Pergamon

Tetrahedron: *Asymmetry* 14 (2003) 453–459

TETRAHEDRON: *ASYMMETRY*

Ephedrine derived reusable chiral auxiliary for the synthesis of optically pure 3-hydroxy-4-aryl-β-lactams

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Received 12 November 2002; accepted 8 January 2003

Abstract—The diastereoselective synthesis of various β-lactams has been achieved using a chiral acid auxiliary derived from (−)-ephedrine. An efficient acid-catalyzed cleavage of the chiral auxiliary from these β-lactams to afford 3-hydroxy-4-aryl-*cis*-β-lactams, which are precursors for analogues of the taxol side chain, is described.

1. Introduction

The β-lactam skeleton has gained significant interest among synthetic as well as medicinal chemists over the years, mainly because it represents the core structure of synthetic and natural β-lactam antibiotics.[1] The importance of the β-lactam unit as a synthon has been recognized in the synthesis of a variety of biologically important β-lactam and non-β-lactam derivatives.[2] It has been shown that a suitably substituted 3-hydroxy-β-lactam can serve as a synthetic equivalent for the phenylisoserine[3] side chain of taxol, an anticancer agent obtained from the bark of *Taxus brevifolia* or can be directly coupled with baccatin III[4] (a precursor of taxol which is available in sufficient quantities from the leaves of the plant) to give taxol. 3-Hydroxy-β-lactams are also a source of enantiomerically pure α-hydroxy-β-amino acids, which are present in many biologically important compounds.[5–7] The preparation of suitably substituted (3*R*,4*S*)-3-hydroxy-β-lactams by diastereoselective cycloaddition reaction,[3,4,8,9] borohydride reduction of 3-ketoazetidinones[10] and the resolution of (±)-3-hydroxy-β-lactams[11] have been reported.

In continuation of our efforts into the synthesis of homochiral β-lactams and their use as synthons,[12] we have recently reported the use of a chiral auxiliary derived from the readily available and naturally abundant (+)-3-carene[12f,j] in an asymmetric synthesis of the taxol side chain. However, the chiral auxiliary is either unrecoverable or lost during the oxidative removal of the auxiliary, thereby making this methodology less attractive. We report herein a solution to this problem by using a chiral auxiliary derived from the readily available (−)-ephedrine, which can be removed under mild conditions and recovered in quantitative yield without racemization and is therefore readily recycled.

2. Results and discussion

The hemiketal **3** was easily prepared from (−)-ephedrine **1** and α-ketopropionoyl chloride.[13] The absolute stereochemistry of this hemiketal has been established previously.[13] Alternatively the same hemiketal can also be prepared by reacting (−)-ephedrine with oxalyl chloride followed by addition of Grignard reagent to the corresponding lactone **2**.[14] The resulting hemiketal **3** was then alkylated with ethyl bromoacetate followed by hydrolysis of the corresponding ester to afford the chiral acid **4**, which was characterized by its spectroscopic data (IR, NMR) (Scheme 1). Cycloaddition reaction of acid **4** with various imines **5** in the presence of triethylamine and triphosgene as an acid activator furnished a diastereomeric mixture of *cis*-β-lactams **6** and **7**) in good yields (Scheme 2, Table 1). The diastereomers were easily separated by flash column chromatography. The stereochemistry of the diastereomer **7b** was confirmed by single crystal X-ray diffraction[15] and the stereochemistry was assigned as 3*S*,4*R* for the β-lactam ring (Fig. 1).

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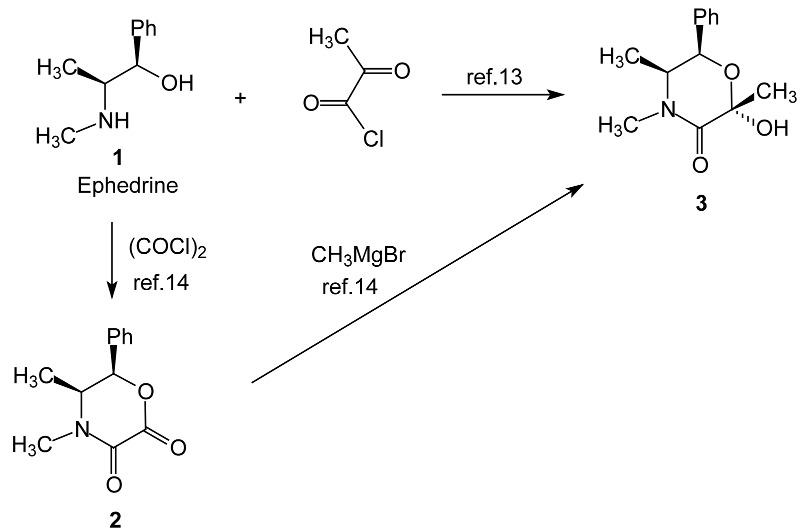
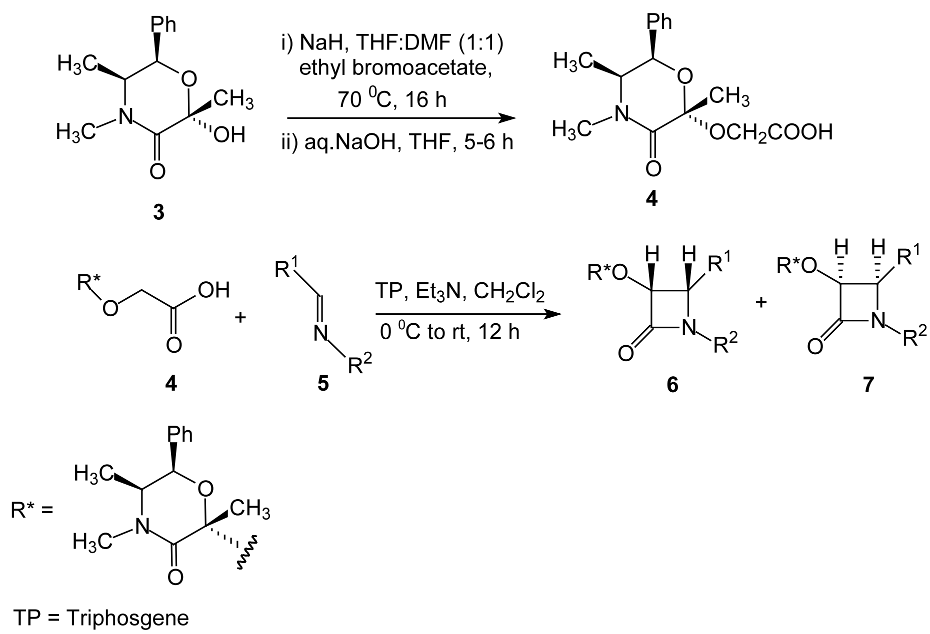
PII: S0957-4166(03)00039-9



Scheme 1.



Scheme 2.

Table 1. Synthesis of *cis*-β-lactams **6a**–**d** and **7a**–**d** from chiral acid **4** and imines **5a**–**d**

Entry no.	Product	R^1	R^2	Yield[a] (%)	Diastereoselectivity[b]
1	**6a** and **7a**	Ph	PMP	70	50:50
2	**6b** and **7b**	PMP	Ph	60	60:40
3	**6c** and **7c**	PMP	PMP	65	65:35
4	**6d** and **7d**	Ph	Ph	65	56:44

[a] Isolated yields of diastereomeric mixture.
[b] Ratio determined from ^{1}H NMR spectral analysis of crude reaction mixture

On heating under reflux with PTSA in aqueous THF for about 10–12 h the pure diastereomers **6** and **7** gave the corresponding enantiomerically pure 3-hydroxy-*cis*-β-lactams **8a**, **9a**–**d** in near-quantitative yields (Scheme 3, Table 2) by column chromatography. The formation of 3-hydroxy-β-lactams **8a** and **9a**–**d** was confirmed from their spectroscopic data (IR, ^{1}H NMR). The absolute configuration of the β-lactams **8** and **9** was assigned as 3*R*,4*S* and 3*S*,4*R*, respectively, by comparing their physical data as well as their specific rotation

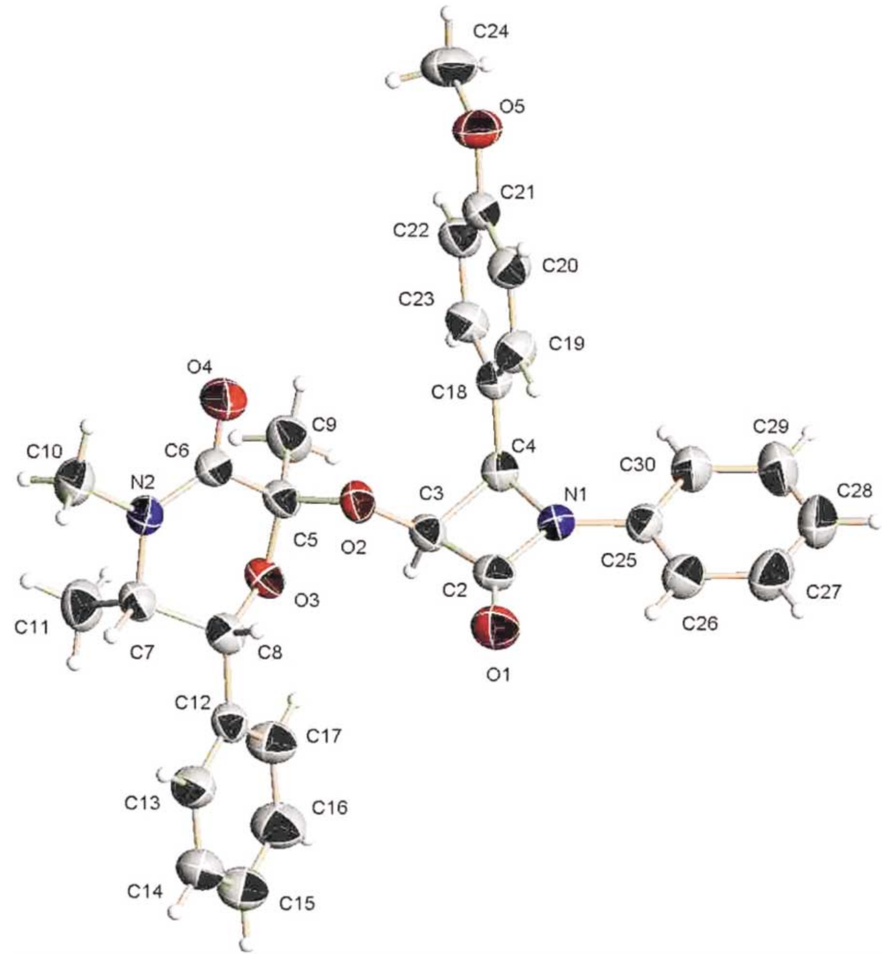
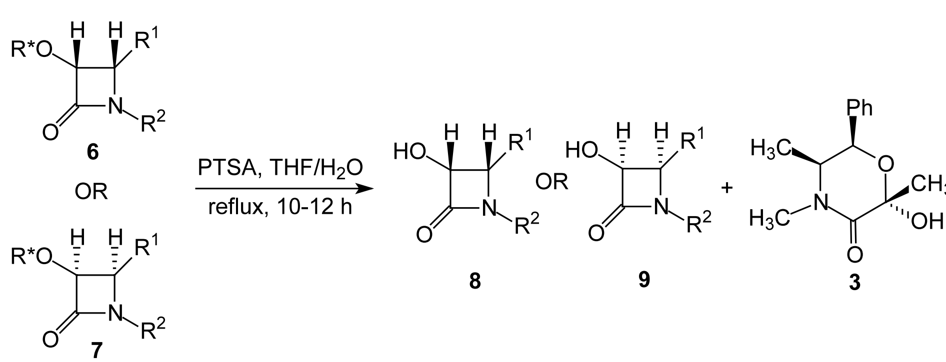


Figure 1. ORTEP drawing of **7b**.



Scheme 3.

Table 2. Synthesis of 3-hydroxy-*cis*-β-lactams **8a** and **9a–d** from enantiomerically pure diastereomers **6a** and **7a–d**

Entry no.	R^1	R^2	Product	Yield (%)[a]	Mp (°C)	$[\alpha]_D$ ($CHCl_3$)	Configuration
1	Ph	PMP	**8a**	90	196–197	+180.0 (*c* 0.40) lit.[12j] +176.0 (*c* 1.00)	3*R*,4*S*
2	Ph	PMP	**9a**	90	201–202	−178.0 (*c* 0.90) lit.[12j] −179 (*c* 1.00)	3*S*,4*R*
3	PMP	Ph	**9b**	85	212–213	−173.7 (*c* 1.00)	3*S*,4*R*
4	PMP	PMP	**9c**	88	132–133	−179.1 (*c* 2.20) lit.[12j] −181.9 (*c* 0.93)	3*S*,4*R*
5	Ph	Ph	**9d**	84	216–217	−188.4 (*c* 0.90) lit.[12j] −188.7 (*c* 0.39)	3*S*,4*R*

[a] Isolated yield of pure enantiomers.

values with those of compounds **8a**, **9a**, **9c** and **9d** reported in the literature.[12j]

The hemiketal **3** formed during the hydrolysis of **6** and **7** was also isolated in quantitative yield by column chromatography and characterized by IR and ^{1}H NMR spectroscopy. There was no loss in enantiomeric purity of the recovered hemiketal **3** as it showed exactly the same specific rotation value {$[\alpha]_D^{25}$ −107.6 (*c* 1.4, $CHCl_3$)} as that of the starting hemiketal.

3. Conclusion

It must be emphasized that the acid-catalyzed hydrolysis regenerates hemiketal as the only other product, which was recycled. Thus, we have demonstrated an efficient use of this (−)-ephedrine derived chiral auxiliary, which significantly improves the practical scope of large-scale preparations of enantiopure 3-hydroxy-*cis*-β-lactams, one of which, **8a**, is a key intermediate in the synthesis of the taxol side-chain.[3,8]

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution on a Bruker AC 200 or MSL 300 spectrometers and chemical shifts are reported in ppm downfield from tetramethylsilane for ^{1}H NMR. Infrared spectra were recorded on Perkin–Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 Elemental analyzer. Optical rotations were recorded on a JASCO-181 digital Polarimeter under standard conditions.

4.2. Preparation of ethyl (2*S*,5*S*,6*R*)-[(2,4,6-trimethyl-3-*oxo*-6-phenylmorpholin-2yl)oxy]acetate

To a suspension of sodium hydride (108 mg, 4.5 mmol) in DMF (2 mL) and THF (2 mL) at 0°C was added methyl hemiketal solution (705 mg, 3 mmol) dropwise in DMF (2 mL) and THF (2 mL) and the resulting solution was stirred at 0°C for 10 min. Ethyl bromoacetate (0.33 mL, 3 mmol) was then added dropwise and the resulting solution was heated at 70°C for 16 h. Ice was added to the reaction mixture. Ethyl acetate (15 mL) and water (15 mL) were added and organic layer was separated. Organic layer was washed with water (3×15 mL), brine (3×15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue upon purification by column chromatography PE/EA (1:1) furnished the ester as a white solid (750 mg, 78%); mp 87–89°C; $[\alpha]_D^{25}=-80.7$ (*c* 1.1, $CHCl_3$); IR 1659, 1753 cm^{-1}; ^{1}H NMR δ 0.96 (d, 3H, $J=6.3$ Hz), 1.11 (t, 3H, $J=7.3$ Hz), 1.67 (s, 3H), 3.04 (s, 3H), 3.43–3.53 (dq, 1H, $J=2.9$, 6.3 Hz), 3.90–4.04 (q, 2H, $J=7.3$ Hz), 4.18 (s, 2H), 5.62 (d, 1H, $J=2.9$ Hz), 7.20–7.47 (m, 5H); ^{13}C NMR δ 12.2, 13.9, 21.4, 33.6, 59.0, 59.8, 60.7, 71.2, 99.3, 125.5, 127.5, 128.2, 137.0, 165.8, 169.8; MS: *m*/*z* 321 (M^+). Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.80; H, 7.50; N, 4.69%.

4.3. Preparation of (2*S*,5*S*,6*R*)-[(2,4,6-trimethyl-3-*oxo*-6-phenylmorpholin-2-yl)oxy]acetic acid, 4

To the solution of ester (963 mg, 3 mmol) in THF (9 mL) was added aqueous NaOH (1 M, 9 mL) and stirred at ambient temperature for 5–6 h. THF was removed under reduced pressure. Aqueous layer was acidified with Conc. HCl dropwise and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine solution (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated to give **4** as a white solid (800 mg, 91%); mp 98–100°C; $[\alpha]_D^{25}=-64.9$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1651, 1738, 3418 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 3H, $J=6.4$ Hz), 1.68 (s, 3H), 3.05 (s, 3H), 3.44–3.60 (dq, 1H, $J=2.9$, 6.4 Hz), 4.12 (d, 1H, $J=16.6$ Hz), 4.30 (d, 1H, $J=16.6$ Hz), 5.46 (d, 1H, $J=2.9$ Hz), 7.10–7.50 (m, 5H), 8.75 (bs, 1H); ^{13}C NMR ($CDCl_3$): 11.7, 20.9, 33.4, 58.6, 58.8, 70.7, 98.7, 125.0, 127.2, 127.9, 136.3, 166.1, 172.1. Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.70; H, 6.72; N, 4.99%.

4.4. Typical procedure for synthesis of 6a and 7a

To a stirred solution of **4** (1.172 g, 4 mmol) in dichloromethane (15 mL) was added triethylamine (3.34 mL, 24 mmol) and **5a** (0.760 g, 3.6 mmol) at 0°C. To the resulting solution was added triphosgene (0.831 g, 2.8 mmol) solution in dichloromethane (10 mL) dropwise over a period of 15 min. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (10 mL) and washed successively with water (2×15 mL), sat. $NaHCO_3$ (2×15 mL), brine (2×15 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue on purification by flash column chromatography (PE/EA, 3:2) gave more polar compound **6a** (610 mg, 35%) and less polar compound **7a** (610 mg, 35%).

4.4.1. (3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1-(4-Methoxyphenyl)-4-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 6a. Isolated as a white solid; yield 35%; mp 113–115°C; $[\alpha]_D^{25}=-51.0$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1649, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 3H, $J=6.8$ Hz), 1.70 (s, 3H), 2.89 (s, 3H), 3.15–3.30 (dq, 1H, $J=2.9$, 6.8 Hz), 3.71 (s, 3H), 4.63 (d, 1H, $J=2.9$ Hz), 5.00 (d, 1H, $J=5.4$ Hz), 5.36 (d, 1H, $J=5.4$ Hz), 6.73 (d, 2H, $J=8.8$ Hz), 7.10–7.50 (m, 12H); ^{13}C NMR ($CDCl_3$): 12.2, 23.4, 33.5, 55.4, 58.9, 62.3, 71.0, 76.0, 99.9, 114.3, 118.7, 125.6, 127.8, 128.4, 130.9, 133.8, 137.1, 156.3, 164.3, 165.2; MS: *m*/*z* 486 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.80; H, 6.00; N, 5.98%.

4.4.2. (3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1-(4-Methoxyphenyl)-4-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 7a. Isolated as a white solid; yield 35%; mp 108–110°C; $[\alpha]_D^{25}=-189.4$ (*c* 1.4, $CHCl_3$); IR ($CHCl_3$): 1649, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.79

(d, 3H, J=6.4 Hz), 1.50 (s, 3H), 2.87 (s, 3H), 2.89–3.05 (dq, 1H, J=2.9, 6.4 Hz), 3.71 (s, 3H), 4.57 (d, 1H, J=2.9 Hz), 5.16 (d, 1H, J=4.9 Hz), 5.57 (d, 1H, J=4.9 Hz), 6.75 (d, 2H, J=8.3 Hz), 7.09–7.50 (m, 12H); ^{13}C NMR ($CDCl_3$): 12.0, 22.2, 33.1, 55.2, 58.8, 63.0, 70.6, 77.7, 98.5, 114.1, 118.6, 125.4, 127.4, 128.0, 128.6, 130.6, 134.3, 136.8, 157.0, 163.7, 165.3; MS: m/z 486 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.83; H, 6.45; N, 5.99%.

Other β-lactams **6b–d** and **7b–d** were prepared using the similar procedure and both the diastereomers were separated by flash column chromatography.

4.4.3. (3*R*,4*S*,2′*S*,5′*S*,6′*R*)-4-(4-Methoxyphenyl)-1-phenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 6b. Isolated as a gum; yield 36%; $[\alpha]_D^{25}$=−64.4 (c 0.9, $CHCl_3$); IR ($CHCl_3$): 1649, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (d, 3H, J=6.4 Hz), 1.73 (s, 3H), 2.91 (s, 3H), 3.16–3.33 (dq, 1H, J=2.9, 6.4 Hz), 3.80 (s, 3H), 4.63 (d, 1H, J=2.9 Hz), 4.99 (d, 1H, J=5.4 Hz), 5.34 (d, 1H, J=5.4 Hz), 6.79 (d, 2H, J=8.8 Hz), 6.90–7.50 (m, 12H); ^{13}C NMR ($CDCl_3$): 12.1, 23.4, 33.5, 55.2, 58.9, 61.9, 71.0, 75.8, 100.0, 113.9, 117.5, 124.0, 125.5, 125.6, 127.7, 128.4, 128.9, 129.7, 137.1, 137.4, 159.8, 165.1, 165.3; MS m/z 486 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.85; H, 6.4; N, 5.96%.

4.4.4. (3*S*,4*R*,2′*S*,5′*S*,6′*R*)-4-(4-Methoxyphenyl)-1-phenyl-3-[(2′,4′,5′-trimethyl-3′-oxo-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 7b. Isolated as a white solid; yield 24%; mp 204–205°C; $[\alpha]_D^{25}$=−181.5 (c 0.6, $CHCl_3$); IR ($CHCl_3$): 1649, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, 3H, J=6.8 Hz), 1.50 (s, 3H), 2.91 (s, 3H), 2.96–3.09 (dq, 1H, J=2.9, 6.8 Hz), 3.84 (s, 3H), 4.57 (d, 1H, J=2.9 Hz), 5.17 (d, 1H, J=4.9 Hz), 5.57 (d, 1H, J=4.9 Hz), 6.92 (d, 2H, J=8.3 Hz), 7.00–7.47 (m, 12H); ^{13}C NMR ($CDCl_3$): 12.2, 22.5, 33.4, 55.2, 59.0, 62.6, 70.8, 77.6, 98.7, 113.6, 117.5, 124.1, 125.4, 126.0, 127.5, 128.2, 129.0, 129.9, 136.9, 137.1, 159.7, 164.6, 165.5; MS: m/z 486 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found C, 71.80; H, 6.48; N, 5.98%.

4.4.5. (3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1,4-Di-(4-methoxyphenyl)-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 6c. Isolated as a gum; yield 42%; $[\alpha]_D^{25}$=−78.5 (c 1.3, $CHCl_3$); IR ($CHCl_3$): 1649, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 3H, J=6.4 Hz), 1.72 (s, 3H), 2.91 (s, 3H), 3.16–3.32 (dq, 1H, J=2.9, 6.4 Hz), 3.70 (s, 3H), 3.80 (s, 3H), 4.63 (d, 1H, J=2.9 Hz), 4.95 (d, 1H, J=5.3 Hz), 5.33 (d, 1H, J=5.3 Hz), 6.72 (d, 2H, J=8.8 Hz), 6.80 (d, 2H, J=8.8 Hz), 7.02–7.60 (m, 9H); ^{13}C NMR ($CDCl_3$): 12.2, 23.4, 33.5, 55.3, 55.4, 59.0, 62.0, 71.0, 75.9, 100.0, 113.9, 114.4, 118.8, 125.6, 125.8, 127.7, 128.4, 129.8, 131.0, 137.2, 156.3, 159.9, 164.5, 165.3; MS: m/z 516 (M^+). Anal. calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42. Found: C, 69.98; H, 6.49; N, 5.71%.

4.4.6. (3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1,4-Di-(4-methoxyphenyl)-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 7c. Isolated as a white solid; yield 23%; mp 207–208°C; $[\alpha]_D^{25}$=−170.9 (c 2.0, $CHCl_3$); IR ($CHCl_3$): 1649, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.80 (d, 3H, J=6.4 Hz), 1.49 (s, 3H), 2.90 (s, 3H), 2.96–3.11 (dq, 1H, J=2.9, 6.4 Hz), 3.72 (s, 3H), 3.84 (s, 3H), 4.57 (d, 1H, J=2.9 Hz), 5.12 (d, 1H, J=4.9 Hz), 5.55 (d, 1H, J=4.9 Hz), 6.75 (d, 2H, J=8.8 Hz), 6.92 (d, 2H, J=8.8 Hz), 7.06–7.45 (m, 9H); ^{13}C NMR ($CDCl_3$): 12.1, 22.5, 33.4, 55.2, 55.3, 59.0, 62.6, 70.7, 77.6, 98.6, 113.6, 114.2, 118.7, 125.4, 126.1, 127.5, 128.2, 129.9, 130.7, 137.0, 156.1, 159.6, 163.9, 165.5; MS: m/z 516 (M^+). Anal. calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42. Found: C, 69.96; H, 6.48; N, 5.70%.

4.4.7. (3*R*,4*S*,2′*S*,5′*S*,6′*R*)-1,4-Diphenyl-3-[(2′,4′,5′-trimethyl-3′-*oxo*-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 6d. Isolated as a gum; yield 36%; $[\alpha]_D^{25}$=−61.0 (c 1.0, $CHCl_3$); IR ($CHCl_3$): 1649, 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 3H, J=6.3 Hz), 1.72 (s, 3H), 2.88 (s, 3H), 3.15–3.30 (dq, 1H, J=2.4, 6.3 Hz), 4.60 (d, 1H, J=2.4 Hz), 5.03 (d, 1H, J=5.4 Hz), 5.37 (d, 1H, J=5.4 Hz), 6.94–7.50 (m, 15H); ^{13}C NMR ($CDCl_3$): 12.4, 23.6, 33.7, 59.2, 62.5, 71.4, 76.2, 100.2, 117.8, 124.4, 125.9, 127.8, 128.5, 129.1, 129.3, 134.0, 136.9, 137.0, 165.1, 165.5; MS: m/z 456 (M^+). Anal. calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.13. Found: C, 73.88; H, 6.44; N, 6.36%.

4.4.8. (3*S*,4*R*,2′*S*,5′*S*,6′*R*)-1,4-Diphenyl-3-[(2′,4′,5′-trimethyl-3′-oxo-6′-phenylmorpholin-2′-yl)oxy]azetidin-2-one, 7d. Isolated as a white solid; yield 29%; mp 99–100°C; $[\alpha]_D^{25}$=−194.6 (c 1.5, $CHCl_3$); IR ($CHCl_3$): 1649, 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.79 (d, 3H, J=6.8 Hz), 1.51 (s, 3H), 2.88 (s, 3H), 2.90–3.03 (dq, 1H, J=3.4, 6.8 Hz), 4.55 (d, 1H, J=3.4 Hz), 5.21 (d, 1H, J=4.9 Hz), 5.60 (d, 1H, J=4.9 Hz), 6.95–7.55 (m, 15H); ^{13}C NMR ($CDCl_3$): 12.2, 22.4, 33.3, 59.1, 63.1, 70.9, 77.9, 98.8, 117.5, 124.2, 125.6, 127.6, 128.2, 128.8, 129.0, 134.5, 137.1, 137.3, 164.5, 165.6; MS: m/z 456 (M^+). Anal. calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.13. Found: C, 73.90; H, 6.42; N, 6.35%.

4.5. Preparation of 3-hydroxy-*cis*-β-lactams 8 and 9

4.5.1. Typical procedure for hydrolysis of β-lactam, 7a to (3*S*,4*R*)-1-(4-methoxyphenyl)-4-phenyl-3-hydroxyazetidin-2-one, 9a. To a stirred solution of **7a** (0.243 g, 0.5 mmol) in a mixture of THF (5 mL) and water (1 mL) was added PTSA (0.951 g, 5 mmol) and refluxed for 10 h. THF was then removed under reduced pressure and reaction mixture was then diluted with water (5 mL). Solid $NaHCO_3$ was added to the reaction mixture until basic pH and extracted with dichloromethane (3×10 mL). Combined organic layers were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue on purification by column chromatography PE/EA (1:1) gave **9a** (0.121 g, 90%) as a white solid and recovered chiral auxiliary **3** (0.103 g, 88%).

4.5.2. (3*S*,4*R*)-1-(4-Methoxyphenyl)-4-phenyl-3-hydroxy-azetidin-2-one, 9a. Isolated as a white solid; yield 90%; mp 201–202°C; $[\alpha]_D^{25}=-178.0$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1713, 3315 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.87 (d, 1H, $J=6.9$ Hz), 3.76 (s, 3H), 5.20 (dd, 1H, $J=5.4$, 6.9 Hz), 5.27 (d, 1H, $J=5.4$ Hz), 6.80 (d, 2H, $J=8.8$ Hz), 7.23–7.55 (m, 7H); ^{13}C NMR ($CDCl_3$): 55.5, 62.3, 77.26, 114.5, 118.9, 127.5, 129.0, 129.1, 130.6, 133.2, 156.5, 165.4; MS: *m*/*z* 269 (M^+). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.60; H, 5.81; N, 5.35%.

Specific rotation of recovered chiral auxiliary 3: $[\alpha]_D^{25}=-107.6$ (*c* 1.4, $CHCl_3$); [(lit.[14] $[\alpha]_D^{25}=-107.4$ (*c* 1.1, $CHCl_3$)].

Other hydroxy β-lactams **8a** and **9b–d** were prepared from **6a** and **7b–d**, respectively, using a similar procedure.

4.5.3. (3*R*,4*S*)-1-(4-Methoxyphenyl)-4-phenyl-3-hydroxy-azetidin-2-one, 8a. Isolated as a white solid; yield 90%; mp 196–197°C; $[\alpha]_D^{25}=+180.0$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 1713, 3315 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.87 (d, 1H, $J=6.9$ Hz), 3.76 (s, 3H), 5.20 (dd, 1H, $J=5.4$, 6.9 Hz), 5.27 (d, 1H, $J=5.4$ Hz), 6.80 (d, 2H, $J=8.8$ Hz), 7.23–7.55 (m, 7H); MS: *m*/*z* 269 (M^+). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.60; H, 5.90; N, 5.45%.

4.5.4. (3*S*,4*R*)-4-(4-Methoxyphenyl)-1-phenyl-3-hydroxy-azetidin-2-one, 9b. Isolated as a white solid; yield 85%; mp 212–213°C; $[\alpha]_D^{25}=-173.7$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1713, 3315 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.65 (bs, 1H), 3.82 (s, 3H), 5.18 (d, 1H, $J=5.4$ Hz), 5.29 (d, 1H, $J=5.4$ Hz), 6.95 (d, 2H, $J=8.3$ Hz), 7.01–7.45 (m, 7H). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.63; H, 5.89; N, 5.48%.

4.5.5. (3*S*,4*R*)-1,4-Di-(4-methoxyphenyl)-3-hydroxyaze-tidin-2-one, 9c. Isolated as a white solid; yield 88%; mp 132–133°C; $[\alpha]_D^{25}=-179.1$ (*c* 2.2, $CHCl_3$); IR ($CHCl_3$): 1728, 3310 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.04 (bs, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 5.15 (d, 1H, $J=5.3$ Hz), 5.21 (d, 1H, $J=5.3$ Hz), 6.79 (d, 2H, $J=8.8$ Hz), 6.92 (d, 2H, $J=8.7$ Hz), 7.10–7.40 (m, 4H). Anal. calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.50; H, 5.82; N, 4.87%.

4.5.6. (3*S*,4*R*)-1,4-Diphenyl-3-hydroxyazetidin-2-one, 9d. Isolated as a white solid; yield 84%; mp 216–217°C; $[\alpha]_D^{25}=-188.4$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1713, 3325 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.65 (bs, 1H), 5.21 (d, 1H, $J=5.4$ Hz), 5.33 (d, 1H, $J=5.4$ Hz), 6.90–7.55 (m, 10H). Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.50; H, 5.69; N, 5.97%.

Acknowledgements

One of the authors (B.A.S.) thanks CSIR for the financial support.

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15. X-Ray crystal data for **7b**: $C_{29}H_{30}N_2O_5$: colorless needles (0.57×0.11×0.03 mm grown from methanol). $M=486.55$, orthorhombic, space group $P2_12_12_1$, $a=5.765(2)$, $b=15.103(5)$, $c=29.301(9)$ Å, $V=2551.2(14)$ Å^3, $Z=4$, $D_{calcd}=1.267$ mg m^{-3}, $\mu=0.087$ mm^{-1}, $F(000)=1032$, $T=293$ K. Data were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation ($\lambda=0.7107$ Å) to a maximum θ range of 23.27°. The structure was solved by direct methods using SHELXTL. Least squares refinement of scale, positional and anisotropic thermal parameters for non hydrogen atom converged to $R=0.0373$. $R_w=0.0748$ for $[I>2\sigma(I)]$, 3673 unique observed reflections out of 18110 measured. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97[16] was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Largest diff. peak and hole 0.115 and −0.110 e Å^{-3}. ORTEP diagram of the molecule along with the crystallographic numbering of atoms. Ellipsoids are drawn with 50% probability. Crystallographic data (excluding structure factors) for the structure **7b** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200549.
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