Pergamon

Tetrahedron, Vol. 52, No. 27, pp. 8989-9004, 1996
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0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00463-2

Application of (+)-(*1S,2S*)-2-Amino-1-phenylpropan-1,3-diol in the Formal Total Synthesis of Carbapenems, Novel 4-Cyano-β-Lactams and β-Hydroxy Aspartates#

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Dedicated to Prof. Ajay K. Bose on the occasion of his 70th birthday.

Abstract: *The imines derived from (+)-(1S,2S)-2-amino-1-phenylpropan-1,3-diol furnished cis-β-lactams stereoselectively on the Staudinger reaction. These homochiral cis-β-lactams were converted in to cis-β-lactams possessing aminol side chain at C-4. These aminols were efficiently transformed in to novel 4-cyano-cis-β-lactams, 4-acetoxy-β-lactam (which are well proven starting materials in the synthesis of carbapenem antibiotics) and advanced starting materials for the synthesis of β-hydroxy aspartates.*
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INTRODUCTION

Continued interest in the asymmetric synthesis of the β-lactam ring stems not only from the variety of antibiotics[1] featuring a β-lactam moiety that one can derive, but its use as a versatile precursor for a number of non-β-lactam molecules[2] of diverse structures and biological activities. Over the last four decades several methodologies have been developed for the construction of the β-lactam skeleton.[3] However, in terms of efficiency and the stereochemical predictability, the Staudinger reaction[4] still remains the most widely used route to β-lactams despite the obscure nature of its exact mechanism.[5]

The stereoselective synthesis of β-lactams using imines derived from *O*-protected-α-hydroxy aldehydes has been widely explored.[6] However the use of homochiral α-amino aldehydes in the Staudinger reaction and related reactions is a topic of current interest.[7] Recent studies by us[8] and others[9] have shown that *N*-Boc protected α-amino imines are attractive starting materials for the synthesis of diversely substituted β-lactams, and various other non-β-lactams of interest.

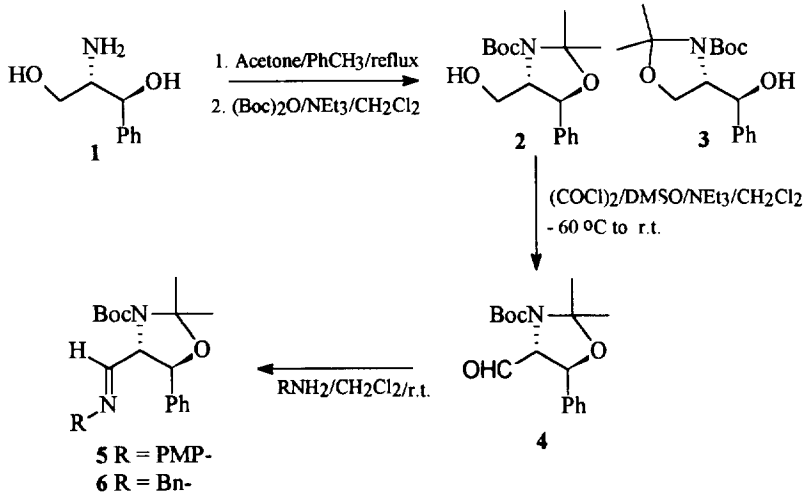
In the course of our ongoing project on the asymmetric synthesis of β-lactams using readily available homochiral starting materials[10] herein we report the detailed account of our work using (+)-(*1S,2S*)-2-amino-1-phenylpropan-1,3-diol, an unwanted antipode in chloramphenicol synthesis and available in optically pure form,

as the starting material for the synthesis of a variety of homochiral *cis*-3-substituted-4-(1-aminoalkyl)-β-lactams and their conversion to homochiral 4-cyano β-lactams *via* a novel lead tetraacetate mediated cleavage of the aminol side chain, 4-formyl β-lactams via a novel lead tetraacetate mediated cleavage in the presence of water and also to 4-carboxy and 4-acetoxy β-lactams which are proven advanced starting materials for the synthesis of β-hydroxy aspartates[9c] and carbapenem antibiotics respectively.[3f, 11]

RESULTS AND DISCUSSION

A aminodiol **1**, on acetonide formation followed by *N*-Boc protection, gave a 3:1 mixture of primary and secondary alcohols **2** and **3** respectively (**Scheme 1**). Column chromatographic separation of this mixture

Scheme 1

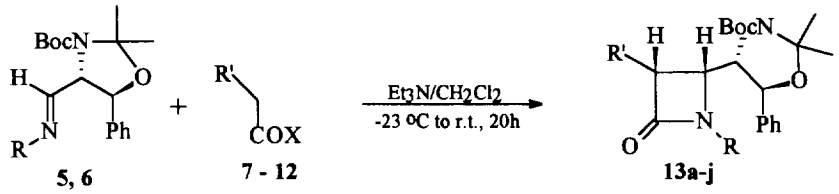


PMP- = *p*-methoxyphenyl; Bn- = benzyl-

gave the desired primary alcohol in an overall yield of 70%. Swern oxidation of the primary alcohol **2** provided the *N,O*-diprotected aldehyde **4** in quantitative yield.[12] Treatment of this aldehyde with *p*-anisidine and benzyl amine provided the imines **5** and **6** respectively. These imines (**5, 6**) were used for the cycloaddition reaction without further purification.

Synthesis of Homochiral β-Lactams 13a-j. The phthalimido, alkoxy and acetoxyacetyl chlorides (**7-11**) on treatment with imines (**5** or **6**) in the presence of excess triethylamine at -20 °C to room temperature provided β-lactams **13a-e,g-j** in 37-94% yields (**Scheme 2**). Azido β-lactam, **13f** was obtained in 53% yield by the mixed anhydride method[6b] using the potassium salt of azidoacetic acid and cyanuric chloride in the presence of triethylamine. In all cases a single *cis*-diastereomer was obtained as the sole product. (**Scheme 2, Table 1**).

Scheme 2



	R'	X
7	PhthN-	Cl
8	PhO-	Cl
9	BnO-	Cl

	R'	X
10	MeO-	Cl
11	AcO-	Cl
12	N_3-	OK

Table 1 **Cycloaddition reaction of imines 5 & 6 with ketene precursors 7 - 12**

Compd.	R	R'	Yield[a] (%)	m.p. (°C)
13a	PMP-	PhthN-	73	235-236
13b	PMP-	PhO-	74	145-146
13c	PMP-	BnO-	91	oil
13d	PMP-	MeO-	68	oil
13e	PMP-	AcO-	37	135-137
13f	PMP-	N_3-	53	oil
13g	Bn-	PhthN-	91	174-175
13h	Bn-	PhO-	94	65-67
13i	Bn-	BnO-	77	158-161
13j	Bn-	MeO-	80	94-96

[a] Isolated yields of pure β-lactams after column chromatography.

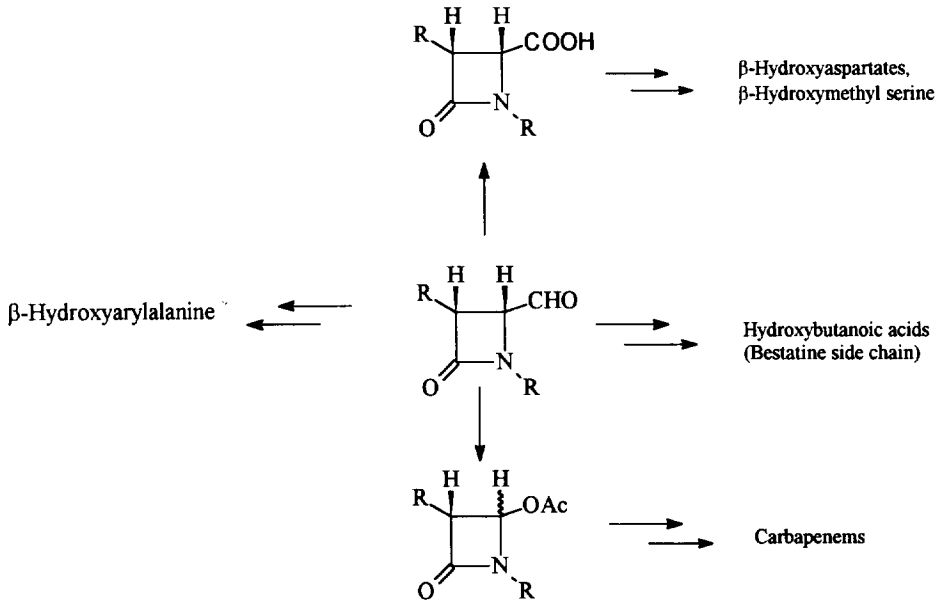
PMP- = *p*-methoxyphenyl; **PhthN-** = phthalimido; **Bn-** = benzyl

The stereochemical assignment was based on the observed H3-H4 proton coupling constant (4.5-6.5 Hz), which is in agreement with previously reported coupling constant values in *cis*-β-lactams.[13] The ^{1}H NMR spectra of most of the *N1-p*-anisyl β-lactams showed dynamic behavior at room temperature. On cooling, these compounds showed two sets of signals, whereas on heating, the two sets coalesced to a single set of sharp signals. Such dynamic behavior with similar compounds has been ascribed to the conformational changes between the two possible rotamers around the carbamate moiety.[9b,14] However, the dynamic behavior was not observed in the ^{1}H NMR spectra of β-lactams (**13g-j**) with the *N*1-benzyl substituent.

As reported earlier[8] the relative configuration within the β-lactam **13a** was established on the basis of single crystal X-ray diffraction analysis. The configurations at C3 and C4 of the β-lactam **13a** were assigned as 3*R*, 4*S* on the basis of the known absolute configuration (4′*S*,5′*S*) of the aminol moiety.

Novel Synthesis of 4-Cyano-β-Lactams and 4-Formyl-β-Lactams.

After suceeding in the synthesis of several homochiral β-lactams bearing diverse substitutions we envisioned that, after deprotection, the aminol side chain at C4 could serve as an excellent functionality for further elaboration. Careful treatment of the β-lactams (**13b-d,h,j**) with 3N HCl in methanol at 60 °C provided the deprotected aminols (**14a-e**) in almost quantitative yields.[15] We reasoned that the oxidative cleavage of the aminol side chain in compounds **14a-e** using an appropriate reagent should provide 4-formyl-β-lactams which were effectively used in the synthesis of several biologically important compounds as depicted below.



It has been reported that 1,2-aminols can undergo C-C bond cleavage by lead tetraacetate (LTA) to provide aldehydes. Similar β-lactams derived from serinal were recently reported to give 4-formyl–β-lactams with lead tetraacetate.[9a] We tried a similar reaction of lead tetraacetate with aminols **14a-c** and to our surprise *cis*-4-cyano-β-lactams **15a-c** (**Scheme 3**) were isolated in almost quantitative yields (**Table 2**)

Scheme 3

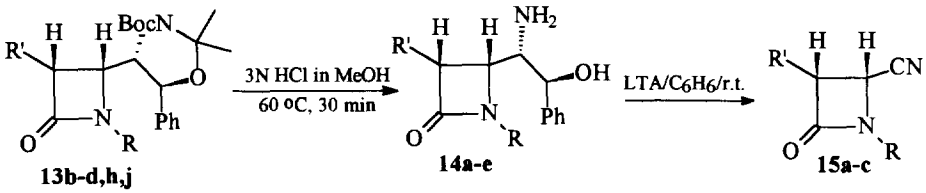


Table 2 **Synthesis of aminols 14a-e and 4-cyano β-lactams 15a-c**

Compd.	**R**	**R'**	Yield[a] (%)	m.p. (°C)
14a	PMP-	PhO-	99	174-176
14b	PMP-	BnO-	97	132-133
14c	PMP-	MeO-	98	137-138
14d	Bn-	PhO-	97	oil
14e	Bn-	BnO-	97	oil
15a	PMP-	PhO-	99	112-114
15b	PMP-	BnO-	97	130-131
15c	PMP-	MeO-	98	109-110

[a] Isolated yields of pure β-lactams after column chromatography.

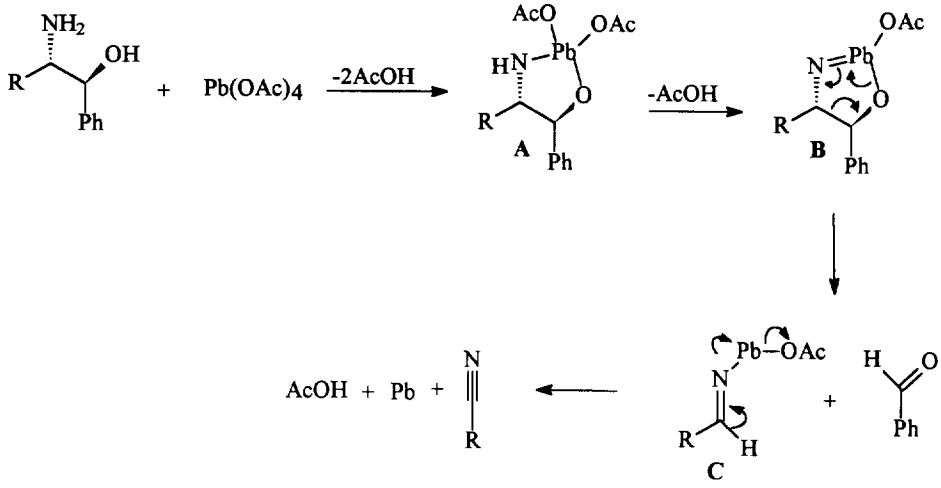
PMP- = *p*-methoxyphenyl; **Bn-** = benzyl

instead of the corresponding 4-formyl-β-lactams. However this cleavage was facile only when the N1 substituent was *p*-anisyl. Similar cleavage was not successful when the N1 substituent of the aminol was benzyl (**14d,e**).

Mechanistic considerations

In all the reactions, we isolated benzaldehyde as a coproduct. If we consider the reported mechanism[16a] for the cleavage of α-aminoketones by lead tetraacetate, a second molecule of lead tetraacetate is necessary to account for the formation of the nitrile moiety and benzaldehyde. However the involvement of a second molecule of lead tetraacetate was ruled out in our case since with one equivalent of lead tetraacetate, the 4-cyano β-lactam was isolated in more than 80% yield. Based on our observations we proposed the following mechanism for the cleavage reaction. The cyclic intermediate B will undergo the cleavage resulting in benzaldehyde and the iminium intermediate C. Under the anhydrous conditions this can undergo an elimination

resulting in the formation of the nitrile, acetic acid and Pb (0). If the reaction conditions are not anhydrous then the iminium intermediate C can undergo hydrolysis resulting in the formation of the expected aldehyde.



To further verify our mechanism and to achieve our goal to synthesize optically active *cis*-4-formyl-β-lactams we examined several reaction conditions for the cleavage of the aminol side chain. When moist benzene was used as solvent, 4-formyl-β-lactams were formed in traces, the major product being the 4-cyano compounds (**15**). The addition of few drops of water to the LTA reaction in benzene provided a 1:1 mixture of 4-cyano and 4-formyl-β-lactams. After investigating several reaction conditions we found that, when the reaction was carried out in methanol and benzene (2:1) in the presence of two equivalents of water, to our delight, the exclusive formation of 4-formyl-β-lactams (**16**) was observed. Under these conditions, no trace of 4-cyano compound could be detected (TLC, ^{1}H NMR of the crude reaction mixture). By employing the above reaction conditions, several 4-formyl-β-lactams (**16a-e**) were synthesized (**Scheme 4, Table 3**).

Scheme 4

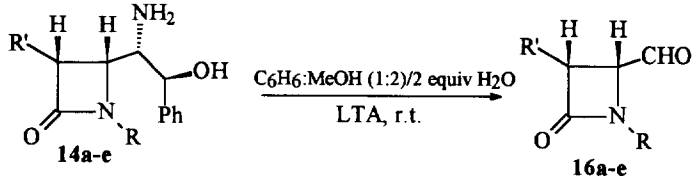


Table 3 **Synthesis of 4-formyl β-lactams 16a-e**

Compd. **16**	**R**	**R'**	Yield[a] (%)	m.p. (°C)
a	PMP-	PhO-	80	138-139
b	PMP-	BnO-	78	153-154
c	PMP-	MeO-	81	128-129
d	Bn-	PhO-	82	oil
e	Bn-	BnO-	78	113-114

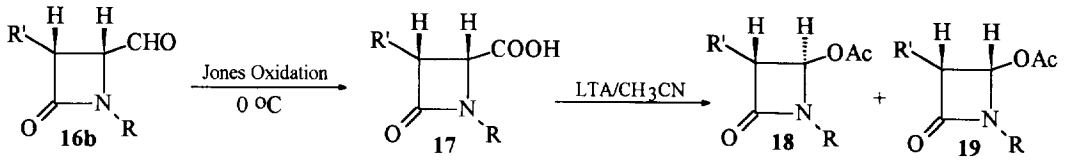
[a] Isolated yields of pure β-lactams after column chromatography.

PMP- = *p*-methoxyphenyl; **Bn-** = benzyl

These β-lactams (**16a-e**) were found to be optically pure by comparing the specific rotations with those of 4-formyl compounds prepared earlier in our laboratory from L-(+)-tartaric acid.[10b]

Synthesis of 4-Carboxy and 4-Acetoxy β-Lactams: The 4-carboxy β-lactam **17** is an important intermediate in the synthesis of β-hydroxyaspartates and β-hydroxymethyl serines. Jones' oxidation of 4-formyl-β-lactam **16b** provided the 4-carboxy-β-lactam **17** in 95% yield (**Scheme 5**).

Scheme 5



In a recent report[9c] unnatural R-serine was used to synthesize **17**, while our methodology provides an easy access for this acid from readily available aminodiol. The treatment of **17** with lead tetraacetate under established reaction conditions[17] provided 4-acetoxy-β-lactam (**18 & 19**) as *trans/cis* (75:25) mixture of isomers in 80% yield (**Scheme 5**). The major *trans* isomer (**18**) could be obtained in 56% yield in pure form by single crystallization (EtOAc/petroleum ether). It is known that Kronenthal's CAN oxidative dearylation[18] of **18&19** will give the *N*-dearylated product which can easily be converted into 3-unsubstituted β-lactam.[19] Alkylation of the 3-unsubstituted β-lactam using ethyl iodide and isopropyl iodide will furnish 3,4-disubstituted β-lactams[20] which have already been converted into (+) PS-5 and (+) PS6 carbapenems.[11,3f] Hence the present

route constitutes a formal total synthesis of optically pure carbapenem antibiotics from readily available aminodiol.

In conclusion, we have demonstrated that the readily available (+)-(1*S*,2*S*)-2-amino-1-phenylpropan-1,3-diol can serve as an efficient starting material for the enantiospecific synthesis of β-lactams. Further, a novel lead tetraacetate cleavage of aminols to 4-cyano β-lactams was also achieved. Further, we have shown that the aminol could serve as a starting material in the synthesis of β-hydroxy aspartates,[9c] β-hydroxy methylserines,[9c] hydroxy butanoic acids,[3h] the C-termenal moiety of renin inhibitors,[3h] a β-hydroxyaryl alanine fragment[9i] and carbapenams.[11]

EXPERIMENTAL PROCEDURE

General. All the melting points were recorded using a Thermonik Campbell melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded, except or otherwise stated, in $CDCl_3$ solution on a Bruker AC 200 instrument at 200 and 50 MHz respectively. The ^1H NMR chemical shifts are reported in ppm downfield from tetramethylsilane. The ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer Model 599-B using sodium chloride optics. Mass spectra were recorded on a Finnigan Mat-1020 spectrometer (electron impact). Elemental analyses were performed on a Carlo-Erba 1100 automatic analyser. Optical rotations were recorded on a JASCO-181 digital Polarimeter under standard conditions. CH_2Cl_2 was distilled over P_2O_5. Silica gel (SD's, 60-120 mesh) was used for column chomatography.

The aminodiol **1** supplied by *Parke Davis India Ltd.* was crystallized (EtOAc) to constant rotation and its optical purity was confirmed by comparing its specific rotation with the literature[21] value {$[\alpha]^{25}_D$ = +38 (c 1.1 N HCl)}. The acetonide protected aminodiol was prepared by following the reported procedure.[12]

Synthesis of Alcohol 2 & 3. To a stirred solution of acetonide protected alcohol (10.35 g, 0.05 mol) in dry CH_2Cl_2 (80 mL), triethylamine (7 g, 0.7 mol) and $(Boc)_2O$ (0.075 mol) was added at -15 °C. The reaction mixture was allowed to warm up to 0 °C and it was stirred further at this temperature for 4h. After the completion of the reaction (TLC), the reaction mixture was poured into 10% aqueous NH_4Cl (150 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were washed with water (50 mL), dried (Na_2SO_4), filtered and concentrated to give a mixture of alcohols **2** and **3** (3:1) in 99% yield. The column chomatography (3% EtOAc in petroleum ether) of this mixture yielded the pure alcohol **2** (10.8 g, 70%) as a yellow oil.

2 : Oil, ^1H NMR (at 50 °C): δ 1.55 (s, 9H); 1.65 (s, 3H); 1.73 (s, 3H); 3.60 - 3.95 (m, 2H); 4.05 - 4.15 (m, 1H); 4.60 (d, *J* = 7 Hz, 1H); 7.30 - 7.55 (m, 5H); IR ($CHCl_3$); ν 3400, 1675 cm^{-1}.

Synthesis of Aldehyde 4. A solution of DMSO (6.2 g, 0.08 mol) in CH_2Cl_2 (15 mL) was added to a stirred solution of oxalyl chloride (4.03 g, 0.032 mol) in CH_2Cl_2 (20 mL) over a period of 30 min at -60 °C under argon and stirred further at this temperature for 30 min. A solution of alcohol **2** (9.2 g, 0.03 mol) in CH_2Cl_2 (90 mL) was then added dropwise over 30 min at -60 °C and stirred further for 30 min. It was then warmed to -15 °C and triethylamine (15 g, 0.15 mol) was added over a period of 20 min. The reaction mixture was allowed to warm up to 0 °C over a period of 2h and then poured into a 10% aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with water (100 mL), dried and concentrated to give aldehyde **4** as an oil (8.96 g, 98%). This compound showed expected ^1H NMR spectrum and IR spectrum. It was immediately used as such for further reaction.

4: Oil, ^1H NMR : δ 1.30 (s, 9H); 1.55 (s, 3H); 1.65 (s, 3H); 4.00 - 4.10 (m, 1H); 4.95 (s, 1H); 7.20 - 7.45 (m, 5H); 9.53 (d, J = 3 Hz, 1H). IR ($CHCl_3$); ν 1720, 1690 cm^{-1}.

General Procedure for the Preparation of Imines 5 & 6. To a solution of amine [20 mmol, *p*-anisidine or benzylamine] in dry CH_2Cl_2 (50 mL), anhyd. $MgSO_4$ (10 g) and the aldehyde **4** (21 mmol) were added and the resulting mixture was stirred at room temperature. After the completion of the reaction (TLC, about 24 h) , the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (25 mL). The filtrate was concentrated under reduced pressure to give imine **5** or **6** in almost quantitative yields. The imines thus obtained were used without further purification.

5: Oil, ^1H NMR : δ 1.28 (s, 9H); 1.55 (s, 3H); 1.65 (s, 3H); 3.75 (s, 3H); 4.00 - 4.15 (m, 1H); 4.98 (bs, 1H); 6.95 - 7.23 (m, 5H); 7.85 (d, J = 3 Hz, 1H). IR ($CHCl_3$); ν 1700, 1610, 1520 cm^{-1}.

6: Oil, ^1H NMR : δ 1.35 (s, 9H); 1.60 (s, 3H); 1.65 (s, 3H); 4.10 - 4.20 (m, 1H); 4.63 (s, 2H); 5.00 (s, 1H); 7.00 - 7.43 (m, 5H); 7.73 (d, J = 3 Hz, 1H). IR ($CHCl_3$); ν 1695, 1620 cm^{-1}.

General Procedure for the Preparation of β-Lactams 13a-j. A solution of the acid chloride (**7-12**, 3 mmol) in anhydrous CH_2Cl_2 (30 mL) was slowly added to a stirred solution of the imine (**6** or **7**, 2 mmol) and triethylamine (10 mmol) in CH_2Cl_2 (30 mL) at -20 °C. The resulting mixture was allowed to warm up to room temperature and stirred further for 20 h. It was then washed successively with water (2 x 30 mL), satd. $NaHCO_3$ (2 x 30 mL) and water (30 mL). The organic layer was then column chromatographed (EtOAc-Petroleum ether mixtures) to give pure β-lactams **13a-e,g-j** in 37-94% yield. 3-Azido-β-lactam **13f** was prepared by adding a solution of cyanuric chloride (1.12 g, 4 mmol) in CH_2Cl_2 to a stirred mixture of potassium azidoacetate (0.556 g, 4 mmol), imine **5** (0.82 g, 2 mmol), triethylamine (1 g, 10 mmol) and CH_2Cl_2 (30 mL) at

-20 °C. The resulting reaction mixture was allowed to warm up to room temperature and stirred further for 20 h. By following above work up procedure, 3-azido-β-lactam **14f** was obtained in 53% yield.

(3*R*,4*S*,4′*S*,5′*S*) *N*-(*p*-Anisyl)-3-phthalimido-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13a). White crystalline solid. $[\alpha]^{25}_D$ = -90.1 (c 1.00, $CHCl_3$). ^1H NMR: δ 1.15 (s, 9H); 1.35 (s, 3H); 1.80 (s, 3H); 3.80 (s, 3H); 4.70 - 4.80 (m, 2H); 5.25 (dd, *J* = 2 & 12 Hz, 1H); 5.55 (d, *J* = 5 Hz, 1H); 6.75 - 7.05 (m, 7H); 7.50 - 7.70 (m, 6H). ^{13}C NMR δ 27.5, 27.9, 29.3, 55.4, 55.7, 60.9, 61.5, 79.8, 81.0, 96.9, 114.7, 118.5, 123.4, 127.1, 128.2, 128.5, 131.3, 132.3, 134.1, 138.6, 151.9, 156.8, 161.1, 167.2. IR ($CHCl_3$), ν 1770, 1730, 1700, 1620, 1600 cm^{-1}. MS: *m/z* 597 (M^+, 5%). Anal. Calcd for $C_{34}H_{35}O_3N_3$: C, 68.30; H, 5.90; N, 7.00. Found: C, 67.84; H, 6.21; N, 6.97.

(3*R*,4*S*,4′*S*,5′*S*) *N*-(*p*-Anisyl)-3-phenoxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13b). Colorless crystals. $[\alpha]^{25}_D$ = +86.7 (c 1.00, $CHCl_3$). ^1H NMR (at 92 °C Toluene d_8): δ 1.25 (s, 9H); 1.52 (s, 3H); 1.75 (s, 3H); 3.42 (s, 3H); 4.72 - 4.85 (m, 1H); 4.88 (d, *J* = 5.5 Hz, 1H); 5.13 (dd, *J* = 5.5 & 10 Hz, 1H); 5.35 (d, *J* = 5.2 Hz, 1H); 6.65 (d, *J* = 9 Hz, 2H); 6.95 - 7.15 (m, 8H); 7.45 (d, *J* = 9 Hz, 4H): ^1H NMR (at -15 °C, CD_2Cl_2): δ 1.00 and 1.25 (two s, total 9H); 1.30 and 1.52 (two s, total 3H); 1.40 and 1.75 (two s, total 3H); 3.70 and 3.75 (two s, total 3H); 4.65 - 4.90 (m, 1H); 4.90 - 5.20 (m, 2H); 5.35 - 5.50 (m, 1H); 6.65 - 7.60 (m, 14H): ^{13}C NMR: δ 27.6, 28.2, 30.9, 55.6, 57.2, 61.8, 79.6, 80.7, 95.6, 114.3, 116.2, 118.9, 122.7, 127.4, 128.3, 128.5, 129.7, 156.6, 158.1, 163.4. IR ($CHCl_3$): ν 1760, 1710, 1530 cm^{-1}. MS: *m/z* 544 (M^+, 5%). Anal. Calcd for $C_{32}H_{36}O_6N_2$: C, 70.56; H, 6.66; N, 5.14. Found: C, 70.47; H, 6.67; N, 4.95.

(3*R*,4*S*,4′*S*,5′*S*)*N*-(*p*-Anisyl)-3-benzyloxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-xazolidin-4′-yl]azetidin-2-one (13c). Isolated as an oil. $[\alpha]^{25}_D$ = +47.9 (c 1.00, $CHCl_3$). ^1H NMR (at 92 °C, Toluene d_8): δ 1.25 (s, 9H); 1.52 (s, 3H); 1.75 (s, 3H); 3.40 (s, 3H); 4.42 (d, *J* = 5.5. Hz, 1H); 4.55 - 4.65 (m, 1H); 4.60 (d, *J* = 11.6 Hz, 1H); 4.80 (d, *J* = 11.6 Hz, 1H); 5.02 (dd, *J* = 5.5 & 10 Hz, 1H); 5.30 (d, *J* = 5.4 Hz, 1H); 6.65 (d, *J* = 9 Hz, 2H); 6.95 - 7.20 (m, 10H); 7.42 (d, *J* = 9 Hz, 2H). ^1H NMR (at -15 °C CD_2Cl_2): δ 1.00 and 1.25 (two s, total 9H); 1.30 and 1.52 (two s, total 3H); 1.40 and 1.75 (two s, total 3H); 3.70 and 3.75 (two s, total 3H); 4.65 - 5.20 (m, 3H); 5.35 - 5.50 (m, 1H); 6.65 - 7.60 (m, 14H). IR (neat): ν 1760, 1700, 1520 cm^{-1}. Anal. Calcd for $C_{33}H_{38}O_6N_2$: C, 70.94; H, 6.85; N, 5.01. Found: C, 70.87; H, 6.76; N, 5.26.

(3*R*,4*S*,4′*S*,5′*S*) *N*-(*p*-Anisyl)-3-methoxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13d). Isolated as an oil. $[\alpha]^{25}_D$ = +51.7 (c 1.00, CH_2Cl_2). ^1H NMR (at 92 °C, Toluene d_8): δ 1.25 (s, 9H); 1.55 (s, 3H); 1.77 (s, 3H); 3.30 (s, 3H); 3.37 (s, 3H); 4.12 (d, *J* = 5 Hz, 1H); 4.60 - 4.73 (m, 1H); 4.92 (dd, *J* = 5 & 7 Hz, 1H); 5.30 (d, *J* = 5 Hz, 1H); 6.60 (d, *J* = 9 Hz, 2H); 6.90 - 7.15 (m, 3H); 7.30 - 7.45 (m, 4H). IR (neat): ν 1760, 1750, 1690 cm^{-1}. Anal. Calcd for $C_{27}H_{34}O_6N_2$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.27; H, 7.23; N, 5.66.

(3*R*,4*S*,4′*S*,5′*S*) 3-Acetoxy-*N*-(*p*-anisyl)-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13e). White crystalline solid. $[\alpha]^{25}_D$ = +34.2 (c 1.00, CH_2Cl_2). ^1H NMR (at 77 °C, Toluene d_8): δ 1.20 (s, 9H); 1.35 (s, 3H); 1.47 (s, 3H); 1.70 (s, 3H); 3.40 (s, 3H); 4.40 (dd, *J* = 5 & 10 Hz, 1H); 4.95 (d, *J* = 2.4 Hz, 1H); 5.05 (dd, *J* = 2.4 & 10 Hz, 1H); 5.87 (d, J = 5 Hz, 1H); 6.72 (d, *J* = 9 Hz, 2H); 6.90 - 7.15 (m, 3H); 7.25 - 7.35 (m, 2H); 7.50 (d, *J* = 9 Hz, 2H). IR ($CHCl_3$): ν 1760, 1750, 1690 cm^{-1}. Anal. Calcd for $C_{28}H_{34}O_7N_2$: C, 65.86; H, 6.71; N, 5.48. Found: C, 65.50; H, 6.72; N, 5.41.

(3*R*,4*S*,4′*S*,5′*S*) *N*-(*p*-Anisyl)-3-azido-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13f). Isolated as a gum. $[\alpha]^{25}_D$ = +86.6 (c 1.00, $CHCl_3$). ^1H NMR (at 82 °C, Toluene d_8): δ 1.25 (s, 9H); 1.52 (s, 3H); 1.77 (s, 3H); 3.85 (s, 3H); 4.15 (d, *J* = 5.2 Hz, 1H); 4.55 - 4.70 (m, 1H); 4.80 (dd, *J* = 5.2 & 10Hz, 1H); 5.67 (d, *J* = 5.9 Hz, 1H); 6.58 (d, *J* = 9 Hz, 2H); 6.85 - 7.15 (m, 3H); 7.20 (d, *J* = 9 Hz, 2H); 7.30 (d, *J* = 9 Hz, 2H). IR ($CHCl_3$): ν 2100, 1760, 1700 cm^{-1}. MS: *m/z* 493 (M^+).

(3*R*,4*S*,4′*S*,5′*S*) *N*-Benzyl)-3-phthalimido-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin- 4′-yl]azetidin-2-one (13g). White crystalline solid. $[\alpha]^{25}_D$ = -138.4 (c 1.000, $CHCl_3$). ^1H NMR: δ 1.25 (s, 3H); 1.30 (s, 3H); 1.65 (s, 9H); 3.90 - 4.00 (m, 1H); 4.05 (d, *J* = 15 Hz, 1H); 4.55 (d, J = 2 Hz, 1H); 5.10 (dd, *J* = 2 & 11 Hz, 1H); 5.25 (d, *J* = 15 Hz, 1H); 5.40 (d, *J* = 5 Hz, 1H); 6.80 - 7.05 (m, 5H); 7.25 - 7.45 (m, 5H); 7.60 (bs, 4H). ^{13}C NMR: δ 27.9, 28.7, 29.0, 45.9, 55.9, 59.6, 60.6, 79.4, 81.3, 96.3, 123.4, 126.9, 128.1, 128.5, 128.8, 129.1, 131.2, 134.2, 139.4, 152.5, 164.3, 167.2. IR ($CHCl_3$): ν 1770, 1700, 1580 cm^{-1}. MS: *m/z* 581 (M^+, 1%). Anal. Calcd for $C_{34}H_{35}O_6N_3$: C, 70.20; H, 6.60; N, 7.22. Found: C, 69.97; H, 6.22; N, 7.64.

(3*R*,4*S*,4′*S*,5′*S*) *N*-Benzyl)-3-phenoxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin- 4′-yl]azetidin-2-one (13h). White crystalline solid. $[\alpha]^{25}_D$ = -29.2 (c 1.00, $CHCl_3$). ^1H NMR: δ 1.40 (s, 3H); 1.45 (s, 3H); 1.57 (s, 9H); 4.55 (d, *J* = 16 Hz, 1H); 4.27 (dd, J = 5 & 10 Hz, 1H); 4.87 (d, J = 16 Hz, 1H); 5.05 (dd, *J* = 2.4 & 10 Hz, 1H); 5.15 (d, *J* = 2.4 Hz, 1H); 5.25 (d, *J* = 5 Hz, 1H); 6.92 - 7.05 (m, 3H); 7.15 - 7.60 (m, 12H). ^{13}C NMR: δ 27.9, 28.0, 28.3, 44.7, 57.4, 61.6, 79.2, 80.7, 81.2, 95.4, 116.0, 122.3, 127.0, 127.7, 128.0, 128.2, 128.3, 128.7, 129.3, 135.0, 139.2, 152.2, 157.6, 166.2. IR ($CHCl_3$): ν 1770, 1700, 1610 cm^{-1}. Anal. Calcd for $C_{32}H_{36}O_5N_2$: C, 72.70; H, 6.86; N, 5.30. Found: C, 72.72; H, 6.91; N, 5.43.

(3*R*,4*S*,4′*S*,5′*S*) *N*-Benzyl)-3-benzyloxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin-4′-yl]azetidin-2-one (13i). White crystalline solid. $[\alpha]^{25}_D$ = -40.5 (c 1.00, $CHCl_3$). ^1H NMR: δ 1.32 (s, 3H); 1.40 (s, 3H); 1.52 (s, 9H); 3.45 (d, *J* = 15.1 Hz, 1H); 3.95 - 4.10 (m, 1H); 4.65 - 4.75 (m, 2H); 4.77 - 5.00 (m, 3H); 5.05 (d, J = 3 Hz, 1H); 7.05 - 7.55 (m, 15H). ^{13}C NMR: δ 28.2, 28.6, 44.6, 57.4, 61.8, 73.1, 79.3, 80.8, 81.1, 95.5, 127.2, 128.0, 128.1, 128.4, 128.5, 128.8, 135.2, 136.7, 139.4, 152.3, 168.0. IR ($CHCl_3$): ν 1770, 1700, 1610 cm^{-1}. Anal. Calcd for $C_{33}H_{38}O_5N_2$: C, 73.03; H, 7.05; N, 5.16. Found: C, 73.12; H, 7.27; N, 4.95.

(3*R*,4*S*,4′*S*,5′*S*) *N*-Benzyl)-3-methoxy-4-[*N*-t-butoxycarbonyl-2′,2′-dimethyl-5′-phenyl-1′,3′-oxazolidin- 4′-yl]azetidin-2-one (13j). White solid. $[\alpha]^{25}_D$ = -24.5 (c 1.00, $CHCl_3$). ^1H NMR: δ 1.40 (s, 3H); 1.45 (s, 3H); 1.49 (s, 9H); 3.20 (d, *J* = 16 Hz, 1H); 3.53 (s, 3H); 4.05 - 4.20 (m, 1H); 4.51 (d, J = 5 Hz, 1H); 4.60 - 4.80 (m, 2H); 5.08 (d, *J* = 4 Hz, 1H); 7.00 - 7.55 (m, 10H). ^{13}C NMR: δ 27.6, 28.4, 44.4, 57.1, 59.6, 62.0, 79.0, 80.6, 84.0, 95.3, 126.2, 127.1, 127.8, 128.1, 128.2, 128.5, 135.0, 139.3, 152.2, 167.8. IR ($CHCl_3$): ν 1750, 1680, 1450 cm^{-1}. Anal. Calcd for $C_{27}H_{34}O_6N_2$: C, 67.23; H, 7.05; N, 5.80. Found: C, 67.12; H, 7.27; N, 5.95.

General Procedure for the Preparation of Aminols 14a-e. To a solution of β-lactams **13b-d,h,j** (2 mmol) in methanol (20 mL), 3N HCl (20 mL) was added and heated under reflux for 20-30 min. The progress of the reaction was carefully monitored by TLC and the reaction mixture was cooled to room temperature immediately after the disappearance of the starting material. The cold reaction mixture was basified with solid $NaHCO_3$ to P^H 9 and it was concentrated on a rotary evaporator. The residue was taken up in CH_2Cl_2 (50 mL) and the organic layer was washed with water (30 mL), brine and dried (Na_2SO_4) and filtered. The removal of solvent under reduced pressure provided the deprotected aminols **14a-e** in 97-99% yields. The solid aminols thus obtained were crystallized from suitable solvents.

Aminol 14a. $[\alpha]^{25}_D$ = +91.7 (c 1.00, CH_2Cl_2). ^1H NMR: δ 1.60 (bs, 3H); 3.62 (dd, *J* = 5 & 6 Hz, 1H); 3.80 (s, 3H); 4.60 (t, *J* = 5 Hz, 1H); 4.70 (d, *J* = 6 Hz, 1H); 5.40 (d, *J* = 5 Hz, 1H); 6.95 (d, *J* = 9 Hz, 2H); 7.14 (d, *J* = 9 Hz, 2H); 7.25 - 7.60 (m, 10H): IR (nujol): ν 3450 and 1760cm^{-1}.

Aminol 14b. $[\alpha]^{25}_D$ = +48.8 (c 1.00, CH_2Cl_2). ^1H NMR: δ 1.80 (bs, 3H); 3.50 (t, *J* = 6 Hz, 1H); 3.80 (s, 3H); 4.36 (t, *J* = 5.2 Hz, 1H); 4.65 (d, *J* = 6 Hz, 1H); 4.77 (d, *J* = 11.5 Hz, 1H); 4.83 (d, *J* = 5.2 Hz, 1H); 5.07 (d, *J* = 11.5 Hz, 1H); 6.88 (d, *J* = 9 Hz, 2H); 7.20 - 7.55 (m, 12H): IR (nujol): ν 3400 and 1750 cm^{-1}.

Aminol 14c. $[\alpha]^{25}_D$ = +50.9 (c 1.00, CH_2Cl_2). ^1H NMR: δ 1.48 (bs, 3H); 3.50 (t, *J* = 5.3 Hz, 1H); 3.70 (s, 3H); 3.80 (s, 3H); 4.35 (t, *J* = 5.3 Hz, 1H); 4.62 (d, *J* = 5.3 Hz, 2H); 6.92 (d, *J* = 9 Hz, 2H); 7.30 - 7.50 (m, 7H): IR (nujol): ν 3100 and 1740 cm^{-1}.

Aminol 14d. $[\alpha]^{25}_D$ = +70.3 (c 1.00, CH_2Cl_2). ^1H NMR: δ 2.10 (bs, 3H); 3.25 (dd, *J* = 5 & 10 Hz, 1H); 3.90 (dd, *J* = 3 & 10 Hz, 1H); 4.45 (d, *J* = 16 Hz, 1H); 4.52 (d, *J* = 3 Hz, 1H); 4.90 (d, *J* = 16 Hz, 1H); 5.25 (d, *J* = 5 Hz, 1H); 7.00 - 7.20 (m, 5H); 7.25 - 7.60 (m, 10H): IR (nujol): ν 3400 and 1750 cm^{-1}.

Aminol 14e. $[\alpha]^{25}_D$ = +46.5 (c 1.00, CH_2Cl_2). ^1H NMR: δ 2.00 (bs, 3H); 3.00 (dd, *J* = 5 & 9 Hz, 1H); 3.75 (dd, *J* = 6 & 9 Hz, 1H); 4.10 - 4.25 (m, 2H); 4.30 - 5.00 (m, 5H); 6.85 - 7.50 (m, 15H): IR (nujol): ν 3450 and 1770 cm^{-1}.

General Procedure for the Synthesis of 4-Cyano-β-Lactams 15a-c. To a stirred solution of the aminol **14a-c** (1 mmol) in dry benzene (20 mL) was added solid $Pb(OAc)_4$ (1.2 mmol) at room temperature under argon. After the disappearance of the starting material (TLC, about 30 min), the reaction mixture was filtered through a pad

of neutral alumina. The filtrate was washed with water (2 X 20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was column chromatographed (silica gel, petroleum ether/EtOAc mixtures) to get 4-cyano-β-lactams **15a-c** in 97-99% yields.

(3*R*,4*S*) *N*-(*p*-Anisyl)-3-phenoxy-4-cyanoazetidin-2-one (15a). $[\alpha]^{25}_D$ = +135.6 (c 1.000, $CHCl_3$). ^1H NMR: δ 3.83 (s, 3H); 5.00 (d, *J* = 5 Hz, 1H); 5.60 (d, *J* = 5 Hz, 1H); 6.95 (d, *J* = 9 Hz, 2H); 7.05 - 7.25 (m, 3H); 7.30 - 7.50 (m, 4H). IR ($CHCl_3$): ν 2060, 1780, 1600 cm^{-1}. MS *m/z* 294 (M^+, 23%). Anal. Calcd for $C_{17}H_{14}O_3N_2$: C, 73.48; H, 6.00; N, 4.63. Found: C, 73.40; H, 6.12; N, 4.58.

(3*R*,4*S*) *N*-(*p*-Anisyl)-3-benzyloxy-4-cyanoazetidin-2-one (15b). $[\alpha]^{25}_D$ = +140.2 (c 1.000, $CHCl_3$). ^1H NMR: δ 3.75 (s, 3H); 4.65 (d, *J* = 5 Hz, 1H); 4.80 (s, 2H); 5.00 (d, *J* = 5 Hz, 1H); 6.85 (d, *J* = 9 Hz, 2H); 7.25 - 7.45 (m, 7H). ^{13}C NMR: δ 47.9, 55.7, 73.9, 82.1, 114.2, 114.9, 118.6, 128.7, 128.8, 129.3, 135.6, 157.6 and 161.3. IR ($CHCl_3$): ν 2260, 1770, 1620 cm^{-1}. MS *m/z* 308 (M^+, 12%). Anal. Calcd for $C_{18}H_{16}O_3N_2$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.30; H, 5.48; N, 9.21.

(3*R*,4*S*) *N*-(*p*-Anisyl)-3-methoxy-4-cyanoazetidin-2-one (15c). $[\alpha]^{25}_D$ = +167.5 (c 1.000, $CHCl_3$). ^1H NMR: δ 3.72 (s, 3H); 3.80 (s, 3H); 4.77 (d, *J* = 5 Hz, 1H); 4.93 (d, *J* = 5 Hz, 1H); 6.92 (d, *J* = 9 Hz, 2H); 7.40 (d, *J* = 9 Hz, 2H). ^{13}C NMR (acetone-d_6): δ 48.7, 56.0, 59.6, 85.7, 115.6, 119.3, 129.3, 130.8, 158.3 and 162.4. IR ($CHCl_3$): ν 2040, 1770 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.17; N, 12.06. Found: C, 62.43; H, 5.14; N, 12.21.

General Procedure for the Synthesis of 4-Formyl-β-Lactams 16a-e. To a stirred solution of the aminol **14a-e** (1 mmol) in benzene (10 mL) and methanol (20 mL), water (2 mmol) followed by solid $Pb(OAc)_4$ (2 mmol) were added at room temperature and stirred further for 1h. After the disappearance of the starting material (TLC), the reaction mixture was filtered through a small pad of alumina and washed with benzene. The combined filtrate was concentrated under reduced pressure. The residue so obtained was taken up in CH_2Cl_2 (50 mL) and it was washed with water (2 X 20 mL), dried (Na_2SO_4), filtered and concentrated. The crude product thus obtained was column chromatographed (silica gel, petroleum ether/EtOAc mixtures) to give the product **16a-e**, which was crystallized from suitable solvent to get pure 4-formyl-β-lactams (**16a-e**) in 78 - 82% yield.

(3*R*,4*R*) *N*-(*p*-Anisyl)-3-phenoxy-4-formylazetidin-2-one (16a). $[\alpha]^{25}_D$ = +173.4 (c 1.000, CH_2Cl_2). ^1H NMR: δ 3.85 (s, 3H); 4.80 (dd, *J* = 3 & 5 Hz, 1H); 5.65 (d, *J* = 5 Hz, 1H); 6.95 (d, *J* = 9 Hz, 2H); 7.05 - 7.20 (m, 3H); 7.30 - 7.45 (m, 4H); 9.87 (d, *J* = 3 Hz, 1H). ^{13}C NMR: δ 55.8, 63.4, 81.9, 115.0, 116.0, 118.5, 123.4, 130.0, 130.7, 157.2, 157.5, 161.7, 197.6. IR ($CHCl_3$): ν 2810, 1750, 1725, 1600 cm^{-1}. MS *m/z* 297 (M^+, 25%). Anal. Calcd for $C_{17}H_{15}O_4N$: C, 68.60; H, 5.08; N, 4.70. Found: C, 68.66; H, 5.12; N, 4.89.

(3*R*,4*R*) *N*-(*p*-Anisyl)-3-benzyloxy-4-formylazetidin-2-one (16b). Mp: 153 - 154 °C [EtOAc-petroleum ether]. $[\alpha]^{25}_D$ = +178.5 (c 1.0, CH_2Cl_2); {lit.[9a] for the antipode: Mp: 152-153 °C (EtOAc). $[\alpha]^{25}_D$ = -178.4 (c 1.000, CH_2Cl_2)}. Other spectroscopic and analytical data were matching well with the reported values.

(3*R*,4*R*) *N*-(*p*-Anisyl)-3-methoxy-4-formylazetidin-2-one (16c). $[\alpha]^{25}_D$ = +244 (c 0.60 CH_2Cl_2). ^1H NMR: δ 3.55 (s, 3H); 3.80 (s, 3H); 4.55 (dd, *J* = 3 & 5 Hz, 1H); 4.85 (d, *J* = 5 Hz, 1H); 6.85 (d, *J* = 9 Hz, 2H); 7.20 (d, *J* = 9 Hz, 2H); 9.75 (d, *J* = 3 Hz, 1H). ^{13}C NMR: δ 55.2, 59.1, 63.0, 84.9, 114.4, 117.8, 130.3, 156.7, 162.5, 198.5. IR ($CHCl_3$): ν 1760, 1600 cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.32; H, 5.62; N, 5.89.

(3*R*,4*R*) *N*-Benzyl-3-phenoxy-4-formylazetidin-2-one (16d). $[\alpha]^{25}_D$ = +57.6 (c 1.00, CH_2Cl_2). ^1H NMR: δ 4.25 (dd, *J* = 2.9 & 5 Hz, 1H); 4.50 (d, *J* = 11.7 Hz, 1H); 4.75 (d, *J* = 11.7 Hz, 1H); 5.45 (d, *J* = 5 Hz, 1H); 7.00 - 7.15 (m, 3H); 7.25 - 7.45 (m, 7H); 9.50 (d, *J* = 2.9 Hz, 1H). ^{13}C NMR: δ 46.2, 63.3, 82.4, 115.7, 123.1, 128.6, 128.9, 129.3, 129.9, 134.3, 157.1, 164.6, 197.2. IR ($CHCl_3$): ν 1750, 1715, 1610 cm^{-1}. MS *m/z* 281 (M^+, 2%). Anal. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.97. Found: C, 72.65; H, 5.43; N, 4.86.

(3*R*,4*R*) *N*-Benzyl-3-benzyloxy-4-formylazetidin-2-one (16e). Mp: 113 - 114 °C [EtOAc-petroleum ether]. $[\alpha]^{25}_D$ = +86.2 (c 1.0, CH_2Cl_2); {lit.[9a] for the antipode: Mp: 112-113 °C (EtOAc). $[\alpha]^{25}_D$ = -85.9 (c 1.00, CH_2Cl_2)}. Other spectroscopic and analytical data were matching well with the reported values.

Preparation of (3*S*,4*R*) *N*-(*p*-Anisyl)-3-benzyloxy-4-carboxyazetidin-2-one (17). To a stirred solution of 4-formyl-β-lactam **16b** (0.311 g, 1 mmol) in acetone (30 mL), Jones' reagent (chromic acid solution) was added dropwise at 0 °C and stirred further for 20 min. After the disappearance of the starting material (TLC), methanol (1 mL) was added and stirred further for 10 min. The reaction mixture was then filtered through a celite pad and the filtrate was evaporated under reduced pressure. The crude product thus obtained was crystallized from CH_2Cl_2-MeOH to give colorless crystals (0.312 g, 95%) of pure acid **17**, Mp. 208-210 °C. $[\alpha]^{25}_D$ = +115.6 (c 1.000, acetone) {lit.[9c] Mp. 211-213 °C; $[\alpha]^{25}_D$ = +117.5 (c 1.0, acetone)}; ^1H NMR (DMSO-d_6): δ 3.72 (s, 3H); 4.67 (d, *J* = 6 Hz, 1H); 4.75 (s, 2H); 4.97 (d. *J* = 6 Hz, 1H); 6.30 (bs, 1H); 6.70 - 7.40 (m, 9H). IR (nujol) ν 3400, 1760, 1715 cm^{-1}. Anal. Calcd for $C_{18}H_{17}O_5N$: C, 62.06; H, 5.17; N, 12.06. Found: C, 62.43; H, 5.14; N, 12.21.

Preparation of (3*R*,4*R*) 4-Acetoxy-*N*-(*p*-Anisyl)-3-benzyloxyazetidin-2-one (18). To a stirred suspension of the acid **17** (0.327 g, 1 mmol) in acetonitrile (25 mL) $Pb(OAc)_4$ (0.880 g, 2.2 mmol)and catalytic amount of $Cu(OAc)_2$ were added. The resulting mixture was refluxed under argon for 40 min. After the completion of the reaction (TLC), the mixture was cooled and filtered through celite pad and the residue was washed with ethyl acetate. After the evaporation of the solvent under reduced pressure, the crude product was filtered over silicagel

(petroleum ether/EtOAc, 4:1). The removal of solvent gave 0.274 g (80%) of product as *trans : cis* mixture of **18** and **19** in the ratio of 75:25. A single crystallization of this mixture from CH_2Cl_2-petroleum ether gave 0.194 g of major *trans* isomer **18** in analytically pure form. Mp. 135-137 °C. $[\alpha]^{25}_D$ = -32.7 (c 0.70, acetone)}; ^{1}H NMR: δ 2.10 (s, 3H); 3.80 (s, 3H); 4.70 (s, 1H); 4.80 (d. *J* = 11.6 Hz, 1H); 4.90 (d. *J* = 11.6 Hz, 1H); 6.32 (s, 1H); 6.85 - 7.50 (m, 9H). IR ($CHCl_3$) ν 1760, 1750 cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_5N$: C, 62.02; H, 5.21; N, 12.02. Found: C, 62.13; H, 5.19; N, 12.07.

ACKNOWLEDGMENTS. We thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Syn.) for his keen interest and encouragement, Dr. A. Sarkar for his help and Mr. A. G. Samuel, for variable temperature NMR spectra. We gratefully acknowledge the referees of this manuscript for useful suggestions. One of the authors (MJ) acknowledges CSIR for a research fellowship

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NCL communication No. 6295.

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(*Received in USA* 15 *January* 1996; *accepted* 3 *May* 1996)