Pergamon

Tetrahedron 56 (2000) 8555–8560

TETRAHEDRON

Stereoselective Synthesis of *cis*-Bis-β-lactams Linked with an Ethylene Bridge

K. Karupaiyan,[a] V. G. Puranik,[b] A. R. A. S. Deshmukh[a] and B. M. Bhawal[a,*]

[a]*Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India*
[b]*Division of Physical Chemistry, National Chemical Laboratory, Pune 411 008, India*

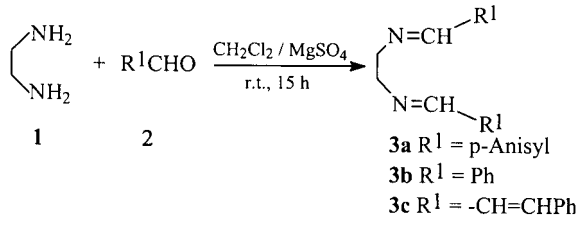
Received 5 June 2000; revised 14 August 2000; accepted 30 August 2000

Abstract—An efficient synthesis of (±)-*cis*-bis-β-lactams (**5** and **6**) via cycloaddition reaction of bisimines (**3a**–**c**) with acid chlorides (**4**) in the presence of triethylamine in very good yield is described. © 2000 Published by Elsevier Science Ltd.

Although β-lactam derivatives are well known for their antibiotic activities,[1] recently they have also been used as a synthon for the synthesis of various natural and unnatural products.[2] Ojima has shown the utility of bis-β-lactams for the synthesis[3] of peptides. The synthesis of bis-β-lactams, in general, have been reported by step-wise construction of β-lactam rings.[4] In continuation of our work on synthesis of bis-β-lactams,[4d,5] we were interested in building bis-β-lactams with spacer groups. Herein, we report the synthesis of bis-β-lactams in single step from bisimines derived from bis-amines.

The starting *N*,*N*′-bis-(*p*-anisylmethylene)ethane diamine (**3a**)[6] and *N*,*N*′-bis-(phenylmethylene)ethane diamine (**3b**)[7] were prepared in excellent yields by stirring a mixture of the aromatic aldehydes (**2a,b**), ethylenediamine and anhydrous $MgSO_4$ in dry dichloromethane (Scheme 1). The bisimine *N*,*N*′-bis-(styrylmethylene)ethane diamine (**3c**)[8] was prepared in quantitative yield by refluxing ethanolic solution of ethylenediamine and cinnamaldehyde.

The bisimines **3a**–**c** on cycloaddition reaction (Staudinger



Scheme 1.

reaction) with various acid chlorides (**4a**–**c**) in the presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-bis-β-lactams[9] (**5a**–**g** and **6a**–**g**) in good to excellent yields (Scheme 2, Table 1). The TLC and ^{1}H NMR spectral analysis of the crude reaction mixture showed the presence two diastereomers. These diastereomers were separated by flash column chromatography. The *C*-symmetric structure for bis-β-lactams **5a**–**g** was assigned from the ^{1}H NMR spectral analysis. The ^{1}H NMR spectra of all these compounds showed two doublets at about δ 2.8 and 3.8 with geminal coupling of 11–12 Hz for the protons of the methylene group joining two β-lactam rings. The *meso* structure was assigned to the other diastereomers **6a**–**g** as ^{1}H NMR spectra of all compounds in this series showed two multiplets (δ ~3.0 and 3.5) due to non-equivalence of two methylenes joining two β-lactam rings.

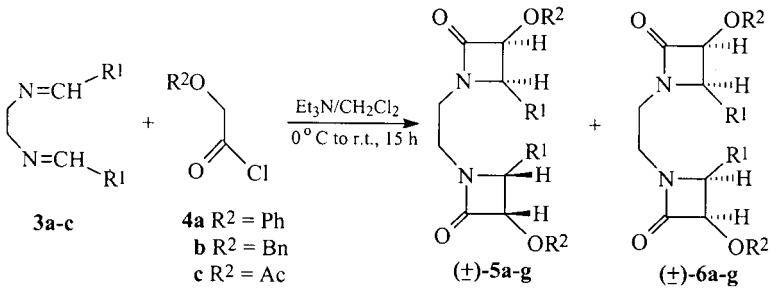
The structures for both C_2-symmetric and *meso* bis-β-lactams (**5a**–**g** and **6a**–**g**) were further confirmed by single crystal X-ray analysis of the representative compounds **5b** and **6c**. The X-ray crystal analysis of isomer (±)-**5b** showed C_2-symmetry in the molecule and the relative stereochemistry of β-lactam ring centres was assigned as 3*S*, 4*R*, 3′*S*, 4′*R* or 3*R*, 4*S*, 3′*R*, 4′*S* (Fig. 1).

The *meso* stereochemistry of the isomer (±)-**6c** was established from its X-ray structure and the relative stereochemistry of β-lactam ring centres was assigned as 3*S*, 4*R*, 3′*R*, 4′*S* or 3*R*, 4*S*, 3′*S*, 4′*R* (Fig. 2).

We have extended the above methodology to the asymmetric synthesis of bis-β-lactams. To achieve the stereoselectivity in β-lactam ring formation via ketene–imine cycloaddition reaction, a sterically demanding chiral acid **7**, derived from camphor sultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **7** was obtained in overall 70% yield from camphor sultam in

Keywords: cycloaddition reaction; azetidinones; Staudinger reaction; bisimines; bis-β-lactams.
* Corresponding author. Tel.: +91-20-5893153; fax: +91-20-5893355; e-mail: bhawal@dalton.ncl.res.in

0040–4020/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4020(00)00800-0



Scheme 2.

Table 1. Synthesis of bis-β-lactams **5** and **6**

Compound	R^1	R^2	Compound **5** and **6**			
			Yield[a] (%)	Ratio[b] of **5** and **6**	mp of **5**[c] (°C)	mp of **6**[c] (°C)
a	Anisyl	Ph	80	42:58	204–205	182–183
b	Anisyl	Bn	86	55:45	138–139	227–228
c	Anisyl	Ac	75	51:49	184–185	194–195
d	Ph	Ph	79	38:62	212–213	195–196
e	Ph	Bn	85	30:70	128–129	242–243
f	Styryl	Bn	60	58:42	Semisolid	151–153
g	Styryl	Ph	66	61:39	196–198	195–196

[a] Isolated yields of diastereomeric mix of **5** and **6**.
[b] The diastereomeric ratio of **5** and **6** was determined from ^{1}H NMR spectral data.
[c] The diastereomers **5** and **6** were separated by flash column chromatography.

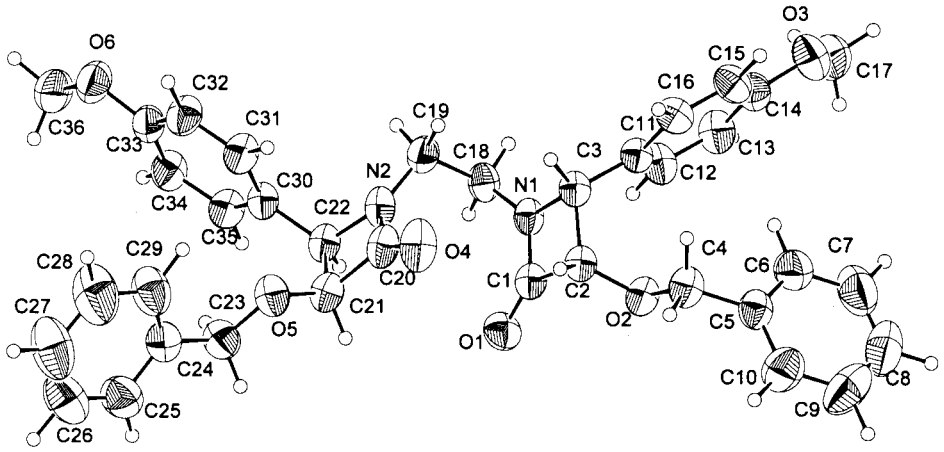


Figure 1. ORTEP diagram of bis-β-lactam **5b** without solvent molecule.

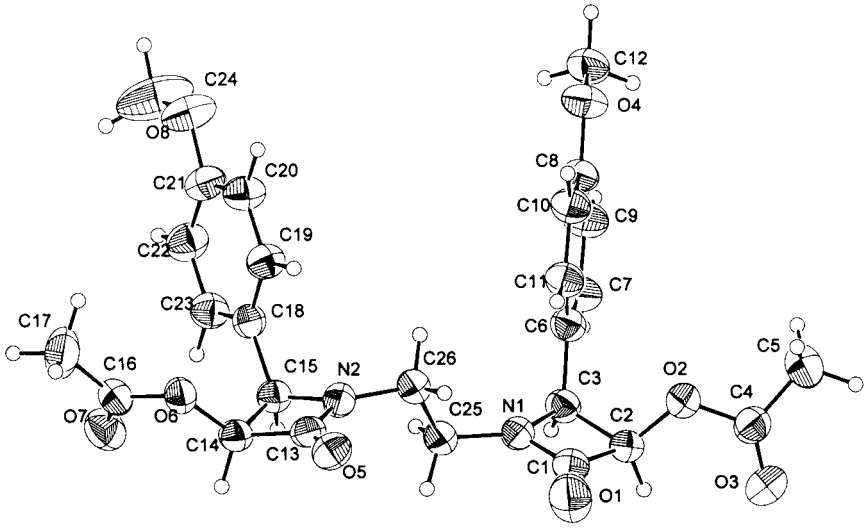
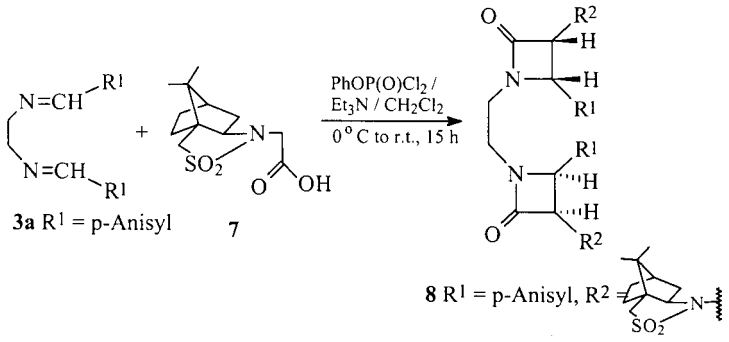


Figure 2. ORTEP diagram of bis-β-lactam **6c**.



Scheme 3.

two steps using our earlier reported procedure.[10] The cycloaddition reaction of ketene derived from the acid **7** with imine **3a** in the presence of triethylamine and phenyldichlorophosphate, as an acid activator, furnished stereospecifically bis-β-lactam **8** in excellent yield (Scheme 3). The formation of a single diastereomer was evident from ^{1}H NMR and HPLC analysis of the crude reaction mixture. The C_2-symmetric structure was assigned to bis-β-lactam **8** based on its ^{1}H NMR spectrum, which compares very well with the ^{1}H NMR spectra of C_2-symmetric bis-β-lactams **5** obtained earlier. The absolute stereochemistry for this bis-β-lactam **8** was assigned as 3*R*, 4*S*, 3′*R*, 4′*S* based on our earlier work on asymmetric synthesis of β-lactams[10] using ketene derived from Oppolzer's sultam and imines.

Experimental

General

^{1}H NMR Spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 spectrometer at 200 MHz and chemical shifts are reported in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 and Bruker MSL 300 instruments and chemical shifts were 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. 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.

General procedure for imines 3a and 3b

A mixture of freshly distilled aldehyde (0.15 mol), ethylenediamine (0.05 mol), anhydrous $MgSO_4$ (24 g) and dry dichloromethane (200 mL) was stirred for 15 h at room temperature. The reaction mixture was then filtered through a bed of celite and the solvent from the filtrate was removed by distillation under reduced pressure. The residue was then treated with a 10% solution of ethyl acetate in petroleum ether (60–80) to remove unreacted aldehyde and filtered to give required imines **3a**,**b** in excellent yield as a crystalline solid.

***N*,*N*′-Bis(*p*-methoxyphenylmethylene)ethane-1,2-diamine 3a.** It was obtained as a white solid, crystallized from EtOAc:petroleum ether (90:10) as needles, yield 88%; mp 109–110°C [lit. mp[6] 110–111°C]; ν_{max} ($CHCl_3$) 830, 1010, 1450, 1630 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.74 (s, 6H); 3.84 (s, 4H); 6.78 (d, *J*=8 Hz, 4H); 7.50 (d, *J*=8 Hz, 4H); 8.06 (s, 2H).

***N*,*N*′-Bis(phenylmethylene)ethane-1,2-diamine 3b.** It was isolated as a white solid and crystallized from EtOAc: petroleum ether (90:10) to give white needles; yield 84%; mp 52–53°C [lit. mp[7] 51.5–53°C]; ν_{max} ($CHCl_3$) 960, 1000, 1350, 1430, 1610 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.88 (s, 4H); 6.92–7.88 (m, 10H); 8.14 (s, 2H).

Preparation of *N*,*N*′-bis(styrylmethylene)ethane-1,2-diamine 3c

A solution of freshly distilled cinnamaldehyde (14.18 g, 0.107 mol) and ethylenediamine (3 g, 0.05 mol) in ethanol (40 mL) was refluxed for 1 h. The solvent was removed by distillation under reduced pressure and the residue was purified by crystallization from ethyl acetate:petroleum ether (90:10) to yield 14.38 g (100%) of pure bisimine **3c** as a crystalline pale yellow solid, mp 108–109°C [lit. mp[8] 109°C]; ν_{max} ($CHCl_3$) 979, 1164, 1218, 1450, 1635, 2846, 2939 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.80 (s, 4H); 6.70–6.95 (m, 4H); 7.15–7.55 (m, 10H); 7.95 (d, *J*=6.6 Hz, 2H).

Typical procedure for the preparation of β-lactams 5a–g and 6a–g

A solution of the acid chlorides (**4a**–**c**, 2.53 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of imines (**3a**–**c**, 3.5 mmol) and triethylamine (10 mmol) in CH_2Cl_2 (15 mL) at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. It was then washed with water (2×20 mL), satd $NaHCO_3$ (15 mL), brine (15 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product of a diastereomeric mixture. The diastereomers were separated by flash column chromatography (silica gel, 230–400, petroleum ether:ethyl acetate, 3:1) to give pure diastereomer of β-lactams (**5a**–**g** and **6a**–**g**).

1,2-Bis[3′-phenoxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]ethane 5a. It was isolated as white solid from diastereomeric mixture by flash column chromatography and

crystallized from dichloromethane:petroleum ether, mp 204–205°C; [Found: C, 72.40; H, 5.49; N, 4.69. $C_{34}H_{32}N_2O_6$ requires C, 72.32; H, 5.71; N, 4.96%]; ν_{max} (Nujol) 1735 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.80 (d, J=11.4 Hz, 2H); 3.75 (s, 6H); 3.82 (d, J=11.4 Hz, 2H); 5.17 (d, J=6.5 Hz, 2H); 5.34 (d, J=6.5 Hz, 2H); 6.60–6.93 (m, 12H); 7.02–7.33 (m, 6H); δ_C (75.2 MHz, $CDCl_3$) 37.36, 55.24, 60.76, 82.55, 113.93, 116.86, 129.16, 129.80, 155.37, 160.14, 166.82; *m/z* (EI) 121(100%), 134, 148, 161, 226.

1-[3-Phenoxy-4-(*p*-anisyl)azetidin-2′-one-1′yl]-2-[3[1]-phenoxy-4[1]-(*p*-methoxy-phenyl)-azetidin-2″-one-1″-yl]ethane 6a. It was obtained as a white solid, which was crystallized from dichloromethane:petroleum ether, mp 182–183°C; [Found: C, 72.50; H, 5.76; N, 4.76. $C_{34}H_{32}N_2O_6$ requires C, 72.32; H, 5.71; N, 4.96]; ν_{max} (Nujol) 1740 cm^{-1}; δ_H (200 MHz $CDCl_3$) 3.00–3.24 (m, 2H); 3.50–3.75 (m, 2H); 3.78 (s, 6H); 4.88 (d, J=5.4 Hz, 2H); 5.24 (d, J=5.4 Hz, 2H); 6.57–7.42 (m, 18H); δ_C (75.2 MHz, $CDCl_3$) 38.24, 55.27, 61.68, 82.16, 113.99, 116.80, 129.16, 129.86, 155.37, 160.23, 165.84; *m/z* (EI) 245 (100%), 148, 161, 226, 254.

1,2-Bis[3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]ethane 5b. It was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 138–139°C; [Found: C, 72.69; H, 6.22; N, 4.58. $C_{36}H_{36}N_2O_6$ requires C, 72.95; H, 6.12; N, 4.72]; ν_{max} (Nujol) 1735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.72 (d, J=10.8 Hz, 2H); 3.72 (d, 10.79 Hz, 2H); 3.81 (s, 6H); 4.14 (d, J=8.1 Hz, 2H); 4.30 (d, J=8.1 Hz, 2H); 4.82 (d, J=4.2 Hz, 2H); 5.00 (d, J=4.2 Hz, 2H); 6.73–7.04 (m, 8H); 7.12–7.41 (m, 10H); δ_C (50.3 MHz, $CDCl_3$) 37.34, 55.64, 60.99, 72.65, 84.69, 114.34, 125.77, 128.16, 128.39, 128.52, 130.12, 136.85, 160.32, 168.32; *m/z* (EI) 91(100%), 149, 261, 281, 331, 484, 501(M^+-Bn).

1-[3-Benzyloxy-4-(*p*-methoxyphenyl)azetidin-2′-one-1′yl]-2-[3′-benzyloxy-4′-(*p*-methoxyphenyl)azetidin-2″-one-1″-yl]ethane 6b. The *title compound* **6b** was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 227–228°C; [Found: C, 72.76; H, 6.17; N, 4.85. $C_{36}H_{36}N_2O_6$ requires C, 72.95; H, 6.12; N, 4.72]; ν_{max} (Nujol) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.81–3.02 (m, 2H); 3.41–3.62 (m, 2H); 3.82 (s, 6H); 4.14 (d, J=10.8, Hz, 2H); 4.26 (d, J=10.8 Hz, 2H); 4.58 (d, J=4.2 Hz, 2H); 4.70 (d, J=4.2 Hz, 2H); 6.78–7.02 (m, 8H); 7.12–7.33 (m, 10H); δ_C (75.2 MHz, $CDCl_3$) 37.81, 55.48, 61.59, 72.33, 83.77, 114.17, 125.22, 128.00, 128.24, 128.36, 129.92, 136.54, 160.22, 167.34; *m/z* (EI) 90 (100%), 148, 240, 268, 501 (M^+-Bn).

1,2-Bis[3′-acetoxy-4′-(*p*-methoxyphenyl)azetidin-2′one-1′-yl]ethane 5c. It was obtained as a white solid, crystallized from ethyl acetate:petroleum ether, mp 184–185°C. [Found: C, 62.77; H, 5.72; N, 5.77. $C_{26}H_{28}N_2O_8$ requires C, 62.90; H, 5.68; N, 5.64]; ν_{max} (Nujol) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.72 (s, 6H); 2.88 (d, J=10.3 Hz, 2H); 3.79 (d, J=10.3 Hz, 2H); 3.82 (s, 6H); 5.13 (d, J=4.5 Hz, 2H); 5.74 (d, J=4.5 Hz, 2H); 6.89 (d, J=8.69 Hz, 4H); 7.17–7.32 (m, 4H); δ_C (50.3 MHz, 1:1DMSO:$CDCl_3$) 19.98, 38.23, 38.77, 39.18, 39.59, 40.01, 40.43, 40.85, 41.27, 55.36, 60.13, 76.26, 77.26, 77.62, 113.98, 124,97, 129.74, 159.85, 161.39, 165.40, 168.66; *m/z* (EI) 121(100%), 161, 262, 304.

1-[3-Acetoxy-4-(*p*-methoxyphenyl)azetidin-2′-one-1′-yl]-2-[3′-Acetoxy-4′-(*p*-meth-oxyphenyl)azetidin-2″-one-1″-yl]ethane 6c. The *title compound* **6c** was obtained as a white crystalline solid, crystallized from ethyl acetate: petroleum ether, mp 194–195°C; [Found: C, 62.62; H, 5.69; N, 5.50. $C_{26}H_{28}N_2O_8$ requires C, 62.89; H, 5.68; N, 5.64]; ν_{max} (Nujol) 1758 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.73 (s, 6H); 3.02–3.18 (m, 2H); 3.46–3.67 (m, 2H); 3.83 (s, 6H); 4.85 (d, J=5.4 Hz, 2H); 5.65 (d, J=5.4 Hz, 2H); 6.92 (d, J=9.7 Hz, 4H); 7.14–7.30 (m, 4H); δ_C (75.2 MHz, $CDCl_3$) 19.84, 38.45, 55.24, 61.31, 77.43, 113.93, 123.82, 129.65, 160.14, 165.26, 168.92; *m/z* (EI) 150 (100%), 121, 135.

1,2-Di-[3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]ethane 5d. It was obtained as a white crystalline solid, crystallized from dichloromethane:petroleum ether; mp 212–213°C; [Found: C, 76.05; H, 5.30; N, 5.40. $C_{32}H_{28}N2O_4$ requires C, 76.17; H, 5.59; N, 5.55]; ν_{max} ($CHCl_3$) 1752 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.86 (d, J=11.5 Hz, 2H); 3.88 (d, J=11.5 Hz, 2H); 5.22 (d, J=3.9 Hz, 2H); 5.38 (d, J=3.9 Hz, 2H); 6.58–7.39 (m, 20H). δ_C (75.2 MHz, $CDCl_3$) 37.54, 61.16, 82.62, 115.64, 116.92, 128.49, 129.01, 129.13, 132.45, 155.28, 166.85; *m/z* (EI) 230 (100%), 196, 224.

1-[3′-Phenoxy-4′-phenylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-phenylazetidin 2″-one-1″-yl]ethane 6d. It was isolated as a white solid, crystallized from dichloromethane:petroleum ether, mp 195–196°C; [Found: C, 76.30; H, 5.36; N, 5.31. $C_{32}H_{28}N_2O_4$ requires C, 76.17; H, 5.59; N, 5.55]; ν_{max} ($CHCl_3$) 1729 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.00–3.23 (m, 2H); 3.55–3.79 (m, 2H); 4.87 (d, J=4.2 Hz, 2H); 5.22 (d, J=4.2 Hz, 2H); 6.52–6.73 (m, 4H); 6.97–7.20 (m, 4H); 7.20–7.43 (m, 12H); δ_C (75.2 MHz, $CDCl_3$) 38.30, 62.08, 82.16, 116.80, 128.55, 129.16, 132.27, 155.28, 165.81; *m/z* (EI) 230 (100%), 196.

1,2-Di[3′-benzyloxy-4′-phenylazetidin-2′-one-1′-yl]ethane 5e. It was obtained from the diastereomeric mixture by column chromatography (silica gel, 230–400) and crystallized from dichloromethane:petroleum ether, mp 128–129°C; [Found: C, 76.43; H, 6.16; N, 4.98. $C_{34}H_{32}N_2O_4$ requires C, 76.67; H, 6.05; N, 5.26]; ν_{max} (Nujol) 1740 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.75 (d, J=10.9 Hz, 2H); 3.80 (d, J=10.9 Hz, 2H); 4.12 (d, J=10.8 Hz, 2H); 4.29 (d, J=10.8 Hz, 2H); 4.90 (d, J=4.4 Hz, 2H); 5.08 (d, J=4.4 Hz, 2H); 6.94 (m, 4H); 7.18–7.46 (m, 16H); δ_C (50.3 MHz, $CDCl_3$) 37.29, 61.32, 69.19, 72.64, 80.16, 81.13, 82.98, 83.11, 84.73, 86.08, 90.09, 128.03, 128.25, 128.38, 128.72, 133.90, 136.56, 166.11, 168.21, 175.39.

1-[3′-Benzyloxy-4′-phenylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-phenylazetidin-2″-one-1″-yl]ethane 6e. It was obtained as a white solid, crystallized from dichloromethane:petroleum ether, mp 242–243°C; [Found: C, 76.51; H, 6.31; N, 5.27. $C_{34}H_{32}N_2O_4$ requires C, 76.67; H, 6.05; N, 5.26]; ν_{max} (Nujol) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.90–3.10 (m, 2H); 3.51–3.71 (m, 2H); 4.12 (d,

J=10.3 Hz, 2H); 4.24 (d, J=10.34 Hz, 2H);.59 (d, J=4.3 Hz, 2H); 4.68 (d, J=4.3 Hz, 2H); 6.84–6.97 (m, 4H); 7.14–7.54 (m, 16H); δ_C (75.2 MHz, $CDCl_3$) 37.72, 61.95, 72.24, 83.71, 127.88, 128.21, 128.46, 128.58, 128.79, 133.34, 136.24, 167.09.

1-[3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-styrylazetidin-2″-one-1″-yl]ethane 5f. Isolated as a semisolid material. [Found: C, 78.17; H, 6.13; N, 4.54. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.20; N, 4.79]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.00 (d, J=11.8 Hz, 2H); 3.62 (d, J=11.8 Hz, 2H); 4.52 (dd, J=4.4, 9.2 Hz, 2H); 4.62 (d, J=7.3 Hz, 2H); 4.68 (d, J=7.3 Hz, 2H); 4.83 (d, J=4.4 Hz, 2H); 6.23 (dd, J=9.2, 16.1 Hz, 2H); 6.72 (d, J=16.1 Hz, 2H); 7.15–7.50 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 37.89, 60.53, 72.59, 83.65, 122.69, 126.37, 127.84, 128.02, 128.31, 135.44, 136.40, 167.17. m/z 494 (M^+-90), 236, 91(100%).

1-[3′-Benzyloxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-benzyloxy-4″-styrylazetidin-2″-one-1″-yl]ethane 6f. The *title compound* **6f** was obtained as a white solid, crystallized from dichloromethane/methanol, mp 158–159°C; [Found: C, 77.87; H, 6.41; N, 4.84. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.20; N, 4.79]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.10–3.27 (m, 2H); 3.39–3.50 (m, 2H); 4.37 (dd, J=4.4, 9.5 Hz, 2H); 4.53 (d, J=11.0 Hz, 2H); 4.64 (d, J=10.8 Hz, 2H); 4.76 (d, J=4.4 Hz, 2H); 6.30 (dd, J=9.5, 15.4 Hz, 2H); 6.63 (d, J=15.4 Hz, 2H); 7.15–7.50 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 38.39, 61.31, 72.82, 83.68, 123.54, 126.87, 128.00, 128.21, 128.39, 128.73, 135.93, 136.51, 136.76, 167.31; m/z (EI) 494 (M^+-90), 236, 91 (100%).

1-[3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl]ethane 5g. It was obtained as a white solid, crystallized from dichloromethane/methanol, mp 196–198°C; [Found: C, 77.56; H, 5.71; N, 4.89. $C_{36}H_{32}N_2O_4$ requires C, 77.67; H, 5.79; N, 5.03]; ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.12 (d, J=11.3 Hz, 2H); 3.76 (d, J=11.7 Hz, 2H); 4.80 (dd, J=4.9, 9.3 Hz, 2H); 5.40 (d, J=4.9 Hz, 2H); 6.25 (dd, J=9.3, 15.6 Hz, 2H); 6.80 (d, J=15.6 Hz, 2H); 6.90–7.60 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 37.57, 38.67, 38.94, 39.22, 59.70, 81.15, 114.42, 121.13, 121.34, 125.65,.127.36, 127.60, 128.46, 134.65, 136.12, 156.14, 164.93; m/z (EI) 292, 222, 128 (100%).

1-[3′-Phenoxy-4′-styrylazetidin-2′-one-1′-yl]-2-[3″-phenoxy-4″-styrylazetidin-2″-one-1″-yl]ethane 6g. It was obtained as white solid, crystallized from dichloromethane/methanol, mp 195–196°C. [Found: C, 77.45; H, 5.68; N, 4.81. $C_{36}H_{32}N_2O_4$ requires C, 77.67; H, 5.79; N, 5.03]; ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.27–3.67 (m, 4H); 4.75 (dd, J=4.3, 9.2 Hz, 2H); 5.42 (d, J=4.4 Hz, 2H); 6.37 (dd, J=9.2, 15.6 Hz, 2H); 6.75 (d, J=15.6 Hz, 2H); 6.88–7.55 (m, 20H); δ_C (75.2 MHz, $CDCl_3$) 38.33, 39.31, 3958, 39.86, 60.89, 81.61, 114.17, 115.09, 121.68, 122.20, 126.35, 127.94, 128.18, 128.97, 135.32, 136.64, 156.78, 165.63. m/z (EI) 292, 222, 128 (100%).

Preparation of bis-β-lactam 8. To a stirred mixture of bisimine **3a** (0.75 g, 2.53 mmol), acid **7** (2.418 g, 8.86 mmol), triethylamine (0.6 mL) and dry CH_2Cl_2 (10 mL), a solution of phenyl dichlorophosphate (2 mL, 0.013 mol) in dry CH_2Cl_2 (40 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred further for 15 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and successively washed with water (30 mL), satd. $NaHCO_3$ solution (30 mL), brine (30 mL) and dried (Na_2SO_4). The CH_2Cl_2 solution was concentrated to give the crude product, which was column chromatographed (silica gel, 60–120, petroleum ether:ethyl acetate) to furnish 1.9 g (93%) of pure **8** as a white crystalline solid, mp 229–231°C; [Found: C, 62.32; H, 6.54; N, 6.85. $C_{42}H_{54}N_4O_8S_2$ requires C, 62.51; H, 6.74; N, 6.94]; $[\alpha]_D^{25}$=+96.56 (c 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.36 (s, 6H); 0.76 (s, 6H); 1.15–1.52 (m, 4H); 1.60–1.90 (m, 10H); 2.80–3.12 (m, 6H); 3.47–3.62 (m, 2H); 3.78 (s, 6H); 3.84 (d, J=10.8 Hz, 2H); 4.94 (d, J=4.8 Hz, 2H); 5.02 (d, J=4.8 Hz, 2H); 6.88 (d, J=8.7 Hz, 4H); 7.19 (d, J=8.7 Hz, 4H); δ_C (50.3 MHz, $CDCl_3$) 19.97, 20.27, 26.99, 32.94, 38.27, 39.10, 45.41, 47.62, 48.92, 50.30, 55.62, 59.71, 63.60, 66.36, 114.38, 126.53, 129.24, 160.17, 165.15; m/z (EI) 121 (100%), 228, 459.

X-Ray diffraction study

X-Ray structure determination of **5b** [$C_{37}H_{36}N_2O_8$]: Single crystals of compound **5b** were grown by slow evaporation of dichloromrthane:petroleum ether. A crystal of size 0.60×0.47×0.06 mm was used for data collection on an Enaraf Nonius CAD-4 single crystal X-ray diffractometer using CuKα radiation (λ=1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M=636.68, monoclinic, space group $C2/c$, a=23.944 (3), b=10.716(3), c=25.821(3) Å, β=95.47(2)°, V=6595(2) $Å^3$, Z=8, D_c=1.282 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by full-matrix least-squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of scale, positional and anisotropic thermal parameters of non-hydrogen atoms was carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 410, converged to R_1=0.0665, R_w=0.190, $w=1/\sigma^2[(Fo^2)+(0.1513P)^2+1.199P]$ where $P=(Fo^2+2Fc^2)/3$ from 5977 unique reflections ([$I>2\sigma(I)$]), from a total of 6806 collected. The residual density in the difference map for peak and hole is 0.390 and -0.612 e $Å^{-3}$, respectively.

X-Ray structure determination of **6c** [$C_{26}H_{28}N_2O_8$]: Single crystals of compound **6c** were grown by slow evaporation of methylene chloride/petroleum ether. A crystal of size 0.62×0.5×0.2 mm was used for data collection on Enaraf Nonius CAD-4 single crystal X-ray diffractometer using CuKα radiation (λ=1.5406 Å) and ω-2θ scan mode to a maximum θ range of 65°. M=496.50, Triclinic, space group P-1, a=6.425 (2), b=14.161 (2), c=14.811(3) Å, α=106.45 (2), β=100.58 (2), γ=98.76 (2)°, V=1240.3 (5) $Å^3$, Z=2, D_c=1.330 Mg m^{-3}. The structure was solved by direct methods using SHELXS and refined by full-matrix least-squares on F^2 using SHELXL-97.[11] Empirical absorption correction was applied. Least squares refinement of

scale, positional and anisotropic thermal parameters of non-hydrogen atoms was carried out while the positions of hydrogen atoms was held fixed. Each H atom was assigned the same isotropic thermal parameter as the atom to which it was bonded. The refinement with number of refined parameters 326, converged to R_1=0.0532, R_w=0.168, w=1/$\sigma^2[(Fo^2)+(0.1075P)^2+0.5243P]$ where $P=(Fo^2+2Fc^2)/3$ from 3934 unique reflections ($[I>2\sigma(I)]$), from a total of 4516 collected. The residual density in the difference map for peak and hole is 0.362 and -0.252 e $Å^{-3}$, respectively.

Acknowledgements

One of the authors (K. K.) thanks CSIR for financial support.

References

1. (a) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (b) Thomas, R. C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990, p 553. (c) Palamo, C. In *Recent Progerss in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, **1990**, p 565. (d) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503. (e) Burckheiner, W.; Blumbach, J.; Latrell, R.; Sheunemann, K. H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180.

2. (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 699. (b) Manhas, M. S.; Wagle, D. R.; Chiang, J. *Heterocycles* **1988**, *27*, 1755. (c) Ojima, I. In *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH: New York, 1993; p 197. (d) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (e) Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5585. (f) Srirajan, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733.

3. (a) Ojima, I.; Hatanaka, N.; Yoda, N.; Abe, R.; Yatabe, M.; Yanashita, M. In *Peptide Chemistry*; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, 1983, pp 29–34. (b) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. In *Peptide Chemistry*; Sakakibara, S., Ed.; Protein Research Foundation: Osaka, 1983; pp 85–90.

4. (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, 56, 5263. (b) Ojima, I.; Nakahashi, K.; Branstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* 1987, 109, 1798. (c) Bose, A. K.; Womensdors, J. F.; Krishnan, L.; Urbanczyk-Lipkowska, Z.; Shelly, D. C.; Manhas, M. S. *Tetrahedron* **1991**, *47*, 5379. (d) Jayaram, M.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 9005.

5. Jayaram, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 932.

6. Billman, J. H.; Chen Ho, J. Y.; Caswell, L. R. *J. Org. Chem.* **1952**, *17*, 1375.

7. Szabo, J. L.; Edwards, C. D.; Bruce, W. F. *Antibiotics and Chemotheraphy* **1951**, *1*, 499–503; *Chem. Abstr.* **1953**, *47*, 3850d.

8. Ferguson, L. N.; Branch, G. E. K. *J. Am. Chem. Soc.* **1944**, *66*, 1467.

9. The formation of only *cis*-isomers was confirmed from the coupling constant (4–5 Hz) of the β-lactam ring protons in ^1H NMR of the crude reaction mixture.

10. Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5579 and references cited therein.

11. (a) Sheldrick, G. M. SHELXS-93 Program for crystal structure solution and refinement, University of Göttingen, Germany, 1993. (b) Sheldrick, G. M. SHELXL-97 Program for crystal structure solution and refinement, University of Göttingen, Germany, 1997.