

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

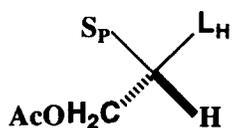
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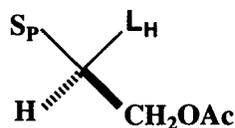
Abstract: 3,4-Disubstituted β -lactam acetates **1a-15a** have been subjected to PPL-catalysed hydrolysis. The stereochemical course of hydrolysis has been shown to depend upon the C3-C4 relative stereochemistry and the length of the chain bearing acetate functionality. © 1998 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Pig Pancreatic Lipase (PPL) has been extensively used to catalyze the hydrolysis of a wide range of acetates¹ and also in transesterification reactions². 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 hydrolysis³. Seebach⁴ and later on Jones⁵ 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 β -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 mimics⁶ and bestatin⁷.



Seebach's Model



Jones' Model

RESULTS AND DISCUSSION

Preparation of Substrates: The substrates used in the present study⁸ 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 Kinugasa⁹ 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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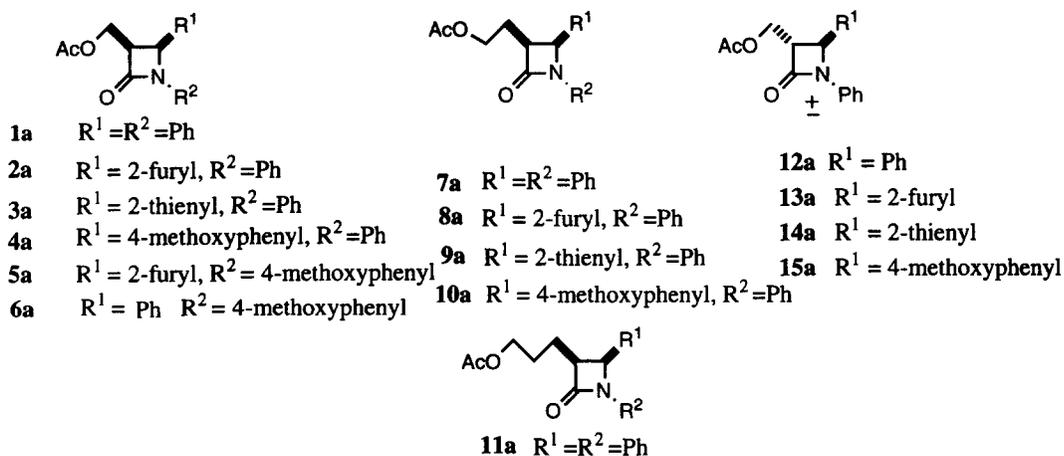
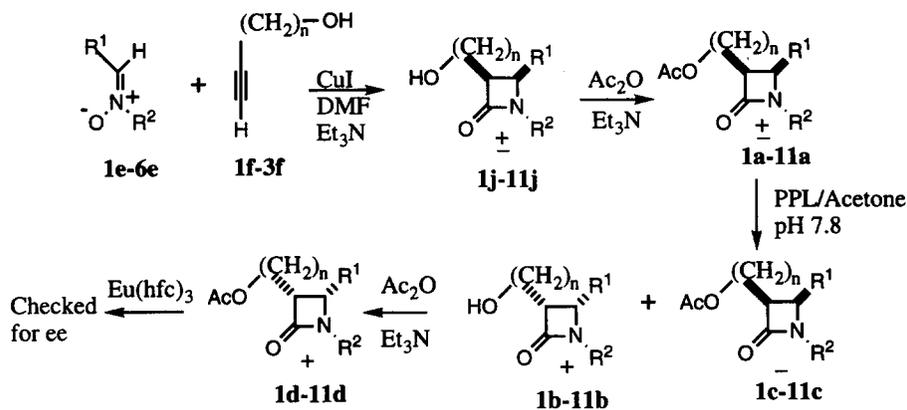
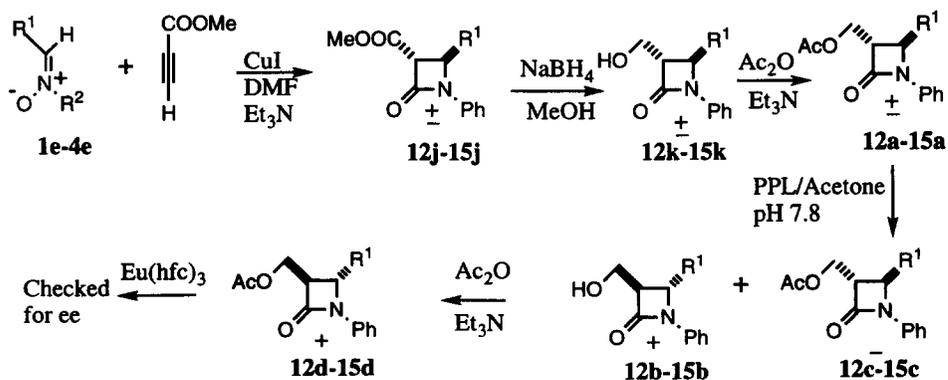


Figure 1



Scheme 1



Scheme 2

PPL-Catalyzed Hydrolysis: The cis β -lactam acetates (**1a-11a**) were subjected to PPL-catalyzed hydrolytic conditions¹⁰ (acetone-phosphate buffer, pH 7.8). The reactions were allowed to go upto 40-50% completion (checked by ¹H NMR); the hydrolysed products and the unconverted acetates were separated by column chromatography. The enantiomeric excesses of the alcohols were determined by recording the ¹H NMR of the corresponding acetates in the presence of Eu(hfc)₃ as shift reagent¹¹. 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 ^o	20	-24.5 ^o
2a	2b	43(22)	84	+69.66 ^o	63	-73 ^o
3a	3b	41(24)	90	+172.98 ^o	50	-70.23 ^o
4a	4b	40(26)	98	+117.40 ^o	58	-37.71 ^o
5a	5b	40(21)	85	+127.88 ^o	40	-34.16 ^o
6a	6b	40(21)	92	+156.75 ^o	60	-37.68 ^o
7a	7b	42(24)	50	+63.66 ^o	30	-
8a	8b	45(25)	20	-25.33 ^o	-	-
9a	9b	43(24)	0	-	-	-
10a	10b	40(24)	0	-	-	-
11a	11b	41(23)	20	+73 ^o	-	-

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 definite 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 ^o
13a	13b	30(28)	33	+25.2 ^o
14a	14b	20(30)	10	+12.5 ^o
15a	15b	20(30)	10	+2.5 ^o

Effect of Stereochemistry

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

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 compounds¹² (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 configuration at C-4.

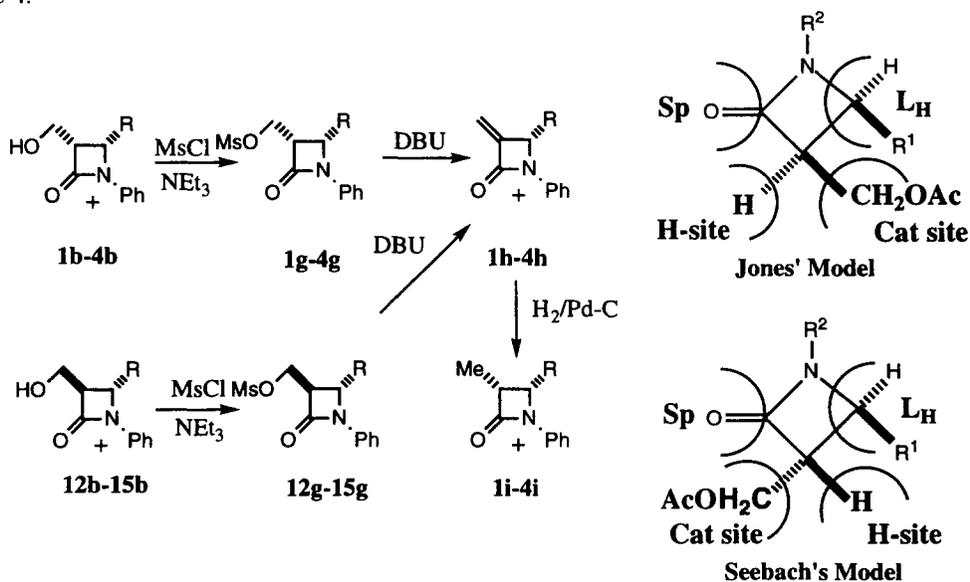


Figure 3

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 binding⁵. 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 β -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. ¹H and ¹³C 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-azetidiones (1j-11j):

To a solution of propargyl alcohol (580 μ l, 10 mmol) in DMF (30 ml), triethyl amine (1.45 ml, 10 mmol) was added under argon. The mixture was stirred for 30 min at 0°C. CuI (1.9 gm, 10 mmol) 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. after which it was poured into water and filtered through celite. The celite bed was thoroughly washed with EtOAc. The organic layer was washed with water and brine and dried over Na₂SO₄. 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 CH₂Cl₂/petroleum ether. Their spectral characteristics are mentioned below:

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

Yield: 55%, m.p. 128°C lit.¹³ 118-121°C; γ_{\max} (KBr): 1751 cm⁻¹; δ_{H} (CDCl₃) 3.56-3.88 (3H, *m*, OCH₂, H-3), 5.27 (1H, *d*, *J* = 5.7 Hz, H-4), 7.01-7.39 (10H, *m*, Ph-H); δ_{C} (CDCl₃/CCl₄) 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 C₁₆H₁₅NO₂ 253.1104 found 253.1110.

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

Yield: 50%, m.p. 122°C; γ_{\max} (KBr): 1749 cm⁻¹; δ_{H} (CDCl₃) 3.65-3.99 (3H, *m*, OCH₂, 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} (CDCl₃/CCl₄) 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 C₁₄H₁₃NO 243.0896 found 243.0892.

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

Yield: 32%, m.p. 82°C; γ_{\max} (KBr): 1748 cm⁻¹; δ_{H} (CDCl₃) 3.79 (3H, *s*, OCH₃), 3.72-3.97 (3H, *m*, OCH₂, 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 (CDCl₃/CCl₄) 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 C₁₅H₁₅NO₄ 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 (CDCl₃) 3.76-3.94 (3H, *m*, OCH₂, H-3), 5.50 (1H, *d*, J = 4.8 Hz, H-4), 7.00-7.35 (8H, *m*, Ph-H, thienyl-H); δ_C (CDCl₃/CCl₄) 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 (CDCl₃) 3.70 (3H, *s*, OCH₃), 3.36-3.75 (3H, *m*, OCH₂, 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 (CDCl₃/CCl₄) 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 C₁₇H₁₇NO₃ 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 (CDCl₃) 3.80 (3H, *s*, OCH₃), 3.5-3.9 (3H, *m*, OCH₂, 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 C₁₇H₁₇NO₃ 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 (CDCl₃) 1.55-1.80 (2H, *m*, CH₂CH₂OH), 3.60-3.75 (3H, *m*, H-3, CH₂OH), 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 (CDCl₃) 1.70-1.95 (2H, *m*, CH₂CH₂OH), 3.66-3.82 (3H, *m*, CH₂OH, 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 (CDCl₃) 1.60-1.90 (2H, *m*, CH₂CH₂OH), 3.73 (3H, *m*, CH₂OH, 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 (CDCl₃) 1.70-1.91 (2H, *m*, CH₂CH₂OH), 3.63 (3H, *m*, CH₂OH, H-3), 3.80 (3H, *s*, OCH₃), 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 (CDCl₃) 1.40-2.02 (4H, *m*, CH₂CH₂CH₂OH), 3.52-3.72 (3H, *m*, H-3, CH₂OH, 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 C₁₈H₁₉NO₂ 281.1417 found 281.1420.

Preparation of Acetates (1a-11a)

To a stirred solution of the β -lactam (**1j-11j**), 1 mmol in dry CH₂Cl₂ (5 ml) freshly distilled acetic anhydride (190 μ l, 2 mmol), dry triethyl amine (290 μ l, 2 mmol) and DMAP (20 mg) were added. The mixture was stirred for 3 h under nitrogen. The products were extracted with CH₂Cl₂, washed with water, aq NaHCO₃ and brine. Drying (Na₂SO₄) and removal of solvent gave the crude products which were purified by column chromatography 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} ($\text{CDCl}_3/\text{CCl}_4$) 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 $\text{C}_{18}\text{H}_{17}\text{NO}_3$ 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} ($\text{CDCl}_3/\text{CCl}_4$) 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 $\text{C}_{16}\text{H}_{15}\text{NO}_4$ 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} ($\text{CDCl}_3/\text{CCl}_4$) 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, OCH_3), 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, $J = 6.8$ Hz, 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} ($\text{CDCl}_3/\text{CCl}_4$) 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, OCH_3), 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} ($\text{CDCl}_3/\text{CCl}_4$) 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, $\text{CH}_2\text{CH}_2\text{O}$), 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-acetoxyethyl]-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, $\text{CH}_2\text{CH}_2\text{O}$), 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-acetoxyethyl]-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, $\text{CH}_2\text{CH}_2\text{O}$), 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 thienyl-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*, $\text{CH}_2\text{CH}_2\text{O}$), 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-acetoxypentyl)-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*, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 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 mmol), Et_3N (580 μl , 4 mmol) in DMF (10 ml) was stirred under argon at 0°C for 30 min. To this mixture a solution of nitrones (**1e-4e**, 1 mmol) 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 β -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 literature¹³; 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 residue 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 $\text{C}_{16}\text{H}_{15}\text{NO}_2$ 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-acetoxymethyl]-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-acetoxymethyl]-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 β -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 ethyl 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 $[\text{Eu}(\text{hfc})_3]$ as chiral shift reagent according to the following procedure:

To a solution of the acetate (0.1 molar) in CDCl_3 , $\text{Eu}(\text{hfc})_3$ (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 CH₂Cl₂ (5 ml), Et₃N (290 μ l, 2 mmol), methane sulphonyl chloride (200 μ l, 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 Na₂SO₄. 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 CH₂Cl₂ (5 ml), DBU (298 μ l, 2 mmol) was added and the mixture was stirred under nitrogen at room temperature for 15 min. The organic layer was evaporated 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} (CDCl₃) 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} (CDCl₃) 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} (CDCl₃) 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} (CDCl₃) 3.80 (3H, *s*, OCH₃), 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 H₂-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 compound as a white solid (20 mg, 98%), [α]_D¹² +124.66°; δ_{H} (CDCl₃) 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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