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Stereoselective Synthesis of Homochiral Pyrrolidinones and *cis, cis-bis-β*-Lactams from (+)-(*1S,2S*)-2-Amino-1-phenylpropan-1,3-diol.

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Dedicated to Dr. Maghar S. Manhas on the occasion of his 73rd birthday

Abstract: *The homochiral β-lactams described in the preceding paper undergone an acid catalyzed rearrangement to 4-aminopyrrolidinones* ***2a-e*** *in excellent yields. A diastereoselective synthesis of cis,cis-bis-β-lactams* ***13*** *&* ***14*** *has been achieved by using imines bearing a β-lactam back bone in good yields and good to excellent selectivities.*

INTRODUCTION

Besides being used for the synthesis of a variety of β-lactam antibiotics,[1] the β-lactam skeleton has been recognized as a useful precursor for various non-β-lactam derivatives (*β-lactam synthon approach*).[2] In the preceding paper we described the stereoselective synthesis of homochiral β-lactams from (+)-(1*S*,2*S*)-2-amino-1-phenylpropan-1,3-diol. In this report we wish to disclose our findings on the further use of this diol for the synthesis of homochiral pyrrolidinones bearing four contiguous chiral centers and *cis,cis-bis*-β-lactams.

Synthesis of 4-Amino-2-pyrrolidinones 2a-f :

Functionalized pyrrolidin-2-ones serve as excellent starting materials for the synthesis of γ-lactam bridged dipeptides,[3] γ-lactam analogs of β-lactam antibiotics,[4] and substituted pyrrolidines.[5] The interest in the stereoselective synthesis of pyrrolidin-2-ones is still an active area of research since they serve as the most potent antagonists with significant in *vivo* activity against cerebral ischaemia and epilepsy.[6] Therefore stereoselective synthesis of pyrrolidin-2-ones with known absolute configuration are of current interest. Herein we report such a synthesis of 3,5-disubstituted pyrrolidin-2-ones in excellent yields.

Our methodology involves the acid catalysed rearrangement of 4-(α-aminoalkyl) β-lactams reported in the preceding paper. The β-lactams **1a-f** on treatment with methanolic HCl (3N) at 60 °C for 2-24 h underwent a facile rearrangement to afford the pyrrolidin-2-ones **2a-f** in almost quantitative yields. The structure of the product was confirmed from its analytical and spectral data. The stereochemical assignment of the pyrrolidinones were based on the coupling constants of the C3, C4, C5 and C1′ protons. The assignment of the protons were made from the results of D_2O exchange, decoupling and COSY experiments. As a representative example, for pyrrolidinone **2f** C3 proton appeared as a singlet at 5.00 ppm indicating the trans stereochemistry between C3 and C4. The C4 proton appeared at 4.10 as a dd before D_2O exchange [$J_{C5\text{-}H\text{-}C4}$ = 7.65 Hz and $J_{C4\text{-}H\text{-}NH}$ = 5.11 Hz] and as a doublet after D_2O exchange. The coupling constant of 7.65 Hz clearly shows the cis geometry between C4 and C5 protons. The C1′ proton appeared as a doublet at 4.03 (J = 3.39 Hz) showing the cis stereochemistry between C5 and C1′ protons. We found that the stereochemistry of the pyrrolidinones were the same as it was observed by others[5] in a similar rearrangement. The pyrrolidin-2-ones **2a-f** were isolated as nice solids which could be crystallized to analytically pure products without column purification. This rearrangement was found to be general and in all the cases the yields were quantitative (**Scheme 1, Table 1**).

Scheme 1

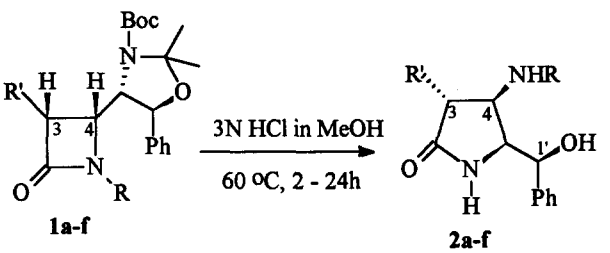

Table 1 **Synthesis of pyrrolidinones 2a-f**

Compound	R	R'	Time[a] (h)	Yield[b] (%)	m p (°C)
2a	PMP	PhO-	7	99	205-206
2b	PMP	BnO-	17	98	185-186
2c	PMP	MeO-	24	99	97-99
2d	Bn-	PhO-	2	97	150-152
2e	Bn-	BnO-	24	99	114-115
2f	Bn-	MeO-	12	99	70-71

[a] reaction time; [b] Isolated yields of pure pyrrolidinones

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

Synthesis of *cis,cis-bis*-β-lactams 13 and 14 :

Imines derived from homochiral aldehydes are known to provide high level of stereoselectivity in the Staudinger reaction.[7] On the other hand the use of imines derived from homochiral amines in the cycloaddition reaction leads to none or modest asymmetric induction.[8] However, the use of imines with a β-lactam back bone were reported to proceed with high levels of selectivity in the cycloaddition reaction.[9] Based on this background it was thought prudent to study the effect of the steric bulk of the β-lactam ring on the diastereoselectivity in the second β-lactam ring formation. Encouraged by recent publications[10] in this area we report our own findings on the diastereoselectivities achieved in the Staudinger reaction by using a chiral amine.

The deprotected aminols **3** were synthesized as reported in the preceding paper. The hydroxy group of the aminols **3** were protected either as trimethylsilyl or t-butyldimethylsilyl ethers **4** (**Scheme 2**). The *O*-protected aminols **4** on treatment with cinnamaldehyde provided the imines **5a-e** in quantitative yields. The cycloaddition reaction of imines **5a,b** with acid chlorides (**6-8**) in the precence of excess triethylamine at -78 °C to rt afforded a diastereomeric mixture of *bis*-β-lactams **9a-d** and **10a-d.** The similar reaction of imines **5c-e** with acid chloride **8** afforded the *bis*-β-lactams **11a-c** and **12a,b**. In the case of TMS protected imines **5a,b** a small amount of corresponding deprotected hydroxy compound was also isolated. Therefore, in all the cases pure *bis*-β-lactams **13a-d** and **14a-d** were isolated after deprotection of either TMS or TBDMS protecting groups. Both the diastereomers were found to be *cis,cis-bis*-β-lactams from the coupling constant of the β-lactam protons in the newly formed β-lactam ring. The ratio of the two diastereomers were determined by HPLC analysis.[11]

The TMS deprotection was effected by stirring the diastereomeric mixture of *bis*-β-lactams **9a-d** and **10a-d** with 1N HCl in methanol for 30 min to give *bis*-β-lactams **13a-d** and **14a-d** which were separated by flash column chromatography. The TBDMS group was removed by stirring an acetonitrile solution of the diastereomeric mixture of *bis*-β-lactams **11a,b** and **12a,b** with 50% HF for 24 h at room temperature to give corresponding *bis*-β-lactams **13a,b** and **14a,b** which were separated by flash column chromatography. The analytical and spectral data of these compounds matched well with that of *bis*-β-lactams **13a,b** and **14a,b** obtained from corresponding TMS protected *bis*-β-lactams **10a,b** and **11a,b**. However, imine **5e** on treatment with acid chloride **8** under usual conditions provided *bis*-β-lactam **11c** as a sole product in 69% yield along with some unreacted imine **5e**. This observation proves that the origin of the selectivity in the second β-lactam ring formation is steric and the bulk of the phthalimido and TBDMS groups in the imine and the phthalimido bulk in ketene precursor provided the necessary steric disposition to achieve total selectivity.

The deprotection of the TBDMS group in **11c** could not be effected under various conditions tried presumably because of steric reasons.

Scheme 2

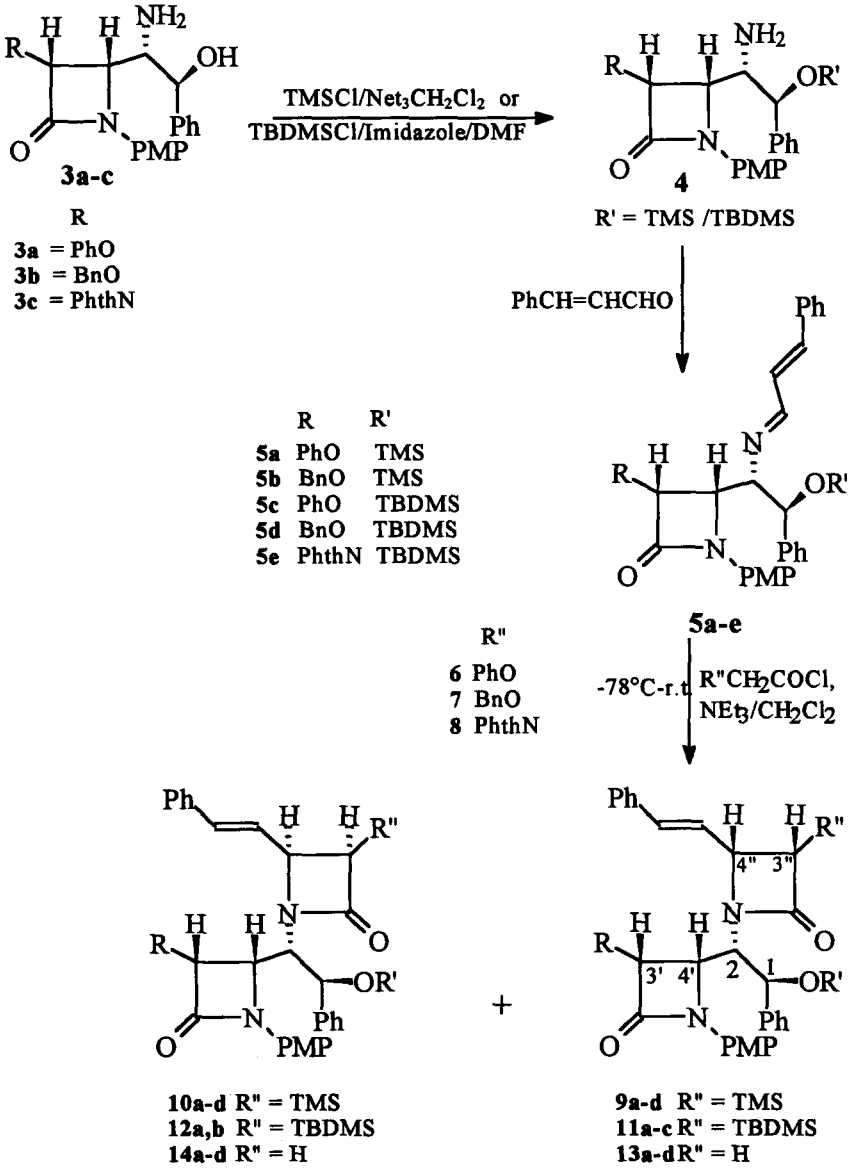

Table 2 **Synthesis of *cis,cis-bis*-β-Lactams 9a-d, 10a-d & 11a-c & 12a,b**

Compound	R	R′	R″	Yield[a] (%)	Ratio (9:10)/ (11:12)
9a & 10a	PhO	TMS	BnO	82	77:23
9b & 10b	PhO	TMS	PhO	78	65:35
9c & 10c	PhO	TMS	PhthN	86	78:22
9d & 10d	BnO	TMS	PhthN	87	75:25
11a & 12a	PhO	TBDMS	PhthN	70	66:34
11b & 12b	BnO	TBDMS	PhthN	96	70:30
11c & 12c	PhthN	TBDMS	PhthN	69	>95[b]:<5

[a] Isolated yield of a mixture of both diastereomers. [b] ^{1}H NMR and HPLC analysis showed only one diastereomer.

PhthN = phthalimido; **Bn** = benzyl; **TMS** = trimethylsilyl; **TBDMS** = t-butyldimethylsilyl

The relative configuration within the *bis*-β-lactam was established by single crystal X-ray diffraction analysis[12] of the *O*-TMS protected *bis*-β-lactam **9c** (**Figure 1**). The configuration at C3″ and C4″ of newly formed β-lactam **9c** was assigned as C3″*S*, C4″*R* on the basis of the known absolute configuration 1*S*,2*S*,3′*R*,4′*S* of the starting aminol. The absolute configuration of the other *bis*-β-lactams in this series were assigned by comparing the ^{1}H NMR, ^{13}C NMR and HPLC data with that of **9c**.

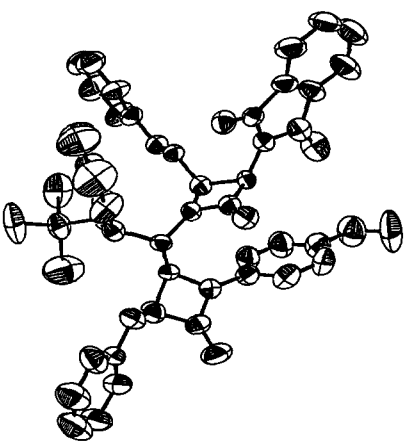

Fig. 1 ORTEP diagram of **9c**

In conclusion we have achieved an easy access to optically pure pyrrolidin-2-ones *via* a β-lactam synthon approach. Novel diversely substituted *bis*-β-lactams were synthesized. Total stereocontrol was observed in the 2nd β-lactam ring formation by using *O*-TBDMS protected imine bearing a phthalimido group at C3 of the β-lactam and ketene derived from phthalimidoacetyl chloride.

EXPERIMENTAL PROCEDURE

General. All the melting points were recorded using Thermonik Campbell melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded, except 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 center 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 (electro 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. Methylene chloride was distilled over P_2O_5. Silica gel (SD's, 60-120 mesh) was used for column chomatography.

General Procedure for the Preparation of Pyrrolidinones 2a-e. To a solution of the β-lactams **1a-f** (1 mmol) in methanol (10 mL), a solution of 3N HCl in methanol (20 mL) was added and the reaction mixture was refluxed for 2 - 24 h. The reaction mixture was cooled after the completion of the reaction (TLC) and the precipitated compound was filtered to get the rearranged products **2a-f**. The filtrate was concentrated under reduced pressure, treated with water (30 mL) and basified with solid $NaHCO_3$ to pH 9. It was then extracted with ethyl acetate (3 X 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the rest of the products **2a-f**. The combined products were crystallized from suitable solvents to give pure products **2a-f** in almost quantitative yields.

(3*R*,4*S*,5*S*,1′*S*)-5-[1′-Hydroxy-1′-phenylmethyl]-4-[(4-methoxyphenyl)amino]-3-phenoxy-2-pyrrolidinone (2a). $[\alpha]^{25}_D$ = +245.9 (c 1.000, acetone). ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.87 (s, 1H, OH, D_2O exchangeable); 3.75 (s, 3H, OCH_3); 4.15 (d, *J* = 7.8 Hz, 1H, C5H); 4.55 (dd, *J* = 9.0 & 15.9 Hz, 1H, C4H); 4.92 (bs, 1H, NH, D_2O exchangeable); 5.05 (s, 1H, C3H); 5.15 - 5.35 (m, 2H, C1′H & NH); 6.75 - 7.05 (m, 5H, arm); 7.10 (d, *J* = 9 Hz, 2H, arm); 7.15 - 7.40 (m, 7H, arm). IR ($CHCl_3$): ν 3400 (bs), 3200 (bs), 1750 cm^{-1}. MS *m/z* 404 (M^+, 100%). Anal. Calcd for $C_{24}H_{24}O_4N_2$: C, 71.30; H, 5.93; N, 6.92. Found: C, 71.40; H, 6.12; N, 7.08.

(3*R*,4*S*,5*S*,1′*S*)-3-Benzyloxy-5-[1′-hydroxy-1′-phenylmethyl]-4-[(4-methoxyphenyl)amino]-2-pyrrolidinone (2b). $[\alpha]^{25}_D$ = +168 (c 1.00, CH_2Cl_2). ^1H NMR : δ 3.00 (s, 1H, OH, D_2O exchangeable); 3.80 (s, 3H,

OCH_3); 3.95 (d, J = 6.97, 1H); 4.30 - 4.50 (m, 2H); 4.80 (d, J = 12.07 Hz, 1H); 4.90 (bs, 2H); 5.02 (d, J = 12.07 Hz, 1H); 6.20 (s, 1H, D_2O exchangeable); 6.70 - 6.85 (m, 4H); 7.15 - 7.50 (m, 10H). IR ($CHCl_3$): ν 3600 (bs), 3400 (bs), 1700 cm^{-1}. Anal. Calcd for $C_{25}H_{20}O_4N_2$: C, 71.78; H, 6.21; N, 6.69. Found: C, 71.63; H, 6.12; N, 6.58.

(3*R*,4*S*,5*S*,1′*S*)-5-[1′-Hydroxy-1′-phenylmethyl]-3-methoxy-4-[(4-methoxyphenyl)amino]-2-pyrrolidinone (2c). $[\alpha]^{25}_D$ = +125.2 (c 1.000, CH_2Cl_2). ^1H NMR: δ 2.70 (s, 1H); 3.42 (s, 3H); 3.50 (s, 3H); 3.53 (bs, 1H); 3.98 - 4.10 (m, 1H); 4.48 - 4.60 (m, 1H); 5.00 - 5.10 (m, 1H); 5.85 (s, 1H); 6.40 - 6.65 (m, 4H); 6.80 - 7.24 (m, 5H). IR ($CHCl_3$): ν 3500 (bs), 3450 (bs), 1710 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_4N_2$: C, 66.68; H, 6.43; N, 8.18. Found: C, 66.63; H, 6.23; N, 8.42.

(3*R*,4*S*,5*S*,1′*S*)-4-Benzylamino-5-[1′-hydroxy-1′-phenylmethyl]-3-phenoxy-2-pyrrolidinone (2d). $[\alpha]^{25}_D$ = +275.5 (c 1.000, CH_2Cl_2). ^1H NMR : δ 1.90 (bs, 1H, D_2O exchangeable); 3.60 - 3.80 (m, 3H); 3.98 (s, 2H); 5.00 - 5.10 (m, 2H); 5.80 (s, 1H, D_2O exchangeable); 7.90 - 7.50 (m, 15H). IR ($CHCl_3$): ν 3400 (bs), 3200 (bs), 1700 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_3N_2$: C, 68.79; H, 6.18; N, 7.21. Found: C, 68.63; H, 6.26; N, 7.34.

(3*R*,4*S*,5*S*,1′*S*)-4-Benzylamino-3-benzyloxy-5-[1′-hydroxy-1′-phenylmethyl]-2-pyrrolidinone(2e). $[\alpha]^{25}_D$ = +125 (c 1.00, CH_2Cl_2). ^1H NMR : δ 3.25 (bs, 2H); 3.60 - 3.75 (m, 1H); 3.65 (s, 2H); 3.95 (d, J = 11Hz, 1H); 4.10 (d, J = 11Hz, 1H); 4.40 - 4.65 (m, 1H); 5.00 (s, 1H); 5.70 (s, 1H); 7.10 - 7.55 (m, 16H). IR (nujol): ν 3400 (bs), 3250 (bs), 1690 cm^{-1}. Anal. Calcd for $C_{25}H_{26}O_3N_2$: C, 74.64; H, 6.46; N, 6.96. Found: C, 74.63; H, 6.58; N, 7.14.

(3*R*,4*S*,5*S*,1′*S*)-4-Benzylamino-5-[1′-hydroxy-1′-phenylmethyl]-3-methoxy-2-pyrrolidinone (2f). $[\alpha]^{25}_D$ = +144.5 (c 1.000, CH_2Cl_2). ^1H NMR : δ 3.05 (bs, 2H, D_2O exchangeable); 350 - 3.60 (m, 3H, CH_2Ph & C5H); 3.70 (s, 3H); 4.03 (d, J = 3.9Hz, 1H, C1′H); 4.10 (dd, J = 5.11 & 7.65Hz, 1H, C4H); 5.00 (s, 1H, C3H); 5.38 (s, 1H, NH, D_2O exchangeable); 7.15 - 7.65 (m, 10H). IR (nujol): ν 3400 (bs), 3300 (bs), 1710 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3N_2$: C, 69.95; H, 6.74; N, 8.58. Found: C, 69.83; H, 6.58; N, 8.47.

General Procedure for the Synthesis of TMS Protected Aminols. To a solution of aminols **3a,b** (1 mmol) and triethylamine (6 mmol) in methylene chloride (30 mL), trimethylsilyl chloride (3 mmol) was added dropwise at -15 °C under argon. The resulting mixture was allowed to warm up to room temperature and stirred overnight. After the completion of the reaction (TLC), saturated NH_4Cl solution (30 mL) was added and the reaction mixture was successively washed with water (50 mL) and brine (40 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the crude product which was then purified by column chromatography (basic alumina, petroleum ether/EtOAc mixtures) to give pure *O*-TMS protected aminols in almost quantitative yields. The spectral and analytical data for these *O*-protected aminols were consistent with their structure.

General Procedure for the Synthesis of *O*-TBDMS Protected Aminols. The TBDMS protection of the aminols were carried out using a reported procedure.[13] The aminols were treated with TBDMSCl and imidazole in DMF. After usual work up and column chromatography (silica gel, petroleum ether/EtOAc, 80/20) the pure *O*-TBDMS protected aminols were obtained in 90 - 96 % yield. The spectral and analytical data for these compounds were consistent with their structure.

General Procedure for the Preparation of Imines 5a-e. To a solution of *O*-protected aminols (1 mmol) in dry methylene chloride (50 mL), anhyd $MgSO_4$ (5 g) and cinnamaldehyde (1.1 mmol) were added. The resulting mixture was stirred overnight at room temperature. After completion of the reaction (TLC), the reaction mixture was filtered and the residue was washed with methylene chloride. The combined filtrate was concentrated to give imines **5a-e** in almost quantitative yields. The imines thus obtained were used as such without further purification.

General Procedure for the Preparation of *bis*-β-Lactams 13 and 14. A solution of the acid chloride (**6-8**, 1.5 mmol) in anhyd methylene chloride (40 mL) was added to a solution of imine **5a-e** (1 mmol) and triethylamine (5 mmol) in methylene chloride (30 mL) at -78 °C under argon. The resulting mixture was allowed to warm up to room temperature and stirred for 14 h. The reaction mixture was then successively washed with water (40 mL), satd $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated to give diastereomeric mixture of either **9a-d** and **10a-d** or **11a-c** and **12a,b.** In the case of *O*-TMS protected compounds **9a-d** and **10a-d** small amounts of *O*-deprotected product was also isolated. Therefore, in all the cases the hydroxy compounds **13** and **14** were isolated after deprotection of the TMS or TBDMS groups.

In the case of TMS protected mixture **9** & **10**, the crude product was taken into methanol (20 mL) and treated with 1N HCl (3 mL) and stirred at room temperature for 30 min. After the completion of the reaction (TLC) the reaction mixture was neutralized with solid $NaHCO_3$. The solvent was removed and the residue was taken in to CH_2Cl_2. The organic layer was then washed with water (20 mL) and dried (Na_2SO_4). The removal of the solvent under reduced pressure provided the products **13a-d** and **14a-d** as a mixture of diastereomers in 78 - 96% yields. The ratio of the two diastereomers was determined by HPLC analysis. The diastereomers were separated by flash column chromatography (silica gel, 240 - 400 mesh, petroleum ether / EtOAc mixtures).

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-2-(3″-benzyloxy-4″-styryl-azetidin-2″-one-1″-yl)-1-phenylethan-1-ol (13a). Mp: 207-210 °C (acetone-petroleum ether). $[\alpha]^{25}_D$ = +113.4 (c 1, CH_2Cl_2). ^1H NMR: δ 3.34 (dd, *J* = 4.4 & 9.6 Hz, 1H, C4″H); 3.68 (d, *J* = 4.4 Hz, 1H, C3″H); 3.77 (s, 3H, OCH_3); 3.84 (dd, *J* = 2.4 & 9.9 Hz, 1H, C2H); 4.32 (s, 2H, OCH_2Ph); 4.56 (dd, *J* = 9.6 & 15.9 Hz, 1H, α CH of styryl group); 5.16 (dd, *J* = 2.4 & 12.5 Hz, 1H, C1H); 5.39 (dd, *J* = 5.3 & 9.9 Hz, 1H, C4′H); 5.58 (d, *J* = 5.3 Hz, 1H, C3′H); 5.97 (d, *J* = 12.5 Hz, 1H, OH); 6.24 (d, *J* = 15.9 Hz, 1H, β CH of

styryl group); 6.90 (d, J = 9 Hz, 2H, arm); 7.00 - 7.55 (m, 22H, arm). IR ($CHCl_3$): ν 3380, 1760, 1730 cm^{-1}. Anal. Calcd for $C_{42}H_{38}O_6N_2$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.87; H, 5.76; N, 4.28.

(1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-2-(3″-benzyloxy-4″-styryl-azetidin-2″-one-1″-yl)-1-phenylethan-1-ol (14a). Mp: 196-198 °C (petroleum ether-EtOAc). $[\alpha]^{25}_D$ = -25.9 (c 1, CH_2Cl_2). ^{1}H NMR: δ 2.90 (dd, J = 4.5 & 9.8 Hz, 1H, C4″H); 3.60 (s, 3H, OCH_3); 3.85 (dd, J = 2.7 & 10 Hz, 1H, C2H); 4.18 (d, J = 4.4 Hz, 1H, C3″H); 4.28 (d, J = 11.4 Hz, 1H, OCH_2Ph); 4.40 (d, J = 11.4 Hz, 1H, OCH_2Ph); 4.97 (d, J = 12.5 Hz, 1H, OH); 5.05 (dd, J = 9.8 & 15.9 Hz, 1H, α CH of styryl group); 5.42 (dd, J = 2.7 & 12.5 Hz, 1H, C1H); 5.50 - 5.60 (m, 2H, C3′H & C4′H); 6.20 (d, J = 15.9 Hz, 1H, β CH of styryl group); 6.85 (d, J = 9 Hz, 2H, arm); 7.05 - 7.50 (m, 22H, arm). ^{13}C NMR: δ 55.3 (C4″), 55.4 (OCH_3), 63.8 (C4′), 64.6 (C2), 72.5 (OCH_2Ph), 73.3 (C3″), 80.3 (C1), 81.8 (C3′), 114.6, 116.2, 120.2, 121.8, 123.1, 124.9, 127.2, 127.7, 127.9, 128.2, 128.4, 128.8, 129.9, 135.5, 136.7, 137.5, 140.4 (αC), 141.5 (βC), 157.2, 157.6, 163.7 (β-lactam CO), 170.6 (β-lactam CO). IR ($CHCl_3$): ν 3400, 1760, 1725 cm^{-1}.

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-2-(3″-phenoxy-4″-styryl-azetidin-2″-one-1″-yl)-1-phenylethan-1-ol (13b). Mp: 236-238 °C (acetone-petroleum ether). $[\alpha]^{25}_D$ = +88.4 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.60 (dd, J = 4.8 & 9.6 Hz, 1H); 3.80 (s, 3H); 3.92 (dd, J = 2.4 & 9.9 Hz, 1H); 4.21 (d, J = 4.8 Hz, 1H); 4.56 (dd, J = 9.6 & 15.9 Hz, 1H); 5.17 (dd, J = 2.4 & 12.5 Hz, 1H); 5.46 (dd, J = 5.3 & 9.9 Hz, 1H); 5.62 (d, J = 5.3 Hz, 1H); 5.87 (d, J = 12.5 Hz, 1H); 6.35 (d, J = 15.9 Hz, 1H); 6.68 (d, J = 9 Hz, 2H); 6.90 - 7.45 (m, 20H); 7.52 (d, J = 9 Hz, 2H). ^{13}C NMR: δ 55.7, 55.9, 63.1, 63.8, 72.9, 79.5, 80.1, 115.0, 115.5, 116.0, 120.4, 122.5, 123.2, 125.2, 127.2, 127.6, 128.4, 128.6, 129.6, 130.1, 135.5, 138.6, 141.2, 157.1, 157.5, 158.0, 164.1, 169.0. IR ($CHCl_3$): ν 3400, 1780, 1770 cm^{-1}. Anal. Calcd for $C_{41}H_{36}O_6N_2$: C, 75.44; H, 5.56; N, 4.29. Found: C, 75.69; H, 5.63; N, 4.43.

(1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-2-(3″-phenoxy-4″-styryl-azetidin-2″-one-1″-yl)-1-phenylethan-1-ol (14b). Oil. $[\alpha]^{25}_D$ = -19.6 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.04 (dd, J = 4.5 & 9.8 Hz, 1H); 3.75 (s, 3H); 3.91 (dd, J = 2.7 & 10 Hz, 1H); 4.72 (d, J = 4.5 Hz, 1H); 4.88 (d, J = 12 Hz, 1H); 4.97 (dd, J = 9.8 & 15.9 Hz, 1H); 5.45 (dd, J = 2.7 & 12 Hz, 1H); 5.50 - 5.60 (m, 2H); 6.22 (d, J = 15.9 Hz, 1H); 6.75 - 7.60 (m, 24H). ^{13}C NMR: δ 55.2, 55.4, 63.5, 64.1, 74.2, 79.9, 80.1, 114.5, 115.3, 116.0, 120.4, 121.0, 122.9, 124.9, 127.0, 128.0, 128.3, 128.5, 128.8, 129.4, 129.8, 130.0, 138.0, 135.4, 141.4, 156.8, 157.1, 157.4, 163.5, 168.9. IR ($CHCl_3$): ν 3380, 1770, 1760 cm^{-1}.

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-1-phenyl-2-(3″-phthalimido-4″-styrylazetidin-2″-one-1″-yl)-ethan-1-ol (13c). Mp: 153-158 °C (CH_2Cl_2 - petroleum ether). $[\alpha]^{25}_D$ = +0.5 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.77 (s, 3H); 4.27 (dd, J = 5.1 & 10 Hz, 1H); 4.42 (d, J = 8.1 Hz, 1H); 4.64 (dd, J = 5.5 & 8.1 Hz, 1H); 4.82 (t, J = 5.5 Hz, 1H); 5.12 (d, J = 5.1 Hz, 1H); 5.30 (d, J = 5.5 Hz, 1H); 5.50 (d, J = 5 Hz, 1H); 5.77 (dd, J = 10 & 15.9 Hz, 1H); 6.00 (d, J = 15.9 Hz, 1H); 6.85 - 7.55 (m, 19H); 7.65 - 7.90 (m,

4H). ^{13}C NMR: δ 55.6, 57.2, 57.7, 60.0, 64.4, 74.0, 80.0, 114.9, 116.1, 120.3, 121.9, 122.9, 123.9, 126.6, 126.9, 128.6, 128.7, 129.1, 129.8, 130.2, 131.5, 134.6, 135.5, 138.0, 140.2, 157.3, 157.5, 163.9, 166.7, 167.2. IR ($CHCl_3$): ν 3540, 1780, 1770, 1730 cm^{-1}. Anal. Calcd for $C_{43}H_{35}O_7N_3$: C, 73.17; H, 4.99; N, 5.95. Found: C, 73.36; H, 5.06; N, 5.87.

(1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-2-(1′-*p*-Anisyl-3′-phenoxyazetidin-2′-one-4′-yl)-1-phenyl-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)-ethan-1-ol (14c). Mp: 118-120 °C, $[\alpha]^{25}_D$ = +151.6 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.80 (dd, *J* = 5 & 10 Hz, 1H); 3.93 (s, 3H); 4.05 (dd, *J* = 2.3 & 10 Hz, 1H); 4.25 (d, *J* = 5 Hz, 1H); 4.90 (dd, *J* = 10 & 15.9 Hz, 1H); 5.25 (dd, *J* = 2.3 & 12 Hz, 1H); 5.43 (dd, *J* = 5.2 & 10 Hz, 1H); 5.60 - 5.75 (m, 2H); 6.30 (d, *J* = 15.9 Hz, 1H); 6.90 - 7.60 (m, 19H); 7.65 - 7.85 (m, 4H). ^{13}C NMR: δ 55.0, 55.5, 55.8, 63.5, 63.9, 72.6, 79.8, 115.0, 115.7, 116.0, 120.4, 120.8, 122.8, 123.4, 125.5, 126.7, 127.2, 128.0, 128.2, 128.3, 128.8, 129.6, 131.1, 134.1, 134.8, 138.2, 140.4, 157.0, 157.6, 163.6, 166.2, 167.0. IR ($CHCl_3$): ν 3380, 1770, 1760 cm^{-1}.

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-2-(1′-*p*-Anisyl-3′-benzyloxyazetidin-2′-one-4′-yl)-1-phenyl-2-(3″-phthalimido-4″-styrylazetidin-2″-one-1″-yl)-ethan-1-ol (13d). Oil. $[\alpha]^{25}_D$ = +151.1 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.75 (s, 3H); 4.05 (dd, *J* = 5 & 10 Hz, 1H); 4.32 (t, *J* = 8 Hz, 1H); 4.57 (d, *J* = 8 Hz, 1H); 4.83 - 4.95 (m, 2H); 5.00 - 5.10 (m, 3H); 5.20 - 5.35 (m, 1H); 5.65 (dd, *J* = 10 & 15.9 Hz, 1H); 5.97 (d, *J* = 15.9 Hz, 1H); 6.85 - 7.00 (m, 4H); 7.15 - 7.55 (m, 15H); 7.70 - 7.90 (m, 4H). ^{13}C NMR: δ 55.6, 57.3, 57.9, 60.8, 64.1, 72.7, 74.5, 81.5, 114.9, 120.2, 121.7, 123.8, 126.1, 126.9, 128.2, 128.5, 128.7, 128.8, 130.0, 131.6, 133.9, 134.6, 135.4, 136.6, 138.2, 148.8, 157.0, 165.5, 166.7, 167.2. IR ($CHCl_3$): ν 3340, 1770, 1720 cm^{-1}. Anal. Calcd for $C_{44}H_{37}O_7N_3$: C, 73.42; H, 5.18; N, 5.84. Found: C, 73.78; H, 5.32; N, 6.07.

(1*S*,2*S*,3′*R*,4′*S*,3″*R*,4″*S*)-2-(1′-*p*-Anisyl-3′-benzyloxyazetidin-2′-one-4′-yl)-1-phenyl-2-(3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl)-ethan-1-ol (14d). Oil. $[\alpha]^{25}_D$ = -41 (c 1, CH_2Cl_2). ^{1}H NMR: δ 3.70 - 3.90 (m, 2H); 3.95 (s, 3H); 4.27 (d, *J* = 5 Hz, 1H); 4.75 - 4.95 (m, 2H); 5.00 - 5.30 (m, 4H); 5.60 (d, *J* = 12 Hz, 1H); 6.20 (d, *J* = 15.9 Hz, 1H); 6.80 - 6.95 (m, 2H); 7.05 (d, *J* = 9 Hz, 2H); 7.15 - 7.60 (m, 15H); 7.60 - 7.85 (m, 4H). ^{13}C NMR: δ 55.2, 55.6, 55.8, 63.9, 72.7, 73.8, 80.6, 115.1, 120.5, 121.2, 123.5, 125.8, 126.8, 127.2, 128.2, 128.3, 128.5, 129.2, 131.3, 134.3, 135.1, 136.4, 138.1, 140.8, 157.5, 165.4, 167.2, 168.4. IR ($CHCl_3$): ν 3340, 1770, 1720 cm^{-1}.

The TBDMS protected diastereomeric mixture of **11** & **12** was dissolved in acetonitrile (6 mL) and treated with 50% HF (4 mL) and stirred for 24 h at room temperature. The reaction was monitored by TLC and after the completion of the reaction the reaction mixture was neutralized with solid $NaHCO_3$. The residue obtained after the removal of solvent was taken into CH_2Cl_2 and washed with water and dried (Na_2SO_4). The removal of the solvent provided the diastereomeric mixture of *O*-deprotected β-lactams (**13a,b** & **14a,b**), which were separated by flash column chromatography. The analytical and spectral data of these compounds matched well with β-lactams **9c,d** & **10c,d** prepared from imines **5a,b**.

In case of *O*-TBDMS protected β-lactam **11c** the deprotection of the TBDMS group could not be effected under various conditions tried.

(1*S*,2*S*,3'*R*,4'*S*,3"*S*,4"*R*)-2-(1'-*p*-Anisyl-3'-phthalimidoazetidin-2'-one-4'-yl)-1-phenyl-2-(3"-phthalimido-4"-styrylazetidin-2"-one-1"-yl)-1-(t-butyldimethylsilyloxy)-ethane (11c). Mp.: 157-159 °C (EtOAc-petroleum ether). $[\alpha]^{25}_D$ = -24 (c 1, CH_2Cl_2). ^{1}H NMR: δ -0.20 (s, 3H); 0.13 (s, 3H); 0.95 (s, 9H); 3.80 - 4.05 (m, 1H); 3.85 (s, 3H); 4.45 (dd, *J* = 2.4 & 10 Hz, 1H); 4.60 (d, *J* = 5.3 Hz, 1H); 4.80 (d, *J* = 2.4 Hz, 1H); 5.15 (d, *J* = 5 & 10 Hz, 1H); 5.70 (d, *J* = 5 Hz, 1H); 5.95 (dd, *J* = 9.9 & 15.9 Hz, 1H); 6.10 (d, *J* = 15.9 Hz, 1H); 7.05 - 7.45 (m, 12H); 7.50 (d, *J* = 9 Hz, 2H); 7.60 - 7.80 (m, 4H); 7.85 - 8.10 (m, 4H). ^{13}C NMR: δ -4.8, -4.1, 18.1, 26.0, 55.7, 56.4, 56.9, 58.0, 60.4, 63.7, 74.4, 115.1, 123.3, 123.7, 124.1, 125.4, 126.2, 126.6, 127.9, 128.4, 128.6, 131.4, 134.2, 134.5, 135.1, 135.9, 140.7, 158.5, 162.3, 165.8, 166.6. IR ($CHCl_3$): ν 1790, 1780, 1730 cm^{-1}. Anal. Calcd for $C_{51}H_{48}O_8N_4Si$: C, 70.17; H, 5.54; N, 6.42. Found: C, 70.32; H, 5.61; N, 6.38.

X-ray Crystallographic Analysis of 9c. Intensity data were collected on PC controlled Enraf-Nonious CAD4 diffractometer with Mo-Kα (λ = 0.7107 A) radiation at 293 K. Crystals belong to monoclinic, Space group $P2_1$ with a = 13.122 (2) A, b = 24.285 (4) A, c = 14.361 (3) A, α = γ = 90°, β = 91.8 (2)°, V = 4574.1 (14)A, Z = 2 , dcalc = 1.192 mgm^{-3}, μ = 0.104 mm^{-1}. Data collection of 6925 unique reflections (θ range 0 to 23.5°), 3881 observed reflections [I ≥ 3.5 σ (I)]. The structure was solved by using SHELEX-86.[13a] Least square refinement of scale factor, positional and anisotropic thermal parameters using NRCVAX package[13b] for non hydrogen atoms (1081 parameters) converge to R = 0.045 and R_W = 0.049. Hydrogen atoms are geometrically fixed during refinement.

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