An Efficient and Eco-friendly Approach to ^{15}N-Unsubstituted β-Lactams: ^{15}N-Labled Synthons for Taxol and Its Analogs

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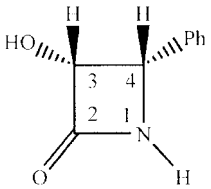
An efficient and eco-friendly approach to *N*-unsubstituted β-lactams has been developed using mostly water as the reaction medium. This methodology was applied to the synthesis of *N*-unsubstituted 3-hydroxy-4-phenyl-2-azetidinone derivatives (including ^{15}N-labeled version) which are suitable precursors for the C-13 side chain of taxol and its analogs.

Keywords : ^{15}N-Labled synthons for taxol, ^{15}N-Unsubstituted β-lactams.

Introduction

Taxol (paclitaxel) and taxotere (docetaxel) are newly introduced drugs that show great promise against ovarian and breast cancer and against several other types of tumor. Taxol and taxotere are manufactured by semi-synthesis. A convenient intermediate[1] for the C-13 side chain of these drugs is (*3R, 4S*)-3-hydroxy-4-phenyl-2-azetidinone **1**. Variants of this α-hydroxy-β-lactam derivative[2] are suitable for the preparation of many types of analog of taxol.



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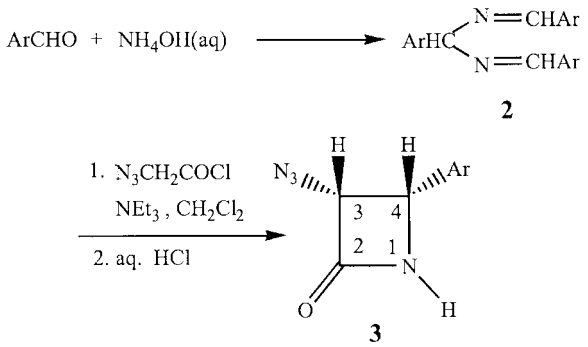
In view of increasing emphasis on environmentally benign organic synthesis, we have sought eco-friendly reactions that could lead to various β-lactam synthons including **1**. We wish to report here an adaptation of simple method (Scheme 1) developed by Wells and coworkers[3] in 1969 that led to *N*-unsubstituted *cis*-3-azido-2-azetidinones **3** in low yield using mostly water as the reaction medium.

The hydrobenzamide **2** used as an intermediate in this synthesis is easily obtained from aromatic aldehydes and strong ammonia.

Results and Discussion

***N*-Unsubstituted 4-aryl-3-hydroxy-2-azetidinones**. The β-lactam formation method of Wells and coworkers[3,4] was modified: toluene was found to be better than methylene chloride for conducting the condensation.



Scheme 1

Acetoxyacetyl chloride **4** was allowed to react with a toluene solution of the hydrobenzamide **2** and triethylamine at 0 °C for several hours. Hydrolysis of this mixture by stirring with silica gel led to the *cis*-β-lactam **7**. The yield based on the acid chloride was 63-88%. We have also used benzyloxyacetyl chloride, methoxyacetyl chloride and various hydrobenzamides to obtain several *N*-unsubstituted α-hydroxy-β-lactam derivatives (Table 1).

The ^{1}H NMR spectrum of the reaction mixture of an acid chloride **4**, hydrobenzamide and triethylamine showed the initial formation of two diastereomeric *cis*-β-lactams **5** and **6**. Obviously, only one of the imino groups in **2** was undergoing cycloaddition at low temperature.

Bis-β-lactams. The reaction of the mixture of **5** and **6** with another equivalent of acid chloride at about 70 °C led to the bis-β-lactams **8** and **9** (Scheme 2). These diastereomers, which were formed in unequal amounts, could be separated by column chromatography or a single crystallization from a suitable solvent. The β-lactam **10** and **11** were obtained by using two different acid chlorides in succession. Attempts to hydrolyze these bis-β-lactams (Table 2) with silica gel or dilute hydrochloric acid have been unsuccessful.

Mild alkaline hydrolysis of the 3-acetoxy-4-phenyl-2-azeti-

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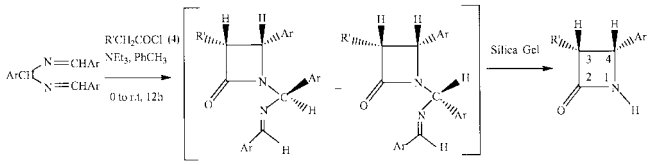
Table 1. Synthesis of *N*-unsubstituted -lactams **7**



2 **5** **6** **7**

Compound	R^1	Ar	Yield (%)	mp (°C)
7a	AcO	Ph	88	139-140
7b	BnO	Ph	63	192-193
7c	MeO	Ph	65	74
7d	AcO	*p*-Methoxyphenyl	81	99-100
7e	BnO	*p*-Methoxyphenyl	69	182-183
7f	MeO	*p*-Methoxyphenyl	72	142-143
7g	AcO	*m*-Bromophenyl	78	130-131

dinone (**7**, R'=OAc) provides **1** in high yield. We have described earlier a convenient method for resolving α-hydroxy-β-lactams *via* the Ferrier reaction involving iodine catalyzed α-glycosylation.[5] Extension of this method for the resolution of *N*-unsubstituded β-lactam is in progress.

***^{15}N*-Labeled β-lactams**. Formation of hydrobenzamide **2** from an aromatic aldehyde and ammonium hydroxide has been conducted under various conditions.[6] In the interest of "atom economy" (reduction of waste chemical production), we have developed a recycling method: the aromatic aldehyde is allowed to react with an excess of NH_4Cl, enough *i*-propyl alcohol is added to ensure a homogeneous solution in the beginning; the pH is 9 or higher. The hydrobenzamide that crystallized out on standing is separated; the mother liquor can be recycled (at least twice) after the addition of fresh NH_4Cl and an aromatic aldehyde.

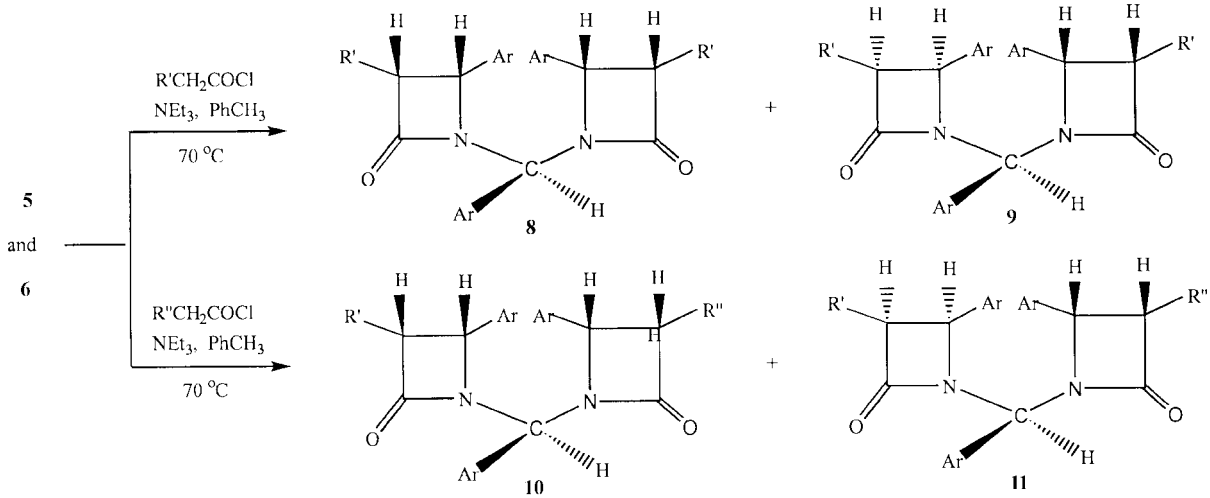
Table 2. Synthesis of bis β-lactams **8**&**9** and mixed bis β-lactams **10**&**11**

Compound	R'	Ar	R''	Yield (%)[a]	mp (°C)[b]	Ratio[c]
8&**9a**	MeO	Ph		66(41)	163-164	70:30
8&**9b**	BnO	Ph		84(61)	103-104	75:25
8&**9c**	MeO	*p*-Methoxyphenyl		66(38)	119-120	70:30
8&**9d**	BnO	*p*-Methoxyphenyl		73(58)	–[d]	80:20
8&**9e**	MeO	*m*-Bromophenyl		74(28)	163-164	70:30
10&**11**	MeO	Ph	BnO	31(17)	157-158	70:30

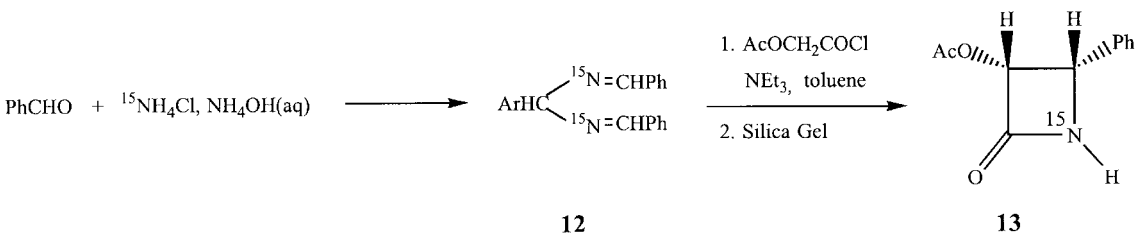
[a]Yield of two diastreomers (Yield of major diastreomer); [b]mp of major diastreomer; [c]Determined from a ^{1}H NMR spectrum; [d]The diastreomers could not be separated.

Since $^{15}NH_4Cl$ is readily available at a reasonable price, we have used it for introducing an ^{15}N label in β-lactam. For this purpose, we have modified the preparation of hydrobenzamides. Thus, benzaldehyde was treated with an aqueous solution (pH=9) of $^{15}NH_4Cl$, NaOH and a small amount of NH_4OH, ^{15}N-labeled hydrobenzamide **12** was collected by filtration. The (+/–)-^{15}N *cis*-3-acetoxy-4-phenyl-2-azetidinone **13** was characterized by ^{1}H NMR and mass spectra (Scheme 3).[7]

The expected ^{15}N-H coupling of 90 Hz was observed and



Scheme 2



Scheme 3

the level of ^{15}N enrichment was deduced to be 80-86% from ^{1}H NMR and mass spectral data. This ^{15}N-labeled β-lactams would be very useful for the preparation of stable isotope labeled taxol, taxotere and analogs for metabolic studies. The ^{15}N-labeled β-lactams and compounds derived from them could also serve as internal standards for quantitation by mass spectral methods.

In summary, a simple, eco-friendly reaction has been devised for the preparation of *N*-unsubstituted α-hydroxy-β-lactam derivatives which are synthons for a variety of physiologically active compounds including taxol and analogs. ^{15}N-labeled intermediates for taxol should be useful for preparing internal standards for mass spectral quantitation and for metabolic studies. The chemical reactions, which are environmentally more benign than many of the alternative processes, are convenient for the large scale preparation of intermediates for taxol and taxotere.

Experimental Section

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a Mel-Temp (50/60 cycles, 110-120 volts, 250 watts) apparatus and are uncorrected. Toluene was distilled from sodium benzophenone ketyl immediately prior to use. Methylene chloride was distilled from calcium hydride immediately prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of Argon in glassware that had been oven and/or flame dried. Infrared spectra were recorded on a Perkin-Elmer 1420 Ratio Recording Infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500- or 200-MHz FTNMR spectrometer. Mass spectra were obtained on a Scientific Research Instruments Biospect mass spectrometer. Flash column chromatography was performed on silica gel 60 (230-400 mesh, Merck) using an ethyl acetate-hexane mixture as the eluent unless specified otherwise. All chromatographic separations were monitored by TLC analyses, performed using glass plates precoated with 0.25-mm 230-400-mesh silica gel impregnated with a fluorescent indicator (254 nm). Solvent removal was accomplished at aspirator pressure using a rotary evaporator.

General procedure for the preparation of imines 2. To an approximately 10-fold excess of an aqueous solution of NH_3 (29-30%), a solution of aldehyde (30 mmol) in ethanol or isopropyl alcohol (20 mL) was added dropwise with stirring. The mixture was then stirred for 12 h. The precipitated product was filtered and dried in a desiccator by connecting it to vaccum. Recrystallization from ethanol or isopropyl alcohol gave **2**.

2a. Benzaldehyde (3.18 g, 30 mmol) in isopropyl alcohol (20 mL) was added to an aqueous solution of NH_3 (200 mL). Recrystallization from isopropyl alcohol gave 2.53 g (85%) of the title compound as a white solid: mp 92°C (lit.[6] 102 °C); IR (KBr) ν 1645 and 1638 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1H, PhCH), 7.20-7.90 (m, 15H, Ar), 8.59 (s, 2H, N=CH); ^{13}C NMR ($CDCl_3$) δ 93.3 (PhCH), 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 130.9, 131.0, 136.2, 141.9, 160.6 (C=N); CIMS (CH_4) 299 $[M+1]^+$, 194 (base peak), 106, 91.

2b. *p*-Anisaldehyde (4.08 g, 30 mmol) in isopropyl alcohol (20 mL) was added to an aqueous solution of NH_3 (200 mL). Recrystallization from isopropyl alcohol gave 3.41 g (88%) of the title compound as a white solid: mp 124-125 °C (lit.[6] 125 °C); IR (KBr) ν 1638 and 1610 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 5.84 (s, 1H, PMPCH), 6.90 (d, J = 8.7 Hz, 2H, Ar), 6.93 (d, J = 8.7 Hz, 4H, Ar), 7.43 (d, J = 8.7 Hz, 2H, Ar), 7.80 (d, J = 8.7 Hz, 4H, Ar), 8.48 (s, 2H, N=CH).

2c. 3-Bromobenzaldehyde (5.55 g, 30 mmol) in isopropyl alcohol (20 mL) was added to an aqueous solution of NH_3 (200 mL). The precipitated gummy product was extracted with methylene chloride and dried over anhydrous sodium sulfate. Removal of solvent by using a rotary evaporator gave 4.82 g (90%) of the title compound as an oil: IR (KBr) ν 1642 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.88 (s, 1H, N=CH), 7.05-8.00 (m, 12H, Ar), 8.44 (s, 2H, N=CH).

Modified preparation of hydrobenzamide 2a.

Method A; Benzaldehyde (3.18 g, 30 mmol) in isopropyl alcohol (10 mL) was added to a solution (pH=9) of water (15 mL), sodium hydroxide (600 mg), conc. ammonium hydroxide (4 mL, approx. 60 mmol) and NH_4Cl (3 g, 56 mmol). The precipitated product was filtered and dried in a desiccator by connecting it to vaccum. Recrystallization from isopropyl alcohol gave 2.6 g (87%) of the title compound as a white solid: mp 92 °C (lit.[6] 102 °C); IR (KBr) ν 1645 and 1638 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1H, PhCH), 7.20-7.90 (m, 15H, Ar), 8.59 (s, 2H, N=CH); ^{13}C NMR ($CDCl_3$) δ 93.3 (PhCH), 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 130.9, 131.0, 136.2, 141.9, 160.6 (C=N); CIMS (CH_4) *m/z* 299 $[M+1]^+$, 194 (base peak), 106, 91.

Method B; Benzaldehyde (3.18 g, 30 mmol) in isopropyl alcohol (10 mL) was added to a solution (pH=9) of water (15 mL), sodium hydroxide (600 mg) and NH_4Cl (3 g, 56 mmol). The precipitated product was filtered and dried in a desiccator by connecting it to vaccum. Recrystallization from isopropyl alcohol gave 1.5 g (50%) of the title compound as a white solid: mp 92 °C (lit.[6] 102 °C); IR (KBr) ν 1645 and 1638 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1H, PhCH), 7.20-7.90 (m, 15H, Ar), 8.59 (s, 2H, N=CH); ^{13}C NMR ($CDCl_3$) δ 93.3 (PhCH), 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 130.9, 131.0, 136.2, 141.9, 160.6 (C=N); CIMS (CH_4) *m/z* 299 $[M+1]^+$, 194 (base peak), 106, 91.

General procedure for the preparation of *N*-unsustituted β-lactams 7. A solution of acid chloride **4** (1.1 mmol) in anhydrous toluene (10 mL) was added to a solution of imine **2** (1 mmol) and triethylamine (2 mmol) in anhydrous toluene (10 mL) at 0-5 °C under Argon. After the addition the reaction mixture was allowed to warm gradually to room temperature and stirred overnight. The reaction mixture was then filtered through Florisil® in order to remove the ammonium salt (triethylammonium chloride). Silica gel (1 g) was added to the filtrate. The mixture was concentrated and left

overnight. Column chromatography on silica gel (hexane-ethyl acetate) gave the *N*-unsustituted β-lactams **7**. Before treating silica gel with the mixture mono-β-lactams **5 & 6** were also isolated to show expected ^{1}H NMR and IR spectra.

***cis*-3-Acetoxy-4-phenylazetidin-2-one (7a)**. The imine **2a** (298 mg, 1 mmol) on treatment with acetoxyacetyl chloride (150 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 180 mg (88%) of the title compound as a white solid: mp 139-140 °C (EtOAc-Hexane); IR (KBr) ν 3200, 1750, 1720 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H, CH_3CO), 5.04 (d, J = 4.6 Hz, 1H, C3 H), 5.88 (dd, J = 2.6 & 4.6 Hz, 1H, C4 H), 6.58 (s, 1H, NH), 7.20-7.40 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 19.7, 57.9, 78.3, 127.5, 127.7, 128.2, 128.5, 134.7, 165.6 (β-lactam CO), 169.0 (acetoxy CO); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.83. Found: C, 64.36; H, 5.27; N, 6.79.

5 & 6a. mp oil (two diastereomers); IR ($CHCl_3$) ν 1775 (C=O), 1755 (C=O), 1645 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, total 3H, CH_3CO), 4.68 and 5.23 (d, J = 4.9 Hz, total 1H, C4 H), 5.69 and 5.75 (d, J = 4.9 Hz, total 1H, C3 H), 6.17 and 6.21 (s, total 1H, PhCH), 6.90-7.80 (m, 15 H, Ar), 8.39 and 8.41 (s, total 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ 60.9, 61.3, 77.9, 78.1, 127.5, 127.6, 127.7, 128.2, 128.5, 128.7, 128.8, 129.1, 131.4, 131.6, 134.2, 135.7, 137.5, 137.9, 163.2 (C=N), 163.8 (C=N), 164.2 (β-lactam CO), 165.0 (β-lactam CO), 168.7 (acetoxy CO).

***cis*-3-Benzyloxy-4-phenylazetidin-2-one (7b)**. The imine (298 mg, 1 mmol) **2a** on treatment with benzyloxyacetyl chloride (203 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 160 mg (63%) of the title compound as a white solid: mp 192-193 °C (EtOAc-Hexane); IR (KBr) ν 3180 (NH) and 1760 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$) δ 4.26 (q, J = 4.4 Hz, 2H, $PhCH_2$), 4.84 (d, J = 4.4 HZ, 1H, C3 H), 4.91 (dd, J = 2.4 & 4.4 Hz, 1H, C4 H), 6.84-7.50 (m, 10H, Arm), 7.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 57.4 (CH_2O), 71.5 (C4), 84.4 (C3), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 136.5, 136.6, 167.5 (β-lactam CO).

5 & 6b. major diastereomer; IR ($CHCl_3$) ν 1755 (C=O), 1645 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.15 (d, J = 11 Hz, 1H, benzyloxy), 4.29 (d, J = 11 Hz, 1H, benzyloxy), 4.85 (d, J = 4.5 Hz, 1H, C4 H), 4.95 (d, J = 4.5 Hz, 1H, C3 H), 6.27 (s, 1H, benzylic), 6.90-7.95 (m, 20H, Ar), 8.43 (s, 1H, N=CH).

***cis*-3-Methoxy-4-phenylazetidin-2-one (7c)**. The imine (298 mg, 1 mmol) **2a** on treatment with methoxyacetyl chloride (119 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 115 mg (65%) of the title compound as a white solid: mp 74 °C (EtOAc-Hexane); IR (KBr) ν 3150 (NH) and 1745 cm^{-1} (NC=O); ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 3H, OCH_3), 4.74 (dd, J = 2.7 & 4.6 Hz, 1H, C4 H), 4.85 (d, J = 4.6 Hz, 1H, C3 H), 6.66 (s, 1H, NH), 7.36 (s, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 58.02, 58.06, 86.63, 127.65, 128.29, 135.82, 167.97 (β-lactam CO); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.23; N, 7.91. Found: C, 68.12; H, 6.05; N, 8.06.

5 & 6c. two diastereomers; IR (KBr) ν 1758 (C=O), 1640 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.04 and 3.07 (s, total 3H, CH_3O), 4.55 and 4.68 (d, J = 4.7 Hz, total 1H, C4 H), 4.63 and 5.10 (d, J = 4.7 Hz, total 1H, C3 H), 6.21 and 6.26 (s, total 1H, PhCH), 7.00-7.85 (m, 15H, Ar), 8.32 and 8.45 (s, total 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ 58.1, 61.2, 61.4, 85.2, 85.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 131.2, 131.4, 135.1, 135.7, 137.7, 137.8, 162.9 (C=N), 163.4 (C=N), 166.8 (β-lactam CO), 167.1 (β-lactam CO); Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.98; N, 7.55. Found: C, 75.87; H, 6.03; N, 7.43.

***cis*-3-Acetoxy-4-(p-anisyl)azetidin-2-one (7d)**. The imine (388 mg, 1 mmol) **2b** on treatment with acetoxyacetyl chloride (150 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 190 mg (81%) of the title compound as a white solid: mp 99-100 °C (EtOAc-Hexane); IR (KBr) ν 3420 (NH), 1780 (CO) and 1755 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 4.98 (d, J = 4.5 Hz, 1H, C3 H), 5.81 (dd, J = 2.6 & 4.5 Hz, 1 H, C4 H), 6.62 (s, 1H, NH), 6.88 (d, J = 8.7 Hz, 2H, Ar), 7.23 (d, J = 8.7 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 19.2, 55.3, 57.4, 78.2, 113.8, 126.6, 128.9, 160.0, 165.7 (β-lactam CO), 169.0 (acetoxy CO); Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.65; H, 5.55; N, 5.79.

***cis*-3-Benzyloxy-4-(p-anisyl)azetidin-2-one (7e)**. The imine (388 mg, 1 mmol) **2b** on treatment with benzyloxyacetyl chloride (203 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 195 mg (69%) of the title compound as a white solid: mp 182-183 °C (CH_2Cl_2-Hexane); IR (KBr) ν 3175 (NH), 1760 (CO) and 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, OCH_3), 4.26 (d, J = 11.4 Hz, benzylic), 4.35 (d, J = 11.4 Hz, 1H, benzylic), 4.80 (d, J = 4.5 Hz, 1H, C3 H), 4.89 (dd, J = 2.6 & 4.5 Hz, C4 H), 6.15 (s, 1H, NH), 6.88-7.10 (m, 3.6H, Ar), 7.20-7.36 (m, 5.4H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.4 (*p*-MeO), 57.9 (C4), 72.2 ($PhCH_2O$), 114.0, 127.8, 128.0, 128.3, 129.2, 137.0, 159.9, 167.7 (β-lactam CO); Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.72; H, 5.85; N, 5.00.

5 & 6e. major diastereomer; mp 105-106 °C (EtOAc and hexane); IR (KBr) ν 1755 (C=O), 1645 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 4.15 (d, J = 12 Hz, 1H, $PhCH_2$), 4.22 (d, J = 12 Hz, 1H, $PhCH_2$), 4.89 (d, J = 4.6 Hz, 1H, C4 H), 4.76 (d, J = 4.6 Hz, 1H, C3 H), 6.15 (s, 1H, PMPCH), 6.80-7.60 (m, 17H, Ar), 8.33 (s, 1H, N=CH).

***cis*-3-Methoxy-4-(p-anisyl)azetidin-2-one (7f)**. The imine (388 mg, 1 mmol) **2b** on treatment with methoxyacetyl chloride (119 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 150 mg (72%) of the title compound as a white solid: mp 142-144 °C (EtOAc-Hexane); IR (KBr) ν 3200 (NH) and 1770 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 3H, C3 OMe), 3.82 (s, 3H, *p*-MeO), 4.71 (dd, J = 2.6 & 4.5 Hz, 1H, C4 H), 4.80 (d, J = 4.5 Hz, 1H, C3 H), 6.26 (s, 1H, NH), 6.92 (d, J = 8.6 Hz, 2H, Ar), 7.31 (d, J = 8.6 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.3 (*p*-MeO), 57.6 (MeO), 58.1 (C4), 86.8 (C3), 113.9, 127.7, 129.0, 159.9, 167.9 (β-lactam CO); Anal. Calcd for

$C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.67; H, 6.15; N, 7.03.

5 & 6f. two diastereomers; IR (KBr) ν 1755 (C=O), 1645 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 and 3.08 (s, total 3H, CH_3O), 3.78-3.85 (m, total 9H, *p*-MeO); 4.49 and 4.63 (d, J = 4.7 Hz, total 1H, C4 H), 4.57 and 5.00 (d, J = 4.7 Hz, total 1H, C3 H), 6.10 and 6.14 (s, total 1H, benzylic), 6.80-7.30 (m, 12 H, Ar), 8.33 and 8.34 (s, total 1H, N=CH).

***cis*-3-Acetoxy-4-(*m*-bromophenyl)azetidin-2-one (7g)**. The imine (535 mg, 1 mmol) **2c** on treatment with acetoxyacetyl chloride (150 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 222 mg (78%) of the title compound as a white solid: mp 130.5-131.5 °C (EtOAc-Hexane); IR (KBr) ν 3200 (NH), 1775 (acetoxy CO) and 1760 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3H, AcO), 4.94 (d, J = 4.7 Hz, 1H, C3 H), 5.85 (dd, J = 2.8 & 4.7 Hz, 1H, C4 H), 6.18 (s, 1H, NH), 7.15-7.44 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 19.8, 57.4, 78.4, 122.5, 126.3, 129.9, 130.6, 131.4, 131.8, 164.9, 169.0 (β-lactam CO), Anal. Calcd for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 47.11; H, 3.83; N, 5.28.

5 & 6g. mp oil (one diastereomer); IR ($CHCl_3$) ν 1775 (acetoxy CO) and 1755 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (s, 3H, AcO), 4.70 (d, J = 4.8 Hz, 1H, C4 H), 5.78 (d, J = 4.8 Hz, 1H, C3 H), 6.24 (s, 1H, benzylic), 7.10-7.80 (m, 12H, Ar), 8.39 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ 19.7 (acetoxy methyl), 60.7 (C4), 76.6, 77.1, 122.0, 122.9, 123.0, 126.0, 127.4, 127.8, 129.3, 130.1, 130.3, 130.5, 131.1, 131.6, 132.0, 132.1, 134.6, 136.4, 136.9, 138.8, 162.6 (N=C), 163.9 (β-lactam CO), 168.6 (acetoxy CO).

General procedure for the preparation of bis-β-lactams 8 & 9a-8 & 9e, 10 & 11. A solution of acetyl chloride (2.2 mmol) **4** in anhydrous toluene (10 mL) was added to a solution of imine (1 mmol) **2** and triethylamine (4 mmol) in anhydrous toluene (10 mL) at 0-5 °C under Argon. After addition the reaction mixture was allowed to warm gradually to room temperature and stirred for 1 h. The reaction mixture was then heated to 70 °C and kept overnight. After cooling it to room temperature, it was filtered through Florisil® in order to remove the ammonium salt (triethylammonium chloride). The filtrate was concentrated by using a rotary evaporator. Recrystallization or column chromatography on silica gel (hexane-ethyl acetate) gave the two diastereomeric bis-β-lactams **8 & 9, 10 & 11** in good yield. Mono-β-lactams **5 & 6** were also isolated to show expected ^1H NMR and IR spectra prior to heating to 70 °C.

8 & 9a. The imine (298 mg, 1 mmol) **2a** on treatment with methoxyacetyl chloride (238 mg, 2.2 mmol) in the presence of triethylamine (400 mg, 4 mmol) gave 181 mg (41%) of the title compound as a white solid: mp (major diastereomer) 163-164 °C (EtOAc-Hexane), IR (KBr) ν 1760 (CO) and 1755 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.03 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 4.63 (d, J = 4.6 Hz, 1H, C 4 H), 4.80(merg. 2 ds, J = 4.6 & 4.8 Hz, 2H, C3 H & C4 H), 5.15 (d, J = 4.8 Hz, 1H, C3 H), 5.68 (s, 1H, NCHN); ^{13}C NMR ($CDCl_3$) δ 58.2, 63.2, 64.1, 66.4, 84.6, 85.2, 127.7, 127.9, 128.3, 128.4, 128.6, 128.8, 33.0, 134.0, 134.5, 167.0 (b-lactam CO), 168.0 (β-lactam CO); Anal. Calcd for: C, 73.28; H, 5.92; N, 6.33. Found: C, 72.21; H, 5.89; N, 6.21.

8 & 9b. The imine (298 mg, 1 mmol) **2a** on treatment with benzyloxyacetyl chloride (406 mg, 2.2 mmol) in the presence of triethylamine (400 mg, 4 mmol) gave 363 mg (61%) of the title compound as a white solid: mp (major diastereomer) 103-104 °C (EtOAc-hexane); IR (KBr) ν 1761 (CO) and 1750 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0-4.35 (m, 4H, $PhCH_2O$), 4.80 (merg. 2 ds, J = 4.6 & 4.7 Hz, 2H, C4 H), 4.96 (d, J = 4.6 Hz, 1H, C3 H), 5.12 (d, J = 4.7 Hz, 1H, C3 H), 5.70 (s, 1H, NCHN), 6.30-7.40 (m, 25H, Ar); ^{13}C NMR ($CDCl_3$) δ 63.4, 64.3, 66.3, 72.3, 72.4, 82.5, 83.1, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.7, 129.0, 133.1, 134.1, 134.3, 136.4, 136.5, 166.6 (β-lactam CO), 167.4 (β-lactam CO); Anal. Calcd for: C, 78.76; H, 5.76; N, 4.71. Found: C, 78.55; H, 5.93; N, 4.59.

8 & 9c. The imine (388 mg, 1 mmol) **2b** on treatment with methoxyacetyl chloride (238 mg, 2.2 mmol) in the presence of triethylamine (400 mg, 4 mmol) gave 202 mg (38%) of the title compound as a white solid: mp (major diastereomer): 119-120 °C (CH_2Cl_2: Hexane); IR (KBr) ν 1775 (CO) and 1755 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (s, 3H, C3 CH_3O), 3.13 (s, 3H, C3 CH_3O), 3.72 (s, 3H, CH_3O), 3.73 (s, 3H, *p*-CH_3O), 3.76 (s, 3H, *p*-CH_3O), 4.60 (d, J = 4.6 Hz, 1 H, C4 H), 4.73 (merg, 2 ds, J = 4.6 Hz, 2H, C3 H & C4 H), 5.07 (d, J = 4.6 Hz, 1H, C3 H), 5.60 (s, 1H, NCHN), 6.50-7.20 (m, 12H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.1, 55.2, 58.0, 58.1, 62.3, 63.3, 65.6, 84.3, 85.0,113.3, 113.6, 113.7, 125.5, 125.8, 125.9, 129.5, 129.6, 129.7, 159.4, 159.8, 166.6 (β-lactam CO), 167.3 (β-lactam CO); Anal. Calcd for: C, 67.65; H, 6.06; N, 5.26. Found: C, 67.70; H, 6.01; N, 5.28.

8 & 9d. The imine (388 mg, 1 mmol) **2b** on treatment with benzyloxyacetyl chloride (406 mg, 2.2 mmol) in the presence of triethylamine (400 mg, 4 mmol) gave 363 mg (61%) of the title compound (a mixture of 2 diastereomers (80 : 20)) as a white solid: IR (KBr) ν 1758 (CO) and 1750 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60-3.90 (m, 9H, OCH_3), 4.05-4.35 (m, 4H, $PhCH_2O$), 4.62 (d, J = 4.6 Hz, C4 H in minor product); 4.75 (m, C4 H in major product & C3 H, C4 H in minor product), 5.58 (s, NCHN in major product), 5.67 (s, benzylic in minor product), 6.50-7.35 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.2 (OCH_3); 62.0 (C4), 62.6 (C4), 63.6 (C4), 63.9 (C4), 65.6 (N-C-N), 72.3 ($PhCH_2O$), 82.3 (C3), 82.4 (C3), 82.9 (C3), 83.0 (C3), 113.3, 113.6, 113.8, 113.9, 125.6, 126.0, 126.1, 126.2, 127.8, 127.9, 128.0, 128.2, 129.0, 129.6, 129.7, 129.9, 130.2, 138.1, 138.2, 138.3, 159.3, 159.5, 159.9, 160.2, 176.4 (β-lactam CO), 176.5 (β-lactam CO), 177.3 (β-lactam CO), 177.4 (β-lactam CO); Anal. Calcd for: C, 73.66; H, 5.89; N, 4.09. Found: C, 73.85; H, 5.72; N, 4.10.

8 & 9e. The imine (535 mg, 1 mmol) **2c** on treatment with methoxyacetyl chloride (238 mg, 2.2 mmol) in the presence of triethylamine (400 mg, 4 mmol) gave 190 mg (28%) of the title compound as a white solid: mp (a diastereomer) 163-164 °C (EtOAc-Hexane); IR (KBr) ν 1768 (CO) and 1754 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, CH_3O), 3.18 (s, 3H, CH_3O), 4.71 (d, J = 4.7 Hz, 1H), 4.80 (d, J = 4.7

Hz, 1H), 4.92 (d, J = 4.7 Hz, 1H), 5.03 (s, 1H, NCHN), 6.94-7.39 (m, 12H, Ar); ^{13}C NMR ($CDCl_3$) δ 58.4 (OCH_3), 58.5 (OCH_3), 62.9 (C4), 63.5 (C4), 65.6 (Benzylic), 84.9 (C3), 85.1 (C3), 121.1, 122.7, 122.8, 126.7, 127.0, 127.1, 129.3, 129.8, 130.0, 131.4, 131.5, 131.7, 131.8, 132.3, 134.8, 136.2, 136.3, 166.7 (β-lactam CO), 167.1 (β-lactam CO); Anal. Calcd for: C, 47.74; H, 3.41; N, 4.13. Found: C, 47.73; H, 3.47; N, 4.09.

Mixed bis-β-lactam 10 & 11. To a solution of imine (298 mg, 1 mmol) **2a** and triethylamine (400 mg, 4 mmol) in anhydrous toluene (10 mL), a solution of methoxyacetyl chloride (119 mg, 1.1 mmol) in anhydrous toluene (10 mL) and a solution of benzyloxyacetyl chloride (203 mg, 1.1 mmol) in anhydrous toluene (10 mL) were added at 0-5 ^{o}C under Argon for 20 min. After addition the reaction mixture was allowed to warm gradually to room temperature and stirred for 1 h. The reaction mixture was then heated to 70 ^{o}C and kept overnight. After cooling it to room temperature, it was filtered through Florisil® in order to remove the ammonium salt (triethylammonium chloride). The filtrate was concentrated by using a rotary evaporator. Crystallization from ethyl acetate and hexane gave 160 mg (31%) of the two diastereomeric bis-β-lactams as a white solid. Recrystallization from ethyl acetate and hexane gave 100 mg of the title compound as a white solid: mp (major diastereomer) 157-158 ^{o}C (EtOAc-Hexane); IR (KBr) ν 1755 (CO) and 1750 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 3H, OCH_3), 4.12 (d, J = 11.1 Hz, 1H, $PhCH_2O$), 4.29 (s, J = 11.1 Hz, 1H, $PhCH_2O$), 4.63 (d, J = 4.63 Hz, 1H, C4 H), 4.86 (d, J = 4.5 Hz, 1H, C4 H), 4.98 (d, J = 4.5 Hz, 1H, C3 H), 5.17 (d, J = 4.5 Hz, 1H, C3 H), 5.71 (s, 1H, NCHPh); 6.80-7.30 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 58.2 (OCH_3), 63.1 and 64.3 (C4), 66.3 (NCHPh), 72.4 ($PhCH_2O$), 83.1 and 84.5 (C3), 127.7, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 132.5, 133.0, 134.0, 134.5, 166.8 (β-lactam CO), 168.0 (β-lactam CO).

^{15}N-Labeled hydrobenzamide 12.

Method A; Benzaldehyde (637 mg, 6 mmol) in isopropyl alcohol (10 mL) was added to a solution (pH=9) of water (7.5 mL), sodium hydroxide (300 mg), conc. ammonium hydroxide (0.6 mL, approx. 9 mmol) and $^{15}NH_4Cl$ (500 mg, 9 mmol). The precipitated product was filtered and dried in a desiccator by connecting it to vaccum. Recrystallization from isopropyl alcohol gave 480 mg (80%) of **12a** as a white solid: mp 92 ^{o}C; IR (KBr) ν 1645 and 1638 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 1H, PhCH), 7.20-7.90 (m, 15H, Ar), 8.59 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ 92.3 (PhCH), 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 128.8, 130.9, 131.0, 136.2, 141.9, 160.6; CIMS (CH_4) m/z 301 $[M+1]^+$, 299, 196, 195 (base peak), 194, 193, 108, 107, 106, 105, 91.

Method B; Benzaldehyde (637 mg, 6 mmol) in isopropyl alcohol (10 mL) was added to a solution (pH=9) of water (7.5 mL), sodium hydroxide (300 mg), conc. ammonium hydroxide (0.1 mL, approx. 1.5 mmol) and $^{15}NH_4Cl$ (500 mg, 9 mmol). The precipitated product was filtered and dried in a desiccator by connecting it to vaccum. Recrystallization from isopropyl alcohol gave 366 mg (61%) of **12b** as a white solid: mp 92 ^{o}C; IR (KBr) ν 1645 and 1638 (C=N) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 5.98 (s, 1H, PhCH), 7.20-7.90 (m, 15 H, Ar), 8.59 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$) δ 92.3 (PhCH), 127.3, 127.7, 128.4, 128.5, 128.6, 128.7, 128.8, 130.9, 131.0, 136.2, 141.9, 160.6; CIMS (CH_4) m/z 301 $[M+1]^+$, 299, 196, 195 (base peak), 194, 193, 108, 107, 106, 105, 91.

^{15}N-Labeled β-lactam 13.

Run 1. The imine **12a** (300 mg, 1 mmol) on treatment with acetoxyacetyl chloride (150 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 169 mg (82%) of **13a** as a white solid: mp 139-140 ^{o}C (EtOAc-Hexane); IR (KBr) ν 3200 (NH), 1750, 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3H, CH_3CO), 5.05 (d, J = 4.7 Hz, 1H, C3 H), 5.88 (dd, J = 2.1 & 4.7 Hz, 1H, C4 H), 6.41 (dd, J = 2.7 & 92.4 Hz, 1H, NH), 7.25-7.36 (m, 5H, Ar); CIMS (CH_4) m/z 207 $[M+1]^+$, 206, 179, 165, 164, 163, 108, 107 (base peak), 106, 91, 89.

Run 2. The imine **12b** (300 mg, 1 mmol) on treatment with acetoxyacetyl chloride (150 mg, 1.1 mmol) in the presence of triethylamine (200 mg, 2 mmol) gave 173 mg (84%) of **13b** as a white solid: mp 139-140 ^{o}C (EtOAc-Hexane); IR (KBr) ν 3200 (NH), 1750, 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3H, CH_3CO), 5.05 (d, J = 4.7 Hz, 1H, C3 H), 5.88 (dd, J = 2.1 & 4.7 Hz, 1H, C4 H), 6.41 (dd, J = 2.7 & 92.4 Hz, 1H, NH), 7.25-7.36 (m, 5H, Ar); CIMS (CH_4) m/z 207 $[M+1]^+$, 206, 179, 165, 164, 163, 108, 107 (base peak), 106, 91, 89.

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