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TETRAHEDRON

PPL-CATALYSED HYDROLYSIS OF 3,4-DISUBSTITUTED β-LACTAMS: EFFECT OF CHAIN LENGTH AND STEREOCHEMISTRY ON THE ENANTIOSELECTIVITY

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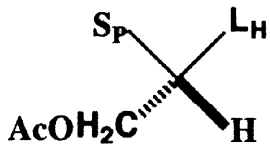
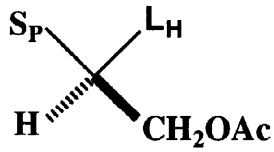
Abstract: 3,4-Disubstituted β-lactam acetates **1a-15a** have been subjected to PPL-catalysed hydrolysis. The stereochemical course of hydrolysis has been shown to depend upon the C3-C4 relative stereochemistry and the length of the chain bearing acetate functionality.

INTRODUCTION

Pig Pancreatic Lipase (PPL) has been extensively used to catalyze the hydrolysis of a wide range of acetates[1] and also in transesterification reactions[2]. The enantioselectivity of such transformations, usually high, depends primarily on the nature and stereochemistry of the substituents near the acetate functionality and the medium of hydrolysis[3]. Seebach[4] and later on Jones[5] have independently proposed active-site models for PPL. Interestingly, although both the models recognize the same four binding pockets they are enantiomeric. Some substrates bind according to Seebach's model whereas there are others whose bindings take place according to the model proposed by Jones. This has led to a complex situation. Study of hydrolysis of a greater variety of substrates differing in the nature of substituents and stereochemistry may help in understanding the active-site better. Primarily with this intention we have undertaken a study of enantioselectivity of PPL-catalyzed hydrolysis of several 3,4-disubstituted ß-lactams containing acetoxyalkyl substituents at C-3 and aromatic/heterocyclic rings at C-4. Another useful aspect of the work is the potential of making β-lactams in chiral forms that may serve as precursors to biologically important entities like taxol sidechain mimics[6] and bestatin[7].



Seebach's Model



Jones' Model

RESULTS AND DISCUSSION

Preparation of Substrates: The substrates used in the present study[8] fall into two groups: one group consisted of cis β-lactams (**1a-11a**) with an acetoxy alkyl group at C-3 with varying alkyl chain length while the other contained 3-acetoxymethyl 4-substituted β-lactams in the trans form (**12a-15a**) (**Figure 1**). The compounds of the cis-series were prepared via Kinugasa[9] reaction involving cycloaddition between nitrones (**1e-6e**) and copper acetylides generated *in situ* from the respective alkynes (**1f-3f**) followed by acetylation under standard conditions. Cycloaddition between the nitrones (**1e-4e**) and methyl propiolate under similar conditions gave the trans β-lactam esters (**12j-15j**). These were reduced with $NaBH_4$ in MeOH and converted into the acetates (**12a-15a**). The reactions are shown in **Schemes 1** and **2**.

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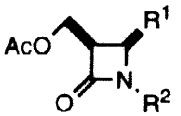


1a $R^1=R^2=Ph$

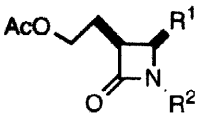
2a R^1 = 2-furyl, $R^2=Ph$

3a R^1 = 2-thienyl, $R^2=Ph$

4a R^1 = 4-methoxyphenyl, $R^2=Ph$

5a R^1 = 2-furyl, R^2 = 4-methoxyphenyl

6a R^1 = Ph R^2 = 4-methoxyphenyl

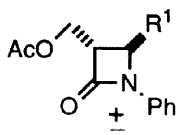


7a $R^1=R^2=Ph$

8a R^1 = 2-furyl, $R^2=Ph$

9a R^1 = 2-thienyl, $R^2=Ph$

10a R^1 = 4-methoxyphenyl, $R^2=Ph$

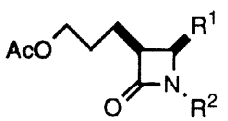


12a R^1 = Ph

13a R^1 = 2-furyl

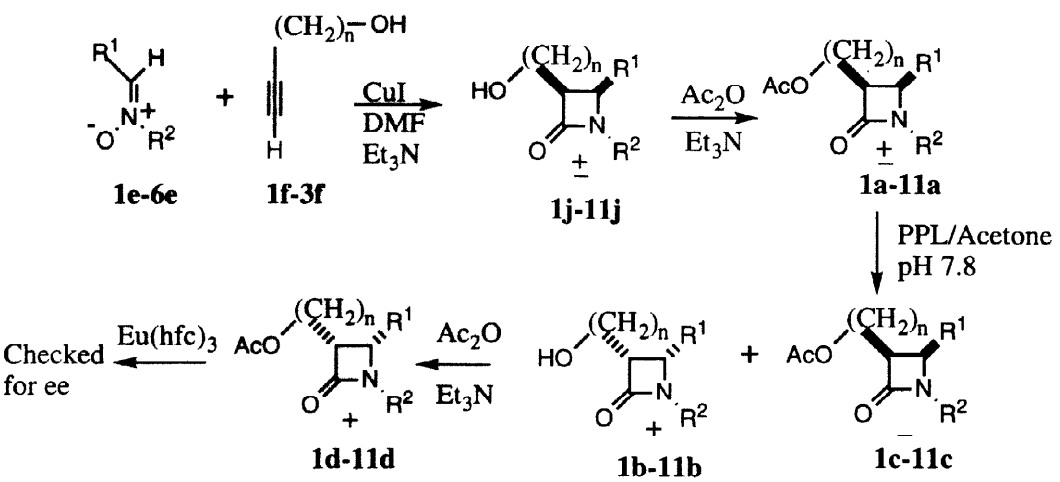
14a R^1 = 2-thienyl

15a R^1 = 4-methoxyphenyl

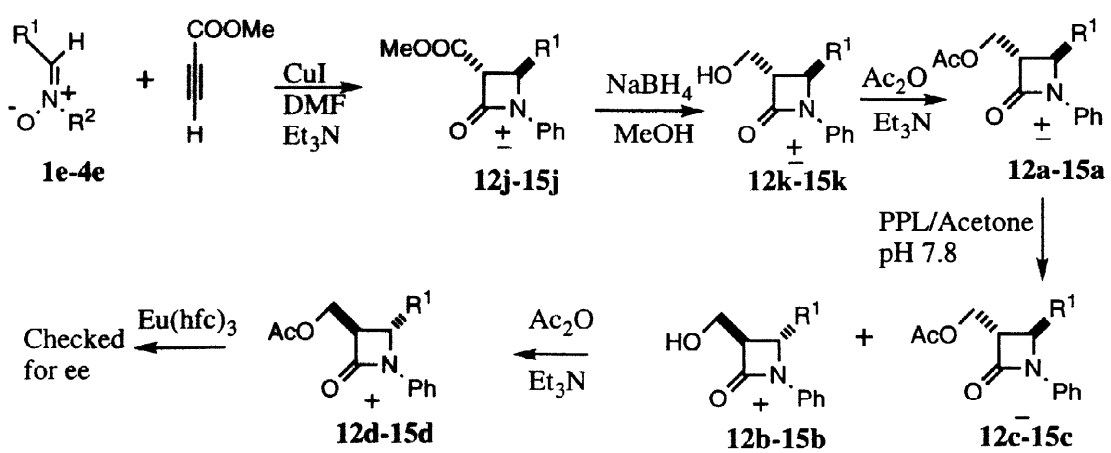


11a $R^1=R^2=Ph$

Figure 1



Scheme 1



Scheme 2

PPL-Catalyzed Hydrolysis: The cis β-lactam acetates (**1a-11a**) were subjected to PPL-catalyzed hydrolytic conditions[10] (acetone-phosphate buffer, pH 7.8). The reactions were allowed to go upto 40-50% completion (checked by ^{1}H NMR); the hydrolysed products and the unconverted acetates were separated by column chromatography. The enantiomeric excesses of the alcohols were determined by recording the ^{1}H NMR of the corresponding acetates in the presence of Eu(hfc)3 as shift reagent[11]. The ees of the recovered acetates (for reactions proceeding with high selectivity) were also determined in a similar manner. The results are shown in **Table 1.** Thus the hydrolysis of cis β-lactam acetates proceeded with high degree of selectivity. Increasing the

Table 1
Hydrolysis of cis-β-Lactams

Substrates	Products	%hydrolysis (rxn time h)	% ee of the alcohol	$[\alpha]_D$	% ee of recovered acetate	$[\alpha]_D$
1a	1b	40(22)	83	+91.42°	20	-24.5°
2a	2b	43(22)	84	+69.66°	63	-73°
3a	3b	41(24)	90	+172.98°	50	-70.23°
4a	4b	40(26)	98	+117.40°	58	-37.71°
5a	5b	40(21)	85	+127.88°	40	-34.16°
6a	6b	40(21)	92	+156.75°	60	-37.68°
7a	7b	42(24)	50	+63.66°	30	-
8a	8b	45(25)	20	-25.33°	-	-
9a	9b	43(24)	0	-	-	-
10a	10b	40(24)	0	-	-	-
11a	11b	41(23)	20	+73°	-	-

carbon chain at C-3 resulted in significant loss of ee. This was expected as the reacting ester functionality is 2 to 3 carbons away from the stereogenic centre. It is only for the 4-phenyl-3-acetoxyethyl β-lactam **7a** we could obtain moderate enantioselectivity. Hydrolysis of β-lactams with a 4-thienyl or 4-methoxyphenyl did not show any selectivity at all! (Table 2). Hydrolysis of the 4-furyl analogue **8a** probably had gone with opposite stereochemistry as revealed by the generation of laevorotatory alcohol. However at this stage we could not have any definte proof in the absence of x-ray data.

Table 2
Hydrolysis of trans-β-Lactams

Substrate	Product	% hydrolysis (rxn time h)	% ee of the alcohol	$[\alpha]_D$
12a	12b	45(30)	50	+42.2°
13a	13b	30(28)	33	+25.2°
14a	14b	20(30)	10	+12.5°
15a	15b	20(30)	10	+2.5°

Effect of Stereochemisty

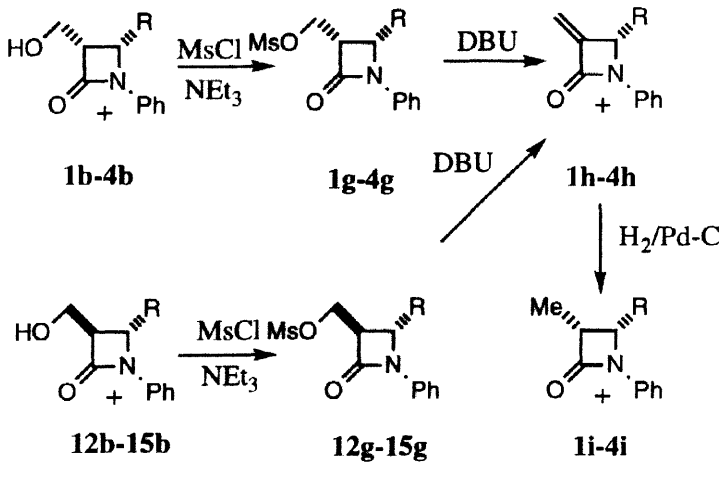
The hydrolysis of trans β-lactam acetates (**12a-15a**) with PPL was significantly slower compared to the cis analogues. The enantiomeric excesses were also much inferior and unlike in the case of cis 3-acetoxymethyl-β-lactams (**1a-6a**), highest ee was obtained for R = Ph (**12a**) (**Table 3**). Thus there is a significant effect of C3-C4 relative stereochemistry on the kinetics and steric course of hydrolysis.

Table 3
Specific Rotations of Exomethylene β-Lactams

Exo methylene ß-Lactams	R	$[\alpha]_D$ from cis series	$[\alpha]_D$ from trans series
1h	phenyl	+65.9°	+30°
2h	2-furyl	+11°	+3.5°
3h	2-thienyl	+27.7°	+2.5°
4h	4-methoxyphenyl	+52.7°	+3.3°

Determination of Absolute Configuration

The absolute stereochemistry of the hydrolysis products (**1b-4b**) from the cis acetoxymethyl β-lactams have been determined by preparing the corresponding cis 3-methyl β-lactams (**1i-4i**) and then comparing the rotation with those for similar compounds[12] (**Scheme 3**). Once we knew the configuration of the cis alcohols (**1b-4b**) the hydrolysis products (**12b-15b**) from the trans series were converted to the exo methylene β-lactams and the rotations checked and compared with those prepared from the cis series. Interestingly both the exomethylene β-lactams obtained from the cis and trans alcohols have the same sign of rotation and hence same configauration at C-4.



Scheme 3

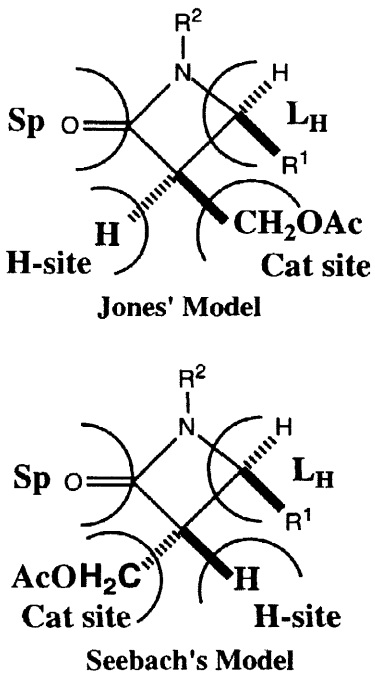


Figure 3

Explanation of Results

The cis β-lactam acetates bind according to the Jones' model as revealed by the absolute configuration of the hydrolysed products. The carbonyl group acts as the small polar group while the C-4 with its large aromatic or heterocyclic rings occupy the large hydrophobic pocket (**Figure 3**).Since the hydrolysis products from the trans series have same configuration at C-4, the stereochemically preferable isomers from the cis and trans β-lactams undergoing hydrolysis must be epimeric at C-3. Also since the cis β-lactam acetates bind according to

the Jones' model, the preferential binding mode for the trans series had to be according to Seebach's model in order to explain the stereochemical results. The explanation for this different mode of binding for the two series of substrates is not clear at the moment. It appears that the large hydrophobic pocket has a chiral recognition element which plays a major role in binding[5]. The catalytic site may be flexible enough to accommodate a β acetate (Jones' model) or an α acetate functionality with some difficulty (For Seebach model). This may explain why the trans acetates are poor substrates compared to the cis counterparts.

In conclusion, we have demonstrated the importance of relative stereochemistry on the enantioselectivity of PPL-catalysed hydrolysis of β-lactam acetates. A switch from Jones' active site model to Seebach's model has been attributed to be due to the dominant role played by the large hydrophobic part in binding. The nature of dependence of ee on the length of the acetate chain for the cis series has also been demonstrated. Some of the chiral ß-lactams may serve as potentially important synthetic intermediates.

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EXPERIMENTAL

General: All solvents were dried prior to use. Methylene chloride, triethyl amine and DMF were distilled from calcium hydride. All reactions were carried out under nitrogen. IR spectra were recorded on Perkin Elmer model 883. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer. Melting points were determined in open capillaries and are uncorrected. PPL was purchased from Fluka, Switzerland. Optical rotations were measured in a Jasco Polarimeter.

General Procedure for the Preparation of Cis 1,4-disubstituted 3-hydroxymethyl-2-azetidinones (1j-11j):

To a solution of propargyl alcohol (580 µl, 10 mmol) in DMF (30 ml), triethyl amine (1.45 ml, 10 mmmol) was added under argon. The mixture was stirred for 30 min at 0°C. CuI (1.9 gm, 10 mmmol) was added and stirring was continued for 5 min at room temperature. Solution of individual nitrones (**1e-6e**, 3 mmol) in DMF (10 ml) were added via syringe in about 15 mins. The reaction mixture was stirred for 24 h at r.t. afterwhich it was poured into water and filtered through celite. The celite bed was throughly washed with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. Filtration followed by removal of solvent gave a solid residue from which the β-lactams were isolated by column chromatography over Si-gel using hexane-EtOAc (1:1) as eluent. The products were crystallised from CH_2Cl_2/petroleum ether. Their spetral characteristics are mentioned below:

Cis (1,4-diphenyl-3-hydroxymethyl)-2-azetidinone (1j)

Yield: 55%, m.p. 128°C lit.[13] 118-121°C; γ_{max} (KBr): 1751 cm-1; δ_H ($CDCl_3$) 3.56-3.88 (3H, *m*, OCH_2, H-3), 5.27 (1H, *d*, J = 5.7 Hz, H-4), 7.01-7.39 (10H, *m*, Ph-H); δ_C ($CDCl_3/CCl_4$) 56.70, 57.35, 58.09, 117.15, 124.07, 126.81, 128.57, 129.0, 129.10, 134.28, 137.42, 165.38; HRMS: calcd for $C_{16}H_{15}NO_2$ 253.1104 found 253.1110.

Cis [N-phenyl-4-(2-furyl)-3-hydroxymethyl]-2-azetidinone (2j)

Yield: 50%, m.p. 122°C; γ_{max} (KBr): 1749 cm^{-1}; δ_H ($CDCl_3$) 3.65-3.99 (3H, *m*, OCH_2, H-3), 5.48 (1H, *d*, J = 5.7 Hz, H-4), 6.41(2H, *bs*, furan H-4, H-5), 7.05-7.49 (6H, *m*, Ph-H, furan H-3); δ_C ($CDCl_3/CCl_4$) 51.45, 57.09, 58.37, 109.94, 110.89, 116.91, 124.27, 129.09, 137.46, 143.29, 148.73, 164.27; HRMS: calcd for $C_{14}H_{13}NO$ 243.0896 found 243.0892.

Cis [N-(4-methoxyphenyl-4-(2-furyl)-3-hydroxymethyl]-2-azetidinone (3j)

Yield: 32%, m.p. 82°C; γ_{max} (KBr): 1748 cm^{-1}; δ_H ($CDCl_3$) 3.79 (3H, *s*, OCH_3), 3.72-3.97 (3H, *m*, OCH_2, H-3), 5.20 (1H, *d*, J = 5.6 Hz, H-4), 6.35-6.37 (3H, *m*, furan H-3, H-4), 6.77 (2H, *d*, J = 9 Hz, Ar-H), 7.25

(3H, *m*, Ar-H, furan H-5); δ_C ($CDCl_3/CCl_4$) 51.55, 55.32, 57.10, 58.46, 109.94, 110.87, 114.15, 118.28, 131.01, 143.14, 148.91, 156.31, 164.43; HRMS: calcd for $C_{15}H_{15}NO_4$ 273.1002 found 273.1005.

Cis [N-phenyl-4-(2-thienyl)-3-hydroxymethyl]-2-azetidinone (4j)

Yield: 51%, m.p. 134°C; γ_{max} (KBr): 1746 cm^{-1}; δ_H ($CDCl_3$) 3.76-3.94 (3H, *m*, OCH_2, H-3), 5.50 (1H, *d*, J = 4.8 Hz, H-4), 7.00-7.35 (8H, *m*, Ph-H, thienyl-H); δ_C ($CDCl_3/CCl_4$) 53.70, 57.37, 58.10, 117.13, 124.17, 126.48, 127.50, 128.91, 129.78, 137.16, 137.66, 165.06; Mass (m/z) 259.

Cis [N-(4-methoxyphenyl-4-phenyl-3-hydroxymethyl]-2-azetidinone (5j)

Yield: 40%, m.p. 119°C; γ_{max} (KBr): 1750 cm^{-1}; δ_H ($CDCl_3$) 3.70 (3H, *s*, OCH_3), 3.36-3.75 (3H, *m*, OCH_2, H-3), 5.22 (1H, *d*, J = 5.4 Hz, H-4), 6.9 (2H, *d*, J = 7.2 Hz, Ar-H), 7.19-7.41 (7H, *m*, Ar-H, Ph-H); δ_C ($CDCl_3/CCl_4$) 55.16, 56.62, 57.40, 57.72, 118.30, 125.96, 126.87, 128.27, 128.70, 130.92, 134.58, 155.98, 165.04; HRMS: calcd for $C_{17}H_{17}NO_3$ 283.1209 found 283.1211.

Cis [N-phenyl-4-(4-methoxyphenyl)-3-hydroxymethyl]-2-azetidinone (6j)

Yield: 34%, m.p. 102°C; γ_{max} (KBr): 1751 cm^{-1}; δ_H ($CDCl_3$) 3.80 (3H, *s*, OCH_3), 3.5-3.9 (3H, *m*, OCH_2, H-3), 5.17, (1H, *d*, J = 5.4 Hz, H-4), 6.9 (2H, *d*, J = 7.2 Hz, Ar-H), 7.10-7.39 (7H, *m*, Ar-H, Ph-H); HRMS: calcd for $C_{17}H_{17}NO_3$ 283.1209 found 283.1212.

Cis (1,4-diphenyl-3-hydroxyethyl)-2-azetidinone (7j)

Yield: 52%, m.p. 107°C; γ_{max} (KBr): 1732 cm^{-1}; δ_H ($CDCl_3$) 1.55-1.80 (2H, *m*, CH_2CH_2OH), 3.60 -3.75 (3H, *m*, H-3, CH_2OH), 5.25 (1H, *d*, J = 5.8 Hz, H-4), 7.10 (1H, *m*, Ar-H), 7.20-7.41 (9H, *m*, Ar-H); Mass (m/z) 267 (M^+).

Cis [N-phenyl-4-(2-furyl)-3-hydroxyethyl]-2-azetidinone (8j)

Yield: 53%, m.p. 104°C; γ_{max} (KBr): 1744 cm^{-1}; δ_H ($CDCl_3$) 1.70-1.95 (2H, *m*, CH_2CH_2OH), 3.66-3.82 (3H, *m*, CH_2OH, H-3), 5.24 (1H, *d*, J = 5.7 Hz, H-4), 6.36 (2H, *m*, furyl-H), 7.07-7.41 (6H, *m*, Ar-H); Mass (m/z) 257 (M^+).

Cis [N-phenyl-4-(2-thienyl)-3-hydroxyethyl]-2-azetidinone (9j)

Yield: 51%, m.p. 125°C; γ_{max} (KBr): 1739 cm^{-1}; δ_H ($CDCl_3$) 1.60-1.90 (2H, *m*, CH_2CH_2OH), 3.73 (3H, *m*, CH_2OH, H-3), 5.49 (1H, *d*, J = 5.7 Hz, H-4), 6.36 (2H, *m*, furyl-H), 7.02-7.12(3H, *m*, thienyl-H), 7.23-7.36 (5H, *m*, Ar-H); Mass (m/z) 273 (M^+).

Cis [N-phenyl-4-(4-methoxyphenyl)-3-hydroxyethyl]-2-azetidinone (10j)

Yield: 47%, m.p. 96°C; γ_{max} (KBr): 1728 cm^{-1}; δ_H ($CDCl_3$) 1.70-1.91 (2H, *m*, CH_2CH_2OH), 3.63 (3H, *m*, CH_2OH, H-3), 3.80 (3H, *s*, OCH_3), 5.18 (1H, *d*, J = 5.7 Hz, H-4), 6.87 (2H, *d*, J = 8.7 Hz,Ar-H), 7.06 (1H, *m*, Ar-H), 7.16 (2H, *d*, J = 8.7 Hz, Ar-H), 7.25 (4H, *m*, Ar-H); Mass (m/z) 297 (M^+).

Cis (1,4-diphenyl-3-hydroxypropyl)-2-azetidinone (11j)

Yield: 49%, m.p. 110°C; γ_{max} (KBr): 1734 cm-1; δ_H ($CDCl_3$) 1.40-2.02 (4H, *m*, $CH_2CH_2CH_2OH$), 3.52-3.72 (3H, *m*, H-3, CH_2OH, H-3), 5.18 (1H, *d*, J = 5.9 Hz, H-4), 6.99-7.06 (2H, *m*, Ar-H), 7.24-7.39 (8H, *m*, Ar-H); HRMS: calcd for $C_{18}H_{19}NO_2$ 281.1417 found 281.1420.

Preparation of Acetates (1a-11a)

To a stirred solution of the β-lactam (**1j-11j,** 1 mmol) in dry CH_2Cl_2 (5 ml) freshly distilled acetic anhydride (190 µl, 2 mmol), dry triethyl amine (290 µl, 2 mmol) and DMAP (20 mg) were added. The mixture was stirred for 3 h under nitrogen. The products were extracted with CH_2Cl_2, washed with water, aq $NaHCO_3$ and brine. Drying (Na_2SO_4) and removal of solvent gave the crude products which were purified by column chromaatography over Si-gel eluting with hexane : ethyl acetate (4:1).

Cis (1,4-diphenyl-3-acetoxymethyl)-2-azetidinone (1a)

Yield: 92%, m.p. 116°C; γ_{max} (KBr): 1747 cm^{-1}; δ_H ($CDCl_3$) 1.85 (3H, s, $COCH_3$), 3.93-4.14 (3H, *m*, OCH_2, H-3), 5.27 (1H, *d*, J = 5.2 Hz, H-4), 7.03-7.54 (10H, *m*, Ph-H); δ_C ($CDCl_3/CCl_4$) 20.40, 53.33, 57.23, 58.85, 117.13, 124.13, 126.86, 128.52, 128.67, 129.06, 133.68, 137.36, 163.87, 169.97; HRMS: calcd for $C_{18}H_{17}NO_3$ 295.1209 found 295.1211.

Cis [N-phenyl-4-(2-furyl)-3-actoxymethyl]-2-azetidinone (2a)

Yield: 95%, m.p. 106°C; γ_{max} (KBr): 1750 cm^{-1}; δ_H ($CDCl_3$) 1.94 (3H, s, $COCH_3$),3.91-3.97 (3H, *m*, OCH_2, H-3), 5.25 (1H, *d*, J = 5.6 Hz, H-4), 6.45(2H, *bs*, furan H-4, H-5), 7.04-7.47 (6H, *m*, Ph-H, furan H-3); δ_C ($CDCl_3/CCl_4$) 20.20, 50.97, 53.33, 59.01, 109.55, 110.41, 116.59, 123.93, 128.75, 137.07, 143.02, 147.85, 163.61, 169.64; HRMS: calcd for $C_{16}H_{15}NO4$ 285.1002 found 285.1003.

Cis [N-phenyl-4-(2-thienyl)-3-actoxymethyl]-2-azetidinone (3a)

Yield: 94%, m.p. 80°C; γ_{max} (KBr): 1746 cm^{-1}; δ_H ($CDCl_3$) 1.93 (3H, s, $COCH_3$),3.91-4.31 (3H, *m*, OCH_2, H-3), 5.55 (1H, *d*, J = 5.6 Hz, H-4), 6.45 (2H, *bs*, furan H-4, H-5), 6.97-7.37 (8H, *m*, Ph-H, thienyl-H); δ_C ($CDCl_3/CCl_4$) 20.17, 53.26, 53.72, 58.69, 116.82, 123.93, 125.62, 126.15, 127.03, 128.73, 136.64, 136.73, 163.16, 169.78; Mass (m/z) 302.

Cis [N-phenyl-4-(4-methoxyphenyl)-3-acetoxymethyl]-2-azetidinone (4a)

Yield: 86%, m.p. 84°C; γ_{max} (KBr): 1748 cm^{-1}; δ_H ($CDCl_3$) 1.80 (3H, s, $COCH_3$), 3.80 (3H, s, OCH_3), 3.80-4.10 (3H, *m*, OCH_2, H-3), 5.22 (1H, *d*, J = 5.4 Hz, H-4), 6.8 (2H, D, J = 7.2 Hz, Ar-H), 6.9-7.4 (7H, m, Ar-H, Ph-H); Mass (m/z) 325 (M^+).

Cis [N-(4-methoxyphenyl)-4-(2-furyl)-3-acetoxymethyl]-2-azetidinone (5a)

Yield: 95%, m.p. 55°C; γ_{max} (KBr): 1752 cm^{-1}; δ_H ($CDCl_3$) 1.94 (3H, s, $COCH_3$), 3.75 (3H, s, OCH3), 3.91-3.97, 4.18-4.34 (3H, *m*, OCH_2, H-3), 5.19 (1H, *d*, J = 5.4 Hz, H-4), 6.35 (2H, *m* , furan H-4, H-5), 6.76 (2H, *d*, J = 6.8Hz, Ar-H), 6.77-7.25 (2H, *m*, Ph-H), 7.41 (1H, t, furan H-3), 7.05-7.49 (6H, *m*, Ph-H, furan H-3); δ_C ($CDCl_3/CCl_4$) 17.92, 50.51, 53.85, 55.21, 59.34, 109.46, 109.81, 114.25, 118.19, 130.82, 143.23, 148.24, 156.2, 162.76, 169.89; Mass (m/z) 315 (M^+).

Cis [N-(4-methoxyphenyl)-4-phenyl-3-acetoxymethyl]-2-azetidinone (6a)

Yield: 89%, m.p. 89°C; γ_{max} (KBr): 1751 cm^{-1}; δ_H ($CDCl_3$) 1.84 (3H, s, $COCH_3$), 3.75 (3H, s, OCH3), 3.77-4.13 (3H, *m*, OCH_2, H-3), 5.22 (1H, *d*, J = 5.2 Hz, H-4), 6.90 (2H, d, J = 7.2 Hz, Ar-H), 7.18-7.35 (7H, m, Ar-H,Ph-H); δ_C ($CDCl_3/CCl_4$) 22.6, 55.26, 56.61, 57.33, 58.03, 114.27, 118.30, 127.67, 128.11, 130.94, 134.37, 141.77, 156.03, 164.63; Mass (m/z) 325 (M^+).

Cis (1,4-diphenyl-3-acetoxyethyl)-2-azetidinone (7a)

Yield: 92%, m.p. 78°C; γ_{max} (KBr): 1736 cm-1; δ_H ($CDCl_3$) 1.60-1.82 (2H, m, CH2CH2O), 2.03 (3H, s, $COCH_3$), 3.67 (1H, m, H-3), 3.96 (2H, m, OCH_2), 5.23 (1H, *d*, J = 5.2 Hz, H-4), 7.05 (1H, m, Ar-H),7.21-7.36 (9H, m, Ar-H); Mass (m/z) 309 (M^+).

Cis [N-phenyl-4-(2-furyl)-3-actoxyethyl]-2-azetidinone (8a)

Yield: 90%, m.p. 94°C; γ_{max} (KBr): 1730 cm^{-1}; δ_H ($CDCl_3$) 1.60-1.82 (2H, m, CH_2CH_2O), 2.05 (3H, s, $COCH_3$),3.73 (1H, m, H-3), 4.03 (2H, t, J = 6.5 Hz, OCH_2), 5.22 (1H, *d*, J = 5.2 Hz, H-4), 6.37 (2H, *m* , furan H-4, H-5), 7.13-7.40 (6H, *m*, Ph-H, furan H-3);Mass (m/z) 299 (M^+).

Cis [N-phenyl-4-(2-thienyl)-3-actoxyethyl]-2-azetidinone (9a)

Yield: 91%, m.p. 97°C; γ_{max} (KBr): 1736 cm^{-1}; δ_H ($CDCl_3$) 1.60-1.82 (2H, m, CH_2CH_2O), 2.04 (3H, s, $COCH_3$),3.71 (1H, m, H-3), 4.03 (2H, t, J = 6.5 Hz, OCH_2), 5.48 (1H, *d*, J = 5.2 Hz, H-4), 7.01-7.09 (3H, m, 2 x thinyl-H, Ar-H), 7.29-7.34 (5H, m, 4 x Ar-H, thienyl-H); Mass (m/z) 315. (M^+)

Cis [N-phenyl-4-(4-methoxyphenyl)-3-(2-acetoxyethyl]-2-azetidinone (10a)

Yield: 90%, m.p. 84°C; γ_{max} (KBr): 1736 cm^{-1}; δ_H ($CDCl_3$) 1.60-1.91 (2H, *m*, CH_2CH_2O), 2.02 (3H, *s*, $COCH_3$), 3.65 (1H, *m*, H-3), 3.80 (3H, *s*, OCH_3), 3.97 (2H, *m*, OCH_2), 5.18 (1H, *d*, J = 5.8 Hz, H-4), 6.89 (2H, *d*, J = 8.17 Hz, Ar-H), 7.06 (1H, *m*, Ar-H), 7.17-7.300 (6H, *m*, Ar-H); Mass (m/z) 339 (M^+).

Cis (1,4-diphenyl-3-(3-acetoxypropyl)-2-azetidinone (11a)

Yield: 90%, m.p. 80°C; γ_{max} (KBr): 1734 cm-1; δ_H ($CDCl_3$) 1.55-1.75 (4H, *m*, $CH_2CH_2CH_2O$), 1.95 (3H, s, $COCH_3$), 3.57 (1H, *m*, H-3), 3.86 (2H, *m*, OCH_2), 5.21 (1H, *d*, J = 5.8 Hz, H-4), 7.05 (1H, *m*, Ar-H),7.20-7.40 (9H, *m*, Ar-H); Mass (m/z) 323 (M^+).

General Procedure for the Synthesis of trans (N-phenyl-4-substituted-3-methoxycarbonyl)-2-azetidinones (12j-15j)

A solution of methyl propiolate (168 µl, 2 mmol), CuI (4 mmmol), Et_3N (580 µl, 4 mmmol) in DMF (10 ml) was stirred under argon at 0°C for 30 min. To this mixture a solution of nitrones (**1e-4e**, 1mmol) in DMF (2 ml) was added at room temperature and stirred for 4 h under argon. The products were extracted following usual procedure (vide preparation of cis ß-lactams). The crude products were purified by chromatography over Si-gel using hexane-EA (3:1) as eluent.

Trans (1,4-diphenyl-3-methoxycarbonyl)-2-azetidinone (12j)

Yield: 72%, m.p. 41°C; γ_{max} (KBr): 1743 cm-1; δ_H ($CDCl_3$) 3.83 (3H, *s*, COOMe), 3.98 (1H, *d*, J = 2.8 Hz, H-3), 5.33 (1H, *d*, J = 2.8 Hz, H-4), 7.02-7.49 (10H, *m*, Ph-H) fully agreed with the spectral data in the literature[13]; Mass (m/z) 281 (M^+).

Trans [N-phenyl-3-methoxycarbonyl-4(2-furyl)-2-azetidinone (13j)

Yield: 68%, viscous oil; γ_{max} (neat): 1749 cm-1; δ_H ($CDCl_3$) 3.81 (3H, *s*, COOMe), 4.29 (1H, *d*, J = 2.8 Hz, H-3), 5.34 (1H, *d*, J = 2.8 Hz, H-4), 6.36 (2H, *d*, J = 1.8 Hz, furan , H-4, H-5), 7.0-7.4 (6H, *m*, Ph-H, furan H-3); Mass (m/z) 271 (M^+).

Trans [N-phenyl-3-methoxycarbonyl-4(2-thienyl)]-2-azetidinone (14j)

Yield: 70%, viscous oil; γ_{max} (neat): 1746 cm-1; δ_H ($CDCl_3$) 3.80 (3H, *s*, COOMe), 4.10 (1H, *d*, J = 2.6 Hz, H-3), 5.40 (1H, *d*, J = 2.6 Hz, H-4), 7.0-7.4 (8H, *m*, Ph-H, thienyl H); Mass (m/z) 287 (M^+).

Trans [N-phenyl-3-methoxycarbonyl-4(4-methoxyphenyl)]-2-azetidinone (15j)

Yield: 71%, viscous oil; γ_{max} (neat): 1742 cm-1; δ_H ($CDCl_3$) 3.80 (3H, *s*, COOMe), 3.83 (3H, *s*, OMe), 3.90 (1H, *d*, J = 2.8 Hz, H-3), 5.50 (1H, *d*, J = 2.8 Hz, H-4), 6.90 (2H, *d*, J = 7.2 Hz, Ar-H), 7.0-7.27 (7H, *m*, Ph-H, Ar-H); Mass (m/z) 311 (M^+).

General Procedure for the Synthesis of Trans N-phenyl-4-substituted-3-hydroxymethyl-2-azetidinones (12k-15k)

To a solution of trans methoxycarbonyl azetidinones in dry methanol (10 ml), sodium borohydride (76 mg, 2 mmol) was added slowly (10 min) and the mixture was stirred for 5 min. The solvent was evaporated and the products were extracted with EtOAc. Evaporation of the solvent gave an oily rsidue which upon column chromatography on Si-gel furnished the products from Hexane:EtOAc (3:1) eluates. The spectral properties are mentioned below:

Trans (1,4-diphenyl-3-hydroxymethyl)-2-azetidinone (12k)

Yield: 25%, m.p. 121°C; γ_{max} (KBr): 1752 cm^{-1}; δ_H ($CDCl_3$) 3.28 (1H, *m*, H-3), 4.05 (2H, *dd*, J = 3.9, 4.4 Hz, OCH_2), 5.05 (1H, *d*, J = 2.6 Hz, H-4), 7.04-7.40 (10H, *m*, Ph-H); HRMS: calcd for $C_{16}H_{15}NO_2$ 253.1104 found 253.1106

Trans [N-phenyl-4-(2-furyl)-3-hydroxymethyl]-2-azetidinone (13k)

Yield: 20%, m.p. 115°C; γ_{max} (KBr): 1748 cm^{-1}; δ_H ($CDCl_3$) 3.61 (1H, *m*, H-3), 4.04 (2H, *dd*, J = 3.9, 4.4 Hz, OCH_2), 5.10 (1H, *d*, J = 2.6 Hz, H-4), 6.36 (1H, *m*, furan H-4), 6.45 (1H, *d*, J = 2.8 Hz, furan H-5), 7.03-7.40 (6H, *m*, Ph-H, furan H-3), δ_C 50.55, 58.45, 58.85, 109.57, 110.65, 116.88, 124.12, 129.02, 137.50, 143.27, 150.11, 165.51; Mass (m/z) 243 (M^+).

Trans [N-phenyl-4-(2-thienyl)-3-hydroxymethyl]-2-azetidinone (14k)

Yield: 21%, m.p. 128°C; γ_{max} (KBr): 1750 cm^{-1}; δ_H ($CDCl_3$) 3.32 (1H, *m*, H-3), 3.96 (2H, *dd*, J = 3.6, 4.0 Hz, OCH_2), 5.21 (1H, *d*, J = 2.6 Hz, H-4), 6.7-7.1 (8H, *m*, Ph-H, thienyl-H), Mass (m/z) 259 (M^+).

Trans [N-phenyl-4-(4-methoxyphenyl)-3-hydroxymethyl]-2-azetidinone (15k)

Yield: 24%, m.p. 98°C; γ_{max} (KBr): 1749 cm^{-1}; δ_H ($CDCl_3$) 3.21 (1H, *m*, H-3), 3.79 (3H, *s*, OCH_3), 4.03 (2H, *dd*, J = 4.0, 4.2 Hz, OCH_2), 4.95 (1H, *d*, J = 2.6 Hz, H-4),6.66 (2H, *d*, J = 8.4 Hz, Ar-H), 7.00-7.31 (7H, m, Ph-H, Ar-H) ;, Mass (m/z) 283 (M^+).

General Procedure for the Preparation of Acetates (12a-15a)

These were prepared following same procedure as described for the cis series. Their spectral characteristics are mentioned below:

Trans (1,4-diphenyl-3-acetoxymethyl)-2-azetidinone (12a)

Yield: 95%; m.p.108°C; γ_{max} (KBr): 1750 cm-1; δ_H ($CDCl_3$) 2.08 (3H, *s*, $COCH_3$), 3.40 (1H, *m*, H-3), 4.52 (2H, *d*, J = 5.6 Hz, OCH_2), 4.99 (1H, *d*, J = 2.4 Hz, H-4), 7.1-7.6 (10H, *m*, Ph-H); 20.79, 58.80, 59.69, 60.59, 117.11, 124.10, 125.85, 128.70, 129.12, 129.30, 137.40, 137.49, 163.61, 170.46; Mass (m/z) 295 (M^+).

Trans [N-phenyl-4-(2-furyl)-3-actoxymethyl]-2-azetidinone (13a)

Yield: 93%; m.p.104°C; γ_{max} (KBr): 1752 cm-1; δ_H ($CDCl_3$) 2.07 (3H, *s*, $COCH_3$), 3.74 (1H, *m*, H-3), 4.49 (2H, *dd*, J = 5.6, 4.2 Hz, OCH_2), 4.96 (1H, *d*, J = 2.6 Hz, H-4), 6.36 (1H, *dd*, J = 1.6, 1.8 Hz, furan H-4), 6.45 (1H, *d*, J = 3.4 Hz, furan H-5), 7.02-7.41 (6H, *m*, furan H-3): Mass (m/z) 285 (M^+).

Trans [N-phenyl-4-(2-thienyl)-3-actoxymethyl]-2-azetidinone (14a)

Yield: 96%; m.p.113°C; γ_{max} (KBr): 1747 cm-1; δ_H ($CDCl_3$) 2.08 (3H, *s*, $COCH_3$), 3.52 (1H, *m*, H-3), 4.51 (2H, *dd*, J = 6.0, 3.6 Hz, OCH_2), 5.19 (1H, *d*, J = 2.6 Hz, H-4), 6.96-7.34 (8H, *m*, Ph-H, thienyl-H): Mass (m/z) 302 (M^+).

Trans [N-phenyl-4-(4-methoxyphenyl)-3-acetoxymethyl]-2-azetidinone (15a)

Yield: 91%, m.p. 83°C; γ_{max} (KBr): 1749 cm-1; δ_H ($CDCl_3$) 2.07 (3H, *s*, $COCH_3$), 3.36 (1H, *m*, H-3), 3.80 (3H, *s*, OCH_3), 4.51 (2H, *d*, J = 5.4 Hz, OCH_2), 4.87 (1H, *d*, J = 2.4 Hz, H-4), 6.89 (2H, *d*, J = 8.4 Hz, Ar-H), 7.01-7.29 (7H, *m*, Ph-H, Ar-H) ;, Mass (m/z) 325 (M^+).

General Procedure for the Hydrolysis of ß-lactam Acetates

To a solution of the acetates (**1a-15a**, 1 mmol) in acetone (20 ml), phosphate buffer (40 ml, pH 7.8) was added. The solution was stirred and PPL (3 gm) in three portions was added in every 6 h. The reaction mixture was stirred for 24 to 36 h at 30°C. The pH was kept constant at 7.8 by addition of 0.1 N NaOH. The mixture was filtered through celite and the solution was partitioned between water and ethy acetate. The organic layer was washed with brine, dried with Na_2SO_4 and evaporated in vacuo. The crude mass was subjected to column chromatography (Si-gel). The unreacted acetates and the alcohols were isolated from the hexane-ethyl acetate (3:1) as eluates while the product alcohols from the hexane:ethyl acetate(1:1) eluates.

Determination of Enantiomeric Excess Using Chiral Shift Reagent

The alcohols obtained after enzymatic hydrolysis (**1b-15b**) were converted to the acetates (**1d-15d**). The enantiomeric excesses were then determined by recording the ^1H NMR in the presence of [Eu(hfc)3] as chiral shift reagent according to the following procedure:

To a solution of the acetate (0.1 molar) in $CDCl_3$, Eu(hfc)3 (0.4 molar) was added. The solution was shaken and ^1H NMR recorded. The acetate peaks for the two enantiomers became resolved into two distinct peaks. The ratio of integrations gave the enantiomeric ratio from which the ee's were calculated. The acetates recovered from the enzymatic hydrolysis were directly checked for ee following the above procedure.

Synthesis of 3-exomethylene [1,4-disubstituted] 2-azetidinones

To a solution of the alcohols (**1b-4b, 12b-15b,** 1 mmol) in CH_2Cl_2 (5 ml), Et3N (290 µl, 2 mmol), methane sulphonyl chloride (200 µl, 2 mmol) and DMAP (10 mg) were added. The reaction mixture was stirred at room temperature for 2 h after which the organic layer was washed with water, brine and then dried with Na_2SO_4. evaporation gave the crude products which were used for the next step without any purification.

To the solution of the mesylates (**1g-4g, 12g-15g,** 1 mmol) in CH_2Cl_2 (5 ml), DBU (298 µl, 2 mmol) was added and the mixture was stirred under nitrogen at room temperature for 15 min. The organic layer was evapoarated and the products were purified by passing through a silica gel column eluting with hexane-ethyl acetate (3:1).

3-Exomethylene-[1,4-diphenyl]-2-azetidinone (1h)

Yield: 78%, m.p.115°C; γ_{max} (KBr): 1752 cm-1; δ_H ($CDCl_3$) 5.16 (1H, *bs*, H-4), 5.40 (1H, *bs*, =CH), 5.84 (1H, *bs*, =CH), 7.04-7.40 (10H, *m*, Ph-H); Mass (m/z) 235 (M^+).

3-Exomethylene-[N-phenyl-4-(2-furyl)]-2-azetidinone (2h)

Yield: 82%, m.p.102°C; γ_{max} (KBr): 1748 cm-1; δ_H ($CDCl_3$) 5.33 (1H, *bs*, H-4), 5.44 (1H, *bs*, =CH), 5.93 (1H, *bs*, =CH), 6.38 (1H, *m*, furan-H), 6.45 (1H, *bd*, furan H-5), 7.05-7.45 (6H, *m*, Ph-H, furan H-3); Mass (m/z) 225 (M^+).

3-Exomethylene-[N-phenyl-4-(2-thienyl)]-2-azetidinone (3h)

Yield: 75%, m.p.86°C; γ_{max} (KBr): 1746 cm-1; δ_H ($CDCl_3$) 5.31 (1H, *bd*, J = 1.2 Hz, H-4), 5.71 (1H, *bs*, =CH), 5.92 (1H, *t*, J = 1.8 Hz, =CH), 7.01-7.43 (8H, *m*, Ph-H, thienyl); Mass (m/z) 325 (M^+).

3-Exomethylene-[N-phenyl-4-(4-methoxyphenyl)]-2-azetidinone (4h)

Yield: 77%, m.p.95°C; γ_{max} (KBr): 1751 cm-1; δ_H ($CDCl_3$) 3.80 (3H, *s*, OCH_3), 5.13 (1H, *t*, J = 1.2 Hz, H-4), 5.34 (1H, *bs*, =CH), 5.82 (1H, *t*, J = 1.6 Hz, =CH), 6.87 (2H, *d*, J = 8.6 Hz, Ar-H), 7.10-7.32 (7H, *m*, Ph-H, Ar-H); Mass (m/z) 265 (M^+).

Preparation of (3R, 4R)-3-methyl-4-phenyl-2-azetidinone (1i)

A solution of **1h** (20 mg) in MeOH (5 ml) was hydrogenated for 15 min with a H_2-balloon in the presence of Pd-C (10%) (5 mg) as catalyst. It was filtered through celite, which was washed with methanol. The combined filtrate and washings were evaporated to leave the title comound as a white solid (20 mg, 98%), $[\alpha]_D^{12}$ +124.66°; δ_H ($CDCl_3$) 0.89 (3H, *d*, J = 7.7 Hz, CH3), 3.63 (1H, *m*, H-3), 3.80 (3H, *s*, OMe), 5.13 (1H, *d*, J = 5.8 Hz, H-4), 6.88 (2H, *d*, J = 8.6 Hz, Ar-H), 7.14 (2H, *d*, J = 8.8 Hz, Ar-H), 7.0 (1H, *m*, Ar-H), 7.23-7.27 (4H, *m*, Ar-H);Mass (m/z) 256 (M^+).

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