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An efficient synthesis of enantiomerically pure 3-hydroxy-β-lactams via zinc induced removal of a chiral auxiliary

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Abstract

The diastereoselective synthesis of various β-lactams **6a–d** and **7a–d** has been achieved using a chiral acid derived from (+)-3-carene. An efficient zinc induced cleavage of the *o*-halo ether linkage of these β-lactams to give enantiomerically pure 3-hydroxy-*cis*-β-lactams **8a**,**b** and **9a–d** is described.

1. 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] It has been shown that suitably substituted 3-hydroxy-β-lactams can serve as a synthetic equivalent for the phenylisoserine[3] side chain of taxol or can be directly coupled with baccatin III[4] to give taxol. The syntheses of suitably substituted (3*R*,4*S*) 3-hydroxy-β-lactams by diastereoselective cycloaddition reactions,[3–6] borohydride reductions[7] of 3-ketoazetidinones and resolutions[8] of (±)-3-hydroxy-β-lactams have been reported.

In our continued efforts towards the asymmetric synthesis of β-lactams and their use as synthons,[9] we have recently reported the use of a chiral auxiliary derived from readily available and naturally abundant (+)-3-carene[9f] for the taxol side chain. However, oxidative cleavage of the chiral auxiliary using MCPBA limited the use of this methodology in large-scale preparations. We herein report a solution to this problem by structural modification of the chiral auxiliary, which permits its removal under mild conditions.

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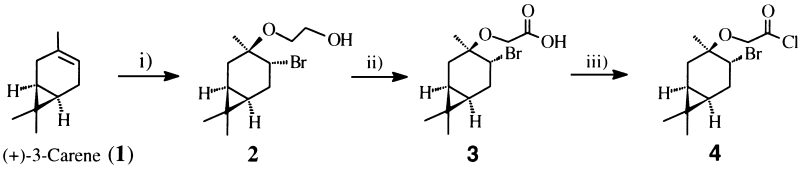
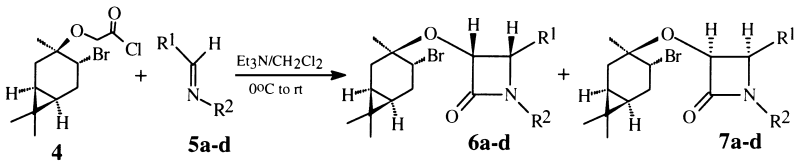
2. Results and discussion

The acid **3** was obtained from (+)-3-carene **1** by NBS reaction[10] in the presence of ethylene glycol followed by Jones oxidation of bromo alcohol **2**. The acid **3** was converted to acid chloride **4** in almost quantitative yield by using thionyl chloride (Scheme 1). The acid chloride **4**, on cycloaddition reaction with various imines **5** in the presence of triethylamine, furnished a diastereomeric mixture of *cis*-β-lactams **6a–d** and **7a–d** in good yields (Scheme 2, Table 1). In most of the cases the diastereomers were separated either by crystallization or column chromatography.



Scheme 1. (i) NBS/ethylene glycol, 0°C, 4 h; (ii) Jones oxidation; (iii) $SOCl_2$/benzene, reflux, 3 h



5,6,7 a R^1 = Ph, R^2 = PMP
5,6,7 b R^1 = R^2 = Ph
5,6,7 c R^1 = R^2 = PMP
5,6,7 d R^1 = Styryl, R^2 = PMP

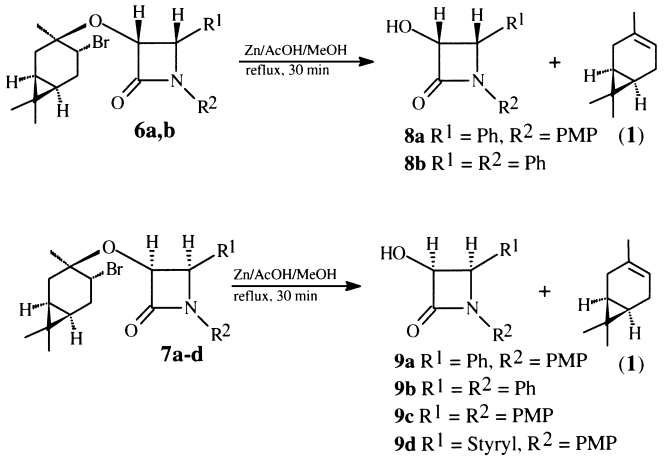
Scheme 2.

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

Entry	Product	R^1	R^2	Yield[a] (%)	Diastereoselectivity[b]
1.	**6a & 7a**	Ph	PMP	70	60:40
2.	**6b & 7b**	Ph	Ph	65	58:42
3.	**6c & 7c**	PMP	PMP	70	64:36
4.	**6d & 7d**	Styryl	PMP	60	60:40

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

The cleavage of the chiral auxiliary was effected by reacting pure diastereomers **6a**,**b** and **7a–d** with zinc/acetic acid (Boord reaction[11]) under reflux for 30 min to give corresponding enantiomerically pure 3-hydroxy-*cis*-β-lactams **8a**,**b** and **9a–d** in nearly quantitative yields (Scheme 3, Table 2). The (+)-3-carene formed in the reaction by cleavage of the chiral auxiliary was also isolated and characterized. The formation of 3-hydroxy-β-lactams **8a**,**b** and **9a–d** was confirmed from their spectral data (IR, ^{1}H NMR). The absolute configuration of the β-lactams **8** and **9** was



Scheme 3.

Table 2
Synthesis of 3-hydroxy-β-lactams **8a**,**b** and **9a**–**d** from optically pure diastereomers **6a**,**b** and **7a**–**d**

Entry No.	Prod.	R^1	R^2	Yield (%)[a]	m.p. (°C)	$[\alpha]_D$ (conc. in g/100 ml)	Config.
1.	**8a**	Ph	PMP	95	197-198	+177.4 (c 0.33, $CHCl_3$) lit.[9f] +176 (c 1, $CHCl_3$)	3*R*, 4*S*
2.	**9a**	Ph	PMP	95	200-201	−177.4 (c 1.0, $CHCl_3$) lit.[8b] −179 (c 1, $CHCl_3$)	3*S*, 4*R*
3.	**8b**	Ph	Ph	96	217-218	+190.9 (c 0.7, $CHCl_3$)	3*R*, 4*S*
4.	**9b**	Ph	Ph	96	216-217	−188.7 (c 0.39, $CHCl_3$)	*3S, 4R*
5.	**9c**	PMP	PMP	98	132-133	−181.90 (c 0.93, $CHCl_3$)	*3S, 4R*
6.	**9d**	Styryl	PMP	96	156	−236 (c 0.01, MeOH) lit.[6e] −237 (c 0.01, MeOH)	*3S, 4R*

[a] Isolated yield of pure enantiomers.

assigned as (3*R*,4*S*) and (3*S*,4*R*), respectively, by comparing their physical data as well as specific rotations with some of the compounds **8b** and **9b**,**d** reported in the literature.[6e,8b,9f]

3. Conclusion

It must be emphasized that the zinc-mediated cleavage of the chiral auxiliary regenerates (+)-3-carene as the only other product, which, in principle, should permit recycling of the chiral auxiliary. Thus, we have demonstrated that a small change in the design of a chiral pool-derived

auxiliary significantly improves the practical scope of the large-scale preparation of enantiopure 3-hydroxy-*cis*-β-lactams, one of which, **9a**, is a key intermediate for the taxol side-chain.[3,5]

4. Experimental

4.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 and MSL-300 spectrometer and chemical shifts are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Bruker AC 200 instruments and chemical shifts are reported in ppm, relative to the centerline of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin–Elmer Infracord Specrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell point apparatus and are uncorrected. The microanalysis was 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 (1′S,3′R,4′R,6′R)-2-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]ethan-1-ol **2**

To a stirred solution of (+)-3-carene (1.36 g, 10 mmol) and ethylene glycol (31 mL, 50 mmol) in dichloromethane (30 mL), powdered NBS (2.23 g, 12.5 mmol) was added in small portions over a period of 30 min at 0°C. The reaction mixture was allowed to warm-up to room temperature and stirred for a further 4 h. After the completion of the reaction (TLC), cold water (50 mL) was added to the reaction mixture and extracted with dichloromethane (3×30 mL). The combined extracts were washed with sat. $NaHSO_3$ (15 mL), water (20 mL), brine (15 mL) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 60–120, pet. ether/ethyl acetate) to give 1.24 g (45%) of pure bromo alcohol **2** as a pale yellow liquid. $[\alpha]_D^{25} = -33.45$ (c 1.65, $CHCl_3$); IR 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65–0.90 (m, 2H), 0.97 (s, 3H), 1.0 (s, 3H), 1.30–1.50 (m, 1H), 1.35 (s, 3H), 2.05–2.25 (m, 1H), 2.40–2.50 (m, 2H), 3.40–3.60 (m, 2H), 3.65–3.75 (m, 2H), 4.07 (t, $J = 8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.48, 17.70, 18.32, 19.50, 21.63, 28.39, 29.97, 31.80, 59.92, 61.83, 62.04, 75.25; MS: *m*/*z* (%) 276 (M^+, 3.5), 92 (100).

4.3. Preparation of (1′S,3′R,4′R,6′R)-2-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]-acetic acid **3**

To a stirred solution of bromo alcohol **2** (276 mg, 1 mmol) in acetone (10 mL), Jones reagent was added drop by drop at 0°C until decolorization of the reagent was stopped. The reaction mixture was further stirred for 3 h at room temperature, the green precipitate of the chromium salt was filtered off and the excess reagent destroyed by adding isopropyl alcohol at 0°C. The solution was concentrated under vacuum and residue was extracted with ether (3×20 mL). The ether extract was washed with brine and dried over Na_2SO_4. It was then filtered and filtrate on concentration under reduced pressure afforded bromo acid **3** (232 mg, 80%). The pure bromo acid was obtained by crystallization from pet. ether/ethyl acetate to give **3** as white crystals, mp 85°C; $[\alpha]_D^{25} = -72$ (c 0.45, $CHCl_3$); IR 1760, 2600, 3700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65–0.90 (m, 2H),

0.98 and 1.00 (2s, 6H), 1.4 (s, 3H), 1.3–1.4 (m, 1H), 2.20 (dd, $J=5.5$, 10 Hz, 1H), 2.35–2.55 (m, 2H), 4.00 (m, 1H), 4.05 (d, $J=18$ Hz, 1H), 4.10 (d, $J=18$ Hz, 1H), 7.30–9.0 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 15.71, 17.34, 18.18, 19.55, 21.85, 28.57, 30.88, 31.99, 59.74, 59.89, 78.12; MS: m/z (%) 210 (M^+–HBr, 2), 135 (82), 107 (37), 93 (100), 77 (40), 71 (52), 67 (38).

4.4. Preparation of (1′S,3′R,4′R,6′R)-2-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]acetyl chloride ***4***

A mixture of acid **3** (5.8 g, 20 mmol) and $SOCl_2$ (2.18 mL, 30 mmol) in dry benzene (40 mL) was refluxed for 3 h. The benzene was removed by distillation to give 5.240 g (85%) of acid chloride **4**, which was used as such in the next step.

4.5. Preparation of β*-lactams* ***6a*** *and* ***7a***

To a stirred solution of imine **5a** (2.10 g, 10 mmol) and Et_3N (7.50 mL, 75 mmol) in dry dichloromethane (50 mL), a solution of acid chloride **4** (7.70 g, 25 mmol) in dry dichloromethane (20 mL) was added drop-wise at 0°C over a period of 1 h. The reaction mixture was allowed to warm-up to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (20 mL) and washed successively with water (30 mL), sat. $NaHCO_3$ (30 mL), brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed by distillation under reduced pressure and residue on column chromatography (silica gel, 60–120, pet. ether/ethyl acetate) gave 3.38 g (70%) diastereomeric mixture of β-lactams (**6a** and **7a**) in a ratio of 60:40 (HPLC and ^{1}H NMR analysis). The flash column chromatography (silica gel, 230–400) of the diastereomeric mixture gave less polar compound **7a** (675 mg, 20%) and more polar compound **6a** (1.35 g, 40%), along with a diastereomeric mixture of **6a** and **7a** (1.10 g).

4.5.1. (3S,4R,1′S,3′R,4′R,6′R)-1-(4-Methoxyphenyl)-3-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)-hept-3′-yloxy]-4-phenylazetidin-2-one ***6a***

Isolated as a white solid; mp 176°C; $[\alpha]_D^{25}=-114.2$ (c 0.48, CH_2Cl_2); IR 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50–0.70 (m, 2H), 0.74 (s, 3H), 0.87 (s, 3H), 0.94 (dd, $J=4.5$, 14.5 Hz, 1H), 1.24 (s, 3H), 1.57 (9.5, 14.5 Hz, 1H), 2.25 (dd, $J=4.5$, 8.7 Hz, 2H), 3.70 (s, 3H), 3.73 (t, $J=8.5$ Hz, 1H), 5.05 (d, $J=4.8$ Hz, 1H), 5.27 (d, $J=4.8$ Hz, 1H), 6.73 (d, $J=9$ Hz, 2H), 7.24 (d, $J=9$ Hz), 7.29–7.39 (m, 3H).

4.5.2. (3R,4S,1′S,3′R,4′R,6′R)-1-(4-Methoxyphenyl)-3-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)-hept-3′-yloxy]-4-phenylazetidin-2-one ***7a***

Isolated as a white solid; mp 148°C; $[\alpha]_D^{25}=+18.7$ (c 0.31, CH_2Cl_2); IR 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.5–0.6 (m, 1H), 0.65–0.80 (m, 1H), 0.87 (s, 3H), 0.91 (s, 3H), 1.19 (s, 3H), 1.32 (dd, $J=5$, 15 Hz, 1H), 2.18 (dd, $J=10$, 15 Hz, 1H), 2.20–2.30 (m, 2H), 3.70 (t, $J=7.5$ Hz, 1H), 3.75 (s, 3H), 5.12 (d, $J=5$ Hz, 1H), 5.19 (d, $J=5$ Hz, 1H), 6.74 (d, $J=9$ Hz, 2H), 7.20–7.40 (m, 7H).

4.5.2.1. Data for mixture of ***6a*** *and* ***7a***. ^{13}C NMR ($CDCl_3$) δ 15.27, 15.40, 17.81, 18.20, 18.86, 19.36, 19.49, 21.24, 21.50, 28.42, 31.42, 31.87, 31.96, 32.08, 35.39, 59.44, 59.60, 63.07, 63.18, 77.48, 77.68, 114.31, 118.73, 128.18, 128.40, 128.48, 128.66, 130.93, 134.04, 134.31, 156.19, 164.91, 165.31. MS: m/z (%) 485 (M^++2, 5), 483 (M^+, 4), 268 (49), 211 (62), 135 (58), 134 (51), 120

(80), 93 (100), 91 (89), 77 (52). Anal calcd for $C_{26}H_{30}BrNO_3$: C, 64.46; H, 6.24; N, 2.89. Found: C, 64.91; H, 6.48; N, 3.02.

Other β-lactams **6b–d** and **7b–d** were prepared using the same procedure except for their method of purification.

The diastereomeric mixture of β-lactams **6b** and **7b** (2.94 g, 65%) was separated by flash column chromatography (silica gel, 230–400), which gave polar **6b** (1.32 g, 45%) and less polar **7b** (529 mg, 18%), along with a mixture of **6b** and **7b** (910 mg).

4.5.2.2. (3S,4R,1′S,3′R,4′R,6′R)-3-[4′-Bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]-1,4-diphenylazetidin-2-one ***6b***. Isolated as a white solid; mp 159°C; $[\alpha]_D^{25} = -100.9$ (c 0.22, CH_2Cl_2); IR 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.45–0.70 (m, 2H), 0.74 (s, 3H), 0.89 (s, 3H), 0.90–1.10 (m, 1H), 1.27 (s, 3H), 1.55–1.75 (m, 1H), 2.25 (dd, $J = 4.4$, 8 Hz, 2H), 3.75 (t, $J = 8$ Hz, 1H), 5.12 (d, $J = 5$ Hz, 1H), 5.31 (d, $J = 5$ Hz, 1H), 7.15–7.50 (m, 10H).

4.5.2.3. (3R,4S,1′S,3′R,4′R,6′R)-3-[4′-Bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yl-oxy]-1,4-diphenylazetidin-2-one ***7b***. Isolated as a white solid; mp 181°C; $[\alpha]_D^{25} = +21$ (c 0.2, CH_2Cl_2); IR 1753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.50–0.65 (m, 1H), 0.65–0.80 (m, 1H), 0.90 (s, 3H), 0.95 (s, 3H), 1.20 (s, 3H), 1.20–1.40 (m, 1H), 2.00–2.40 (m, 3H), 3.70 (t, $J = 9$ Hz, 1H), 5.18 (d, $J = 5$ Hz, 1H), 5.25 (d, $J = 5$ Hz, 1H), 6.95–7.50 (m, 10H).

4.5.2.4. Data for mixture of ***6b*** *and* ***7b***. MS: *m/z* (%) 455 (M+2, 3), 453 (M^+, 3), 238 (68), 182 (90), 135 (66), 120 (79), 93 (100), 91 (99), 77 (72), 55 (45); ^{13}C NMR ($CDCl_3$) δ 15.25, 15.39, 17.77, 18.21, 18.83, 19.33, 19.46, 21.21, 21.47, 28.41, 31.40, 31.84, 31.93, 32.05, 59.16, 59.37, 62.91, 63.01, 76, 77.61, 117.42, 124.07, 128.18, 128.42, 128.61, 128.97, 133.87, 134.13, 137.34, 165.54, 166. Anal. calcd for $C_{27}H_{32}BrNO_4$: C, 66.08; H, 6.21; N, 3.08. Found: C, 66.32; H, 6.49; N, 3.17.

The diastereomeric mixture of β-lactams **6c** and **7c** (3.59 g, 70%) was separated by flash column chromatography to give polar **6c** (1.540 g, 43%) and less polar **7c** (789 mg, 22%), along with a mixture of **6b** and **7b** (1.1 g).

4.5.2.5. (3S,4R,1′S,3′R,4′R,6′R)-3-[4′-Bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]-1,4-di-(4-methoxyphenyl)azetidin-2-one ***6c***. Isolated as a white solid; mp 167°C; $[\alpha]_D^{25} = -123.6$ (c 0.23, CH_2Cl_2); IR 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.50–0.70 (m, 2H), 0.75 (s, 3H), 0.90 (s, 3H), 0.95 (dd, $J = 6$, 15 Hz, 1H), 1.25 (s, 3H), 1.50–1.70 (m, 1H), 2.30 (dd, $J = 3$, 12 Hz, 2H), 3.70 (s, 3H), 3.70–3.75 (m, 1H), 3.80 (s, 3H), 5.0 (d, $J = 6$ Hz, 1H), 5.25 (d, $J = 6$ Hz, 1H), 6.72 (d, $J = 9$ Hz, 2H), 6.85 (d, $J = 9$ Hz, 2H), 7.22 (d, $J = 9$ Hz, 2H), 7.25 (d, $J = 9$ Hz, 2H).

4.5.2.6. (3R,4S,1′S,3′R,4′R,6′R)-3-[4′-Bromo-3′,7′,7′-trimethylbicyclo(4.1.0)hept-3′-yloxy]-1,4-di-(4-methoxyphenyl)azetidin-2-one ***7c***. Isolated as a white solid; mp 157°C; $[\alpha]_D^{25} = +20$ (c 0.23, CH_2Cl_2); IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.50–0.60 (m, 1H), 0.65–0.80 (m, 1H), 0.90 (s, 3H), 0.92 (s, 3H), 1.18 (s, 3H), 1.30 (dd, $J = 6$, 12 Hz, 1H), 2.15 (dd, $J = 12$, 15 Hz, 1H), 2.20–2.35 (m, 2H), 3.70 (s, 3H), 3.60–3.75 (m, 1H), 3.78 (s, 3H), 5.05 (d, $J = 4.9$ Hz, 1H), 5.15 (d, $J = 4.9$ Hz, 1H), 6.75 (d, $J = 9$ Hz, 2H), 6.85 (d, $J = 9$ Hz, 2H), 7.25 (d, $J = 8$ Hz, 4H).

4.5.2.7. Data for mixture of ***6c*** *and* ***7c***. ^{13}C NMR ($CDCl_3$) δ 15.51, 15.69, 18.01, 18.63, 18.98, 19.60, 21.46, 21.71, 28.65, 31.64, 32.06, 55.46, 59.65, 62.98, 76, 77.70, 113.19, 114.48, 118.97, 126.19, 126.41, 130.07, 130.22, 131.19, 156.34, 159.96, 165.23, 165.58; MS: *m/z* (%) 515 (M^++2,

0.18), 513 (M^+, 0.2), 241 (39), 134 (60), 121 (57), 93 (57), 77 (38). Anal. calcd for $C_{27}H_{32}BrNO_4$: C, 63.04; H, 6.27; N, 2.72. Found: C, 62.79; H, 6.31; N, 3.01.

The diastereomeric mixture of β-lactams **6d** and **7d** (3.05 g, 60%) was separated by flash column chromatography to offer polar **6d** (915 mg, 30%) and less polar **7d** (450 mg, 15%), along with a mixture of **6b** and **7b** (1.5 g).

*4.5.2.8. (3*S*,4*R*,1′*S*,3′*R*,4′*R*,6′*R*)-1-(4-Methoxyphenyl)-3-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)-hept-3′-yloxy]-4-(2″-phenylethynyl)azetidin-2-one* ***6d***. Isolated as a white solid; mp 158–160°C; $[\alpha]_D^{25} = -122.9$ (c 1.85, CH_2Cl_2); IR 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55–0.85 (m, 2H), 0.93 (s, 3H), 0.95 (s, 3H), 1.45 (s, 3H), 1.45–1.60 (m, 1H), 2.20 (dd, $J = 12.5$, 15 Hz, 1 H), 2.40 (dd, $J = 6$, 10 Hz, 1H), 3.75 (s, 3H), 4.05 (t, $J = 10$ Hz, 1H), 4.75 (dd, $J = 5$, 10 Hz, 1H), 5.20 (d, $J = 5$ Hz, 1H), 6.35 (dd, $J = 10$, 15 Hz, 1H), 6.70–6.90 (m, 3H), 7.20–7.55 (m, 7H).

*4.5.2.9. (3*R*,4*S*,1′*S*,3′*R*,4′*R*,6′*R*)-1-(4-Methoxyphenyl)-3-[4′-bromo-3′,7′,7′-trimethylbicyclo(4.1.0)-hept-3′-yloxy]-4-(2″-phenylethenyl)azetidin-2-one* ***7d***. Isolated as a white solid; mp 166°C; $[\alpha]_D^{25} = +33$ (c 1.85, CH_2Cl_2); IR 1520, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55–0.75 (m, 1H), 0.75–0.95 (m, 1H), 1.00 (s, 3H), 1.05 (s, 3H), 1.35 (s, 3H), 1.50 (dd, $J = 5$, 15 Hz, 1H), 2.20–2.50 (m, 3H), 3.75 (s, 3H), 4.05 (dd, $J = 8$, 10 Hz, 1H), 4.75 (dd, $J = 5$, 10 Hz, 1H), 5.15 (d, $J = 5$ Hz, 1H), 6.45 (dd, $J = 10$, 15 Hz, 1H), 6.70–6.95 (m, 3H), 7.20–7.60 (m, 7H).

4.5.2.10. Data for mixture of ***6d*** *and* ***7d***. MS: *m/z* (%) 511 (M^++2, 1.8), 509 (M^+, 2), 294 (28), 236 (35), 146 (69), 115 (100), 93 (83), 91 (69), 77 (38); ^{13}C NMR ($CDCl_3$) δ 15.36, 15.52, 17.82, 17.88, 19.35, 19.44, 19.60, 21.36, 21.70, 28.39, 31.62, 31.87, 32.01, 55.37, 58.85, 60.14, 61.71, 62.33, 77.43, 77.70, 77.87, 114.26, 118.56, 118.63, 125.11, 126.62, 126.78, 128.03, 128.14, 128.48, 128.60, 131.41, 135.76, 135.89, 136.73, 156.20, 164.70, 164.79. Anal. calcd for $C_{28}H_{32}BrNO_3$: C, 65.99; H, 6.33; N, 2.75. Found: C, 65.85; H, 6.52; N, 2.70.

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

*4.6.1. Preparation of (3*S*,4*R*)-3-hydroxy-1-(4′-methoxyphenyl)-4-phenyl*-cis-β-*lactam* ***9a***

To a solution of β-lactam **7a** (5 g, 10.35 mmol) in methanol (150 mL), activated Zn (6.35 g, 100 mmol) and glacial acetic acid (2.5 mL) were added with stirring. The reaction mixture was then heated at 80°C with continuous removal of methanol over a period of 3 h.

4.6.1.1. Isolation of (+)-3-carene. The distilled methanol from reaction mixture was diluted with ice-cold water (500 mL) and extracted with pet. ether (4×100 mL). The combined pet. ether extract was washed with sat. $NaHCO_3$ (50 mL), water (50 mL) and finally with brine (50 mL) and dried over sodium sulphate. The solvent was removed by distillation and residue was purified by Kugelrohr distillation to give 1.26 g (90%) of pure (+)-3-carene. The IR, NMR and optical rotation were identical with the authentic (+)-3-carene sample.

4.6.1.2. Isolation of β-*lactam* ***9a***. The residue from the reaction mixture was treated with dichloromethane (100 mL) and filtered; the solid was washed with dichloromethane (3×50 mL). The combined filtrate was successively washed with dilute HCl (5%, 50 mL), satd $NaHCO_3$ (2×30 mL), water (2×40 mL), brine (20 mL)) and dried over anhydrous Na_2SO_4. The removal of solvent gave 2.50 g (90%) of **9a** as a white crystalline solid, mp 200–201°C; $[\alpha]_D^{25} = -177.4$ (c 1,

$CHCl_3$); IR 1716, 3328 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (d, $J=8.5$ Hz, 1H), 3.75 (s, 3H), 5.20 (dd, $J=5.4$, 8.8 Hz, 1H), 5.30 (d, $J=5.4$ Hz, 1H), 6.80 (d, $J=9$ Hz, 2H), 7.15–7.60 (m, 7H). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.84; H, 5.86; N, 5.02.

Using a similar procedure as described for **9a**, the following 3-hydroxyazetidin-2-ones were prepared.

4.6.2. (3R,4S)-1-(4-Methoxyphenyl)-4-phenyl-3-hydroxyazetidin-2-one ***8a***

Isolated as a white solid; mp 197–199°C; $[\alpha]_D^{25}=+178.2$ (c 0.33, $CHCl_3$); IR 1716, 3328 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 5.15 (d, $J=5.2$ Hz, 1H), 5.25 (d, $J=5.2$ Hz, 1H), 6.80 (d, $J=9$ Hz, 2H), 7.15–7.50 (m, 7H). Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.65; H, 5.80; N, 5.49.

4.6.3. (3R,4S)-1,4-Diphenyl-3-hydroxyazetidin-2-one ***8b***

Isolated as a white solid; mp 217–218°C; $[\alpha]_D^{25}=+190.9$ (c 0.7, $CHCl_3$); IR 1740, 2852, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.15 (d, $J=5.4$ Hz, 1H), 5.18 (d, $J=5.4$ Hz, 1H), 6.90–7.50 (m, 10H). Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.14; H, 5.43; N, 5.89.

4.6.4. (3S,4R)-1,4-Diphenyl-3-hydroxyazetin-2-one ***9b***

Isolated as a white solid; mp 216–217°C; $[\alpha]_D^{25}=-188.7$ (c 0.39, $CHCl_3$); IR 1716, 2852, 3328 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.15 (d, $J=5.4$ Hz, 1H), 5.20 (d, $J=5.4$ Hz, 1H), 6.80–7.55 (m, 10H). Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.68; H, 5.65; N, 6.10.

4.6.5. (3S,4R)-1,4-Di-(4-methoxyphenyl)-3-hydroxyazetidin-2-one ***9c***

Isolated as a white crystalline solid; mp 132°C; $[\alpha]_D^{25}=-181.9$ (c 0.93, $CHCl_3$); IR 1726, 2852, 3301 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.80 (s, 3H), 5.15 (dd, $J=5.4$, 8 Hz, 1H), 5.25 (d, $J=5.4$ Hz, 1H), 6.80 (d, $J=8$ Hz, 2H), 6.95 (d, $J=8$ Hz, 2H), 7.20–7.40 (m, 4H). Anal. calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.06; H, 5.98; N, 4.55.

4.6.6. (3S,4R)-3-Hydroxy-1-(4-methoxyphenyl)-4-(2-phenylethenyl)azetidin-2-one ***9d***

Isolated as a white solid; mp 156–157°C; $[\alpha]_D^{25}=-236$ (c 0.01, CH_3OH); IR 1737, 3340 cm^{-1}; ^1H NMR δ 3.75 (s, 3H), 4.85 (dd, $J=5.2$, 7.4 Hz, 1H), 5.15 (bd, $J=5.2$ Hz, 1H), 6.40 (dd, $J=8.1$, 16.1 Hz, 1H), 6.65–7.00 (m, 3H), 7.20–7.65 (m, 7H). Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.59; H, 6.02; N, 5.00.

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