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TETRAHEDRON

Synthesis of N1-unsubstituted β-lactams *via* a facile deprotection of N1-[(α-thiophenyl)benzyl] group

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Abstract : A diastereoselective synthesis of (±) *cis*-β-lactams (**5** & **6**) *via* cycloaddition reactions of N1-(α-thiophenyl)benzyl imines (**3**) with acid chlorides (**4**) in the presence of triethylamine is described. The deprotection of N1-(α-thiophenyl)benzyl group has been achieved by oxidation using potassium persulfate to give N-unsubstituted β-lactams (**7**) in good yields.

N1-Unsubstituted β-lactams are key intermediates for the synthesis of monocyclic as well as bicyclic β-lactam antibiotics.[1] In most cases, the β-lactam nitrogen is protected during the synthesis. The choice of the protective group is based on the ease of selective removal of these protective groups at an appropriate time. Among the various groups,[2] benzyl,[3] *p*-methoxyphenyl,[4] allyl[5] and silyl[6] groups are more popular owing to their easy accessibility and convenience of removal under mild reaction conditions.

As a part of our project on β-lactam as a synthon[7] for the synthesis of natural and unnatural products, we were interested in developing methods for the preparation of NH-β-lactams. In our recent communication[8] we have reported the use of (α-thiophenyl)benzyl as a novel N-protective group in the synthesis of β-lactams and its oxidative removal using potassium persulfate to yield N-unsubstituted β-lactams. In this paper, we wish to report the detailed account of this work.

The starting 1-phenyl-N,N′-bis(phenylmethylene)methanediamine (**2a**) and 1-*p*-anisyl-N,N′-bis(*p*-anisylmethylene)mehtanediamine (**2b**) were prepared in excellent yields[9] by stirring a mixture of the aromatic aldehydes (**1a,b**) with a 10 fold excess of ammonia solution (30%) for 3 h (Scheme 1). The imines **2a,b** on reaction with the appropriate thiophenol in dioxane under reflux conditions gave the imines **3a,b** in good yields.[10]

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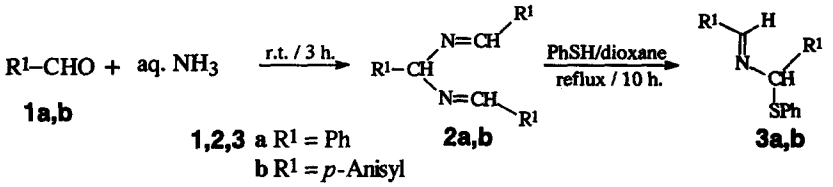
Scheme 1



The imines **3a,b** on cycloaddition reaction (Staudinger reaction) with various acid chlorides (**4a-c**) in presence of triethylamine gave diastereomeric mixtures of (±)-*cis*-β-lactams[11] (**5a-e** & **6a-e**) in 50-79% yields (Scheme 2, Table 1). The diastereomeric ratio was determined by the HPLC[12] and ^{1}H NMR analysis of a crude reaction mixture. The major (**5**) and minor (**6**) diastereomers were separated by crystallization.

Scheme 2

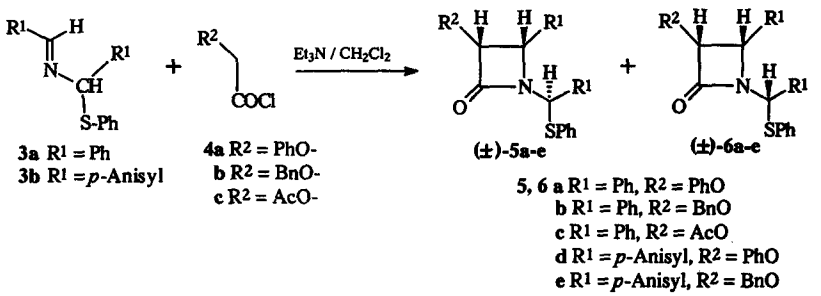


Table 1. Synthesis of β-lactams **5** & **6** and N^1-unsubstituted β-lactams **7**.

Compd	R^1	R^2	Compound 5 & 6			Compound 7	
			Yield[a] (%)	Ratio[b] of 5 & 6	m.p.[c] of 5 (°C)	yield[d] (%)	m.p. (°C)
a	Ph	PhO	74	74:26	214-215	70	159-160
b	Ph	BnO	58	64:36	119-120	64	188-189
c	Ph	AcO	50	74:26	153-154	--	--
d	*p*-Anisyl	PhO	79	83:17	157-159	70	165-167
e	*p*-Anisyl	BnO	57	78:22	149-151	--	--

[a] Isolated yields of diastereomeric mixture of **5** & **6**; [b] Ratio of **5** & **6** from HPLC and ^{1}H NMR spectral data; [c] The diastereomers **5a-e** were obtained by column chromatography in pure form. [d] Isolated yield.

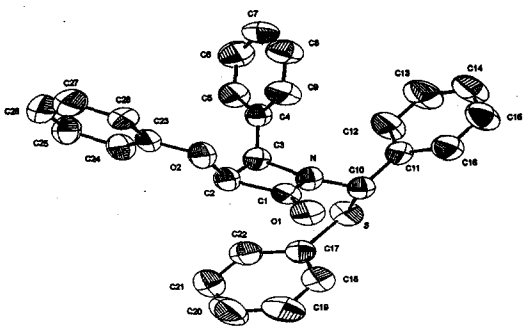
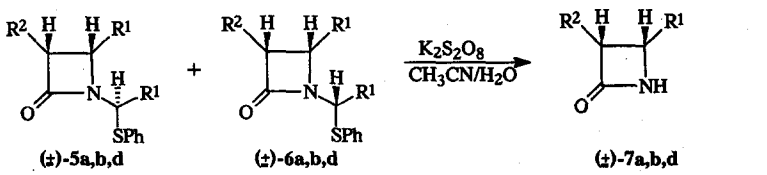


Fig. 1. The ORTEP diagram of the β-lactam **5a**

The relative configuration of the major diastereomer (±)-**5a** was established by single crystal X-ray analysis[13,14] as 1′*S*, 3*S*, 4*R* (Fig. 1).

N-Deprotection of pure major diastereomers **5** was carried out under mild oxidative conditions using potassium persulfate in acetonitrile/water at reflux temperature to give N1-unsubstituted β-lactams **7** in good yields (Scheme 3). The diastereomeric mixture of **5** and **6** on oxidative N-deprotection under similar conditions also gave the same β-lactams **7**. This further establishes that the β-lactams **5** and **6** are diasteromeric at (α-thiophenyl)benzylic position.

Scheme 3



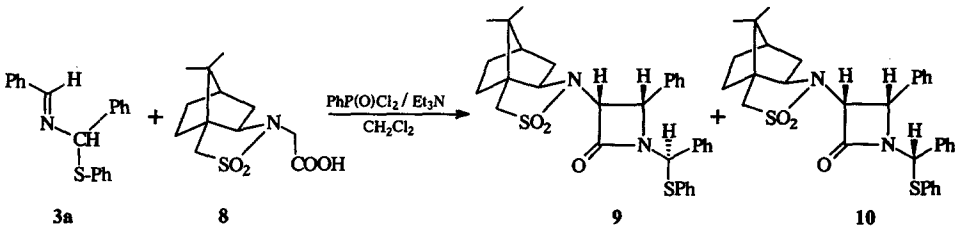
(±)-5a,b,d (±)-6a,b,d (±)-7a,b,d

5, 6 a R^1 = Ph, R^2 = PhO
b R^1 = Ph, R^2 = BnO
d R^1 = *p*-Anisyl, R^2 = PhO

7 a R^1 = Ph, R^2 = PhO
b R^1 = Ph, R^2 = BnO
d R^1 = *p*-Anisyl, R^2 = PhO

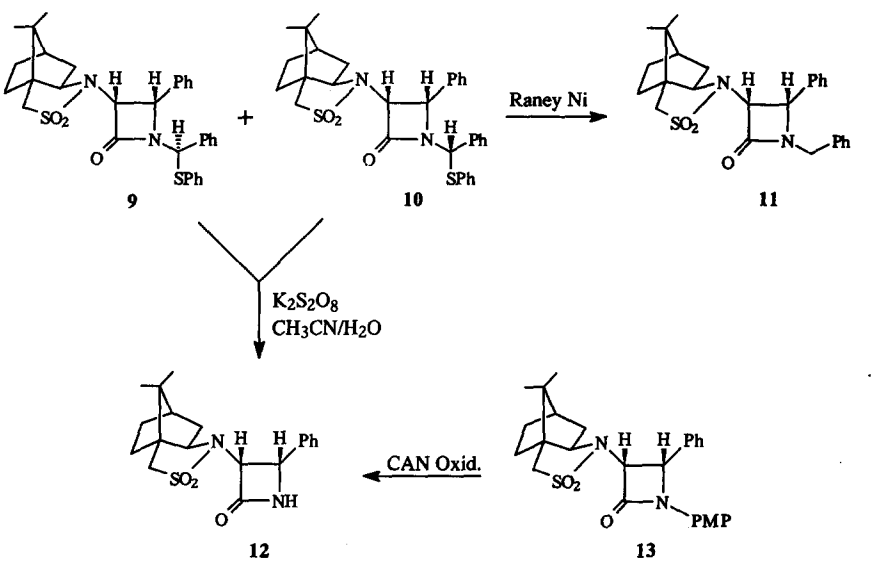
We have extended the above methodology for asymmetric synthesis of N1-unsubstituted β-lactams. To achieve the diastereoselectivity in β-lactam ring formation *via* ketene-imine cycloaddition reaction, a sterically demanding chiral acid **8**, derived from camphorsultam (Oppolzer's sultam) was chosen as a ketene precursor. The starting acid **8** was obtained in overall 70% yield from camphorsultam[15] in two steps using our earlier reported procedure.[16] The cycloaddition reaction of ketene derived from the acid **8** with imine **3a** in presence of triethylamine and phenyldichlorophosphate, an acid activator, offered a diastereomeric mixture of β-lactams **9** and **10** (Scheme 4) in the ratio of 92:8 (HPLC).

Scheme 4



In this reaction diastereospecific *cis*-β-lactam[11]ring formation was observed. The isomers (**9** & **10**) obtained were diastereomeric at N1-(α-thiophenyl)benzylic position, which was confirmed by converting them to N1-benzyl-*cis*-β-lactam via reductive removal of thiophenyl group. Thus, elimination of thiophenyl group of distereomeric mixture of β-lactams **9** and **10** using Raney Ni gave N1-benzyl-*cis*-β-lactam (**11**) as a single diastereomer (^{1}H NMR) in high yield (Scheme 5). The spectral data and rotation of the β-lactam **11** were found to be identical with a compound of known absolute configuration reported earlier.[16] Therefore, the absolute stereochemistry at 3 and 4 positions of β-lactam ring in **9** and **10** was assigned as 3*R*, 4*S*.

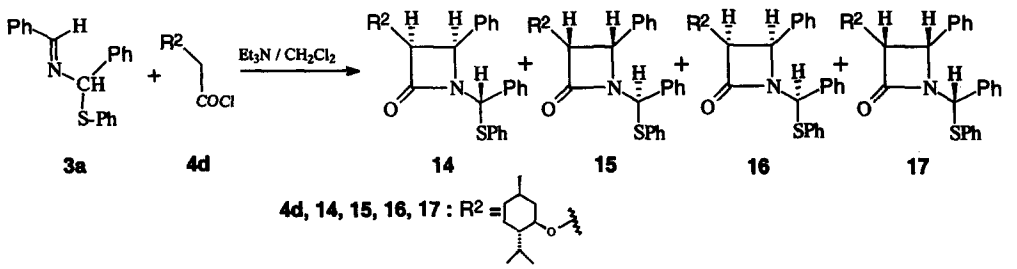
Scheme 5



These assignments were further confirmed by deprotection of the N1-(α-thiophenyl)benzylic group. The oxidative removal of the N1-(α-thiophenyl)benzylic group of the diastereomeric mixture of β-lactams **9** and **10** using potassium persulfate in acetonitrile/water under reflux conditions gave the N1-unsubstituted β-lactam (**12**) as a single diastereomer (^{1}H NMR) in good yield (Scheme 5). This N1-unsubstituted β-lactam (**12**) was also prepared from the N1-(*p*-methoxyphenyl)-β-lactam (**13**) known to have (3*R*, 4*S*) absolute configuration. Thus, **13** on treatment with ceric(IV)ammonium nitrate (CAN) in acetonitrile/water gave the NH-β-lactam **12** in 86.8% yield (Scheme 5) which showed identical spectral (NMR) and analytical (m.p., rotation) data with the NH-compound **12** prepared from the diastereomeric mixture of β-lactams **9** & **10**. From the above chemical transformations the absolute configuration at the 3 and 4 positions of β-lactam ring in **9**, **10** & **12** was unambiguously established as 3*R*, 4*S*.

We have also studied the effect of the chiral ketene derived from menthyloxyacetyl chloride (**4d**) on diastereoselective β-lactam ring formation. The starting chiral menthyloxyacetic acid was obtained in good yield by alkylation[17] of *l*-menthol with chloroacetic acid using sodium metal in dry toluene under refluxing conditions. The menthyloxyacetic acid on treatment with thionyl chloride gave the required chiral acid chloride **4d** in high yield. The acid chloride **4d** on reaction with imine **3a** in presence of triethylamine gave a diastereomeric mixture of *cis*-β-lactams (**14-17**) in good yield (Scheme 6).

Scheme 6

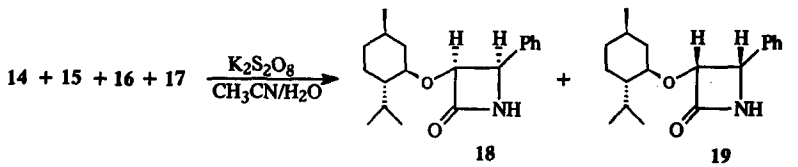


^{1}H NMR analysis of the crude reaction product showed the presence of four *cis*-β-lactams (**14**, **15**, **16** & **17**) in the diastereomeric ratio of 35:35:18:12, the diastereomeric ratio due to N1-(α- thiophenyl)benzyl group being found to be 70:30 (**14** + **15** : **16** + **17**). However, this chiral acid chloride **4d**, did not give appreciable asymmetric induction in β-lactam ring formation and almost equal amounts of two major (**14** & **15**) and two minor (**16** & **17**) diastereomers were formed. Crystallization of diastereomeric mixture from pet. ether : acetone (96:4) gave only one diastereomer, out of the four, in pure form as a white solid, which was found to be one of the minor diastereomers (**16** or **17**) by ^{1}H NMR spectral analysis. The absolute stereochemistry could not be determined as this pure compound failed to give X-ray quality crystals.

The N1-deprotection of the diasteromeric mixture of β-lactams **14**, **15**, **16** & **17** using potassium persulfate in acetonitrile/water under reflux condition gave a mixture two diastereomers **18** & **19** in almost equal amounts (Scheme 7). This further confirms that the diastereomeric ratio of 70:30 is due to the chiral

center of N1-(α-thiophenyl)benzyl group and there is no diastereoselectivity in β-lactam ring formation. Similarly, the potassium persulfate oxidation of pure diastereomer (**16** or **17**) gave one of the N-unsustituted β-lactam **18** or **19** in good yield.

Scheme 7



In conclusion, we have developed a useful method for the synthesis of N1-unsubstituted β-lactams, which can be prepared with high diastereoselectivity in certain set of substrates.

Acknowledgment : We thank Dr. A. Sarkar for valuable suggestions and the authors (KK & VS) thanks CSIR for the financial support.

Experimental Section

^{1}H NMR Spectra were recorded in $CDCl_3$ solution on a Brucker 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. Methylene chloride was distilled over P_2O_5 under argon. Silica gel (SD's, 60 - 120 mesh) was used for column chromatography.

Preparation of Hydrazamides (2a & 2b) : Freshly distilled aldehyde was added to a ca. 10 fold excess of aq. NH_3 (30%). The reaction mixture was stirred for 3 h. at room temperature. The supernatant liquid was decanted off and the lumps were crushed, treated with water and filtered. The crude solid so obtained was crystallized from ethanol to give pure hydrazamides **2a,b** in very high yield.

1-Phenyl-N,N'-bis(phenylmethylene)methanediamine(2a): Yield : 92%. M.p. 101-102 °C [lit.[9a] m.p. 101-102 °C]. ^{1}H NMR : δ 5.80 (s, 1H); 7.18 (m, 9H); 7.62 (m, 6H); 8.30 (s, 2H). IR : 1630, 754, 693 cm^{-1}.

1-*p*-Anisyl-N,N'-bis(*p*-anisylmethylene)mehtanediamine(2b) : Yield : 89%. M. p. 126-128 °C [lit.[9b] m.p. 128.5-130.5 °C]. ^{1}H NMR : δ 3.68 (s, 3H); 3.75 (s, 6H); 5.73 (s, 1H); 6.73 (d, J = 9 Hz, 6H); 7.27 (d, J = 9 Hz, 2H); 7.62 (d, J = 9 Hz, 4H); 8.28 (s, 2H). IR : 1610, 1030, 760 cm^{-1}.

Synthesis of N-[(α-thiophenyl)benzyl]imine (3a) : A mixture of hydrobenzamide (**1a**, 5.96 g, 0.02 mol), thiophenol (3.34 g, 0.03 mol) and 1,4-dioxane (30 mL) was refluxed for 10 h. The dioxane was removed by distillation under reduced pressure and the residue was treated with pet. ether (10 mL) and kept in refrigerator over night. The precipitated solid was filtered and washed with cold pet. ether (5 mL) to get 9 g (99%) of imine **3a**, which was sufficiently pure so as to be used in next step with out further purification. M. p. 79-80 °C [lit.[10] m.p. 79.5 °C]. ^{1}H NMR : δ 5.93 (s, 1H); 7.30 (m, 11H); 7.48 (d, J = 7.5, 2H); 7.61 (d, J = 7.5, 2H); 8.0 (s, 1H). IR : 1628, 749, 694 cm^{-1}.

N-[(α-Thiophenyl)-*p*-methoxybenzyl]imine (3b) : Using the above procedure the imine **3b** was prepared from **2b** in 98% yield. M. p. 94 - 95 °C. ^{1}H NMR : δ 3.80 (s, 3H); 3.86 (s, 3H); 5.90 (s, 1H); 6.95 (d, J = 8.8 Hz, 4H); 7.25 (m, 3H); 7.43 (m, 2H); 7.52 (d, J = 8.8 Hz, 2H); 7.70 (d, J = 8.8 Hz, 2H); 7.95 (s, 1H). IR : 1605, 836, 736 cm^{-1}.

Typical procedure for the preparation of β-lactams (5a-e & 6a-e) : A solution of the acid chloride (**4a-c**, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imines (**3a,b**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was then allowed to warm-up to r.t. and stirred further for 13 h. It was then washed with water (2x15 mL), satd. $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether:acetone, 9:1) to give diastereomeric mixture of β-lactams (**5a-e** & **6a-e**) in good yields. The major and minor diastereomers were separated by crystallization from pet. ether - acetone.

3-Phenoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5a) : M. p. 214 - 215 °C. ^{1}H NMR : δ 5.0 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.47 (s, 1H); 6.8 (d, J = 10 Hz, 2H); 6.83 (t, J = 10 Hz, 1H); 6.95 - 7.70 (m, 17H). ^{13}C NMR : 61.20, 62.34, 81.22, 115.64, 122.00, 127.55, 127.85, 128.08, 128.22, 128.57, 128.81, 129.08, 129.42, 132.49, 133.03, 135.07, 156.87, 165.98. MS : m/z 328 (M^+- SPh), 199, 132 (100%), 109. IR : 1740 cm^{-1}. Anal. Cald for $C_{28}H_{23}O_2NS$: C, 76.86; H, 5.30; N, 3.20. Found : C, 76.68; H, 5.37; N, 3.27.

3-Phenoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (6a) : Isolated as an oil. ^{1}H NMR : δ 4.45 (d, J = 5 Hz, 1H); 5.2 (d, J = 5 Hz, 1H); 6.15 (s, 1H); 6.6 (d, J = 10 Hz, 2H); 6.85 (t, J = 10 Hz, 1H); 6.95 - 7.60 (m, 17H). ^{13}C NMR : 63.23, 63.93, 80.30, 115.56, 121.95, 127.84, 128.06, 128.64, 128.75, 129.05, 129.44, 132.28, 133.04, 133.54, 135.78, 156.79, 164.91. IR : 1740 cm^{-1}.

3-Benzyloxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5b) : M.p. 119 - 120 °C. ^{1}H NMR : δ 4.0 (d, J = 10.5 Hz, 1H); 4.15 (d, J = 10.5 Hz, 1H); 4.5 (d, J = 4.8 Hz, 1H); 5.05 (d, J = 4.8 Hz, 1H); 6.43 (s, 1H); 6.76 - 6.85 (m, 2H); 7.00 - 7.65 (m, 18H). ^{13}C NMR : 61.00, 62.17, 72.24, 82.83, 127.73, 127.86, 127.99, 128.14, 128.46, 128.75, 129.32, 132.50, 133.02, 133.85, 135.25, 136.25, 167.0. MS : m/z 342 (M^+-SPh), 199, 132, 109, 91 (100%). IR : 1740 cm^{-1}. Anal. Cald for $C_{29}H_{25}NO_2S$: C, 77.13; H, 5.58; N, 3.10. Found : C, 77.07; H, 5.77; N, 3.07.

3-Benzyloxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (6b) : Isolated as an oil. ^{1}H NMR : δ 4.05 (d, J = 10.8 Hz, 1H); 4.15 (d, J = 10.8 Hz, 1H); 4.35 (d, J = 4.8 Hz, 1H); 4.65 (d, J = 4.8 Hz, 1H); 6.15

(s, 1H); 6.82 - 7.50 (m, 20H). ^{13}C NMR : 62.91, 63.43, 72.04, 82.67, 127.65, 127.89, 128.44, 128.60, 128.85, 131.91, 133.76, 165.92. IR : 1740 cm^{-1}.

3-Acetoxy-N1-[(α-thiophenyl)benzyl]-4-phenylazetidin-2-one (5c) : M. p. 153 -154 °C. ^{1}H NMR : δ 1.55 (s, 3H); 5.22 (d, *J* = 5.3 Hz, 1H); 5.40 (d, *J* = 5.3 Hz, 1H); 6.44 (s, 1H); 6.85 - 7.70 (m, 15H). ^{13}C NMR : 19.57, 60.40, 62.66, 76.12, 127.54, 127.81, 128.05, 128.22, 128.42, 128.63, 128.76, 129.42, 132.59, 133.39, 134.78, 164.89, 168.76. IR : 1750 cm^{-1}. Anal. Cald for $C_{24}H_{21}O_3NS$: C, 71.44; H, 5.25; N, 3.47. Found : C, 71.32; H,5.14; N,3.54.

3-Phenoxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (5d) : M.p. 157 - 159 °C. ^{1}H NMR : δ 3.70 (s, 3H); 3.72 (s, 3H); 4.95 (d, *J* = 4.8 Hz, 1H); 5.12 (d, *J* = 4.8 Hz, 1H); 6.4 (s, 1H); 6.50 - 7.65 (m, 18H). ^{13}C NMR : 54.97, 55.05, 60.66, 61.43, 81.05, 113.02, 113.43, 115.50, 121.78, 125.02, 127.31, 128.23, 128.95, 129.19, 129.96, 132.64, 156.82, 159.32, 159.47, 165.71. MS : m/z 388 (M^+- SPh), 254, 162 (%), 109. IR : 1740 cm^{-1}. Anal. Cald for $C_{30}H_{27}O_4NS$: C, 72.41; H, 5.47; N, 2.81. Found C, 72.44; H, 5.56; N, 2.87.

3-Benzyloxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (5e) : M. p. 149-151 °C. ^{1}H NMR : δ 3.71 (s, 3H); 3.77 (s, 3H); 4.02 (d, *J* = 11 Hz, 1H); 4.16 (d, *J* = 11 Hz, 1H); 4.43 (d, *J* = 5.4 Hz, 1H); 4.96 (d, *J* = 5.4 Hz, 1H); 6.35 (s, 1H); 6.53 - 6.72 (m, 4H); 6.83 - 7.45 (m, 12H); 7.53 - 7.64 (m, 2H). ^{13}C NMR : 55.29, 60.59, 61.50, 72.21, 82.74, 113.37, 113.60, 125.98, 127.72, 127.80, 128.03, 128.16, 128.33, 129.17, 129.33, 130.11, 132.85, 159.61, 167.02. IR : 1750 cm^{-1}. Anal. Cald for $C_{31}H_{28}O_4NS$: C, 72.92; H, 5.53; N, 2.74. Found C, 72.24; H, 6.07; N, 2.76.

3-Benzyloxy-N1-[(α-thiophenyl)-*p*-methoxybenzyl]-4-*p*-anisylazetidin-2-one (6e) : Isolated as an oil .^{1}H NMR : δ 3.80 (s, 3H); 3.83 (s, 3H); 4.07 (d, *J* = 10.8 Hz, 1H); 4.15 (d, *J* = 10.8 Hz, 1H); 4.25 (d, *J* = 5.5 Hz, 1H); 4.63 (d, *J* = 5.5 Hz, 1H); 6.10 (s, 1H); 6.80 - 7.45 (m, 18H). IR : 1745 cm^{-1}.

Preparation of N1-unsubstituted β-lactams (7a-c) : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of β-lactams 5 (0.2 mmol) in acetonitrile (8 mL) was added and the reaction mixture was refluxed with stirring for 4 h. After completion of the reaction (TLC), the acetonitrile was removed by distillation under reduced pressure and the residue was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was washed with water (15 mL), brine (10 mL) and dried over Na_2SO_4. It was filtered and filtrate on removal of solvent provided the crude product, which was column chromatographed to get of pure unsubstituted β-lactams 7.

3-Phenoxy-4-phenylazetidin-2-one (7a) : Yield 70%. M.p. 160 °C. ^{1}H NMR : δ 5.05 (d, *J* = 4.8 Hz, 1H, C3H); 5.5 (dd, *J* = 2.5 & 4.8 Hz, 1H, C4H); 6.6 (bs, 1H, NH); 6.8 (d, *J* = 9 Hz, 2H, Ar); 6.9 (t, J = 9 Hz, 1H, Ar); 7.10 - 7.40 (m, 7H, Ar). IR : 2800 - 3500, 1770 cm^{-1}. Analysis Cald for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found : C, 75.51; H, 5.73; N, 5.62.

3-Benzyloxy-4-phenylazetidin-2-one (7b) : Yield 64%. M. p. 188-189 °C. ^{1}H NMR : δ 4.25 (d, *J* = 12 Hz, 1H); 4.35 (d, *J* = 12 Hz, 1H); 4.85 (d, *J* = 4.8 Hz, 1H); 4.95 (m, 1H); 6.25 - 6.30 (bs, 1H); 6.9 - 7.8 (m, 10H). IR : 1750, 3195 cm^{-1}. Anal. for Cald $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found : C, 75.48; H, 6.01; N, 5.46.

3-Phenoxy-4-*p*-anisylazetidin-2-one (7c) : Yield 70%. M. p. 165 - 167 °C. ^{1}H NMR : δ 3.80 (s, 3H); 5.03 (d, J = 4.5 Hz, 1H); 5.42 (dd, J = 2.4 & 4.5 Hz, 1H); 6.50 (s, 1H); 6.75 - 6.97 (m, 5H); 7.11 - 7.23 (m, 2H); 7.30 (d, J = 8.2 Hz, 2H). IR : 1720 & 3190 cm^1. Anal. for Cald $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found : C, 71.78; H, 5.27; N, 5.46.

Preparation of diastereomeric mixture of {N1'-[(α-thiophenyl)benzyl]-4'-phenylazetidin-2'-one-3'-yl}-2,10-comphorsultam (9 & 10) : To a stirred mixture of acid **8** (0.4 g, 1.46 mmol), imine **3a** (0.653 g, 2.15 mmol), triethylamine (0.6 mL) and dry CH_2Cl_2 (10 mL), a solution of phenyl dichlorophosphate (0.32 mL, 2.15 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C. The reaction mixture was then allowed to warm-up 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 (15 mL), satd. $NaHCO_3$ solution (15 mL), brine (15 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, pet. ether/acetone) to furnish 0.614 g (75.4%) of the diastereomeric mixture of **9** & **10** as a white solid, m. p. 98 - 100 °C. This mixture was used for deprotection without separation. ^{1}H NMR (diastereo-meric mixture **9** & **10**) : δ 0.12 (s, 3H); 0.68 (s, 3H); 0.82-1.03 (m, 1H); 1.1-1.47 (m, 4H); 1.50-1.85 (m, 2H); 2.82 & 3.00 (2xdd, J = 4.8 & 13.2 Hz, total 2H, CH_2); 3.39 & 3.54 (2xdd, J = 3.9 & 6.8 Hz, total 1H); 4.27 & 4.67 (2xd, J = 4.8 Hz, total 1H); 4.78 and 5.23 (2xd, J = 4.8 Hz, total 1H); 5.97 and 6.38 (2xs, total 1H); 6.71 - 6.82 (m, total 2H, Ar); 6.92 - 7.84 (m, total 13H, Ar). IR (diastereomeric mixture) : 1755 cm^{-1}. $[\alpha]^{25}_D$ (diastereomeric mixture) : +96.086° (c 1, CH_2Cl_2). Anal. Cald for $C_{32}H_{34}N_2O_3S_2$: C, 68.79; H, 6.13; N, 5.01. Found C, 68.67; H, 6.71; N, 4.50.

Preparation of (2R, 3S, 6R, 3'R, 4'S)-[N1'-benzyl-4'-phenylazetidin-2'-one-3'-yl}-2,10-comphorsultam (11) from diastereomeric mixture of 9 & 10 : To a solution of diastereomeric mixture of β-lactams **9** & **10** (0.050 g , 0.089 mmol) in ethanol (5 mL) was added Raney nickel (0.8 mL suspension in ethanol) and the resultant mixture was stirred for 30 min at room temperature. After completion of the reaction (TLC), it was filtered through celite pad, washed with ethanol. The filtrate on removal of solvent yielded 0.040 g (99.3%) of N1-benzyl-β-lactam (**11**) as a white crystalline solid, m. p. 222 - 223 °C [lit.[16] m.p. 221-222 °C]. ^{1}H NMR : δ 0.20 (s, 3H); 0.75 (s, 3H); 1.30 (m, 2H); 1.7(m, 5H); 2.95 (d, J = 14 Hz, 1H); 3.05 (d, J = 14 Hz, 1H); 3.55 (t, J = 7 Hz, 1H); 4.05 (d, J = 16 Hz, 1H); 4.7 (d, J = 5.4 Hz, 1H); 5.0 (d, J = 16 Hz, 1H); 5.05 (d, J = 5.4 Hz, 1H); 7.10 - 7.45 (m, 10H). IR : 1760 cm^{-1}. $[\alpha]^{25}_D$: +62.87° (c 1.1, CH_2Cl_2); {lit.[16] $[\alpha]^{25}_D$: +62.0° (c 1, CH_2Cl_2)}.

Preparation of (2R, 3S, 6R, 3'R, 4'S)-[4'-phenylazetidin-2'-one-3'-yl]-2,10-camphorsultam (12) from diastereomeric mixture of 9 & 10 : To a solution of potassium persulfate (0.850 g, 3.11 mmol) in water (10 mL), a solution of diastereomeric mixture of β-lactams **9** & **10** (0.7 g, 1.25 mmol) in acetonitrile (25 mL) was added and the reaction mixture was refluxed with stirring for 4 h. After completion of the reaction (TLC), the reaction mixture was work-up as described for compound **7**. The crude product obtained was column chromatographed to get 0.341 g (75.8%) of pure NH β-lactam **12** as a white solid, which was crystallized from acetone/pet. ether, m. p. 234 - 236 °C. ^{1}H NMR : δ 0.09 (s, 3H); 0.71 (S, 3H); 0.77 - 0.99 (m, 1H); 1.03 - 1.47 (m, 4H); 1.52 - 1.89 (m, 2H); 2.98 (dd, J = 13.66 Hz, and 33.17 Hz, 2H); 3.57 (t, J =

5.36 Hz, 1H); 5.00 (d, 4.8 Hz, 1H); 5.21 (bd, 1H); 6.67 (bs, 1H); 7.17 - 7.68 (m, 5H). IR : 1760, 3300 cm^{-1}. $[a]^{25}_D$: +43.85° (c 1, CH_2Cl_2).

Preparation of (2R, 3S, 6R, 3'R, 4'S)-[4'-phenylazetidin-2'-one-3'-yl]-2,10-comphorsultam (12) from (2R, 3S, 6R, 3'R, 4'S)-[N1'-(p-Anisyl)-4'-phenylazetidine-2'-one-3'-yl]-2,10-comphorsultam (13) : A solution of β-lactam 13 (0.074 g, 0.16 mmol) in acetonitrile/tetrahyrofuran (3:1mL) was cooled to 0°C and treated with a solution of ceric (IV) ammonium nitrate (0.482 mmol) in water (1.5 mL) over 3 min. The solution was stirred at 0 - 5 °C for 45 min. and diluted with 10 mL of water. The mixture was extracted with ethyl acetate (3x5 mL). The organic extracts were washed with satd. sodium bicarbonate (5 mL) and the aqueous solution back extracted with ethyl acetate (5 mL). The combined organic extracts were washed with sodium sulfite (10%, 2x10 mL), satd. sodium bicarbonate (5 mL), and brine (10 mL), It was then dried over Na_2SO_4) and filtered through celite. The filtrate on removal of solvent furnished crude product, which was purified by column chromatography to give 0.050 g (86.8%) of NH-β-lactam 12 as a white solid, m. p. 233 - 234 °C. $[\alpha]^{25}_D$: + 43.6° (c 0.9, CH_2Cl_2). The spectral data for this compound was identical to that of NH-β-lactam 12 prepared from diastereomeric mixture of 9 & 10.

3-Menthyloxy-N1-[(1'-thiophenyl)benzyl]-4-phenylazetidin-2-one (14-17) : A solution of the menthyl-oxyacetyl chloride (**4d**, 2 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of imine (**3a**, 1.5 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was then allowed to warm to r.t. and stirred further for 15 h. It was then washed with water (2x15 mL), satd. $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). The removal of organic solvent by distillation under reduced pressure gave crude product, which was purified by column chromatography (silica gel, 60-120 mesh, pet. ether:acetone, 9:1) to give 0.77 g (62.2%) of a semi solid mixture of β-lactams (**14-17**) with diastereomeric ratio of 35:35:18:12. ^1H NMR (mixture of **14-17**) : δ 0.02 - 1.01 (m, total 13H); 1.02 - 1.24 (m, 2H); 1.24 - 1.58 (m, 2H); 1.85 - 2.17 (m, 1H); 2.72 - 2.83 and 3.02 - 3.22 (2xm, total 1H); 4.28, 4.31, 4.40 and 4.43 (4xd, J = 4.5 Hz, total 1H); 4.60, 4.67, 4.97 and 4.99 (4xd, J = 4.5 Hz, total 1H); 6.11, 6.16, 6.27 and 6.29 (4xs, total 1H); 6.87 - 7.88 (m, 15). IR : 1745 cm^{-1}.

The diastereomeric mixture of **14 - 17** was crystallized from pet. ether - acetone to give 60 mg of one of the minor diastereomer (**16** or **17**) in pure form. M. p. 158 - 160 °C. ^1H NMR : δ 0.1 (d, J = 8 Hz, 3H); 0.48 (d, J = 8 Hz, 3H); 0.60 - 0.75 (m, 2H); 0.82 (d, J = 8 Hz, 3H); 0.9 - 1.3 (m, 3H); 1.35 - 1.50 (m, 1H); 1.85 - 2.05 (m, 1H); 2.75 (m, 1H); 4.40 (d, J = 5.2 Hz, 1H); 5.00 (d, J = 5.2 Hz, 1H); 6.4 (s, 1H); 6.9 - 7.6 (m, 15H). ^{13}C NMR : 15.61, 20.61, 22.13, 22.86, 24.47, 31.17, 31.41, 34.16, 40.87, 47.53, 61.68, 61.89, 80.77, 82.19, 127.39, 127.59, 127.84, 128.05, 128.18, 128.30, 128.67, 128.88, 128.97, 129.21, 131.94, 132.70, 134.37, 135.50, 168.96. IR : 1740 cm^{-1}. $[a]^D_{23}$: +98.58° (c 1, $CHCl_3$). Anal. Cald for $C_{32}H_{37}O_2NS$: C, 76.91; H, 7.46; N, 2.80. Found C, 76.53; H, 7.52; N, 2.92.

Preparation of NH-β-lactams 18 and 19 form diastereomeric mixture of β-lactams 14-17 : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of diastereomeric mixture of β-lactams **14-17** (0.1g, 0.2mmol) in acetonitrile (8 mL) was added and the reaction mixture was refluxed with stirring for 4 h. The usual work-up as described for compound 7 gave crude product, which was purified by column chromatography to give 45 mg (75%) of NH-β-lactams (**18 & 19**) as a mixture of two diastereomers.

^{1}H NMR (mixture of 18 & 19) : δ 0.21 - 1.08 (m, 13H); 1.12 - 1.32 (m, 2H); 1.42 - 1.68 (m, 2H); 1.92 - 2.18 (m, 1H); 2.98 and 3.29 (2xtd, *J* = 4.5 & 9.9 Hz, total 1H); 4.82 and 4.85 (2xd, *J* = 4.5 Hz, total 1H); 4.90 - 4.93 and 4.95 - 4.99 (2xdd, *J* = 2.2, & 4.8 Hz, total 1H); 6.30 (bs, 1H); 7.20 - 7.49 (m, 5H). IR : 3410, 1750 cm^{-1}.

Preparation of 3-menthyloxy-4-phenylazetidin-2-one (18 or 19) from pure β-lactam 16 or 17 : To a solution of potassium persulfate (0.162 g, 0.6 mmol) in water (3 mL), a solution of pure β-lactam 16 or 17 (0.1 g, 0.2 mmol) in acetonitrile (8 mL), was added and the reaction mixture was refluxed with stirring for 4 h. The usual work-up as described for compound 7 gave crude product, which was purified by column chromatography to give 39 mg (65%) of pure NH-β-lactam (18 or 19) as a white solid. M.p. 173-174 °C. ^{1}H NMR : δ 0.26 (d, *J* = 8 Hz, 3H); 0.55 (d, *J* = 8 Hz, 3H); 0.76 (m, 2H); 0.88 (d, *J* = 8 Hz, 3H); 0.97 (m, 2H); 1.26 (m, 2H); 1.52 (m, 2H); 2.15 (m, 1H); 2.95 (td, *J* = 4. 5 &10.2, IH); 4.81 (d, *J* = 4.8 Hz, 1H); 4.88 (dd, *J* = 2.2, & 4.8 Hz, 1H); 6.30 (bs, 1H); 7.42 (m, 5H). ^{13}C NMR : 15.87, 20.70, 22.21, 23.02, 24.68, 31.55, 34.28, 41.22, 47.61, 58.79, 81.37, 84.56, 127.80, 128.12, 136.48, 169.89. IR : 1759, 3413 cm^{-1}. Anal. for Cald $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65. Found : C, 75.92; H, 9.15; N, 4.64. $[a]^{25}_D$: +25.51° (c 0.97, CH_2Cl_2).

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11. The ^{1}H NMR of the crude reaction mixture indicated the formation of only *cis*-isomers ($J_{3,4}$ = 4 -5 Hz).

12. HPLC : Perkin-elmer 410-pump, H.P. 1050 MWD at 254 nm connected to HP 3396 Ser-II integrater. Col. MN-C-18, 8 mm X 100 mm length. Solvent system (v/v) : 80:20 (MeOH:H_2O) flow rate 1.5 mL/min.

13. Data was measured on a PC-controlled Enraf-Nonius CAD-4 single crystal X-ray diffractometer[13] with Mo-Kα (λ= 0.7093 A°) radiation at 293 K. Crystal belongs to monoclinic, space group $P2_1$ /c with a = 11.813 (2), b = 6.410 (2), c = 30.552 (4) A°; V = 2312.6 A° 3, Z = 4, dcalc = 1.257 Mgm^{-3}, μ = 0.165 mm^{-1}. The structure was solved by direct methods using MULTAN-80 Least squares refinement of scale factor, positional and anisotroic thermal parameters for non hydrogen atoms converged to R = 0.068. Hydrogen atoms geometrically fixed and confirmed by difference fourier were held fixed during refinement. Structure solution and refinements were carried out using NRCVAX programs.

14. *For details of the X-ray data see* : Srirajan, V.; Bhawal, B. M; Puranik, V. G. *Acta. Cryst. C* **1997**, *C53*, 358.

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