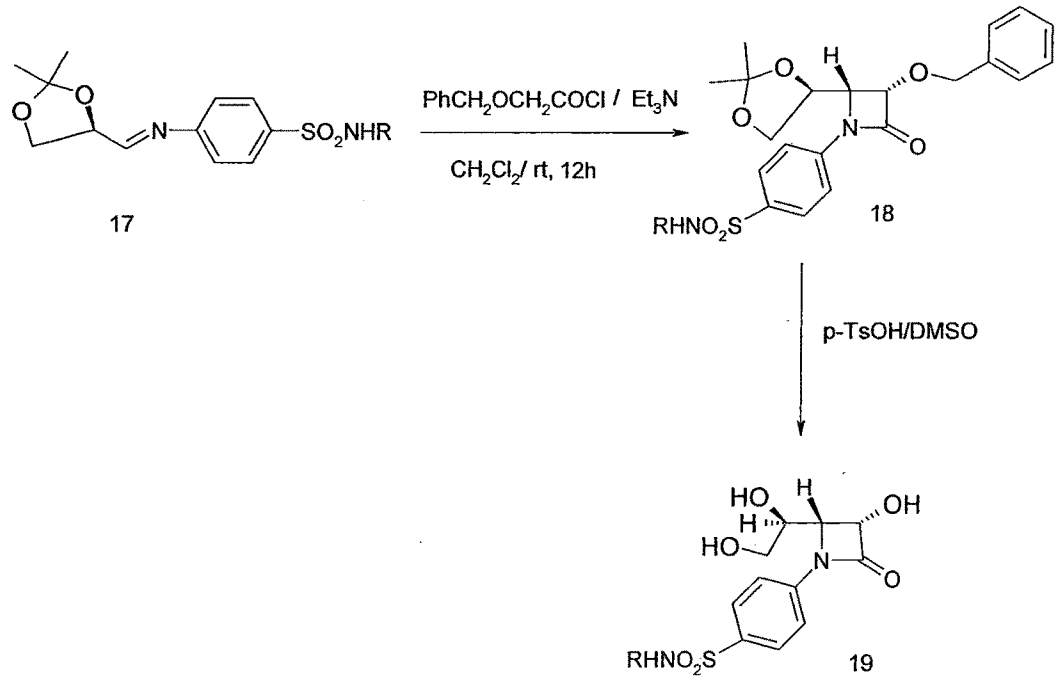
Synthesis of cis –N – 2 – hydroxyethyl – 2 – azetidinones (16) has been reported by Sharma and Bhaduri[33] using phenoxy acetic acid in the presence of benzene sulphonyl chlorides. The protection of the hydroxyl group in imine 15 is a necessity for a reaction to proceed and it has been achieved with trimethylsilyl chlorides (**Scheme III.5**)



15 16

Scheme III.5

Chiral aldimines obtained from D-glyceraldehyde acetonide and some biologically important heterocyclic amines, have been reacted with benzyloxyacetyl chloride in the presence of triethyl amine to give optically pure cis-3-benzyloxy-2-azetidinones 18. The latter compounds yield 3-hydroxy-2-azetidinones 19 having an N-sulfonamido drug side chain on hydrolysis (**Scheme III.6**).[34]

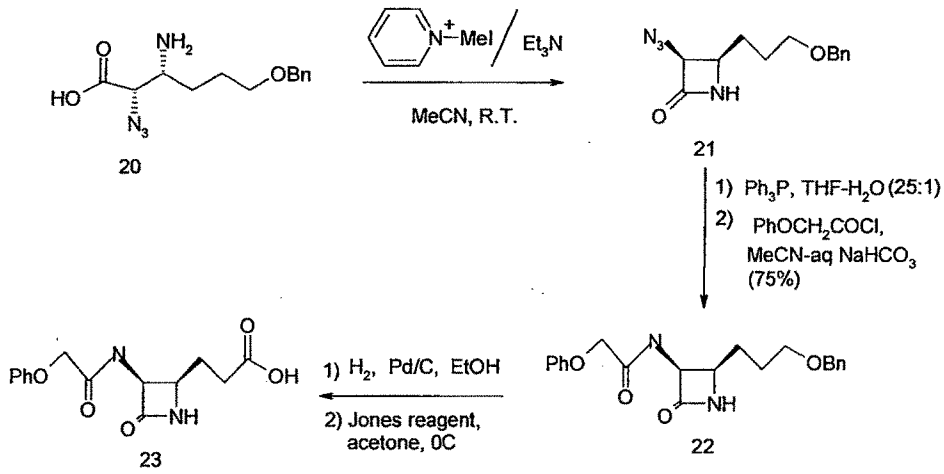


Scheme III.6

Straudinger ketene-imine cycloaddition has been used to synthesize 2-azetidinones with a broad range of substituents including various heterocycles. These azetidinones have been screened for different biological activities such as antibacterial, antifungal, anticancer and antitubercular activities.

b) **Cyclisation and other methods**

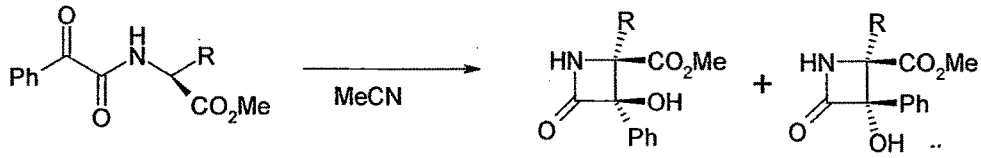
β– Amino acid cyclisation has been utilized by Lee and co-workers to synthesize the cis – (*3S, 4R*) azetidinone 23 as a precursor for the antibiotic, loracarbef[35]. The required α-azido- β-amino acid 20 was synthesized by asymmetric amino hydroxylation of theα,β-unsaturated ester followed by the introduction of azide. (**Scheme III.7**)



20 21 22 23

Scheme III.7

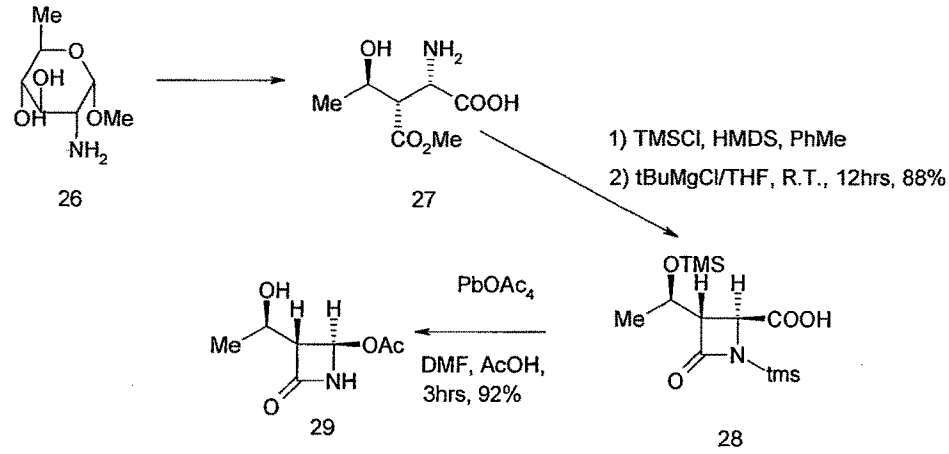
The formation of 3-hydroxy –2 – azetidinones 24 in a reversible photocyclisation of phenylglyoxamides 25 of enantiomerically pure α-amino acid methyl ester has been reported by Aries beck and heckroth.[36] In many cases they have isolated the azetidinone in moderate to high diastereoselectivity with the cis –isomer as the major component. The presence of a catalytic amount of HCl in the reaction mixture stabilizes the azetidinones but reduces and inverts the diastereomeric ratios **(Scheme III.8).**



25 24

Scheme III.8

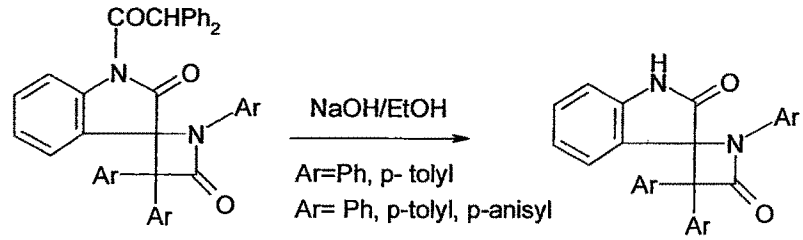
Synthesis of (+)-4- Acetoxy – 3 – hydroxyethyl – 2 – azetidinone (29) which is key intermediate for the synthesis of the carbapenem antibiotic, (+) thienamycin has been reported by Tatsuta and co-workers (**Scheme III.9**).[37]



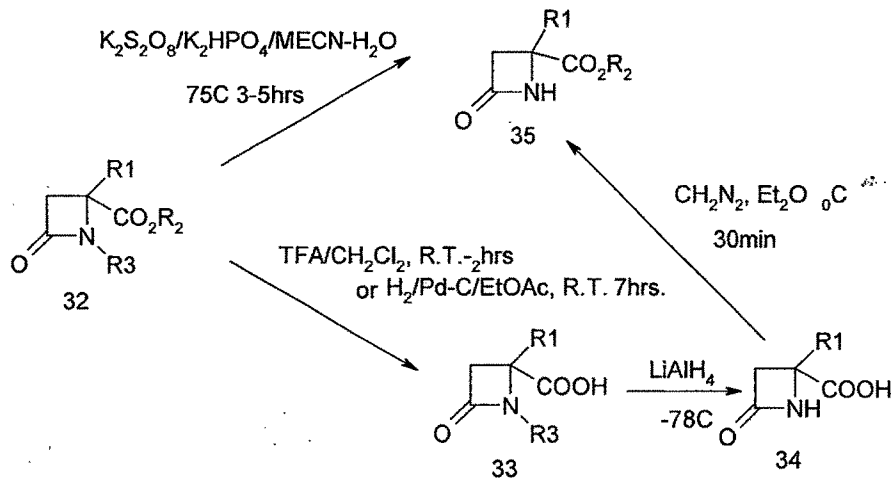
Scheme III.9

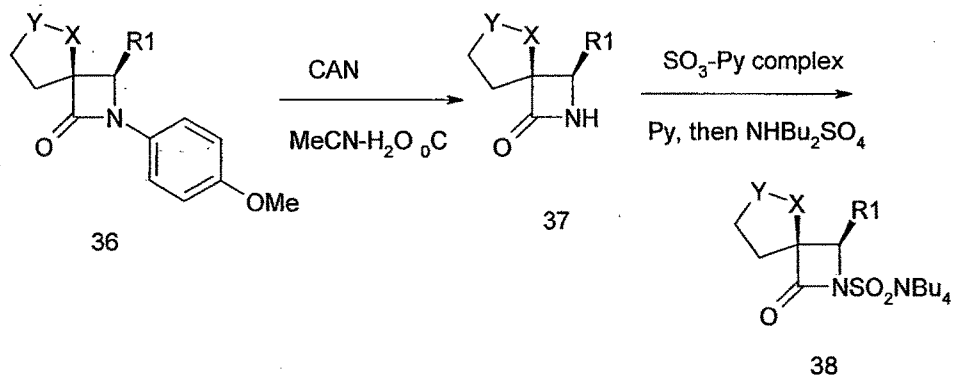
3.1.2 Chemical Transformations Of Azetidinone Derivatives

The synthesis of some novel spiroazetidinones containing an indolinone ring has been reported by Singh.[38] The spiroazetidinones 30 undergoes selective N – decarbonylation in ethanolic NaOH to give the products. The spiroazetidinone have significant anticonvulsant activity. Gonzalez – Muniz[39] have reported selective C and N-deprotection in 4–alkyl-4 –carboxy – azetidinones 32 leading to the formation of the N - unsubsituted azetidinones 33–35. An oxidative N – dearylation in the spiro – azetidinones 36 using ceric ammonium nitrate followed by treatment with a SO_3 pyridine complex, leads to the formation of the spiro N – sulfonyl azetidinone derivatives 38 (**Scheme III.10**).[40]



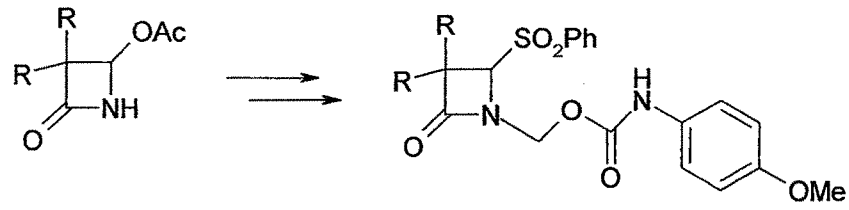
30 31





Scheme III.10

Clamente and co-workers[41] have transformed the azetidinones 39 to 40 in a few simple steps. These compounds have been found to exhibit the inhibitory potency and selectivity for the enzyme, human – leucocyte elastase (**Scheme III.11**).[41]



39 40

Scheme III.11

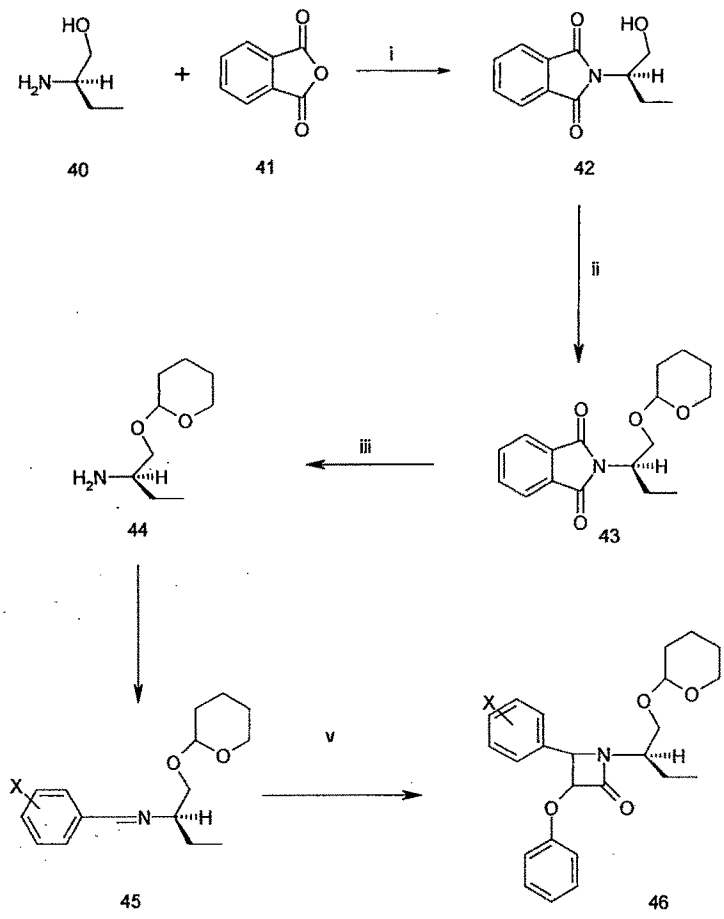
The antibiotic activity of azetidinones, their effectiveness in cholesterol absorption, enzyme inhibition and their application as synthons for various biologically important compounds make them an appealing target for medicinal synthetic chemist. Several literature reports the stereo and enantioselective reaction employing different conditions and reagents e.g. chiral amines, ketenes and catalyst.

3.2 RESULTS AND DISCUSSION

We have studied the enantioselective synthesis of a few substituted azetidinones using 2-Amino-1- butanol as a chiral template for the construction of the four membered ring using phenoxy acetyl chloride as a ketene precursor in the Staudinger reaction.

The free amino group of (*R*)-2-Amino-1-butanol (40) is protected by using phthalic anhydride (41) to obtain (*R*)-2-(1-hydroxymethylpropyl) isoindol-1, 3-dione (42) in good yield. The free hydroxyl group of 42 is protected using 3, 4-Dihydro-2H-pyran in CH_2Cl_2 as a solvent using PTSA as a catalyst. Deprotection of the phthaloyl group of 43 with hydrazine hydrate in absolute alcohol results in the formation of O-THP-protected-

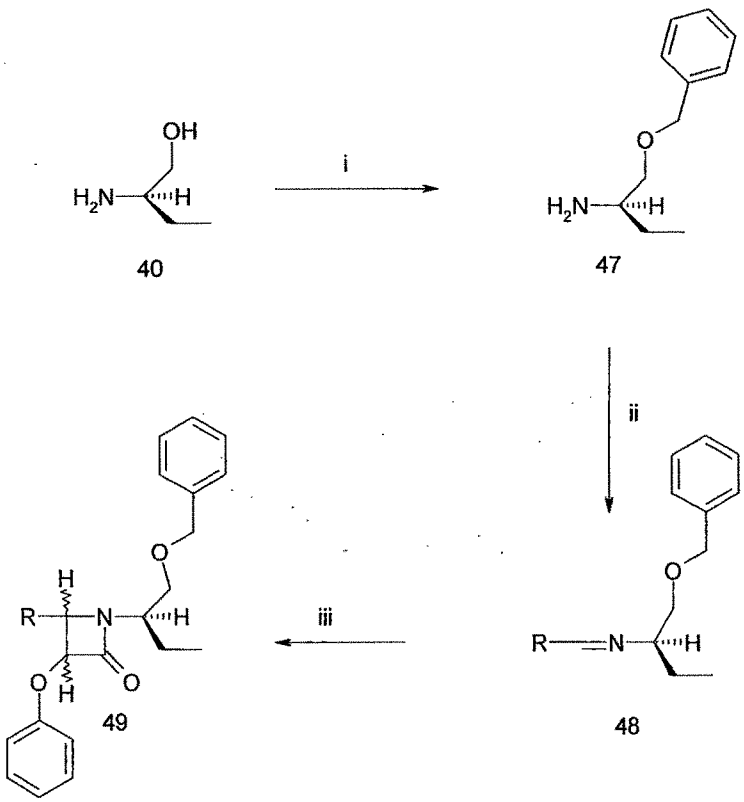
2-Amino-butanol 44. Three different aromatic aldehydes were reacted with O-THP-protected-2-Amino-butanol 44 in toluene under dean and stark conditions to give the corresponding Schiff bases 45a-45c which was directly used for the formation of azetidinones 46a-46c by reaction with phenoxy acetyl chloride and triethyl amine at 0 °C **(Scheme III.12)**.

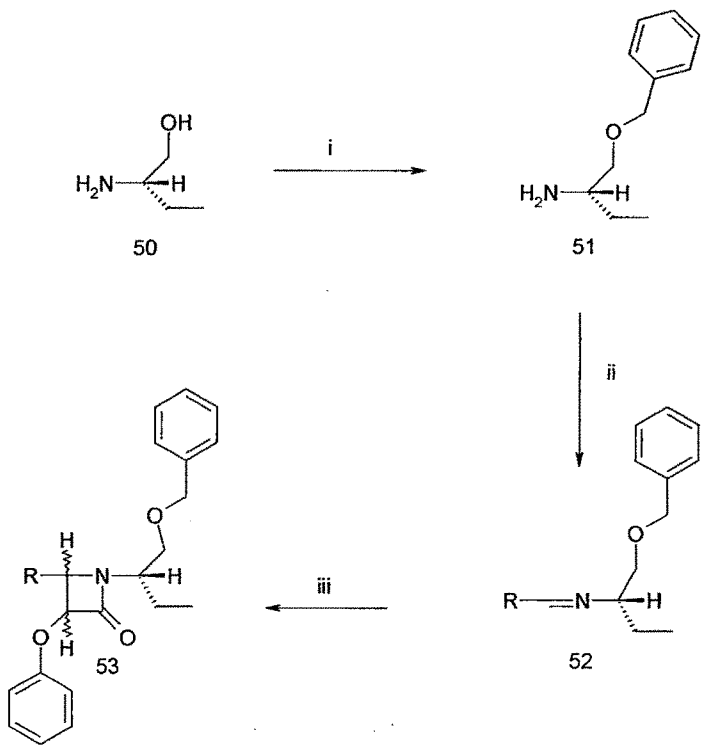


X=- NO_2 (46a), -Cl (46b), -H (46c)

Scheme III.12: i. 140°C, Neat, oil bath ii. DHP, PTSA/CH_2Cl_2 iii. $N_2H_4.H_2O$, absolute alcohol, reflux. iv. a. 4-$NO_2C_6H_5CHO$, b. 4-ClC_6H_5CHO, c. C_6H_5CHO toluene, reflux, dean-stark v. $PhOCH_2COCl$, Et_3N, 0°C

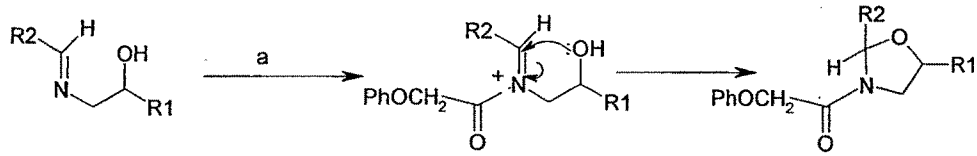
We have also studied the reaction using benzyl chloride as a protecting group. The reaction of the aldehydes with (*R*) & (*S*)-O-Benzyl-2-amino-1-butanols 47 & 51 resulted in the formation of the corresponding schiff bases. The Schiff bases were directly allowed to react with a mixture of phenoxy acetyl chloride and triethyl amine in dichloromethane at 0 °C to give the corresponding azetidinone derivatives 49a-49d & 53a-53d (**Scheme III.13**).





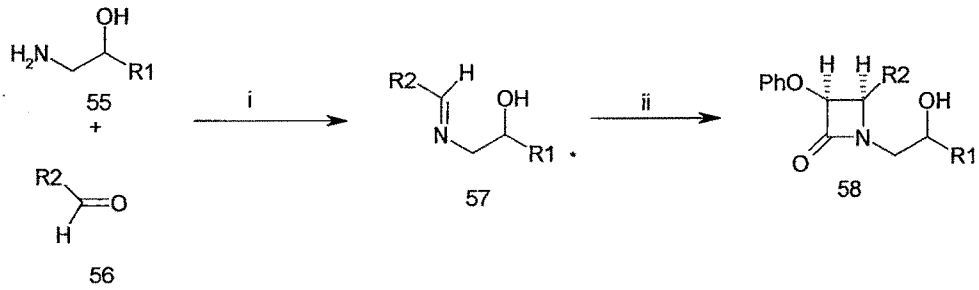
Scheme III.13 i.NaH, dry THF, 17 hours reflux; benzyl chloride, 24 hours reflux ii.a. C_6H_5CHO, b. 4-ClC_6H_4CHO, c. 4-$OCH_3C_6H_4CHO$, d.C_6H_5CH=$CHCHO$, PTSA, Toluene 7-8hours dean-stark iii. $PhOCH_2COCl$, Et_3N, 0°C-r.t.

The protection of hydroxyl group by a protecting group is an essential feature of this reaction. This was observed by Sharma *et al.*[33], who while carrying out reaction of ethanolimines with phenoxy acetic acid promoted by benzene sulfonyl chloride found out that the imines in which the hydroxyl group was left unprotected resulted in the formation of N-acylated oxazolidines(**Scheme III.14**), while the imines in which the hydroxyl of the imines is protected leads to the formation of β-lactams **(Scheme III.15).** Trimethyl silyl chloride was used as the protecting group.



a. $PhOCH_2CO_2H/Et_3N/ PhSO_2Cl$

Scheme III.14



i. Anhyd. Na_2SO_4, MeOH reflux ii. Me_3SiCl/Et_3N, $PhOCH_2CO_2H/ PhSO_2Cl$

Scheme III.15

Our aim was to study the formation of β-lactams using (*R*) and (*S*)-2-Amino-1-butanols for the synthesis of imines and using phenoxy acetyl chloride and triethyl amine for the generation of the ketene. We have used two protecting groups, dihydropyran and benzyl group for the synthesis of the protected imines to obtain the corresponding protected azetidinones.(*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl)isoindol-1,3-dione(43) show -ed a triplet at δ0.9 for three protons of $-CH_3$ group, a multiplet for six protons of methylene of tetrahydropyran group, another multiplet at δ1.7-2.1 for two protons of the methylene group, a multiplet at δ3.4-4.4 for six protons of $-CH_2$-O of tetrahydropyran group, for -CH_2-O group, for –CH-O group of tetrahydropyran and another –CH-O group. A multiplet was observed for four protons in the aromatic region (**Figure III.1**). (*R*)-1-(tetrahydropyran-2-yloxymethylpropyl) amine (44) also showed similar PMR pattern (**Figure III.2**), only the aromatic region showed no peaks.

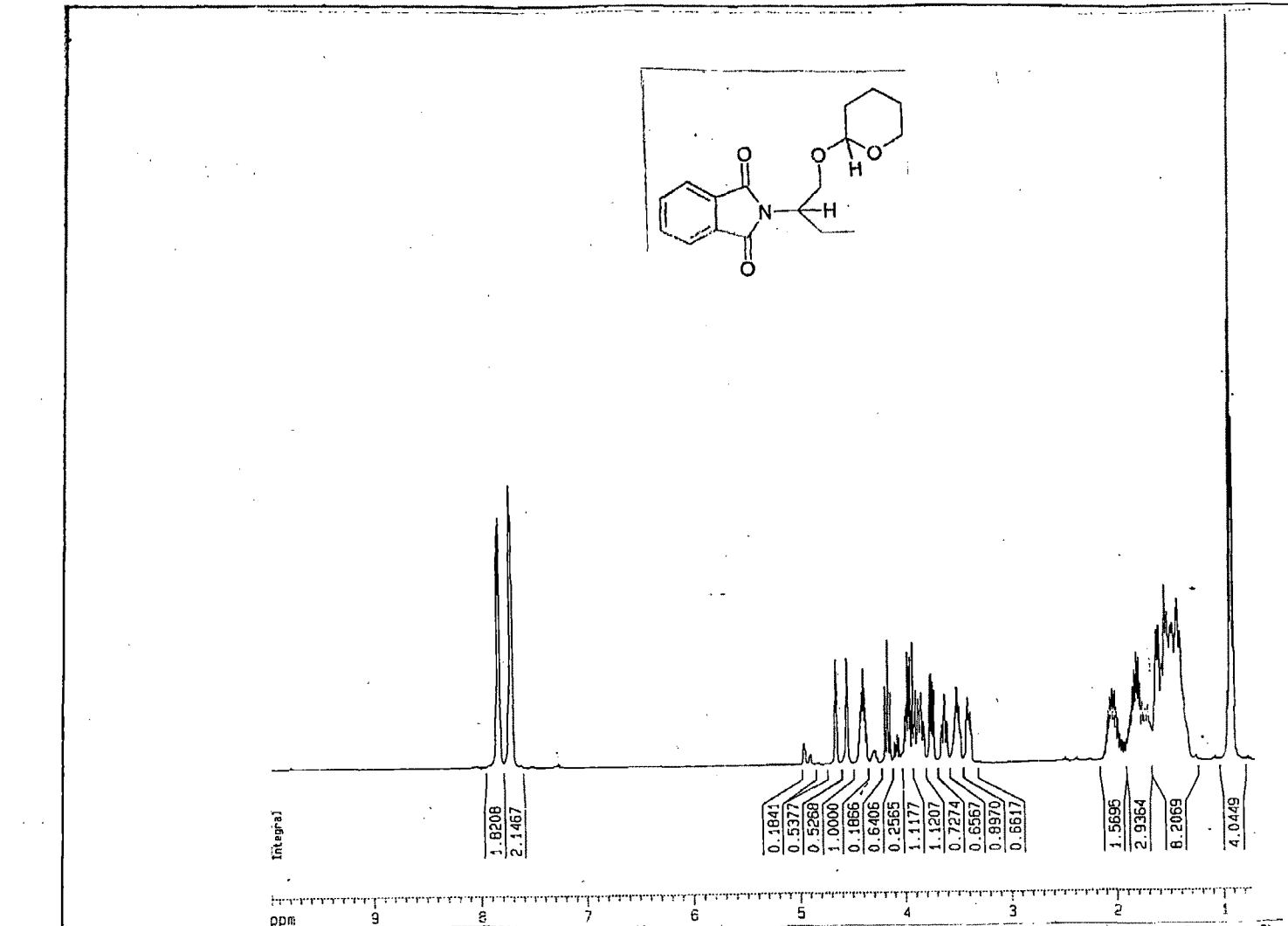


Figure III.1 1H NMR($CDCl_3$) spectrum of (*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl) isoindol -1,3-dione (43)

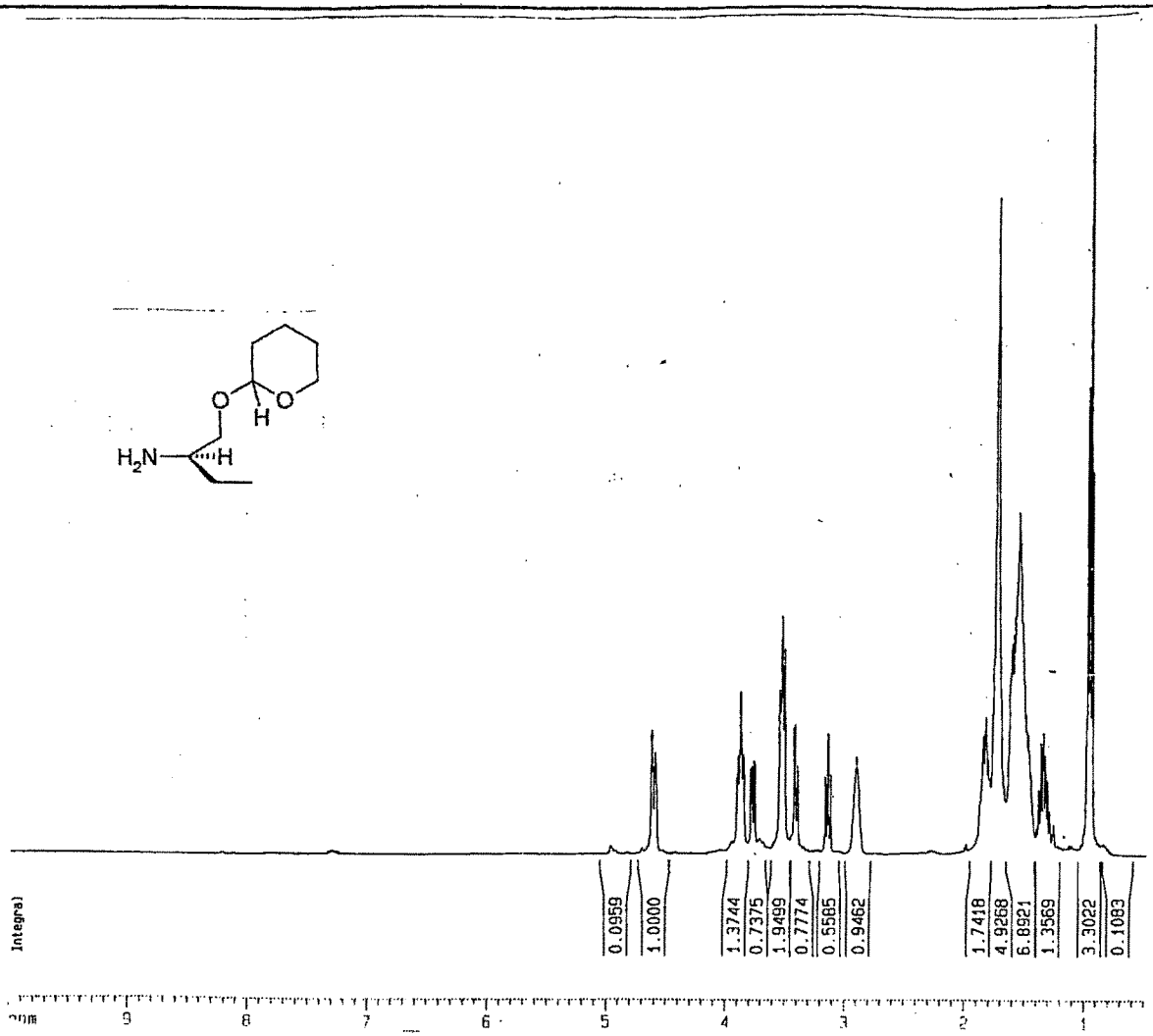


Figure III.2 1H NMR($CDCl_3$) spectrum of (*R*)-1-(tetrahydropyran-2-yloxymethylpropyl) amine (44)

The thp-protected azetidinones 46a-46c was formed in poor yields and the diastereoselectivity of the products was extremely poor reflected by the very complex pmr spectra (**Figure III.3**) and hplc data of the isolated compounds (**Figure III.4**). The IR spectra clearly showed the presence of the required carbonyl peak of the β-lactam ring in the region of 1745 -1750cm^{-1}(**Figure III.5**). However in case of the benzyl protected imines, when the reaction was carried out with phenoxy acetyl chloride and triethyl amine, the reaction proceeded smoothly with extremely good yields and with very good diastereoselectivity. All the azetidinones showed the typical band for the carbonyl of the β-lactam ring in the region of 1745-1755cm^{-1}(**Figure III.6**).

The proton nmr of 49a (**Figure III.7**) showed a triplet at δ 1.0 for the protons of the methyl group, a multiplet at δ1.6-2.0 for the two methylene protons. A quartet was obtained for the methylene of the benzyl group of the azetidinone. A double doublet was observed at δ3.28 for one of the non equivalent methylene protons and another double doublet was observed at δ 3.44 for the other proton. A doublet was observed at δ4.26 was observed for the –CH of the four membered ring and another doublet at δ5.36 was observed for the other –CH of the azetidinone. The coupling constant values for the protons were found to be 4.5Hz. This clearly shows a cis relationship in between the two protons. The aromatic region shows a multiplet for fifteen protons for the phenyl protons.

The p-chloro substituted compound 49b also showed similar pmr spectral pattern (**Figure III.8**). It also showed a doublet at δ4.94 and δ5.36 for the –CH groups of the four membered ring. Again the coupling constant was found to be 4.5 which again indicated a cis relationship in between the two protons. The aromatic region showed a multiplet at δ6.6-7.4 for the fourteen protons. The methoxy substituted compound 49c showed other than the required peaks a singlet at δ3.8 for the methoxy group (**Figure III.9**). The azetidinone 49d showed in addition to the required peaks as a double doublet at δ6.3 for =CH of the cinnamyl group and a doublet at δ6.5 for the other =CH group (**Figure III.10**). The azetidinone 53a synthesized by using (S)-2-amino-1-butanol 51 showed a similar spectral pattern as the (R) counterpart (**Figure III.11**). The coupling constant was

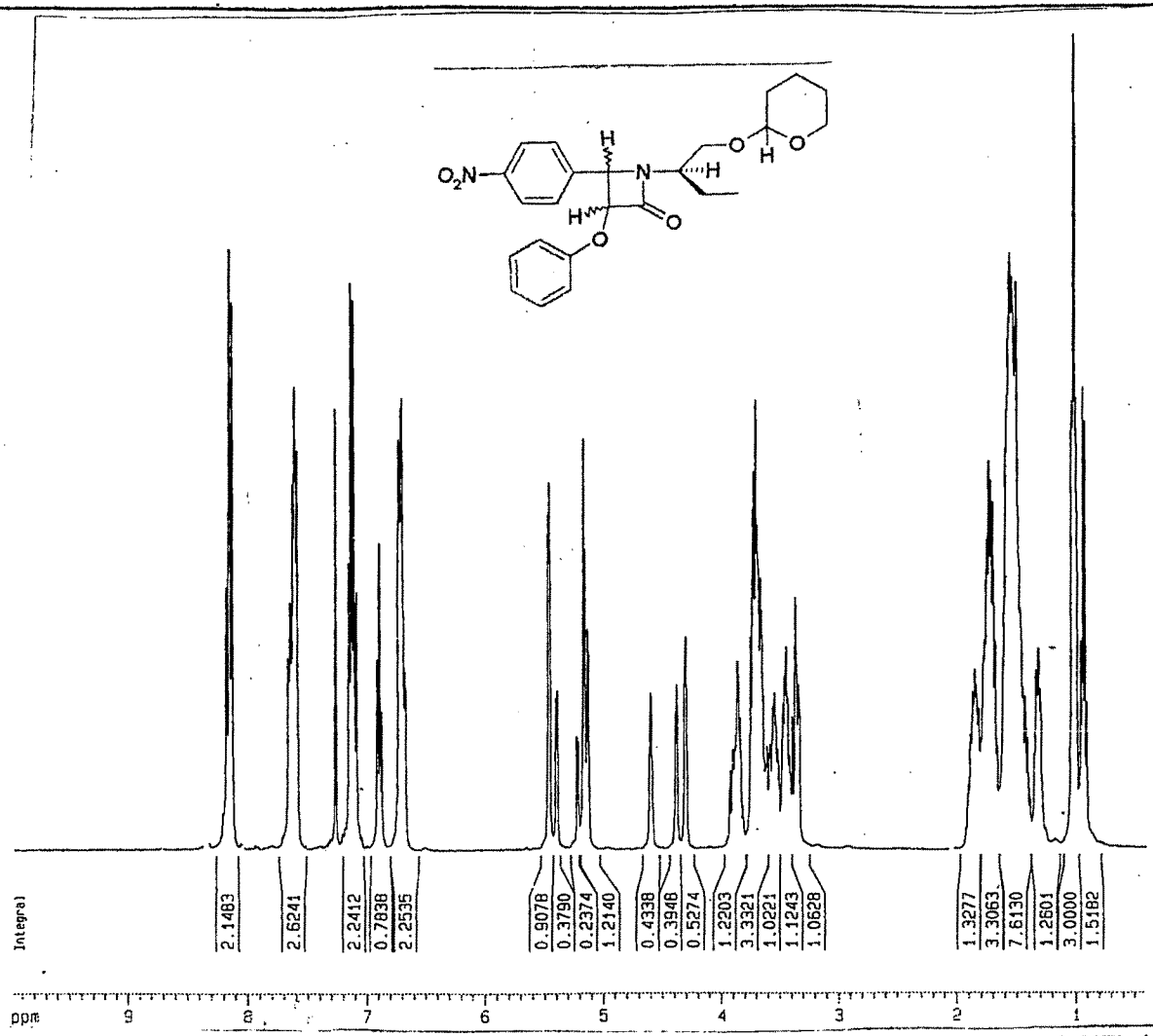
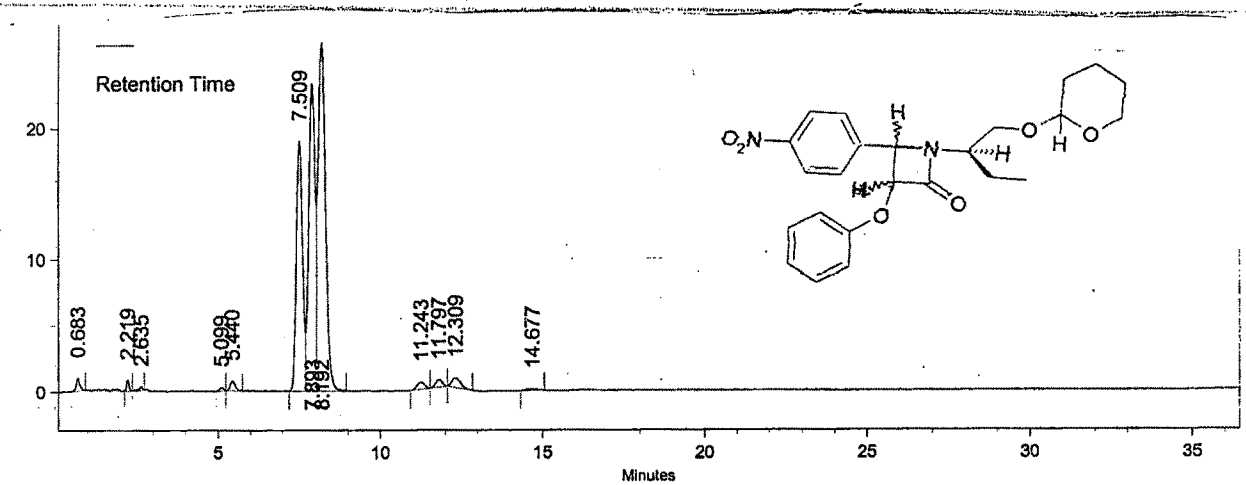


Figure III.3 1H NMR($CDCl_3$) spectrum of 4-(4-Nitrophenyl)-3-phenoxy-1-[(*R*)-1-(tetrahydropyran-2-yloxymethyl)propyl]azetedin-2-one (46a)



1: 254 nm, 8 nm

Pk #	Retention Time	Area	Area Percent
1	0.683	7907	0.76
2	2.219	4407	0.42
3	2.635	2008	0.19
4	5.099	2264	0.22
5	5.440	8188	0.79
6	7.509	248968	23.88
7	7.893	312331	29.96
8	8.192	422677	40.54
9	11.243	8774	0.84
10	11.797	8325	0.80
11	12.309	13752	1.32
12	14.677	3003	0.29
Totals		1042604	100.00

Figure III.4 HPLC DATA OF 4-(4-Nitrophenyl)-3-phenoxy-1-[(*R*)-1-(tetrahydropyran-2-yloxymethyl)propyl] azetedin-2-one (46a)

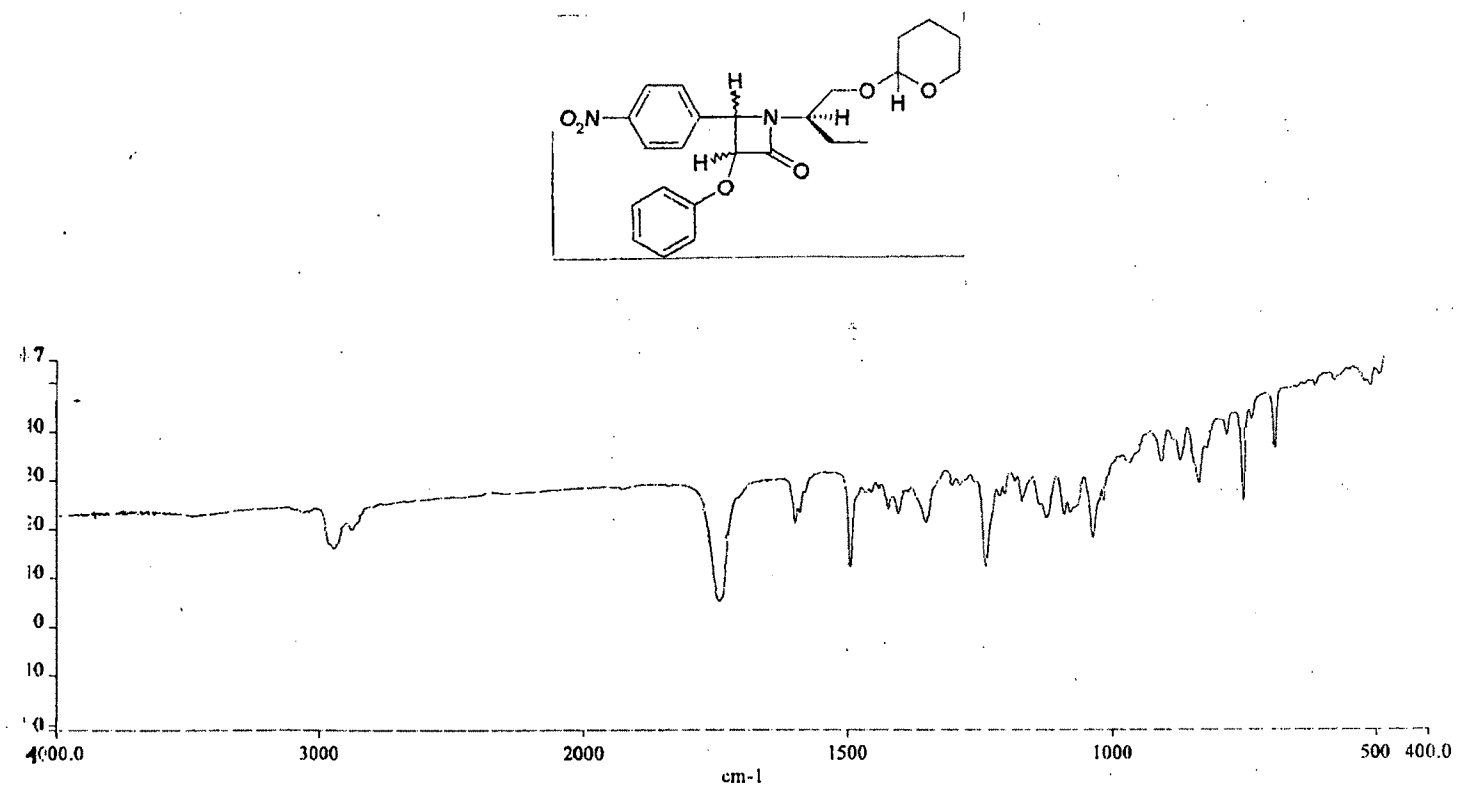


Figure III.5 IR spectrum (KBr) of 4-(4-Nitrophenyl)-3-phenoxy-1-[(*R*)-1-(tetrahydropyr an-2-yloxymethyl)propyl]azetedin-2-one (46a)

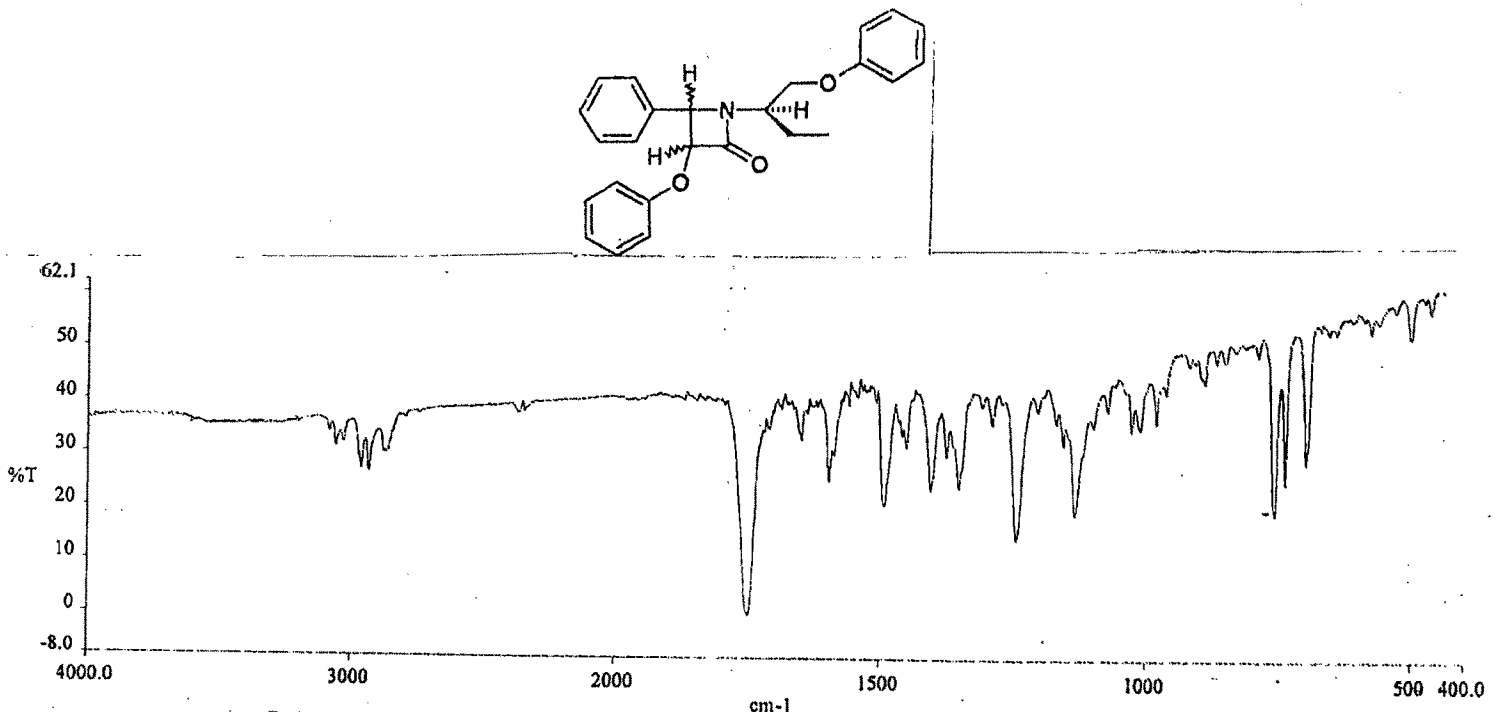


Figure III.6 IR spectrum (KBr) of 4-Phenyl-3-Phenoxy-1-((R)-1-phenoxymethylpropyl) azetedin-2-one (49a)

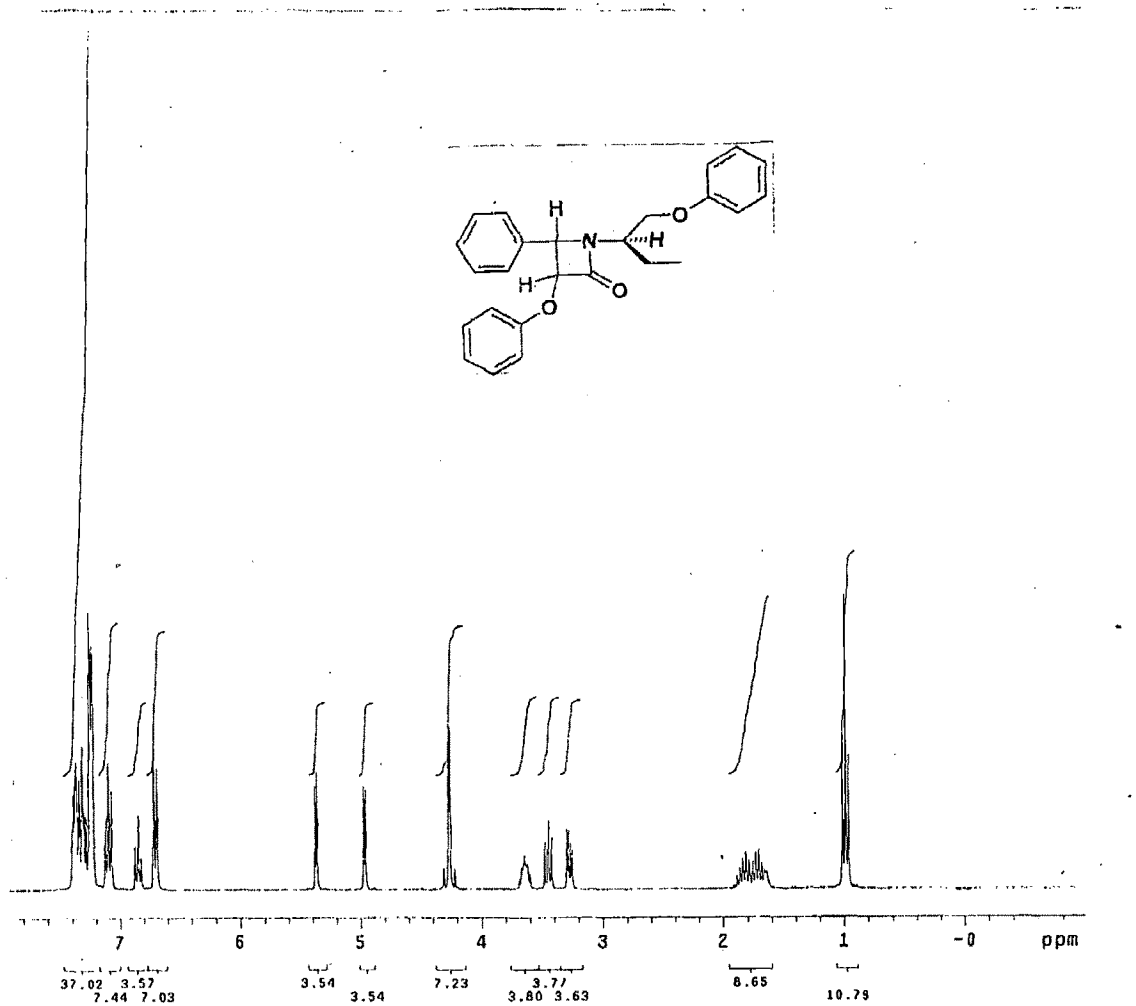


Figure III.7 1H NMR($CDCl_3$) spectrum of 4-Phenyl-3-Phenoxy-1-((R)-1-phenoxymethyl propyl)azetedin-2-one (49a)

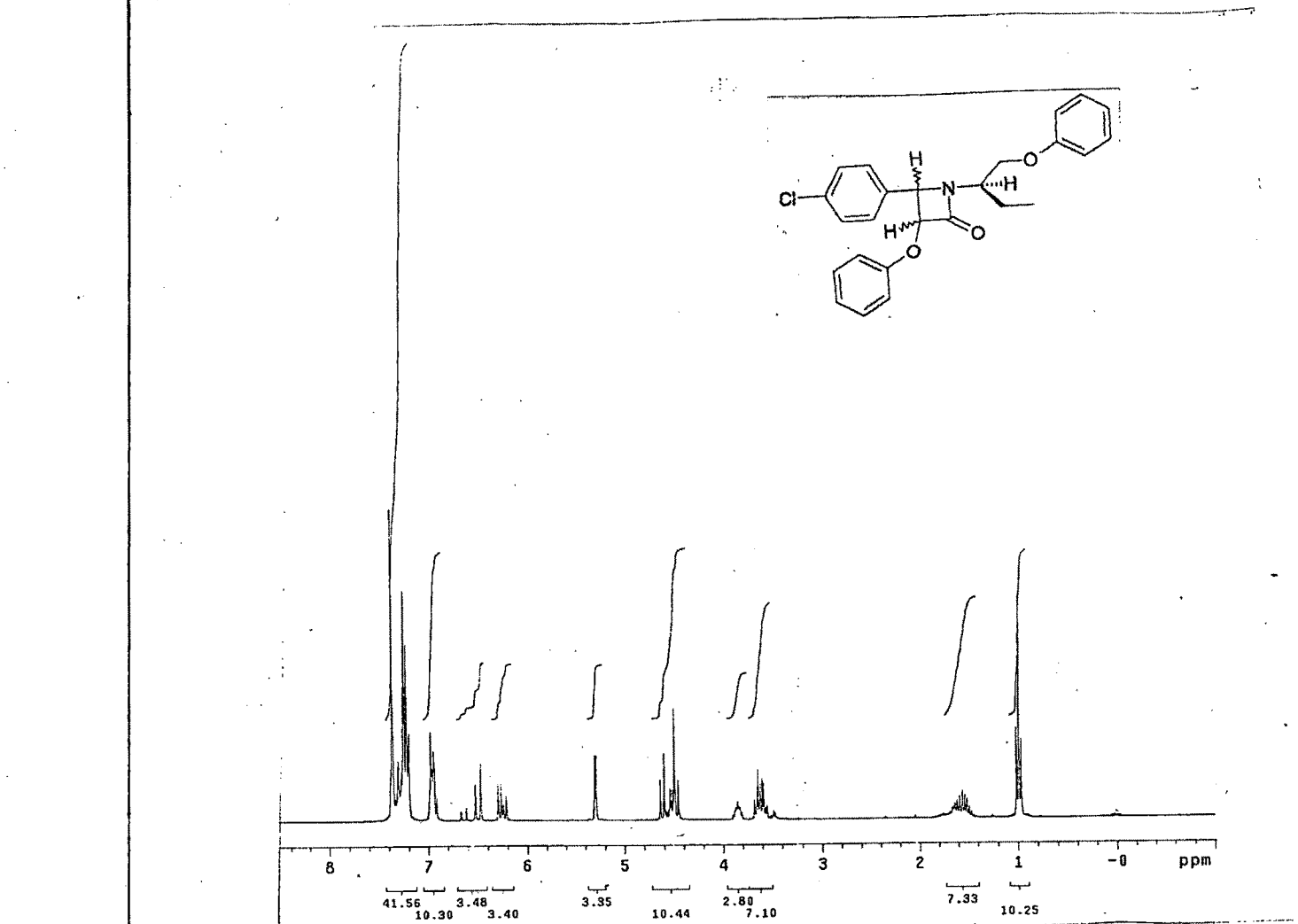


Figure III.8 1H NMR($CDCl_3$) spectrum of 4-(4-Chlorophenyl)-3-phenoxy-1-((R)-1-phenoxy methylpropyl)azetidin-2-one (49b)

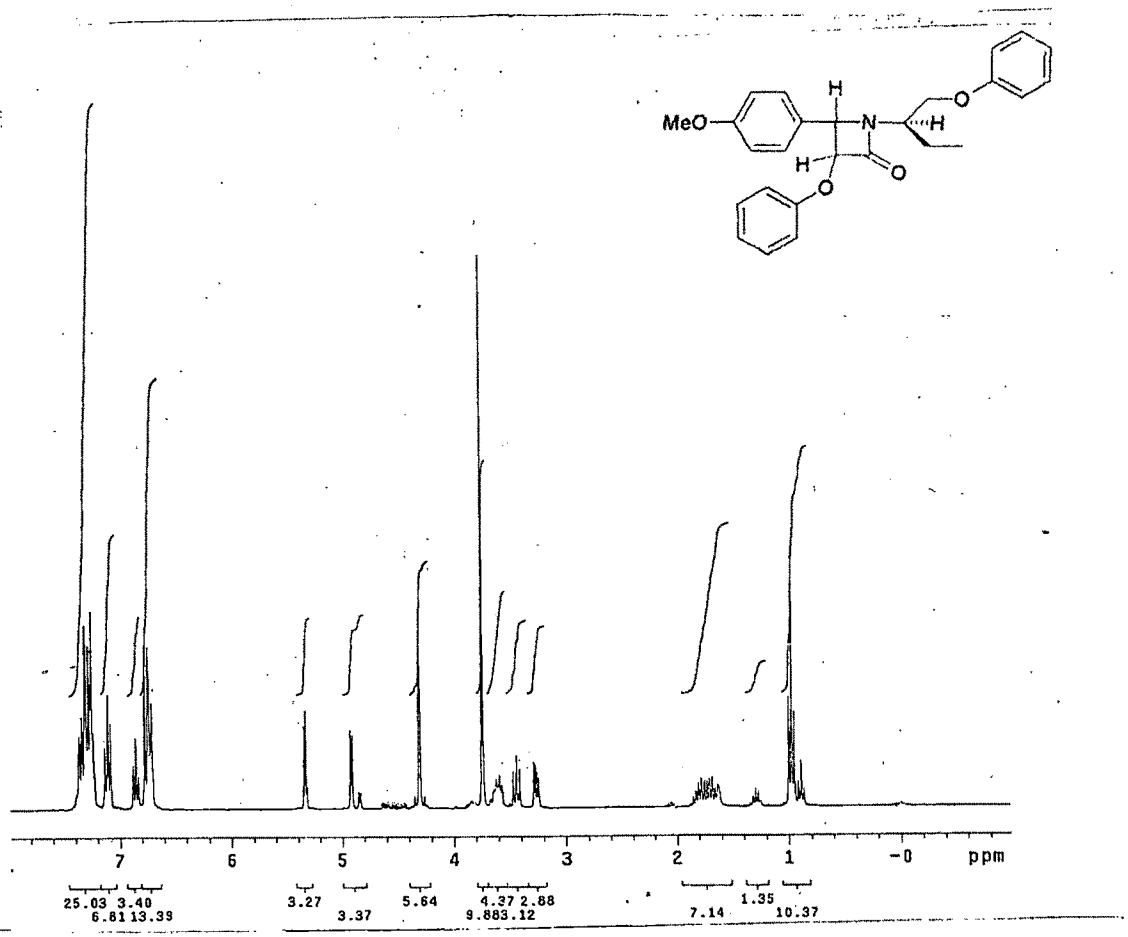


Figure III.9 1H NMR($CDCl_3$) spectrum of 4-(4-Methoxyphenyl)-3-phenoxy-1-((R)-1-phenoxymethyl-propyl)azetidin-2-one (49c)

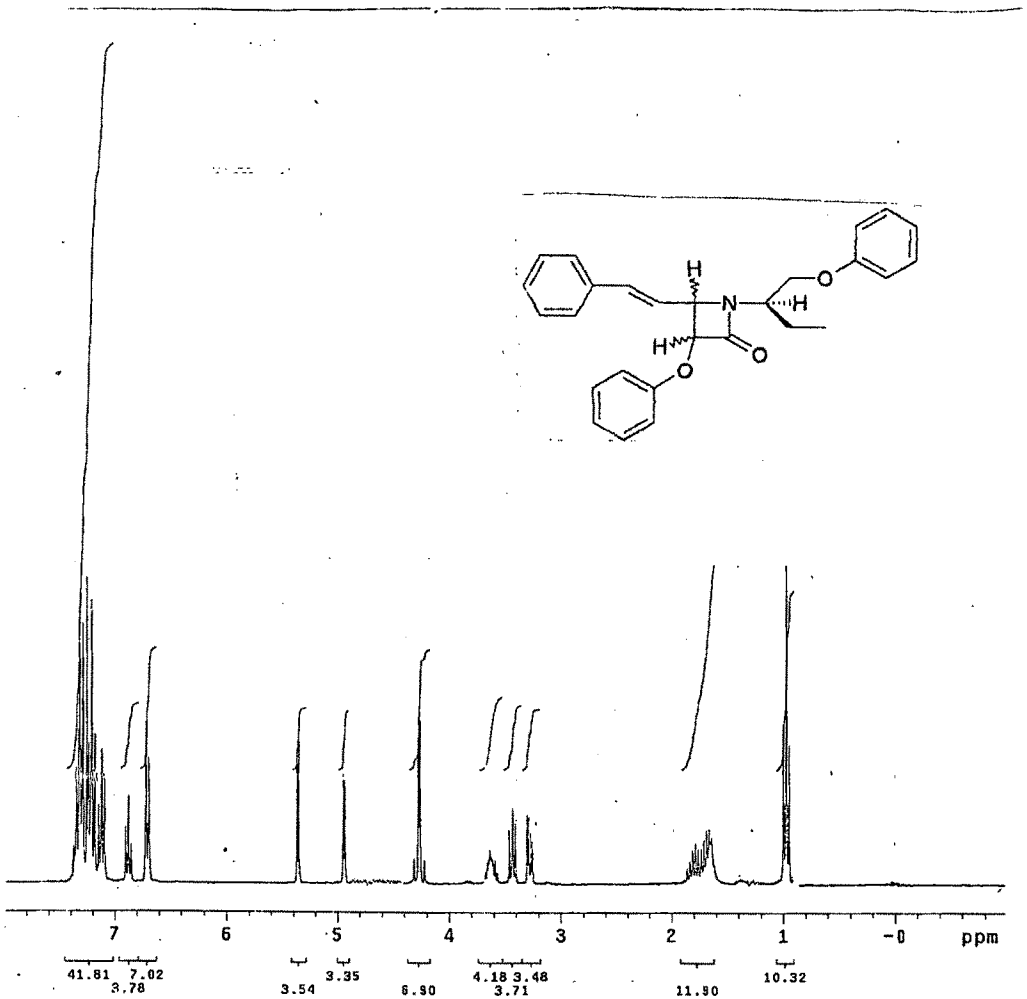


Figure III.10 1H NMR($CDCl_3$) spectrum of 4-Styryl-3-phenoxy-1-((R)-1-phenoxymethyl-propyl)azetidin-2-one (49d)

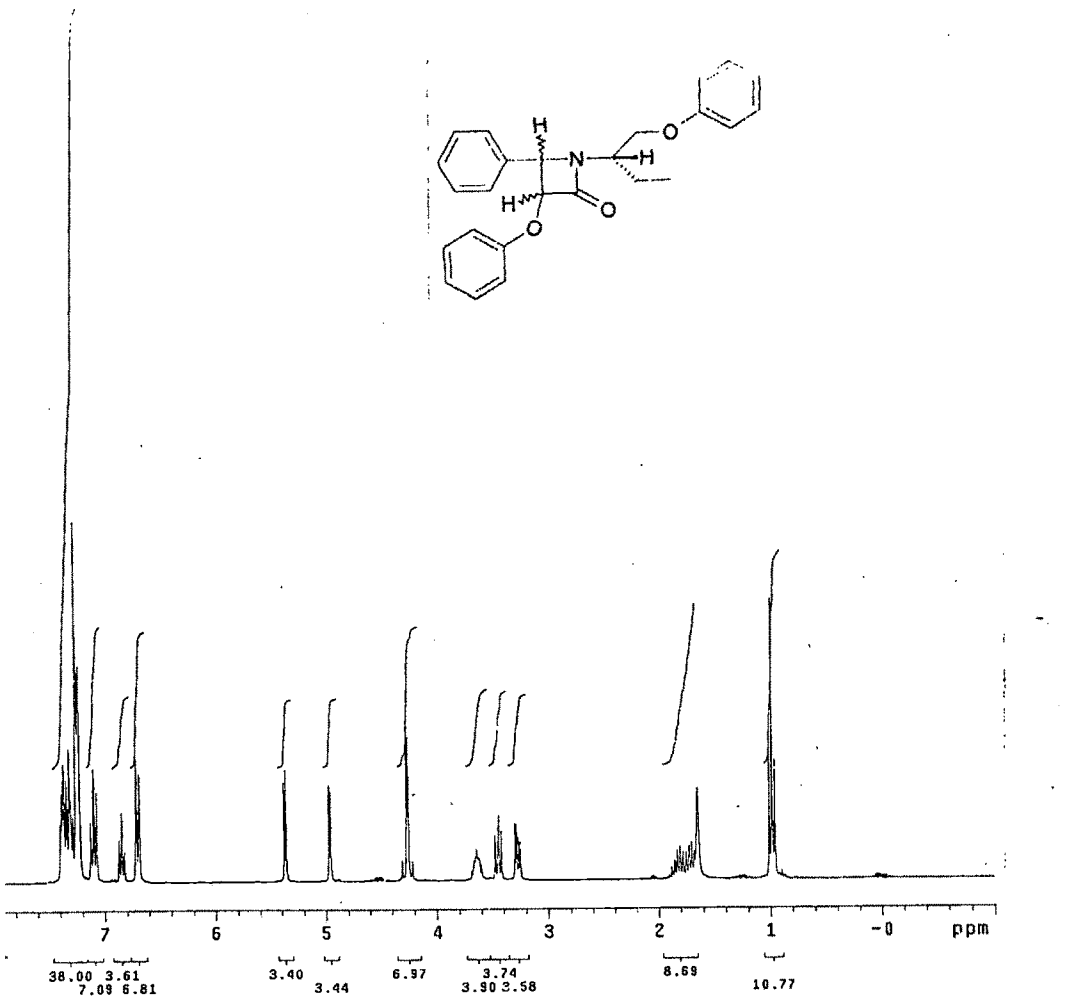
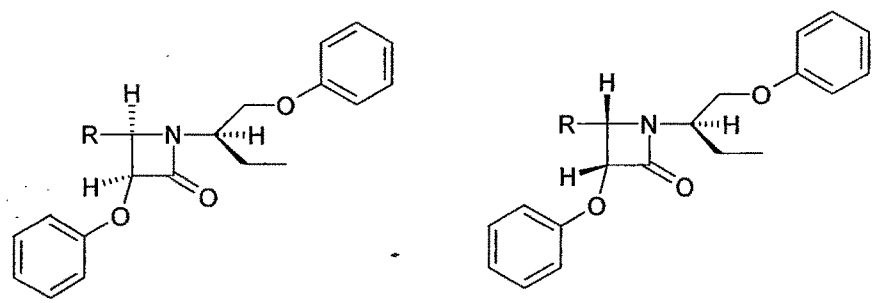


Figure III.11 1H NMR($CDCl_3$) spectrum of 4-Phenyl-3-Phenoxy-1-((S)-1-phenoxymethyl propyl)azetidin-2-one (53a)

also found to 4.5Hz for the protons indicating a cis relationship in between the two protons.

The styryl derivative 53d also showed a similar spectral pattern as its (R) isomer (**Figure III.12**). In case of the p-chloro derivative (53b) two triplets were observed at δ0.89 and δ0.97 indicating the presence of two methyl groups of two diastereomers (**Figure III.13**). Also the –CH of the four membered ring showed a double doublet at δ4.2 and another double doublet at δ5.35 indicating the presence of two diastereomers. The coupling constant values were found to be 4.5 indicating a cis relationship in between the protons of both the diastereomers. A similar observation was made in the case of the methoxy substituted azetidinone 53c (**Figure III.14**). The structures of the two diastereomers 49 consistent with the observed pmr of the products are as shown in **Figure III.15**



49

Figure III.15

Whereas complete diastereoselectivity is observed in 49a, 49b, 49c, 49d, 53a and 53d resulting in the formation of only one diastereomer, in case of 53b and 53c a mixture of two diastereomers is formed. The probable reason for the very good diastereoselectivity for the reaction may be linked to the presence of the chiral centre. Though the chiral centre is far away from the reacting site, the bulky benzyl protecting group and the ethyl group must be oriented in such a way as to block one of the faces of the imine from cyclisation. Thus the cyclisation must be taking place only from one of the faces resulting in formation of one of the diastereomers.

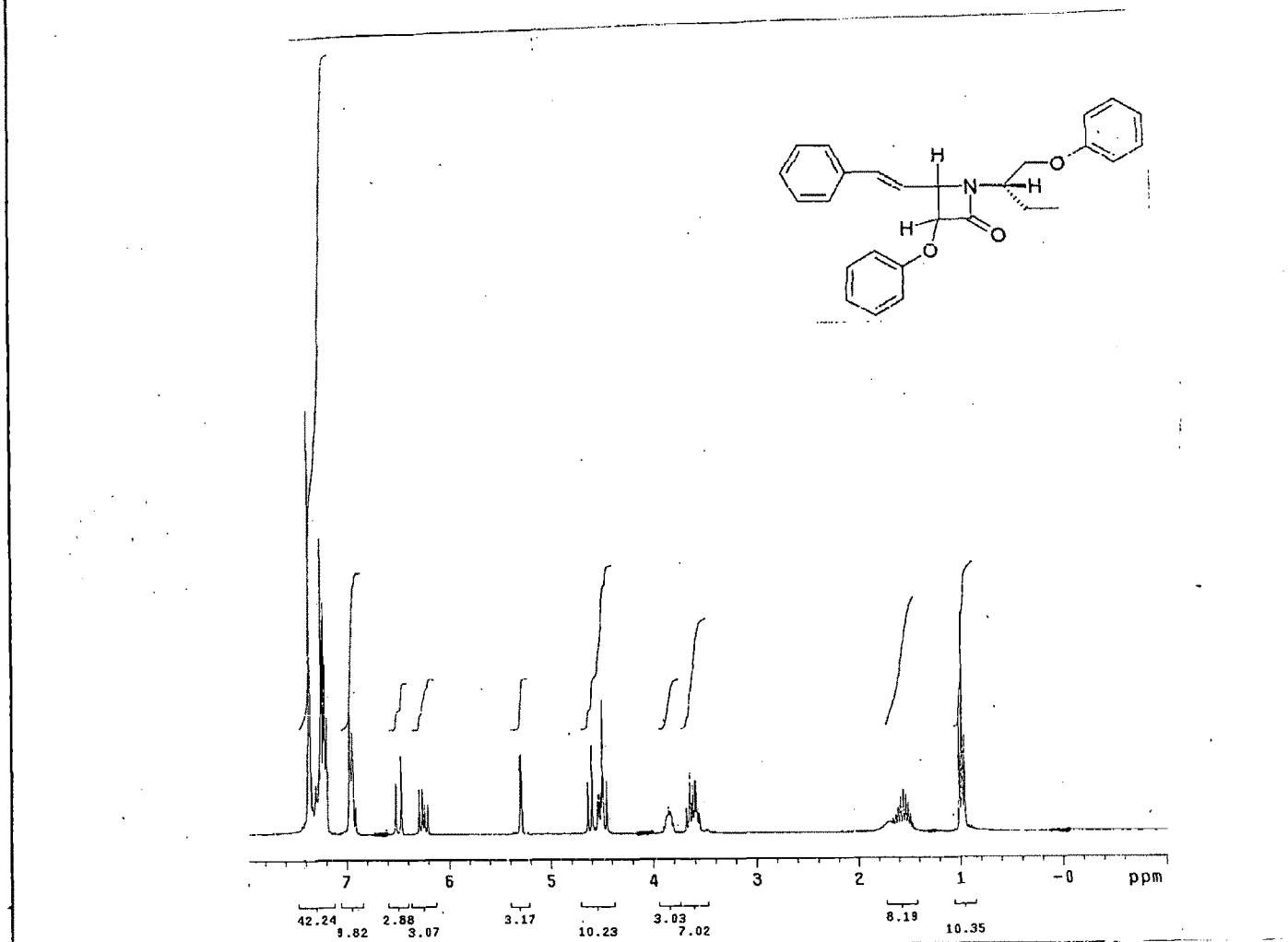


Figure III.12 1H NMR($CDCl_3$) spectrum of 4-Styryl-3-phenoxy-1-((S)-1-phenoxymethyl-propyl)azetidin-2-one (53d)

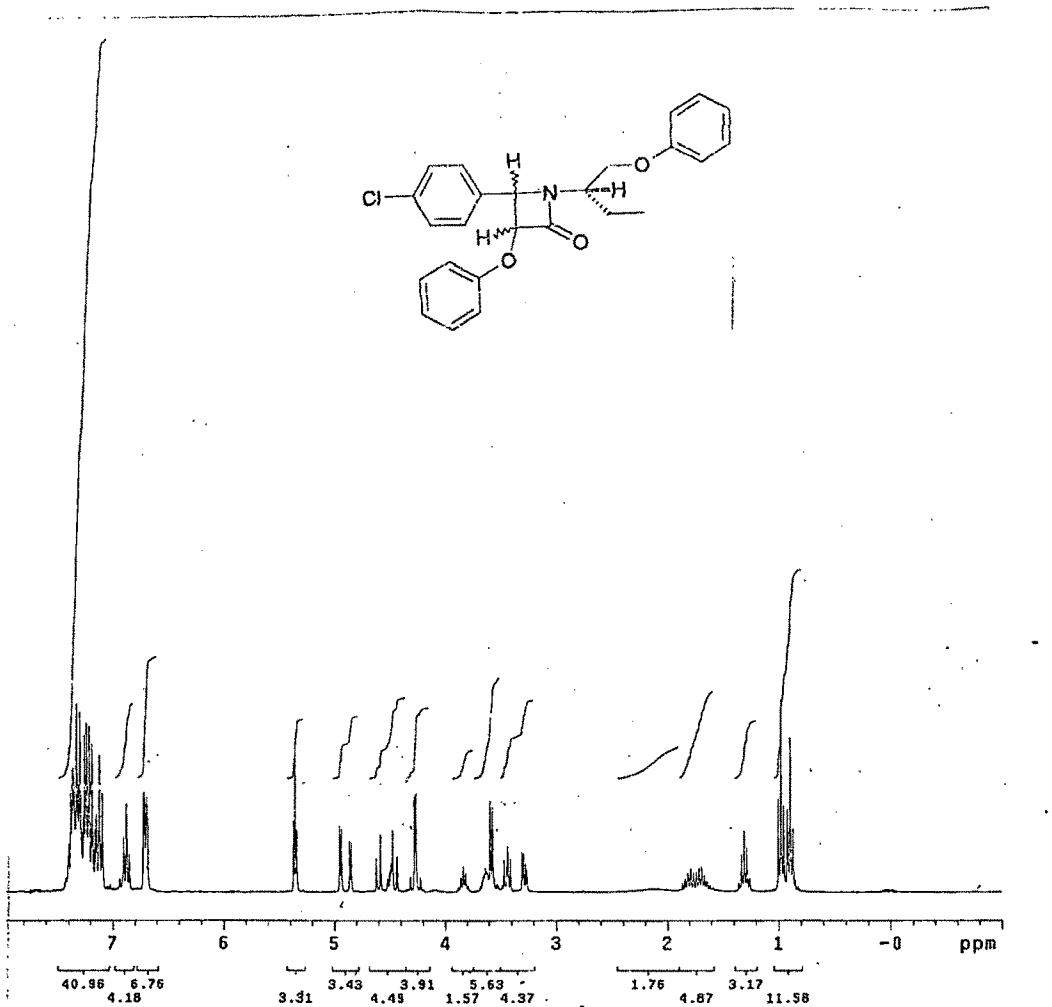


Figure III.13 1H NMR($CDCl_3$) spectrum of 4-(4-Chlorophenyl)-3-phenoxy-1-((S)-1 phenoxymethylpropyl)azetidin-2-one (53b)

III .13

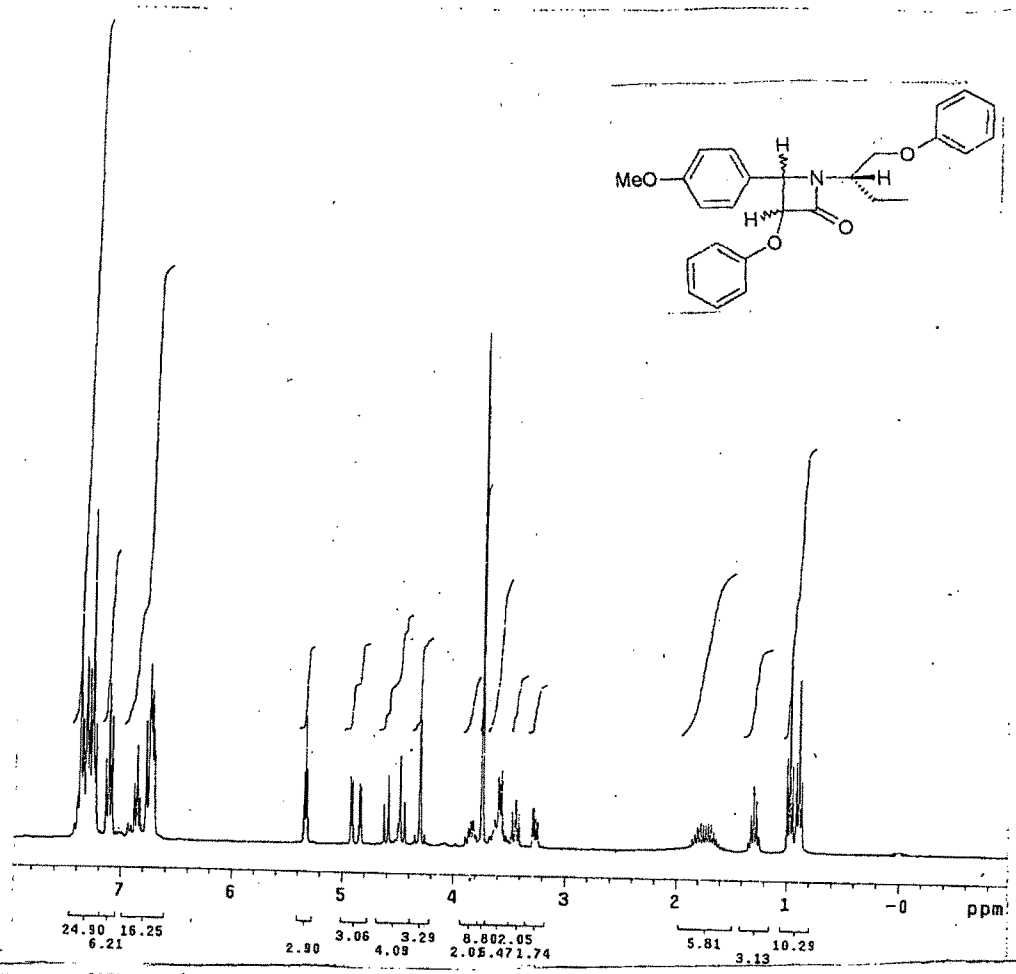


Figure III.14 1H NMR($CDCl_3$) spectrum of 4-(4-Methoxyphenyl)-3-phenoxy-1-((S)-1-phenoxymethylpropyl)azetidin-2-one (53c)

III . 14

Thus the procedure gives rise to benzyl substituted azetidinones which can be modified by further ring opening of the β-lactam. The excellent diastereoselectivity of the reaction and high yield makes it an excellent procedure for synthesis of these β-lactam derivatives. The actual configuration of the azetidinone derivatives can be determined by x-ray crystallographic techniques. Also these β-lactam derivatives can be investigated for various medicinal activities

3.3 EXPERIMENTAL

Reagent chemicals were purchased from Lancaster synthesis ltd. and Aldrich chemical co. ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Tetrahydrofuran (THF) was distilled over sodium wire and stored over sodium wire. Dichloromethane (DCM) was dried, distilled and stored over 4A° molecular sieves before use. Column chromatography was carried out using silica gel (60-120 mesh). Thin layer chromatography (TLC) was carried out using silica gel (75μ). Infrared spectra for the solids were recorded in the range 4000-600cm^{-1} using Perkin-Elmer FT-IR16PC spectrometer using the KBr pellet technique or neat in case of liquids. Proton NMR was recorded using Bruker 300 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer C, H, and N elemental analyzer. Specific rotations were measured using JOSCO P-1030 polarimeter.

SECTION I

3.3.1 Synthesis of (*R*)-2-(1-hydroxymethylpropyl) isoindol-1, 3-dione (42)

A mixture of (*R*)-2-Amino-1-butanol (40) (22.2g, 249.8mmole) and 37g phthalic anhydride (41) (37.0g, 249.8mmole) was heated for one hour at 140° C. The solution was cooled and 200ml of ether solution was added to it. The ether solution was washed successively with 10% potassium carbonate solution, 10% HCl and saturated salt solution. The ether solution was dried over anhydrous sodium sulphate. Removal of the solvent gave (*R*)-2-(1-hydroxymethylpropyl) isoindol-1, 3-dione (42), 49g.

3.3.2 Synthesis of (*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl) isoindol -1, 3-dione (43)

(*R*)-2-(1-hydroxymethylpropyl) isoindol-1, 3-dione (42) (23.5g, 107.3mmoles) was taken in 35 mL dichloromethane in a two necked round bottom flask. 3,4- Dihydro-2H-pyran (10.83g,128.8mmoles) with 15mL dichloromethane was added drop wise to the solution of (*R*)-2-(1-hydroxymethylpropyl)isoindol-1,3-dione followed by 2.35g of PTSA. After complete addition the mixture was stirred for 8-10 hours at room temperature and the solution was refluxed for 8-10hours. The dichloromethane layer was washed with sodium carbonate solution to remove excess of PTSA. The DCM layer was separated and concentrated to get oil. The resulting oil was purified by column chromatography on silica gel using pet-ether and ethyl acetate as solvent system to give 16g of pure (*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl)isoindol-1,3-dione(43) as a colourless oil.

3.3.3 Synthesis of (*R*)-1-(tetrahydropyran-2-yloxymethylpropyl) amine (44)

(*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl)isoindol-1,3-dione(43) (16g, 52.8 mmoles) was treated with hydrazine hydrate (5.28g, 105.6mmoles) in 100 mL of absolute alcohol and the resulting mixture was refluxed on a water bath for 2 hours. The solid mass is removed from the solution by filtration and the solid was washed twice with cold ethanol solution. The ethanol solution was concentrated to furnish a residue. The residue was washed four to five times with ether and was filtered to remove the spongy mass. Removal of the solvent furnished (*R*)-1-(tetrahydropyran-2-yloxymethylpropyl)amine (44) as a colourless oil.

3.3.4 Synthesis of O-THP azetidinone derivatives (46a-46c)

Aromatic aldehyde (20 m.moles) and (*R*)-1-(tetrahydropyran-2-yloxymethylpropyl) amine (44) (20 m.moles) in toluene was refluxed using dean stark apparatus for 7-8 hours. Toluene was distilled off under vacuum. The corresponding Schiff bases were used as such.

A solution of phenoxy acetyl chloride (12 m.moles) in dichloromethane was added dropwise below 10°C to a well stirred solution of the Schiff base (10 m.moles) and triethylamine (30 m.moles) in dichloromethane. The solution was stirred for 24 hours. Removal of the solvent furnished a crude product which was purified by doing column chromatography on alumina support using pet ether to obtain the pure compounds (46a-46c) as solids.

SECTION II

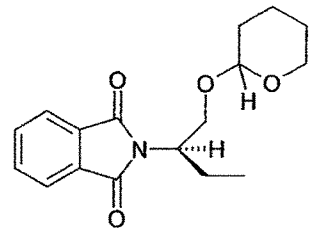
3.3.5 Synthesis of (*R*) & (*S*)-O-benzyl-2-amino-1-butanol (47 & 51)[42]

A solution of (*R*) & (*S*)-2-Amino-1-butanol (50g, 560.9 mmol) in anhydrous THF (400mL) was taken in a three necked 1 litre flask equipped with a water condenser with a calcium chloride guard tube and a dropping funnel. A positive pressure of nitrogen was maintained throughout the reaction. Sodium hydride (20.16g, 840mmol) was added portion wise over a period of one hour. The reaction mixture is refluxed, with stirring on an oil bath for 17 hours. Benzyl chloride (64.44mL, 560.9mmol) in THF (100mL) is added drop wise to the reaction mixture over a period of 1hour and refluxed for 20 hours. The resulting reaction mixture was washed with 250mL distilled water and concentration of the THF extract after drying gave the product which was distilled under vacuum to give (*R*) & (*S*)-O-Benzyl-2-Amino-1-butanol as a colourless viscous oil(47 & 61) 75g.

3.3.6 Synthesis of O-benzyl 2-azetidinone derivatives (General Methodology) (49a-49d) & (53a-53d)

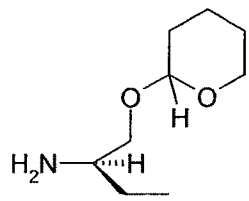
(*R*) & (*S*)-O-benzyl-2-amino-1-butanol (3g, 16.75mmoles) and the corresponding aldehyde (16.75mmole) with a pinch of PTSA was taken in toluene. Mixing resulted in toluene becoming hazy. The reaction mixture is refluxed using dean stark apparatus for 7-8 hours on an oil bath maintained at 120-125°C. The toluene layer is then washed with a solution of 10%$NaHCO_3$ and with distilled water. The toluene layer is then dried over anhydrous Na_2SO_4 and toluene is distilled off under vacuum. The resulting residue is dissolved in 35mL dry dichloromethane and taken in a 100mL three necked flask equipped with a nitrogen inlet and a dropping funnel with a guard tube. Triethyl amine (3.5mL, 25mmol) was added to it and the reaction mixture was cooled to 0°C. Phenoxy acetyl chloride (2.7765mL, 20mmol) in 15mL dry DCM is added drop wise to the reaction mixture for a period of 30 minutes. The temperature is maintained at 0° C for one hour. The ice bath is then removed and the stirring is continued at room temperature for 4-5 hours. The DCM layer is dried and distilled giving a residue which on scratching under cold conditions gave a solid. The solid was recrystallised in an appropriate solvent to give the pure products **49a-49d** or **53a-53d**.

(*R*)-2-(1-tetrahydropyran-2-yloxymethylpropyl) isoindol -1, 3-dione (43)



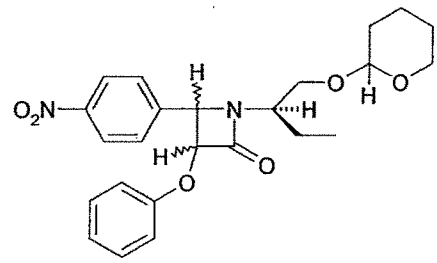
State	Colourless liquid
Molecular formula	$C_{17}H_{21}NO_4$
Yield	70%
$[\alpha]_D^{20}$	+ 14.91° (*c* 1.0, $CHCl_3$)
CHN found(calculated)	C-67.33(67.33); H-6.93(6.77); N-4.62(4.38)
ν_{max} (KBR)/ cm^{-1}	1775,1713,1467, 1373
δ_H (200MHz, $CDCl_3$)	0.9(3H,t,-CH_3); 1.3-1.6(6H,m,-CH_2); 1.7-2.1(2H, m,-CH_2); 3.4-4.4(6H, m,-CH_2-O (thp),-CH_2-O,-CH-O (thp),-CH-O); 7.7-7.9(4H, m, Ar-H).

(*R*)-1-(tetrahydropyran-2-yloxymethyl) propylamine (44)



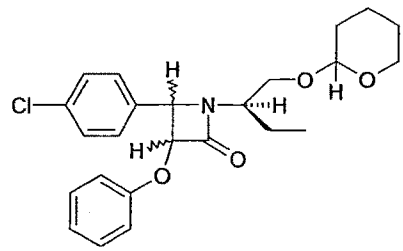
State	Colourless liquid
Molecular formula	$C_9H_{19}NO_2$
Yield	80%
$[\alpha]_D^{20}$	+ 6.51° (*c* 1.0, $CHCl_3$)
CHN found (calculated)	C-61.21(62.43); H-10.75(10.98); N-8.28(8.68)
ν_{max} (KBR)/ cm^{-1}	3381, 3324,1775, 1713
δ_H (200MHz, $CDCl_3$)	0.9(3H, t, CH_3); 1.2-1.8(10H, m,-CH_2-O (thp),-CH_2-O,-NH_2); 2.9-4.0(6H, m, -CH_2-O (thp),-CH_2-O,-CH-O (thp),-CH-O).

4-(4-Nitrophenyl)-3-phenoxy-1-[(*R*)-1-(tetrahydropyran-2-yloxymethyl) propyl] azetedin-2-one (46a)



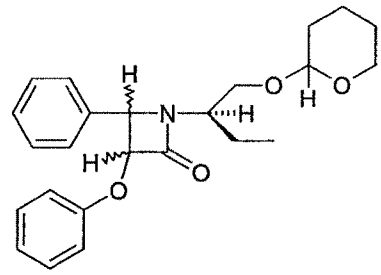
State	White solid
Molecular formula	$C_{24}H_{28}N_2O_6$
Yield	70%
Melting point	112°C
$[\alpha]_D^{20}$	+3.14° (*c* 1.0, $CHCl_3$)
CHN found(calculated)	C-63.92(65.45); H-6.36(6.36); N-3.16(3.18)
ν_{max} (KBR)/ cm^{-1}	1746, 1521,1348,1236,1035

4-(4-Chlorophenyl)-3-phenoxy-1-[(*R*)-1-(tetrahydropyran-2yloxymethyl) propyl] azetedin-2-one (46b)



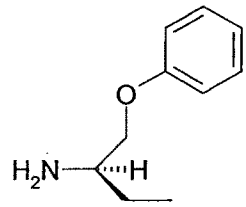
State	White solid
Molecular formula	$C_{24}H_{28}NO_4Cl$
Yield	65%
Melting point	135°C
$[\alpha]_D^{20}$	+8.32° (*c* 1.0, $CHCl_3$)
CHN	C- 66.78(67.05); H- 6.39(6.52);
found (calculated)	N-3.61(3.26)
ν_{max} (KBR)/ cm^{-1}	1745,1236,1035

3-Phenoxy-4-phenyl-1-[(*R*)-1-(tetrahydropyran-2yloxymethyl) propyl]-azetedin-2-one (46c)



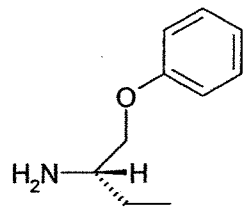
State	Solid
Molecular formula	$C_{24}H_{28}NO_4$
Yield	60%
Melting point	91°C
$[\alpha]_D^{20}$	+12.44°(*c* 1.0, $CHCl_3$)
CHN found (calculated)	C-72.96(73.09); H-7.36(7.10); N-3.47(3.55)
ν_{max} (KBR)/ cm^{-1}	1745

(*R*)-1-Phenoxymethyl-propylamine (47)



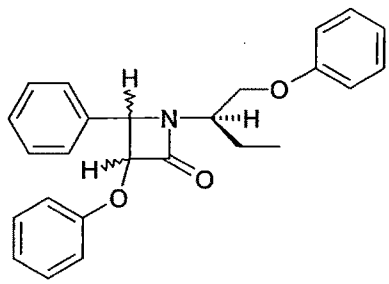
State	Liquid
Molecular formula	$C_{11}H_{17}NO$
Yield	75%
CHN	C-73.20(73.74); H-9.40(9.49);
found (calculated)	N-7.60(7.821)
δ_H (200MHz, $CDCl_3$)	0.93(3H,t,-CH_3);1.25-1.5(2H,m,-CH_2);1.67(2H,s, NH_2); 2.9(1H,m,-CH); 3.2-3.5(2H,m,CH_2); 4.5(2H,s,CH_2); 7.4(5H,m,Ar-H)

(*S*)-1-Phenoxymethyl-propylamine (51)



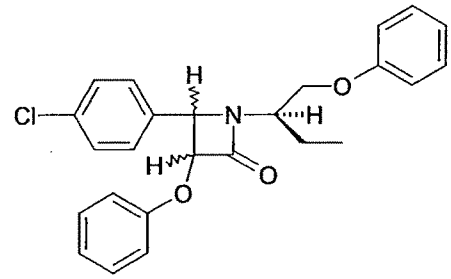
State	Liquid
Molecular formula	$C_{11}H_{17}NO$
Yield	70%
CHN found (calculated)	C-73.60(73.74); H-9.30(9.49); N-7.81(7.821)
δ_H (200MHz, $CDCl_3$)	0.93(3H,t,-CH_3);1.25-1.5(2H,m,-CH_2);1.67(2H,s,-NH_2);2.9(1H,m,-CH);3.2-3.5(2H,m,CH_2);4.5(2H, s,CH_2); 7.4(5H,m,Ar-H)

4-Phenyl-3-Phenoxy-1-((R)-1-phenoxymethylpropyl) azetidin-2-one (49a)



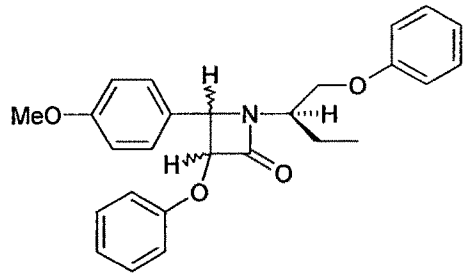
State	Solid
Molecular formula	$C_{25}H_{27}NO_3$
Yield	85%
Melting point	116-118°C
$[\alpha]_D^{20}$	-
CHN	C-77.40(77.12); H-6.46(6.94);
found (calculated)	N-3.09(3.59)
ν_{max} (KBR)/ cm^{-1}	1752
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.6-2.0(2H,m,-CH_2), 3.28(1H, dd,-CH_AH_B), 3.45(1H,dd, -CH_AH_B), 3.64(1H ,m,CH), 4.26(2H,q,-CH_2), 4.96(1H,d,CH J=4.5), 5.37(1H,d,CH J=4.5), 6.6-7.4(15H, M,Ar-H).

4-(4-Chlorophenyl)-3-phenoxy-1-((R)-1-phenoxymethyl-propyl)-azetidin-2-one (49b)



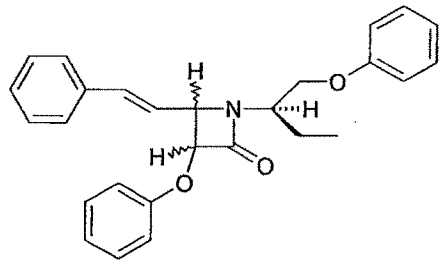
State	Solid
Molecular formula	$C_{25}H_{26}NO_3Cl$
Yield	90%
Melting point	82°C
$[\alpha]_D^{20}$	+10.989°(*c* 0.1, $CHCl_3$)
CHN	C-70.17(70.83); H-6.80(6.139);
found (calculated)	N-2.84(3.30)
ν_{max} (KBR)/ cm^{-1}	1747
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.6-2.0(2H,m,-CH_2), 3.29(1H, dd,-CH_AH_B), 3.44(1H,dd, -CH_AH_B), 3.64(1H ,m,CH), 4.26(2H,q,-CH_2), 4.94(1H,d,CH J=4.5), 5.36(1H,d,CH J=4.5), 6.6-7.4(14H, M, Ar-H).

4-(4-Methoxyphenyl)-3-phenoxy-1-((R)-1-phenoxymethyl-propyl)-azetidin-2-one (49c)



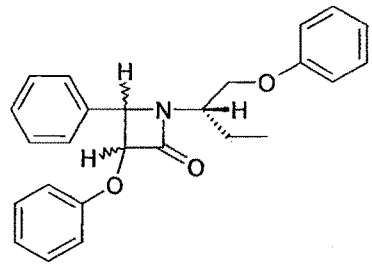
State	Solid
Molecular formula	$C_{26}H_{29}NO_4$
Yield	80%
Melting point	74°C
$[\alpha]_D^{20}$	+10.789 °(*c* 0.1, $CHCl_3$)
CHN found (calculated)	C-74.21(74.46); H-6.96(6.92); N-2.86(3.30)
ν_{max} (KBR)/ cm^{-1}	1749
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.6-2.0(2H,m,-CH_2), 3.29(1H, dd,-CH_AH_B), 3.45(1H,dd, -CH_AH_B), 3.64(1H ,m,CH),3.8(3H,s,-CH_3),4.30(2H,q,-CH_2), 4.92(1H,d,CH J=4.2), 5.33(1H,d,CH J=4.5), 6.6-7.4(14H,m,Ar-H).

4-Styryl-3-phenoxy-1-((R)-1-phenoxymethyl-propyl)-azetidin-2-one (49d)



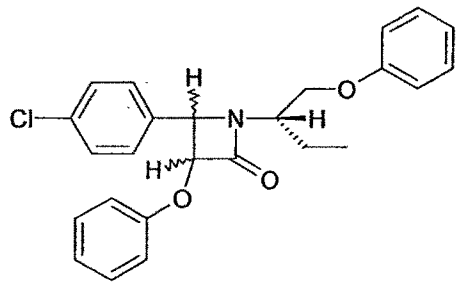
State	Solid
Molecular formula	$C_{28}H_{29}NO_3$
Yield	85%
Melting point	133°C
$[\alpha]_D^{20}$	-20.77 °(*c* 0.1, $CHCl_3$)
CHN	C-79.62(78.68); H-6.84(6.79);
found (calculated)	N-2.68(3.27)
ν_{max} (KBR)/ cm^{-1}	1748
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.4-1.8(2H,m,-CH_2), 3.48-3.68 (2H,m,CH_2), 3.85(-1H,m,-CH), 4.4-4.6(2H ,m,-CH_2), 4.7(1H,d,-CH), 5.3(1H,d-CH J=4.5), 6.3(1H,dd,=CH), 6.5(1H,d,=CH), 7.0-7.6(15H,m,Ar-H) .

4-Phenyl-3-Phenoxy-1-((S)-1-phenoxymethylpropyl)-azetidin-2-one (53a)



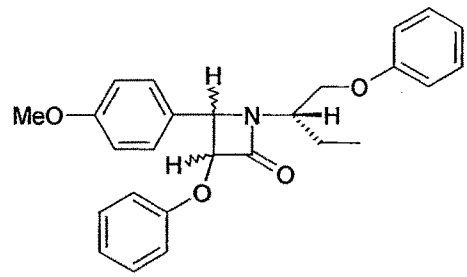
State	Solid
Molecular formula	$C_{25}H_{27}NO_3$
Yield	90%
Melting point	116-118°C
$[\alpha]_D^{20}$	-3.397°(*c* 0.1, $CHCl_3$)
CHN	C-78.15(77.12); H-6,44(6.94);
found (calculated)	N- 3.20(3.59)
ν_{max} (KBR)/ cm^{-1}	1751
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.6-2.0(2H,m,-CH_2), 3.28(1H, dd,-CH_AH_B), 3.44(1H,dd, -CH_AH_B), 3.63(1H ,m,CH), 4.26(2H,q,-CH_2), 4.96(1H,d,CH J=4.5), 5.37(1H,d,CH J=4.5), 6.6-7.4(15H, M,Ar-H).

4-(4-Chlorophenyl)-3-phenoxy-1-((S)-1-phenoxymethyl-propyl)-azetidin-2-one (53b)



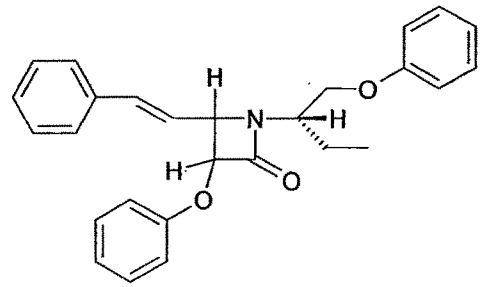
State	Solid
Molecular formula	$C_{25}H_{26}NO_3Cl$
Yield	92%
Melting point	83°C
$[\alpha]_D^{20}$	-2.198° (*c* 0.1 $CHCl_3$)
CHN	C-70.38(70.83); H-6.10(6.139);
found (calculated)	N-3.24(3.30)
ν_{max} (KBR)/ cm^{-1}	1740
δ_H (200MHz, $CDCl_3$)	0.89(3H,t,-CH_3), 0.97(3H,t,-CH_3), 1.304(2H, m,-CH_2), 1.73(2H, m,-CH_2), 3.2-3.8(3H,m,-CH_2,-CH), 4.2(2H, q,-CH_2), 4.84-4.96(1H,dd,-CH J=4.5), 5.35(1H,dd, -CH J=4.5), 6.6-7.5(14H,m, Ar-H).

4-(4-Methoxyphenyl)-3-phenoxy-1-((S)-1-phenoxymethyl-propyl)-azetidin-2-one (53c)



State	Solid
Molecular formula	$C_{26}H_{29}NO_4$
Yield	73%
Melting point	72°C
$[\alpha]_D^{20}$	-2.797 °(*c* 0.1, $CHCl_3$)
CHN found (calculated)	C-75.21(74.46); H-6.70(6.92); N-3.01(3.30)
ν_{max} (KBR)/ cm^{-1}	1747
δ_H (200MHz, $CDCl_3$)	0.89(3H,t,-CH_3), 0.97(3H,t,-CH_3), 1.304(2H, m,-CH_2), 1.73(2H,m,-CH_2), 3.2-3.8(3H,m,-CH_2,-CH), 3.75(3H,s,-CH_3), 4.2(2H,q,-CH_2), 4.84-4.96(1H,dd,-CH J=4.5), 5.33(1H,dd, -CH J=4.2), 6.6-7.5(14H,m, Ar-H).

4-Styryl-3-phenoxy-1-((S)-1-phenoxymethyl-propyl)-azetidin-2-one (53d)



State	Solid
Molecular formula	$C_{28}H_{29}NO_3$
Melting point	132°C
Yield	90%
$[\alpha]_D^{20}$	-12.388 °(*c* 0.1 $CHCl_3$)
CHN	C-79.19(78.68); H-6.82(6.79);
found (calculated)	N-2.89(3.27)
ν_{max} (KBR)/ cm^{-1}	1748
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_3),1.4-1.8(2H,m,-CH_2), 3.48-3.68 (2H,m,CH_2), 3.85(-1H,m,-CH), 4.4-4.6(2H ,m,-CH_2), 4.8(1H,dd,-CH J=11.7), 5.3(1H,dd-CH J=4.5), 6.3(1H,dd,=CH), 6.5(1H,dd,=CH), 7.0-7.6(15H,m,Ar-H) .

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