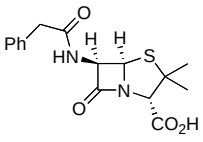
β–LACTAMS: A MEANS AND AN END IN SYNTHESIS

Reported by Iulia I. Strambeanu April 19, 2010

INTRODUCTION

Biological Relevance and Mode of Action

β-lactams (azetidin-2-ones) are four-membered cyclic amides, first synthesized by Staudinger in 1907.[1] With the discovery of penicillin **(1)** in 1928 by Sir Alexander Fleming and its structural confirmation by X-ray crystallography,[2] the scientific community recognized the potent biological activity of compounds containing the β-lactam subunit. Classification of β-lactam derivatives is based on the ring system present: penicillins and carbapenems have a five-membered ring fused to the β-lactam subunit, cephalosporins have a four-six ring system, and monobactams are comprised of only the β-lactam ring. These aforementioned classes all contain natural and synthetic β-lactam derivatives, and they share similar mechanisms of action against bacteria. Specifically, they act by inhibiting the final step of bacterial cell wall biosynthesis by interrupting the crucial cross-linking of the peptidoglycan (ptgn) strands in the cell wall (Scheme 1a). This is achieved by an irreversible acylation of the hydroxy group of the catalytic serine unit within the enzyme active site (Scheme 1b). The cell is then susceptible to osmotic pressure damage, leading to cell wall rupture and death.[3,4]



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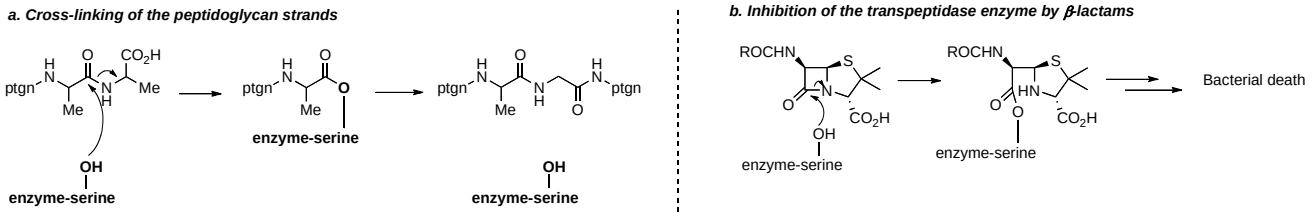
Scheme 1. Mode of Action of the β-lactam Antibiotics



Although many β-lactam antibiotics and β-lactamase inhibitors have been developed over time, their effectiveness in certain bacteria has declined due to the rapid evolution of β-lactamase enzymes, which catalyze the hydrolytic destruction of the β-lactam ring.[5] Therefore, scientists have begun to look at other applications of the β-lactam functionality. For example, the inhibition of other serine protease enzymes (cytomegalovirus protease, [6a] prostate specific antigen, [6b] thrombin, [6c] elastase, [6d] etc) is a very

promising area and holds potential for control of the human cytomegalovirus, thrombotic episodes, and prostate and breast cancers.

METHODS FOR THE SYNTHESIS OF THE β-LACTAM RING

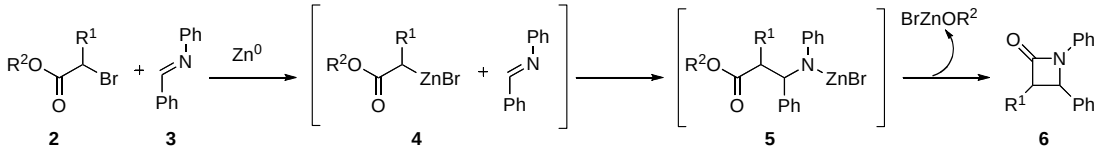
Introduction

As a consequence of the wide-ranging biological and structural significance of the β-lactams, great efforts have been dedicated to the development of methods for the stereoselective synthesis of the β-lactam unit. Although considerable progress has been achieved, many of the described approaches are based on the use of chiral, non-racemic precursors and are largely limited to chiral auxiliary based systems.[7] In fact, until the last decade, direct catalytic enantioselective and/or diastereoselective β-lactam forming reactions were rare, and, despite efforts devoted to their development, each suffered from certain limitations. In this report, the focus will be on those stereoselective methods that are most efficient and of most use for the synthesis of bioactive β-lactam-containing molecules.

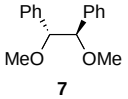
The Enolate-Imine Condensation

In 1943, Gilman and Speeter described the first example of an enolate-imine condensation approach to β-lactams by the use of a Reformatsky reagent **(4)**.[8] The course of the reaction begins with the formation of the zinc bromide enolate **(4)** upon addition of zinc metal to a mixture of α-bromoester **(2)** and imine **(3)**; this enolate then adds to the imine to form adduct **(5)**. Subsequent ring closure via attack of the N atom at the carbonyl of the ester unit forms the final product **6**, with the release of a zinc alkoxide (Scheme 2). This multistep reaction affords β-lactam product **6** in 56-85% yield, in one pot.

Scheme 2. The Gilman-Speeter Reaction Mechanism



Lithium ester and lithium thioester enolates are also used for these types of reactions.[9] The first catalytic asymmetric example of a Gilman-Speeter reaction was reported rather late relative to its discovery.[10] In 1997, Tomioka and coworkers used chiral ether ligands, such as **7**, and lithium amide bases to form a ternary complex reagent **8** in solution that induced asymmetry in the final β-lactam product. Although the exact structure and the catalytic mechanism of **8** are not well



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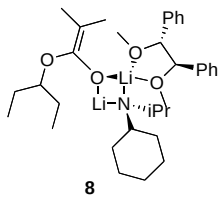

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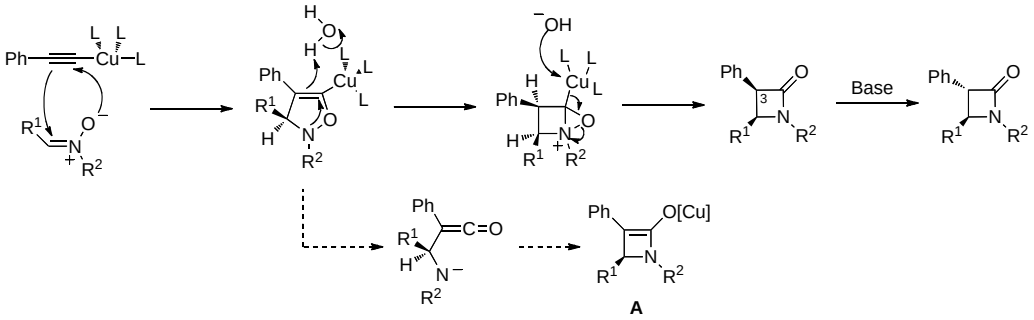
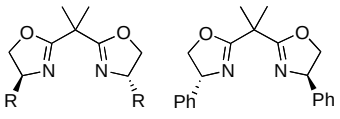
understood, it is known that both **7** and the lithium amide base are needed for high rates of reaction; the one example presented showed *β*-lactam formation in 80% yield and 75% ee. Replacing the lithium amide base and **7** with a chiral tridentate ligand resulted in higher yields (~99%), but comparable enantiomeric excesses (65-89% ee).[11]

The Kinugasa Reaction

Among the different approaches to the preparation of *β*-lactams, the Kinugasa reaction – a reaction of nitrones and alkynes – has been largely neglected in current synthetic practice, even though it provides a useful and economical entry to azetidin-2-ones. The first description of this type of reaction afforded exclusively *cis* products from preformed copper(I) phenylacetylide and a nitrone under nitrogen atmosphere.[12] Normally, the reaction of an alkyne and a nitrone yields pyrrolinediones or isoxazolines, hence the need for a preformed copper(I) acetylide. Preliminary mechanistic studies were done by Ding and Irwin[13] who used isotopic labeling (D_2O and $H_2{}^{18}O$) to show that the carbonyl oxygen originated from the oxygen of the nitrone (i.e., there was no incorporation of ^{18}O in the product) and that the proton α to the carbonyl was derived from the solvent (i.e., D incorporation was observed). Based on these observations, they proposed a regioselective [3+2] cycloaddition leading to a highly strained intermediate comprised of a three-membered oxaziridine and a four-membered azetidine (Scheme 3). Ding and Irwin also established that *cis*-*β*-lactams can undergo base-catalyzed epimerization to the *trans* isomer, especially if there is a carbonyl substituent at C_3. Alternatively, the [3+2] cycloaddition adduct can rearrange to a ketene, as shown in Scheme 3, which then forms the copper enolate intermediate **(A)**.

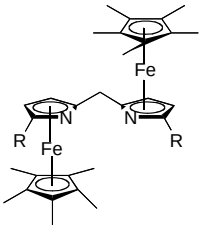
Scheme 3. The Kinugasa Reaction Mechanism





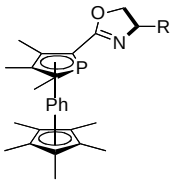
Miura and coworkers reported an interesting modification to the original protocol of the Kinugasa reaction based on the reaction of phenylacetylene and a variety of C,*N*-diarylnitrones in the presence of catalytic amounts of copper iodide, catalytic or stoichiometric amounts of

chiral bis-oxazoline type ligands **9** and potassium carbonate.[14] With stoichiometric amounts of **9a**, the reaction of phenylacetylene with C,*N*-diphenylnitrone provided the *β*-lactam product in 45% yield and a 35:65 cis:trans ratio. Each isomer showed only 40% ee, which upon addition of stoichiometric CuI increased to 68% ee. Ligands **9b** and **9c** generated similar products, with enantiomeric excesses of 67% and 45%, respectively. In 2002, Fu and coworkers reported the first highly diastereo- and



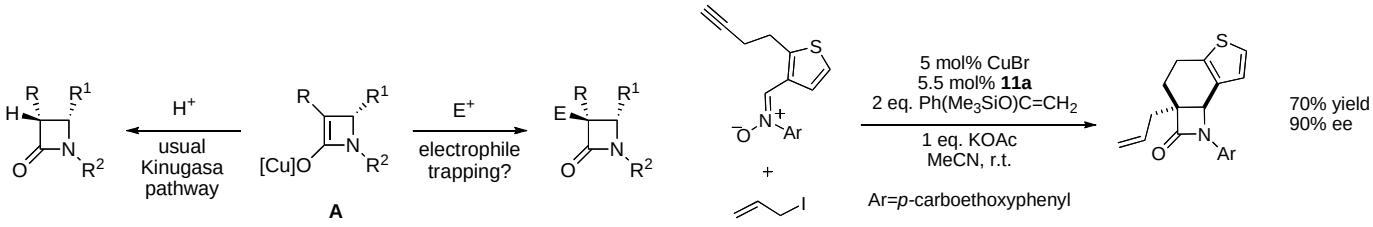
10a R=H, (+)-(R,R)
10b R=Me, (+)-(R,R)

enantioselective catalytic Kinugasa reaction, using the sterically hindered base *N*,*N*-dimethylcyclohexylamine and new C_2-symmetric planar chiral bis(azaferrocene) ligands **(10)**.[15] While **10a** gave only moderate stereoselection, formation of the *β*-lactam products proceeded with excellent *cis* diastereoselectivity (>95:5) and good *ee* (67-93%) upon use of **10b**. Using more electron-rich aromatic groups on the nitrone helped to increase the enantioselectivity. A year later, the same group described the first example of an intramolecular asymmetric Kinugasa reaction.[16] Use of planar chiral phosphaferrocenyl-substituted oxazolines **(11)** improved overall enantioselectivities compared to those obtained under the previously documented reaction conditions (i.e., using ligands **10**). The Fu group further enhanced the utility of this type of Kinugasa reaction by intercepting an intermediate **(A)** in the reaction sequence with an electrophile, thereby creating a quaternary stereocenter (Scheme 4). Intermediate **A** is most likely formed by a rearrangement of the [3+2] adduct (Scheme 3).



11a R=iPr
11b R=tBu

Scheme 4. Formation of Quaternary Centers by Trapping with Electrophiles

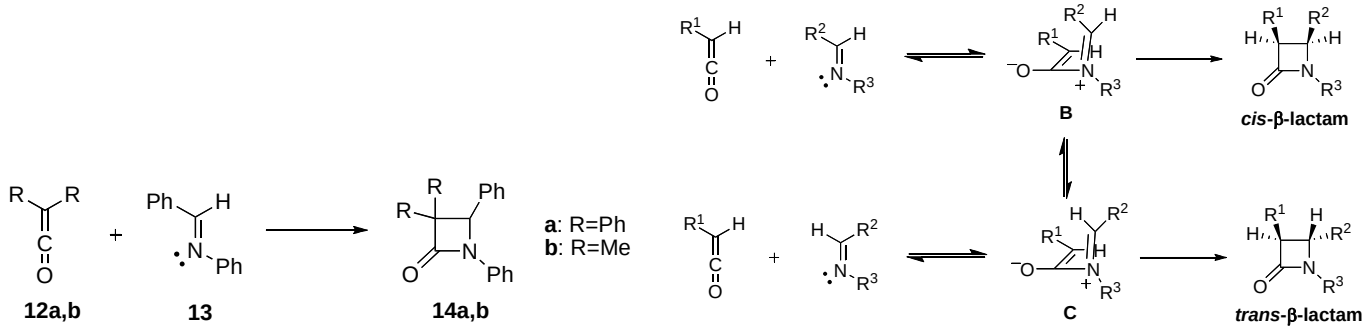


The Staudinger Reaction

The most versatile and efficient route to *β*-lactams, namely the ketene-imine cycloaddition or Staudinger reaction, has been the method of choice for the synthesis of these strained heterocycles ever since its discovery in 1907.[1] Staudinger reported the reaction of diphenyl- **(12a)** or dimethylketene **(12b)** and N-phenylbenzylidineamine **(13)**, yielding 1,3,3,4-tetraphenylazetidin-2-one **(14a)** and 3,3-dimethyl-1,4-diphenylazetidin-2-one **(14b)**, respectively (Scheme 5). The generally accepted mechanism for this reaction involves a nucleophilic attack of the imine on the central carbon of the ketene, giving rise to a

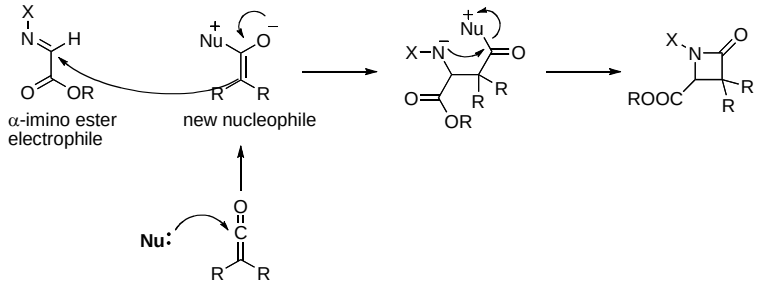
zwitterionic intermediate **(B, C)**, followed by a conrotatory electrocyclic ring closure to produce the *β*-lactam product. This stepwise mechanism can produce two stereogenic centers whose formation can be effected with complete stereocontrol (Scheme 5).

Scheme 5. Typical Staudinger Reaction and Accepted Mechanism

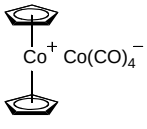


Normally, the Staudinger reaction of a ketene and an imine proceeds without a catalyst.[17] Therefore, the classical pathway has to be modified in order to render this reaction catalytic. This can be achieved by reversing the electronic properties (altering the substituents) on the two starting materials (umpolung) so that the imine acts as the electrophile while the ketene becomes nucleophilic (Scheme 6).

Scheme 6. Staudinger Reaction '*Umpolung*'



Using this approach, Lectka and coworkers developed the first catalytic Staudinger reaction in 1999 by making use of a cobaltocenium cobaltate catalyst **(15)**. [18] This nucleophilic catalyst adds to the ketene and forms a metalloenolate intermediate, thus umpoling the reaction. This proof-of-principle report was limited in scope to just one example. Taking it a step even further, the Lectka group reported the first highly enantioselective synthesis of the *β*-lactam ring system from electron-deficient ketenes and imines, employing chiral amines such as benzoylquinine **(16)** and benzoylquinidine as catalysts.[19] These "pseudoenantiomeric" catalysts provided substituted *β*-lactams in moderate yields (36-65%) and excellent enantioselectivities (95:5 to 99:1 er). The yields are greatly improved upon use of an achiral Lewis acid that works in



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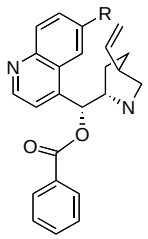

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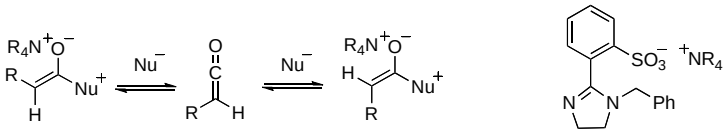
concert with the chiral nucleophilic amine catalyst, forming a bifunctional catalyst system.[20] Optically enriched β-lactams were formed in excellent yields (92-98%), with diastereomeric ratios ranging from 9:1 to 60:1 favoring the *cis* isomer.

β-lactams with a *trans* relationship between the ring substituents of an α,β-disubstituted core remained elusive targets at the time, but are certainly so not today. In this regard, the Lectka group developed an anionic nucleophilic catalyst **(17)** that allowed for the formation of *trans*-β-lactams in good yields (35-70%) and good to excellent diastereoselectivities.[21]

Scheme 7. Sterics Leading to a *trans*-β-lactam Favoring Transition State



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In this instance, the usually *cis*-favoring transition state (TS) is reorganized due to steric interactions to favor the formation of the *trans* isomer (Scheme 7). The reorganization of the *trans*-favoring TS was also effected by phosphonium fluoride precatalysts, whose steric bulk was essential for high diastereoselectivity.

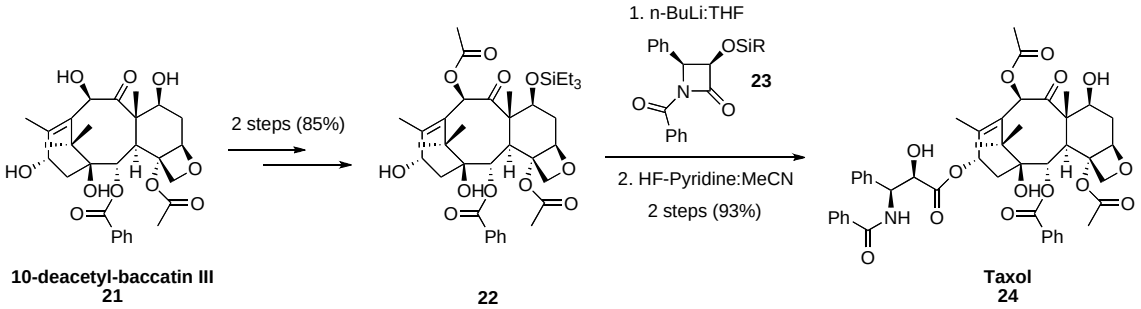
After Lectka's first asymmetric synthesis of β-lactams, Fu and coworkers reported that the a planar-chiral heterocycle could catalyze the same reaction, giving the *cis* isomer as the major product.[22] The broad scope with respect to the imine as well as the ketene is noteworthy, as are the yields and stereoselectivities of this method (82-98% yield, 81-98% ee, and 8:1 to 15:1 d.r.). Fu shows the utility of the reaction by opening the β-lactams to furnish β-amino acids and N-protected γ-amino alcohols. Fu and coworkers also made the interesting discovery that by choosing an appropriate protecting group on the N atom of the imine, the cis/trans selectivity of the reaction can be effectively controlled.[23] This was the first example of a catalytic enantioselective Staudinger reaction leading to *trans*-β-lactams.

β-LACTAM: SYNTHON FOR COMPLEX MOLECULES

In addition to their potent bioactivities, β-lactams are versatile building blocks for the synthesis of a variety of natural products. Because of the highly strained β-lactam ring, the cleavage of any of the four bonds is possible. Mosts commonly, β-Lactams act as potent acylating agents towards nucleophiles that effect cleavage of the N_1-C_2 bond. The most representative example of the utility of β-lactams as acylating agents is the coupling of β-lactam **23** with the protected baccatin III derivtive **22** to produce Taxol **(24)**, a potent anti-cancer drug isolated from the bark of the Pacific Yew (*Taxus brevifolia*) that is

in short supply (Scheme 9). Holton accomplished this remarkable breakthrough,[25] thus solving the Taxol supply problem along with bringing forth a more efficient method for installing the β-amino ester group. This method proved to be superior to the previous esterification routes, and it is now the method used commercially for the synthesis of Taxol and Docetaxel. An enolate-imine condensation was used by Ojima and coworkers[26] to synthesize the β-lactam precursor **23**, and this is, to date, the most efficient method for the preparation of the Taxol side chain.

Scheme 9. Semisynthesis of Taxol Using the β-Lactam Synthon Method



10-deacetyl-baccatin III
21

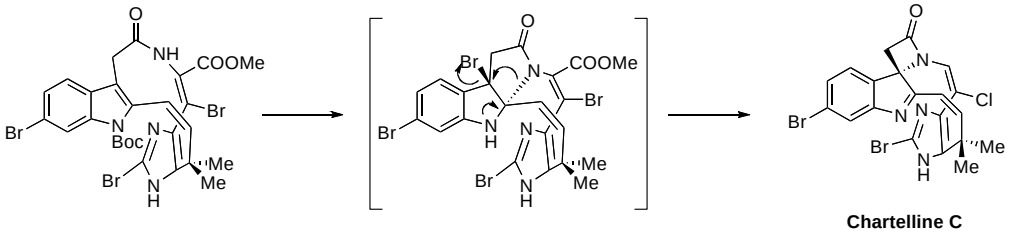
22

Taxol
24

SYNTHESIS OF COMPLEX MOLECULES CONTAINING THE β-LACTAM SUBUNIT

A variety of molecules endowed with biological activity and exquisite structures are continuously produced by marine fauna. The chartellines are members of an architecturally unique class of natural products that have, until recently, remained unconquered from a synthetic perspective, ever since their isolation by Christophersen more than two decades ago. Chartelline C **(20)** is the scarcest member of the family, and its first total synthesis was accomplished by Baran and coworkers in 2006.[24] The synthesis relied on a critical rearrangement that had no precedent in the literature: a halogen-induced ring contraction of pyrroloindoline **18** to a spiro β-lactam, specifically Chartelline C (Scheme 8).

Scheme 8. The Critical Last Step of the Total Synthesis of Chartelline C



18

19

Chartelline C
20

CONCLUSION

Natural and synthetic β-lactam derivatives occupy a central place in medicinal chemistry, and the necessity for augmenting the β-lactam antibiotic realm comes from the emergence of various strains of pathogens resistant to the already existing compounds. The diverse antibiotic activities as well as interesting new biological actions of some *β*-lactam derivatives, the low host toxicity, their good pharmacokinetics, and the synergy with other classes of antibiotics make the *β*-lactams a very interesting class of molecules. Even though they have a long history of development starting in 1928, the quest for new synthetic methods and the refinement of those already known remain appealing.

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