Heterocyclic Letters
Vol. 8| No.2|287-295|Feb-April |2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

STEREOSELECTIVITY OF PHTHALIMIDO β-LACTAMS FORMATION: SYNTHESIS OF 3-AMINO β-LACTAMS THROUGH A FACILE DEPROTECTION REACTION

Armando Paniagua[1], Ram Naresh Yadav,[1, 2] Sunena Chandra[1] and Bimal Krishna Banik[1, 3 *^]

[1]Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, TX 78539, USA; [2]Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur-222003, U.P., India; [3]Current Address: Vice President, Community Health Systems of South Texas, Edinburg, Texas 78539; Email: bimalbanik10@gmail.com; bimal.banik@chsst.org

Key words: Cycloaddition, Phthalimido group, Amino β-lactam, Deprotection

Abstract:
Synthesis of amino β-lactams is a crucial objective because of the medicinal properties associated with them and the products derived from of them. Stereocontrolled synthesis of phthalimido β-lactams is performed and *cis* and *trans*-phthalimido β-lactams are deprotected with ethylene diamine (and other reagents) to amino β-lactams of diverse structures in excellent yield. This reaction is also conducted under solventless conditions to afford identical products.

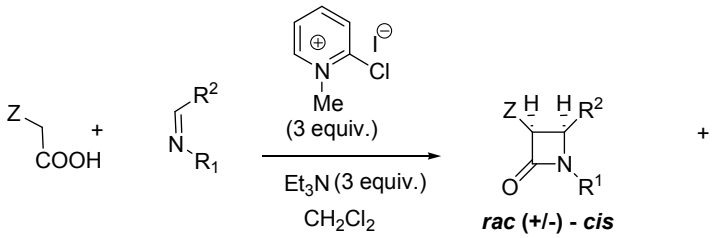
Introduction:
Penicillins, cephalosporins, cephamycins, monobactams and nocardicines are functionalized α-amino β-lactams systems of monocyclic and bicyclic ring structures with cis stereochemistry at the ring junction [1]. Examples of *trans* β-lactams with antibacterial properties are also available [2]. α-Amino β-lactam with *trans* stereochemistry is also active against various cancer cell lines *in vitro* [3]. Similarly *cis* β-lactams with anticancer properties are also identified [4]. These types of molecules are used as the starting compounds for the preparation of diverse natural products, alkaloids, amino sugars, amino acids and other antibiotics [5]. In this paper, a simple and highly convenient synthesis of *cis*- and *trans*-phthalimido β-lactams is described. Preparation of α-amino β-lactams is also reported here by a deprotection reaction of α-phthalimido β-lactams by ethylene diamine and other reagents [6].

Results and Discussions:

Synthesis of α-phthalimido β-lactams by cycloaddition reaction was investigated [7]. The stereochemistry of this reaction depended on the temperature of the process except for N-polyaromatic systems. Our interest in the synthesis of 3-phthalimido substituted β-lactams was initiated many years ago when we discover unprecedented stereochemical outcome of the Staudinger cycloaddition reaction [3, 7]. The *trans* amino β-lactam derived from *trans* 3-phtalimido β-lactam was obtained by a deprotection reaction [3]. Several β-lactams analogues (for example, α-acetoxy, α-hydroxy, α-amido, α-unsubstituted, α-tosylate, α-sulfonamide, α-alkoxy, α-ether, α-benzyl ether, α-halo, α-carboxylate, α-amino, and α-mesylate with diverse functional group at C-4 and N-1) were

synthesized and were tested at the University of Texas M. D. Anderson Cancer Center Core research laboratory against numerous cancer cell lines [8; also see the US patent]. Some of these new molecules were also screened *in vitro* at the US National Cancer Institute Drug Discovery Program against a panel of 60 cancer cell lines in 2001-2002 [3]. Later, this study was extended for the preparation of phthalimido β-lactams with imines for the preparation of diverse pyrrole derivatives appended with a β-lactam ring [9]. In this paper, preparation of α-phthalimido β-lactams by cycloaddition of imines derived from monocyclic primary amines and monocyclic aromatic aldehydes is described [1, 10]. In addition, deprotection of the α-phthalimido β-lactams to α-amino β-lactams is also investigated [9, 10]. The results of this investigation were reported at the American Chemical Society National Meeting as a part of our long-term goal of using β-lactams as therapeutic agents and other useful compounds [10].

SCHEME 1: Synthesis 3-Amino-β- Lactam from N-Phthalimidoglycine with Schiff bas of monocyclic amine



1 **2** **3** **4**

2 a R^1 = Ph R^2 = Ph **100%**
2 b R^1 = PMP R^2 = Ph **100%**
2 c R^1 = Ph R^2 = Cinnamyl **95%**
2 d R^1 = PMP R^2 = Cinnamyl **100%**

3 a R^1 = Ph R^2 = Ph **25%**
3 b R^1 = PMP R^2 = Ph **20%**
3 c R^1 = Ph R^2 = Cinnamyl **90%**
3 d R^1 = PMP R^2 = Cinnamyl **90%**

4 a R^1 = Ph R^2 = Ph **75%**
4 b R^1 = PMP R^2 = Ph **80%**
4 c R^1 = Ph R^2 = Cinnmyl **10%**
4 d R^1 = PMP R^2 = Cinnamyl **10%**

z =

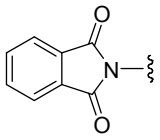


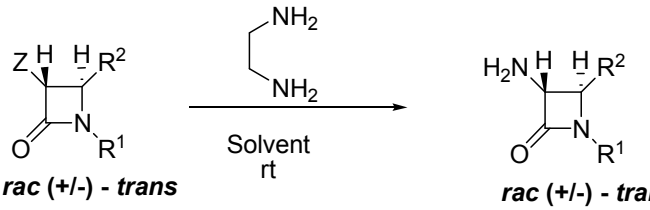
Table 1 : N-Phthalimido β-lactam with N(benzelidine) aniline and its derivatives

S.No	Z	R^1	R^2	*cis*-Isomer	*trans*-Isomer	3/4 ratio	Time (hrs.)	Yield (Major & Minor) (%)
1	PhthN	Ph	Ph	**3a**	**4a**	25/75	**4**	**90**
2	PhthN	PMP	Ph	**3b**	**4b**	20/80	**4**	**90**
3	PhthN	Ph	Cinnamyl	**3c**	**4c**	90/10	**4**	**85**
4	PhthN	PMP	Cinnamyl	**3d**	**4d**	90/10	**4**	**85**

It was found that reaction of phthalimido acetic acid **1** with N-methyl-2-chloropyridinium iodide in the presence of triethylamine with imine **2** in an organic solvent produced a mixture of *cis* and *trans* β-lactams (**3a-d** and **4a-d**) at room temperature (**Scheme 1**) [10]. The *cis*-isomer became the predominant compounds at 0^0C (not shown in the Scheme 1). High temperature (40^0C) favored the formation of the *trans*-isomer. The ratio of the isomers is given in Scheme 1 next to the structure of the products. The cinnamyl group, however, produced mostly *cis* isomers regardless of the temperature of the process.

A number of methods (hydrazine hydrate, sodium borohydride, methyl hydrazine and ethylene diamine) for the deprotection of the phthalimido group in compounds **3** and **4** were attempted. The best reagent was ethylene diamine. The yield of the racemic amino *trans* and *cis* compounds is given in **Scheme 2** and **Scheme 3** at room temperature. The reactions proceeded without the change of the

SCHEME 2 : Mild and efficient Ethylenediiamine mediated deprotection of N-Phthalimido group. A facile Synthesis of (+/-) rac-*trans*-3-amino β-lactam



rac* (+/-) - *trans

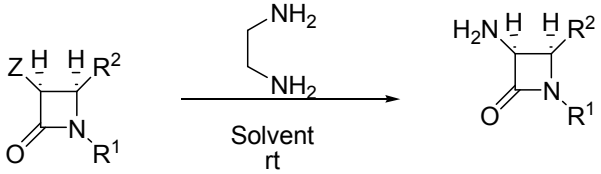
rac* (+/-) - *trans

4 a R^1 = Ph R^2 = Ph
4 b R^1 = PMP R^2 = Ph
4 c $\mathbf{R^1}$ **=** Ph R^2 = Cinnmyl
4 d R^1 = PMP R^2 = Cinnamyl

5 a R^1 = Ph R^2 = Ph **90%**
5 b R^1 = PMP R^2 = Ph **85%**
5 c $\mathbf{R^1}$ **=** Ph R^2 = Cinnmyl **85%**
5 d R^1 = PMP R^2 = Cinnamyl **75%**

stereochemistry at the C-3 and C-4 centers. The success of the reactions was independent in the choice of the solvents (**Table 2**) [10].

SCHEME 3 : Mild and efficient Ethylenediamine mediated deprotection of N-Phthalimido group. A efficient Synthesis of (+/-) rac-*cis*-3-amino β-lactam



rac* (+/-) - *cis

rac* (+/-) - *cis

3 a R^1 = Ph R^2 = Ph
3 b R^1 = PMP R^2 = Ph
3 c $\mathbf{R^1}$ **=** Ph R^2 = Cinnamyl
3 d R^1 = PMP R^2 = Cinnamyl

6 a R^1 = Ph R^2 = Ph **90 %**
6 b R^1 = PMP R^2 = Ph **90 %**
6 c $\mathbf{R^1}$ **=** Ph R^2 = Cinnamyl **85%**
6 d R^1 = PMP R^2 = Cinnamyl **85%**

Table 2: Solvent optimization for the deprotection of the N-Phthalimido group.

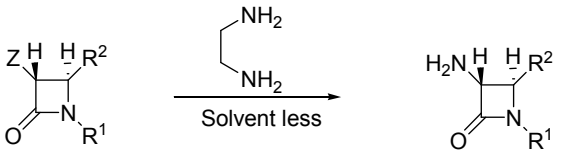
Entry	R^1	R^2	Reagents	Solvent	*trans* (**5**)	*cis* (**6**)	Time (hrs)	Yield **5** & **6** (%)[a]
1	Ph	Ph	$MeNH_2$ (40%)	THF	**5a**	**6a**	5	70 &70
2	PMP	Ph	$MeNH_2$ (40%)	CH_2Cl_2	**5b**	**6b**	5	70 & 70
3	Ph	Cinnamyl	$MeNH_2$ (40%)	Toluene	**5c**	**6c**	5	60 & 65
4	PMP	Cinnamyl	$MeNH_2$ (40%)	Benzene	**5d**	**6d**	6	60 & 65
5	Ph	Ph	$NaBH_4$	EtOH	**5a**	**6a**	4	45 & 35
6	PMP	Ph	$NaBH_4$	MeOH	**5b**	**6b**	4	55 & 25
7	Ph	Cinnamyl	$NaBH_4$	THF	**5c**	**6c**	3	60 & 35
5	PMP	Cinnamyl	$NaBH_4$	Diglyme	**5d**	**6d**	5	50 &35
6	Ph	Ph	$NH_2.NH_2.H_2O$	THF	**5a**	**6a**	4	45 &35
10	PMP	Ph	$NH_2.NH_2.H_2O$	EtOH	**5b**	**6b**	3	40 & 25
11	Ph	Cinnamyl	$NH_2.NH_2.H_2O$	MeOH	**5c**	**6c**	5	30 & 20
12	PMP	Cinnamyl	$NH_2.NH_2.H_2O$	Benzene	**5d**	**6d**	6	35 & 30
13	Ph	Ph	EDA	Dioxane	**5a**	**6a**	1	80 & 80
14	PMP	Ph	EDA	Dioxane	**5b**	**6b**	2	80 &80

15	Ph	Cinnamyl	EDA	Dioxane	**5c**	**6c**	3	80 & 80
16	PMP	Cinnamyl	EDA	Dioxane	**5d**	**6d**	3	80 &80
T(^{0}C)	0 ^{0}C - rt							

a : isolated yield of isomer separately. EDA: Ethylenediamine

The *trans* and *cis* β-lactams (**4** to **5** and **3** to **6**) were also converted to the corresponding amino compounds in excellent yield with ethylene diamine in the absence of any solvent (**Scheme 4** and **Scheme 5**; **Table 3**) [10].

SCHEME 4 : Mild and efficient Ethylenediaminemediated deprotection of N-Phthalimido group without solvent. Synthesis of (+/-) rac-*trans*-3-amino β-lactam

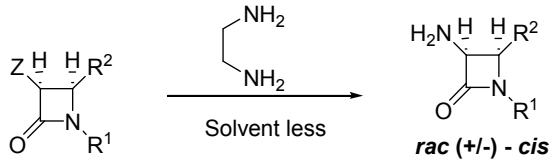


rac* (+/-) - *trans ***rac* (+/-) - *trans***

4 a R^1 = Ph R^2 = Ph
4 b R^1 = PMP R^2 = Ph
4 c $\mathbf{R^1}$ = Ph R^2 = Cinnmyl
4 d R^1 = PMP R^2 = Cinnamyl

5 a R^1 = Ph R^2 = Ph **90%**
5 b R^1 = PMP R^2 = Ph **90%**
5 c $\mathbf{R^1}$ = Ph R^2 = Cinnmyl **85%**
5 d R^1 = PMP R^2 = Cinnamyl **55%**

SCHEME 5: Mild and efficient Ethylenediamine mediated deprotection of N-Phthalimido group without solvent. Synthesis of (+/-) rac-*trans*-3-amino β-lactam



rac* (+/-) - *cis ***rac* (+/-) - *cis***

3 a R^1 = Ph R^2 = Ph
3 b R^1 = PMP R^2 = Ph
3 c $\mathbf{R^1}$ = Ph R^2 = Cinnamyl
3 d R^1 = PMP R^2 = Cinnamyl

6 a R^1 = Ph R^2 = Ph **90 %**
6 b R^1 = PMP R^2 = Ph **85 %**
6 c $\mathbf{R^1}$ = Ph R^2 = Cinnamyl **90%**
6 d R^1 = PMP R^2 = Cinnamyl **85%**

Table 3: Solvent less condition for N-Phthalimido deprotection

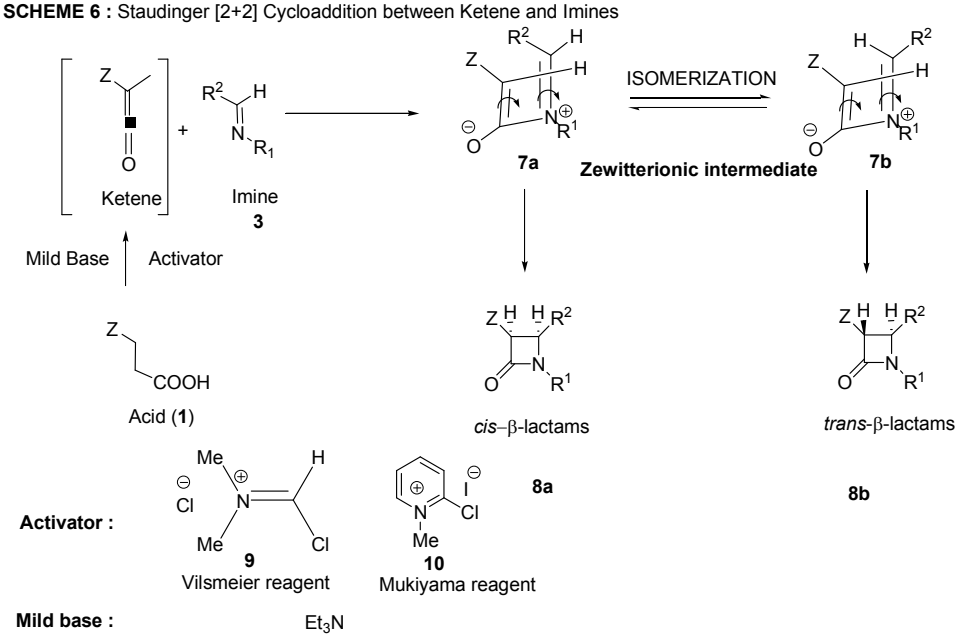
Entry	R1	R2	Reagents	*trans* (5)	*cis* (6)	Time (hrs)	Yield **5 and 6** (%)[c]
1	Ph	Ph	[a]$MeNH_2$ (40% aq)	**5a**	**6a**	3	70&65
2	PMP	Ph	[a]$MeNH_2$ (40% aq)	**5b**	**6b**	3	70 & 70
3	Ph	Cinnamyl	[a]$MeNH_2$ (40% aq)	**5c**	**6c**	3	65 &65
4	PMP	Cinnamyl	[a]$MeNH_2$ (40% aq)	**5d**	**6d**	3	65 &65
6	Ph	Ph	[b]$NH_2.NH_2.H_2O$	**5a**	**6a**	1	60& 65
10	PMP	Ph	[b]$NH_2.NH_2.H_2O$	**5b**	**6b**	2	65& 65
11	Ph	Cinnamyl	[b]$NH_2.NH_2.H_2O$	**5c**	**6c**	3	65 &60
12	PMP	Cinnamyl	[b]$NH_2.NH_2.H_2O$	**5d**	**6d**	3	60 &65
13	Ph	Ph	[d]EDA	**5a**	**6a**	1	90 & 90
14	PMP	Ph	[d]EDA	**5b**	**6b**	1.5	90 &90
15	Ph	Cinnamyl	[d]EDA	**5c**	**6c**	1	90 & 90
16	PMP	Cinnamyl	[d]EDA	**5d**	**6d**	1/2	90&90
T(^{0}C)	0 ^{0}C - rt						

a: 40 wt.% of Methylamine in water was used without additional solvent
b: 1.0 M Hydrazine Hydrate in THF was used without additional solvent
c: isolated yield of both isomer separately.

d: 1.0 M solution of EDA was used without additional solvent

The mechanism of β-lactams formation with phthalimido acetic acid was investigated. But, because of the sensitivity of the process, a clear explanation for the formation of isomeric *cis* and *trans* β-lactams was not possible [1, 11]. The reaction of the phthalimidoacetic acid under the above conditions was temperature dependent. A lower temperature favored the formation of the *cis*-isomer and high temperature produced the *trans*-compound as the major isomer. The mechanism was shown with a general scheme to explain the different stereochemical behavior of the imine **3** with acid **1** for the preparation of **8a** and **8b**. Because of the activation, the acid was able to form zewitterionic intermediates **7a** and **7b** through a reaction with the ketene [3]. These two intermediates were responsible for the formation of **8a** and **8b**. However, it appeared that the intermediates **7a** and **7b** are in equilibrium therefore, they were able to isomerize under different conditions [12]. The intermediates **7a** produced *cis* product **8a**, and **7b** produced **8b**. The intermediate **7b** was more stable than **7a** at high temperature (**Scheme 6**).

SCHEME 6 : Staudinger [2+2] Cycloaddition between Ketene and Imines



Experimental:

General procedure for the synthesis of Schiff base 2:

Equimolar amounts of aldehyde (5 mmol) and primary amine (5 mmol) where dissolved in anhydrous dichloromethane (20 mL). Dry molecular sieves (5 g) were added to it and the reaction was stirred at room temperate for 12-24 h. The progress of the reaction was monitored *via* TLC. After completion of the reaction, it was filtered and the solid mass was washed with dichloromethane (10 mL). The organic portion (the filtrate) was evaporated under vacuum to obtain **2** in almost quantitative yield. No further purification was performed.

General procedure for the synthesis of 3-phthalimido β-lactams 3 and 4 via the Staudinger reaction:

N-phthaloylglycine (**1**, 2 mmol), 2-chloro-1-methylpyridinium iodide (4 mmol) and triethylamine (6 mmol) were dissolved in dry dichloromethane (20 mL) under an inert atmosphere. The mixture was stirred for 2h under ice-cold conditions. The imine **2** was added dropwise to the reaction mixture and the reaction was kept between 0^0C-room temperature for 4h (or the reaction mixture was refluxed for 4h). The reaction was monitored *via* TLC. The reaction mixture was washed with dilute hydrochloric acid (10%, 5 mL), saturated aqueous sodium bicarbonate solution (5 mL), and brine (5 mL). The organic part was dried over sodium sulfate (5 g) and it was then filtered. The solvent was evaporated

under vacuum to produce a crude product. NMR was taken to identify the isomeric rations of the crude products. Column chromatography was performed over silica gel using hexanes-ethyl acetate as solvent (80:20) to afford the pure products **3** and **4**.

General procedure for the synthesis of 3-amino β-lactams 5 and 6.

An identical procedure was used for the deprotection of *cis* and *trans* β-lactams **3** and **4** (with solvent or without solvent). However, the time required for the completion of the reaction depends on the nature of the reagents (**Table 2** and **3**). A representative procedure was given for *cis* 3-pthalimido β-lactam. The β-lactam (1 mmol) was dissolved in 1,4-dioxane (2 mL). Ethylene diamine (2 mmol) was added to the reaction and the reaction was monitored through TLC. Usually it took approximately 1 h for completion. Dichloromethane (10 ml) was added to the reaction mixture and the organic part was washed with brine (5 mL). The resulting organic layer was dried over sodium sulfate (5 gm) and evaporated under vacuum to yield the crude product. It was then filtered through a short column of silica gel using ethyl acetate-hexanes (20:80) to obtain the pure product.

It is surprising that sodium borohydride was capable of doing deprotection reaction [**Table 2**, 13]

Phthalimido and amino *cis* and *trans* β-lactams as reported herein are all known compounds. The compounds obtained from this study demonstrated satisfactory spectral data and melting point reported earlier by other methods [6].

Conclusions:

Stereocontrolled synthesis of monocyclic 3-phthalimido and 3-amino β-lactams were prepared following our own protocol in high yield [3, 10]. The stereochemistry of the 3-phthalimido β-lactams was controlled by a judicial selection of the reaction conditions. Preparation of many other 3-substituted β-lactams (hydroxy, acetoxy, mesylate, amide and many others) was also demonstrated by our group [3, 5, US patent]. Considering the anticancer and antibacterial properties of the 3-amino β-lactams and their derivatives, our methods and compounds as reported herein would find wide application in synthetic organic chemistry, medicinal chemistry and drug discovery program following our exciting research in this field [1-8].

Acknowledgements: AP, an undergraduate student thanks HHMI for funding to complete this research and allow him to present a part of this work at the ACS National Meeting in Dallas (March, 2014). BKB gratefully acknowledges the funding support from Kleberg Foundation of Texas. RNY and SC were financially supported by grant obtained from the Kleberg Foundation of Texas.

References:

1. For synthetic and biological studies studies on β-lactams, see: (a) Banik, B. K., Ed. "*Heterocyclic Scaffolds I. Top. Heterocycl. Chem., Springer*, **2010**, 22, 1-376; (b) Banik, B. K., Ed. "β-Lactams: Synthesis and Biological Evaluation", *Top. Heterocycl. Chem., Springer*, **2012,** 30, 1-226; (c) Banik, I.; Banik, B. K., "Microwave-Induced Chemical Manipulation of β-Lactam"*, Springer*; **2012,** 55, 751-1007; (d) Banik, B. K., "Beta Lactams: Novel Synthetic Pathways and Applications", *Ed. Springer*, **2017,** 1-416; (e) Parvatkar, P. T.; Parameswaran, P. S.; Banik, B. K., "Solid Phase Synthesis of β-Lactams: Results and Scope in Banik, B. K., *Beta Lactams: Novel Synthetic Pathways and Applications, Ed. Spinger*, **2017**, 253-254; (f) Basu, S.; Banik, B. K., "Beta Lactams as Clinically Active Molecules" in Banik, B. K., *Beta Lactams: Novel Synthetic Pathways and Applications, Ed. Springer*, **2017**, 255-310; (g) Banik, B. K., "Synthesis and Biological Studies of Novel β-Lactams", CRC Book, **2013**, 31-72.

2. For a few examples of *trans* antibacterial β-lactams, see: (a) Banik, B. K.; Manhas, M. S.;

Newaz, S. N.; Bose, A. K., "Facile Preparation of Carbapenem Synthons via Microwave Induced Rapid Reaction", *Bioorg. Med. Chem. Lett.* (Symposium-in-Print on β-Lactam Antibiotics), **1993**, 3, 2363-2368; (b) Banik, B. K.; Zegrocka, O.; Manhas, M. S.; Bose, A. K., "A Facile Iodine-Catalyzed Stereospecific Glycosylation: Enantiomerically Pure β-Lactams with the Thienamycin Side Chain", *Heterocycles*, **2009**, 78, 2443-2454; (c) Troisi, L.; Granito, C.; Pindinelli, E., "Novel and Recent Synthesis and Applications of β-Lactams", *Top. Heterocycl. Chem.* **2010**, 22, 101-209.

3. Banik, I.; Becker, F. F.; Banik, B. K., "Stereoselective Synthesis of β-Lactams with Polyaromatic Imines: Entry to New and Novel Anticancer Agents", *J. Med. Chem*., **2003**, 46, 12-15.

4. (a) Turos, E., "The Chemistry and Biology of N-Thiolated β-Lactams", *Top. Heterocycl. Chem.* **2013**, 30, 147-182; (b) Olazaran-Santibanez, F.; Bandyopadhyay, D.; Carranza-Rosales, P.; Rivera, G.; Balderas-Renteria, I., "Stereochemical Preference Toward Oncotarget; Design, Synthesis, and In Vitro Anticancer Evaluation of Diastereomeric β-Lactams", *Oncotarget*, **2017**, 8, 37773-37782. For some additional example, see: (a) Kazi, A.; Hill, R.; Long, T. E.; Kuhn, D. J.; Turos, E.; Dou, Q. P., Novel N-Thiolated β-Lactam Antibiotics Selectively Induce Apoptosis in Human Tumor and Transformed, But Normal or Nontransformed, Cells, *Biochemical Pharmacology*; **2004**, 67, 365-374; (b) Meegan, M. J.; Carr, M.; Knoxx, A. J. S. Zisterer, D. M.; Lloyd, D. G., "β-Lactam Type Molecular Scaffolds for Antiproliferarive Activity: Synthesis and Cytotoxic Effects in Breast Cancer Cells", *J. Enzyme Inhibition and Med. Chem*., **2008**, 23, 679-682; (c) Ruf, S.; Neudert, G.; Gurtler, S.; Grunert, R.; Bednarski, P. J.; Otto, H. H., "β-Lactam Derivatives as Potential Anticancer Compounds", *Monatsh Chem*., **2008**, 139, 848-849.

5. For studies of bioactive β-lactams and products obtained from them from our group, see: (a) Banik, B. K., Ed. "β-Lactams: Synthesis, Stereochemistry, Synthons and Biological Evaluation", *Curr. Med. Chem*., **2004**, Volume 12; (b) Banik, B. K.; Ghatak, A.; Becker, F. F., "Indium-Mediated Facile Synthesis of 3-Unsubstitttuted β-Lactams", *J. Chem. Soc., Perkin Trans. 1*., **2000**, 14, 2179-2181; (c) Ghatak, A.; Becker, F. F.; Banik, B. K., "Indium-Mediated Facile Synthesis of 3-Unsubstituted Ferrocenyl β-Lactams", *Heterocycles*, **2000**, 53, 2769-2773; (c) Banik, B. K.; Samajdar, S.; Banik, I., "A Facile Synthesis of Oxazines by Indium-Induced Reduction-Rearrangement of the Nitro β-Lactams", *Tetrahedron Lett*., **2003**, 44, 1699-1701; (d) Banik, B. K.; Lecea, B.; Arrieta, A.; Cozar, A.; Cossio, F. P., "On the Stereodivergent Behavior Observed in The Staudinger Reaction Between Methoxyketene and (E)-N-Arylbenzylidenearyl Amines", *Angew. Chem. Int. Edn*., **2007**, 46, 3028-3031; (e) Bandyopadhyay, D.; Xavier, M.; Banik, B. K., "Highly Stereoselective β-Lactam Synthesis via the Staudinger Reaction Using Polyaromatic Imines", *Heterocyclic Communications*; **2009**, 229-231; (f) Sanchez, G.; Bandyopadhyay, D.; Jaggi, S.; Gonzalez, C. G.; Banik, B. K., "An Expeditious Synthesis of 3-Amino β-Lactams Derived from Polyaromatic Compounds", *Heterocyclic Communications*, **2009**, 323-325; (g) Aguilar**,** H.; Banik, B. K., "Stereoselectivity of 3,3-Disubstituted β-Lactam Formation via Staudinger Reaction", *Heterocyclic Communications*, **2009**, 15, 365-368; (h) Banik, B. K.; Negi, M.; Manhas, M. S.; Bose,A. K., "Chemoenzymatic Preparation of Intermediates for The Taxol Side Chain and Analogs", *Mol. Med. Rep*., **2010**, 3, 317-318; (i) Bandyopadhyay, D.; Banik, B. K., "Microwave-Induced Stereoselectivity of β-Lactam Formation with Dihydrophenanthrenyl Imines via Staudinger Reaction", *Helv. Chim. Acta*., **2010**, 298-302; (j) Rodriguez, R.; Banik, B. K., "Diasteroselectivity in β-Lactam Formation with Conjugated Imines", *Heterocyclic Letters*, **2011**, 31-34; (k) Banik, I.; Becker, F. F.; Banik, B. K., "Stereoselective Synthesis of β-Lactams Derived From Chrysenyl Imine", *Heterocyclic Letters*, **2011**, 79-81; (l) Banik, I.; Okawa, A.; Banik, B. K., "Synthesis of Racemic and Optically Active β-Lactams Derived From Allyl- and Propargyl Imine", *Heterocyclic Letters*, **2011**

, 83-85; (m) Solano, R.; Mukherjee, S.; Banik, B. K., "Asymmetric Synthesis of β-Lactam Using S-Citronellal"; *Heterocyclic Letters*, **2011**, 97-98; (n) Mohamed, H.; Banik, B. K., "Vinyl β-Lactams: Mechanism of Their Formation", *Heterocyclic Letters*, **2011**, 23-26; (o) Banik, B. K.; Manhas, M. S.; Bose, A. K., "Versatile β-Lactam Synthons: Enantiospecific Synthesis of Polyoxamic Acid", *J. Org. Chem*., **1993**, 58, 307-309; (p) Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S., "Polyhydroxy Amino Acid Derivatives via β-Lactams Using Enantiospecific Approaches and Microwave Techniques", *Tetrahedron*, **2000**, 56, 5603-5619; (q) Shaikh, A. L.; Esparza, O.; Banik, B. K., "An Efficient Synthesis of Optically Active Trans (3R,4R)-N-(Chrysenyl)-3-Acetoxy-4-Aryl-2-Azatidinones Using Carene as a Chiral Auxiliary", *Helv. Chim. Acta.,* **2011**, 94, 2188-2193.

6. For the synthesis of 3-amino β-lactams, see: (a) Sheehan, J. C.; Ryan, J.; *J. Am. Chem. Soc.* **1951**, 73, 4367; (b) Bose, A. K.; Anjaneyulu, B.; Bhattacharya, S. K.; Manhas, M. S.; *Tetrahedon*, **1967**, 23, 4766; (c) Bose, A. K.; Ram, B.; Amin, S. G.; Mukkavilli, L.; Vincent, J.; Manhas, M. S., *Synthesis*, **1979**, 543; (d) Bose, A. K.; Manhas, M. S.; Amin, S. G.; Kapur, J. C.; Kreder, J. ; Mukkavilli, L.; Ram, B.; Vincent, J., *Tetrahedron Lett.* **1979**, 2771; (d) Bose, A. K.; Chawla, H. P. S.; Dayal, B.; Mangas, M. S., "One Step Synthesis of α-Amido beta-Lactams", *Tetrahedron Letters*, **1973**, 27, 2503-2506; (e) Bose, A. K.; Manhas, M. S.; Van Der Been, J. M.; Amin, S. G.; Fernandez, I. F.; Gala, K.; Gruska, R.; Kapur, J. C.; Khajavi, M. S.; Kreder, J.; Mukkavilli, L.; Ram, B.; Sugiura, M.; Vincent, J. E., "A Convenient Synthesis of alpha-Amino-beta-lactams", *Tetrahedron*, **1981**, 37, 2321-2334; (f) Greenlee, M. L.; DiNinno, F. P.; Salzmann, T. N., *Heterocycles* **1987**, 28, 195; (g) Bose, A. K.; Manhas, M. S.; Van der Veen, J. M.; Bari, S. S.; Wagle, D. R., "Stereocontrolled Synthesis of Beta Lactams from Schiff Bases Derived From Threonine Esters", *Tetrahedron* **1992**, 48, 4831-4844; (h) Bose, A. K.; Jayaraman, M.; Okawa, A.; Bari, S. S.; Robb, E. W. Manhas, M. S., "Microwave-Assisted Rapid Synthesis of Alpha-Amino Beta Lactams", *Tetrahedron Lett.* **1996**, 37, 6989-6992.

7. Banik, B. K.; Becker, F. F., "Unprecedented Stereoselectivity in the Staudinger Reaction with Polycyclic Aromatic Imines", *Tetrahedron Lett.,* **2000**, 41, 6551-6554.

8. (a) Banik, B. K.; Becker, F. F.; Banik, I., "Synthesis of Anticancer β-Lactams: Mechanism of Action", *Bioorg. Med. Chem*., **2004**, 12, 2523-2525; (b) Banik, B. K.; Banik, I.; Becker, F. F., "Stereocontrolled Synthesis of Anticancer β-Lactams via the Staudinger Reaction", *Bioorg. Med. Chem*., **2005**, 13, 3611-3622; (c) Banik, B. K.; Becker, F. F., "Selective Anticancer Activity of β-Lactams Derived from Polyaromatic Compound", *Mol. Med. Rep*., **2010**, 3, 315-316; (d) Banik, B. K.; Banik, I.; Becker, F. F., "Asymmetric Synthesis of Anticancer β-Lactams *via* Staudinger Reaction: Utilization of Chiral Ketene from Carbohydrate", *Eur. J. Med. Chem*., **2010**, 45, 546-545; (e) Banik, B. K.; Samajdar, S.; Becker, F. F., "Asymmetric Synthesis of Anticancer β-Lactams Via Staudinger Reaction", *Molecular Medicine Reports*, **2010**, 3, 316-321. For a recent example, see: F. F. Becker and B. K. Banik, "Polycyclic β-Lactam Derivatives for the Treatment of Cancer", *US Patent, Number US8946409*, **2015**.

9. (a) Bandyopadhyay, D.; Cruz, J.; Banik, B. K., "Microwave-Induced Synthesis of 3-Pyrrole Substituted β-Lactams Via Bismuth Nitrate-Catalyzed Reactions", *Tetrahedron Symposium-in-Print***, 2012**, 65, 10656-10665; (b) Bandyopadhyay, D.; Rhodes, E.; Banik, B. K., "A Green, Chemoselective, and Practical approach Toward N-(2-azetidinonyl)-2,5-disubstituted Pyrroles", *Royal Society Advance* **2013**, 3, 16756-16764.

10. Yadav, R. N.; Paniagua, A.; Chandra, S.; Banik, B. K., "Indium (III)-Catalyzed Amino

Glycosydation of 1,2-Anhydrosugar With 3-Amino Azetidinone: A Novel Method for Optical Resolution", Presented at the 247th American Chemical Society National Meeting, Dallas, Texas, March 16-20, Carbohydrate Chemistry Section-66, 2014. A. Paniagua and S. Chandra had synthesized the phthalimido and amino beta lactams for the glycosylation study. A. Paniagua had presented a part of this paper at the HHMI meeting conducted by the University of Texas-Pan American on Friday, October 25, 2013.

11. (a) Morin, R. B.; Goldman, M.; (Editors), *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 1-3, Academic Press, New York, **1982**; (b) Demain, A. L.; Solomon, N. A.; (Editors), Antibiotics Containing the β-Lactam Structure, parts 1 & 2, *Springer, Berlin*; **1983**; (b) Bentley, P. H.; Ponsford, R.; (Editors), *Recent Advances in the Chemistry of Anti-infective Agents*, The Royal Society of Chemistry, Cambridge, **1993**; (c) Niccolai, D.; Tarsi, L.; Thomas, R. J.; The Renewed Challenge of Antibacterial Chemotherapy, *Chem. Commun*., **1997**, 2333-2342; (d) Bronston, J. J.; Barrett J. F.; Quinolone, Eveminomycin, Glycylcycline, Carbapenem, Lipopeptide and Cephem; Antibacterials in Clinical Development, *Curr. Med. Chem*., **2001**, 8, 1775-1793.

12. Arrieta, A.; Lecea, B.; Cossio, F. P. "Computational Studies on the Synthesis of β-Lactams via [2+2]Thermal Cycloadditions", *Top Heterocycl Chem.* **2010**, 22, 313-347.

13. Osby, J,O.; Martin, M.G. ;Ganem, B., "$NaBH_4$ Phtalimide Deprotection of Amines An Exceptionally Mild Procedure", *Tetrahedron Lett*.**, 1984,** *25***,** 2093-96

Received on April 14, 2017.