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Heterocyclic Scaffolds I

β-Lactams

Volume Editor:
Bimal K. Banik

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will also be included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.
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Aims and Scope

The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences etc. Metabolism is also included which provides information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic ring are also dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.

Overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which suits a larger heterocyclic community.

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Preface

The significance of the stereocontrolled synthesis of chiral and achiral β-lactams with their mechanism of formation has gained attention in connection with the structure–activity relationship study and the development of β-lactam antibiotics, β-lactam anticancer agents, cholesterol-lowering drugs, nitrogen-containing heterocycles and inhibitors of β-lactamases. However, β-lactam antibiotics have still occupied a major role in the treatment against pathogenic bacteria and thus improve in quality of human life. But, the extensive use of common β-lactam antibiotics (e.g., penicillins and cephalosporins) in medicine has created severe obstacles because of an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. Due to the increased bacterial as well as tumor cell resistance, there has been enormous effort devoted to prepare new structural types of compounds having the 2-azetidinone ring as a common feature. The diversity of this book by Springer "Heterocyclic Scaffolds I: β-Lactams" in "Topics in Heterocyclic Chemistry" is confirmed in the wide range of significant topics written by experts in this field.

Each one of the seven chapters presented in this book has focused on the very recent aspects in the β-lactam research. Alcaide and Almendros as well as Bari and Bhalla have described very powerful strategies for the preparation of unusual spirocyclic β-lactams. Troisi et al. and Palomo and Oiarbide have described the synthesis and application of β-lactams for the preparation of nitrogen-containing molecules. Basu et al. describe the preparation of β-lactams using solid-supported reagents. Cossio's group has studied computational approach to identify the mechanistic routes on the synthesis of a variety of β-lactams. Development of novel anticancer β-lactams along with their mechanisms of action has been provided by our group.

I take this opportunity to sincerely thank and congratulate the authors for their very significant and useful contribution. This book provides a deeper understanding of the art of β-lactam research to the chemists, biologists, pharmacologists, and clinicians at industrial and/or academic research institutions throughout the world.

Edinburg, Texas TX, USA — Bimal K. Banik
April 2010

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Novel Aspects on the Preparation of Spirocyclic and Fused Unusual β-Lactams

Benito Alcaide and Pedro Almendros

Abstract β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. However, the extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. The resistance of bacteria to the classical β-lactam antibiotics can be overcome, e.g., by using novel β-lactam moieties in drugs, which show much higher stability towards these resistance bacteria. In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition to gene activation. These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest, provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. The aim of this chapter is to provide a survey of the types of reactions used to prepare nonconventional spirocyclic and fused β-lactams, concentrating on the advances that have been made in the last decade, particularly in the last 5 years. We will draw special attention to radical cyclizations, cycloaddition reactions, and transition metal-catalyzed reactions.

Keywords β-Lactams · Cycloadditions · Fused-rings · Metals · Spirocycles

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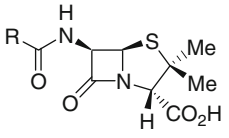
Contents

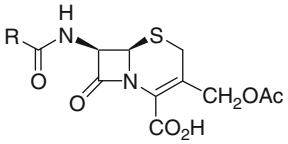
1 Introduction

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within the scientific as well as the public sectors [1–7]. β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. However, the extensive use of common β-lactam antibiotics such as penicillins and cephalosporins (Fig. 1) in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. It is well known that bacterial resistance to β-lactam antibiotics stems from the expression of a β-lactamase that catalyzes the hydrolytic cleavage of the substrate amide bond. β-Lactamases can be classified into four different classes (A–D) according to structure. Class A, C, and D β-lactamases are serine enzymes, the serine residue acting as the nucleophile in the hydrolysis reaction. Class A β-lactamases are also known as "penicillinases" on account of the ease with which they can hydrolyse penicillins, and class C β-lactamases as "cephalosporinases" by virtue of their increased activity against cephalosporins. Of the four structural classes of this enzyme, metallo-β-lactamases (class B) contain zinc and other divalent cations as cofactors.

Two main therapeutic strategies have been adopted to counteract bacterial resistance to β-lactam antibiotics. One strategy consists of modifying the structure



penicillins



cephalosporins

Fig. 1 Common β-lactam antibiotics

of the β-lactam antibiotic, aiming to render it insensitive to the β-lactamase attack. Recently, trinems antibiotics (depicted in Fig. 2) have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamases, and stability to renal dehydropeptidases [8–13]. As a result of their impressive biological activity, tricyclic β-lactams have become interesting targets for synthesis. A second approach uses a reagent, typically a β-lactam derivative, that incapacitates the β-lactamase, in synergy with the β-lactam antibiotic. Clavulanic acid (depicted in Fig. 2) is the archetype of β-lactamase inhibitors [14]: in synergistic mixture with amoxicillin (depicted in Fig. 2), under the name "augmentin", it arrived in the field some years ago. Both approaches have produced results and a new generation of antibiotics has been developed.

In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition [15–21] to gene activation [22]. Systems containing one carbon atom common to two rings, spirocyclic compounds, represent an important structural organization. Spirocyclic β-lactams (Fig. 3) behave as β-turn mimetics [23–26] as well as enzyme inhibitors [27, 28], they are precursors of α,α-disubstituted β-amino acids [29–32], and the spiranic β-lactam moiety is present in chartellines and chartelamides [33–38], a family of marine natural products. Synthetic studies and biosynthetic speculation inspired by an unexpected reaction on the marine alkaloid chartelline C have been described [38].

These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest [39–47], provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core.

The cyclic 2-azetidinone skeleton has been extensively used as a template on which to build the carbo(hetero)cyclic structure joined to the four-membered ring, using the chirality and functionalization of the β-lactam ring as a stereocontrolling element. This review embraces the gamut of unusual β-lactams, including spiranic and fused 2-azetidinones. Without a doubt, this contribution does not include every report of unusual β-lactams, nor does it fully summarize all aspects of the cited references. Instead, examples have been chosen based on their demonstrated and potential usefulness, in the opinion of the authors. The aim of this review is to provide practicing and aspirant β-lactam chemists with a survey and flavor of the types of reactions used to prepare nonconventional β-lactams, and an insight into why certain methodologies are advantageous under particular circumstances,

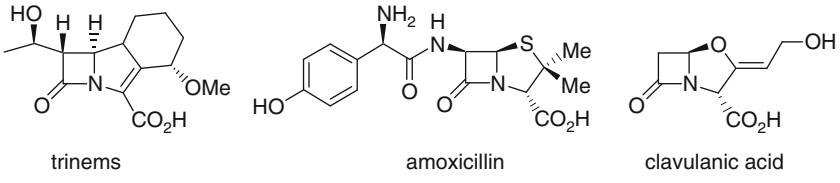


Fig. 2 β-Lactam antibiotics and β-lactamase inhibitor

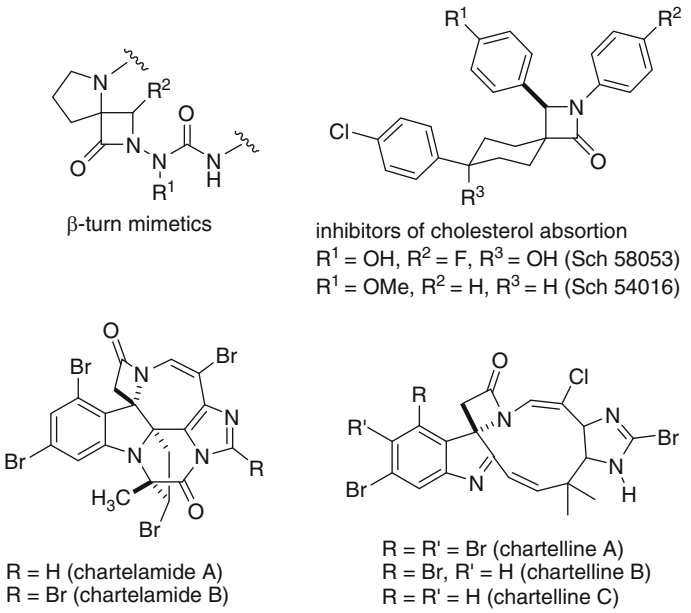


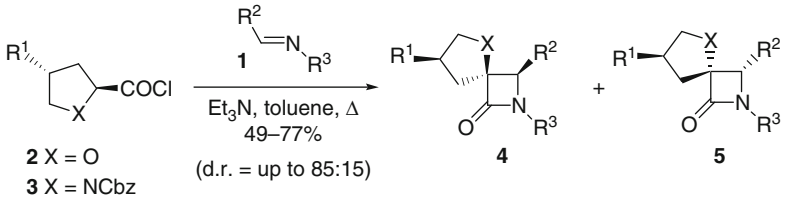
Fig. 3 Biologically relevant spirocyclic β-lactams

concentrating on the advances that have been made in the last decade, particularly in the last 5 years. We will draw special attention to radical cyclizations, cycloaddition reactions, and transition metal-catalyzed reactions.

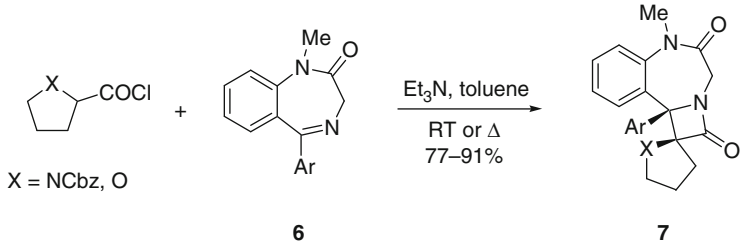
2 Preparation of Spirocyclic-β-Lactams with Nonclassical Structure

2.1 Using Cycloaddition Reactions

The synthesis of pyrrolidine and tetrahydrofuran spiro-β-lactams by a Staudinger-type process [48] has been reported. The β-lactams **4** and **5** were prepared by reaction of either 2-tetrahydrofuroyl chloride **2** or 3-tetrahydrofuroyl chloride **3** with imines **1** (Scheme 1). The acid chloride was added to a stirred, refluxing solution of the imine and triethylamine in toluene. After refluxing of the solution overnight and aqueous work-up, a mixture of *cis*- and *trans*-spiro-β-lactams **4** or **5** was obtained in good to moderate yields. When other solvents such as dichloromethane and lower temperatures were used, the starting materials were always recovered. The β-lactams **4** and **5** are the expected products of the [2+2] cycloaddition reaction of imines with the corresponding cyclic ketenes. In all cases, the



Scheme 1 Preparation of spirocyclic β-lactams through Staudinger reaction



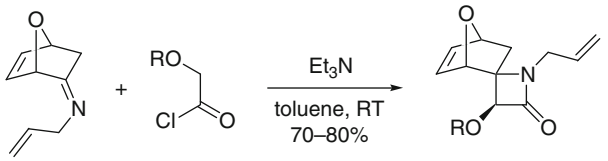
Scheme 2 Preparation of spirocyclic diazepan-β-lactam hybrid **7** through Staudinger reaction

diastereomeric mixtures of spiro-β-lactams **4** and **5** were separated by column chromatography. The relative configuration in the stereogenic centres of the azetidinone ring was established by nuclear overhauser effect (NOE) difference NMR experiments.

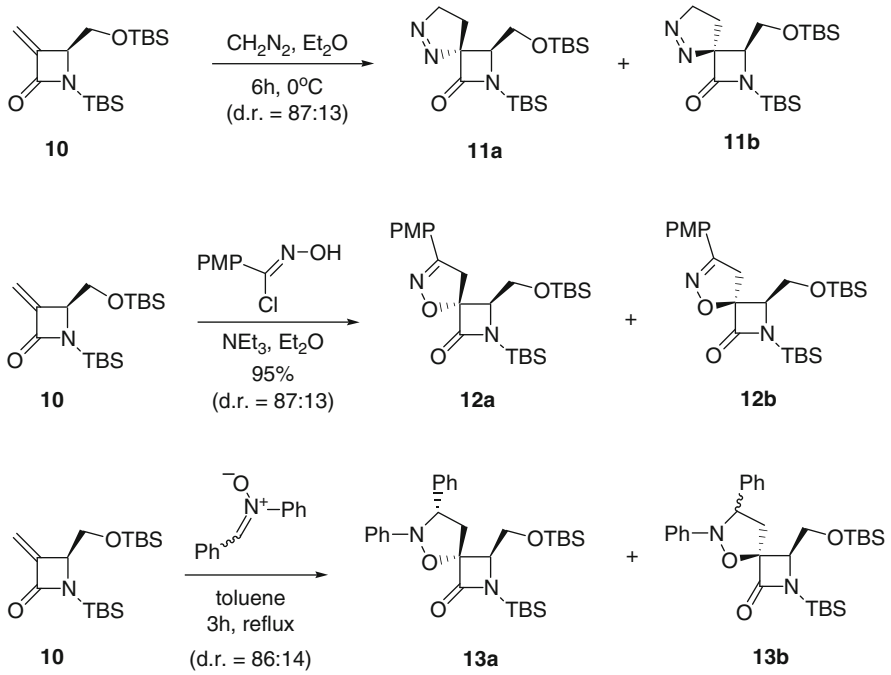
This protocol was also applied to diazepam derivatives **6** [49]. When these compounds were treated with *N*-benzyloxycarbonyl-L-proline acid chloride and tetrahydrofuroyl chloride, the expected spirocyclic systems **7** (Scheme 2) were obtained in good yields. In the case of the *N*-benzyloxycarbonyl-L-proline acid chloride, the reaction was carried out at room temperature, while the process involving the tetrahydrofuroyl chloride needed to be performed in refluxing toluene. This higher temperature was the likely cause of the loss of selectivity observed in the latter case, in which a 10:1 mixture of diastereoisomers was obtained.

Staudinger reaction of imine **8** derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides in the presence of Et_3N (toluene, RT), afforded β-lactams **9** (Scheme 3). These were obtained as single diastereomers, and no traces of the corresponding isomeric *exo*-β-lactams were detected in the crude reaction products [50]. It is worth mentioning that this stereochemical outcome of β-lactam formation with acid chlorides under Staudinger reaction conditions was opposite to the one expected from a *simple* [2+2]-cycloaddition reaction, which should have taken place from the *exo* face of compound **8**.

Optically active α-methylene-β-lactam **10** was synthesized and submitted to 1,3-dipolar cycloadditions with diazomethane, 4-methoxybenzonitrile oxide, and diphenylnitrone [51]. All cycloadditions proceed with complete regioselectivity giving products **11–13** in an *anti*fashion with respect to the substituent at the



Scheme 3 Preparation of spirocyclic 7-oxanorbornene-β-lactam **9** through Staudinger reaction



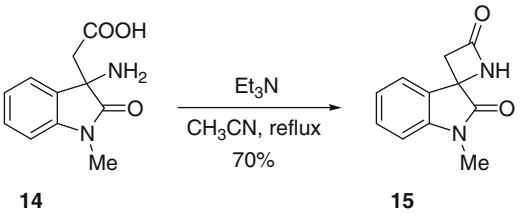
Scheme 4 Preparation of spirocyclic β-lactams using cycloadditions

C4-position of the starting β-lactam in diastereomeric ratios of about 85:15 (Scheme 4). Pure optically active compounds could be obtained in almost all cases after chromatography. Unambiguous structure elucidation could be achieved by X-ray crystal analysis and NOE investigations.

2.2 Using Cyclization and Rearrangement Reactions

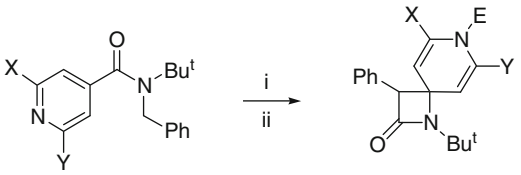
A model compound **15** containing an indole β-lactam moiety in chartellines was synthesized from the Mannich reaction of isatin imine with ketene silyl acetal, followed by β-lactam formation through cyclization of the resulting β-amino acid **14** (Scheme 5) [52]. L-Proline-catalyzed direct asymmetric Mannich reactions of

Scheme 5 Preparation of spirocyclic oxindole-β-lactam **15**



14 **15**

Scheme 6 Preparation of spirocyclic dihydropyridine β-lactam **17** (**i**) LDA, –40°C; (**ii**) E–Cl

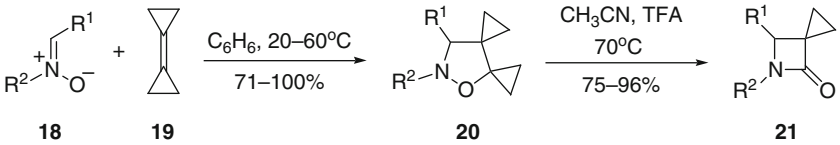


16 **17** (39–91%)

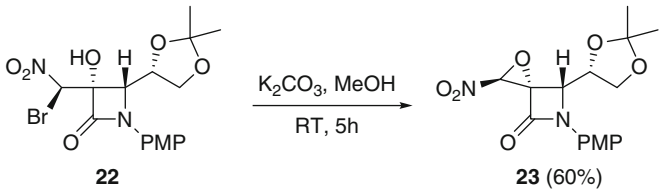
N-PMP protected α-imino ethyl glyoxylate with various α, α-disubstituted aldehydes affords quaternary β-formyl α-amino acid derivatives with excellent yields and enantioselectivities. The Mannich products are further converted to the corresponding spiranic β-lactams [53].

The synthesis of spiro-linked β-lactam-dihydropyridines **17** through the cyclization of lithiated pyridine carboxamides **16** has been achieved (Scheme 6) [54]. Thus, treatment of **16** with LDA at −40°C and addition of methyl chloroformate led to the formation of the corresponding dearomatized product in 91% yield. Other acylating agents, namely, benzyl chloroformate and benzoyl chloride, were equally effective at promoting this new type of cyclization as was methyl triflate. Methyl iodide gave significantly lower yields, and no dearomatized product was obtained on quenching with ammonium chloride – a good indication that electrophilic attack at the pyridine nitrogen is needed to promote the cyclization. It is presumed that the electrophile attacks the lithiated amide at the pyridine nitrogen rather than the considerably more basic organolithium center, presumably for steric reasons. The resulting pyridinium system is activated towards attack at C4, and the spirocyclic β-lactam results.

1,3-Dipolar cycloaddition of nitrones **18** to bicyclopropylidene **19** gave the corresponding cycloadducts **20**. Treatment of these bis-spirocyclopropanated isoxazolidines with trifluoroacetic acid in acetonitrile furnished the corresponding 3-spirocyclopropanated β-lactams **21** in good yields. The structure of the β-lactam derived from *N*-benzyl-*C*-(methoxycarbonyl)nitrone was proved by X-ray crystal structure analysis. Thus, this new method furnishes compounds with a 5-azaspiro [2.3]hexan-4-one skeleton in 68–94% overall yield in two simple steps (Scheme 7) [55]. The one-pot three-component reaction for the direct conversion of certain alkylhydroxylamine hydrochlorides (alkyl = benzyl, *p*-methoxybenzyl, benzhydryl, *tert*-butyl), formaldehyde or an alkyl glyoxylate and bicyclopropylidene **19**

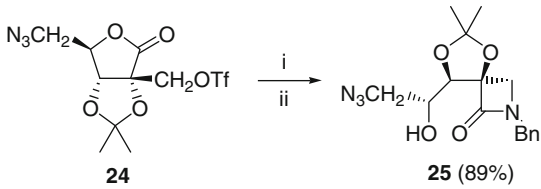


Scheme 7 Preparation of spirocyclic cyclopropane β-lactam **21**



Scheme 8 Preparation of spirocyclic oxirane β-lactam 23

Scheme 9 Preparation of spirocyclic 1,3-dioxolane β-lactam **25** (**i**) $BnNH_2$, 1,4-dioxane, RT; (**ii**) K_2CO_3, THF, RT, 8 days



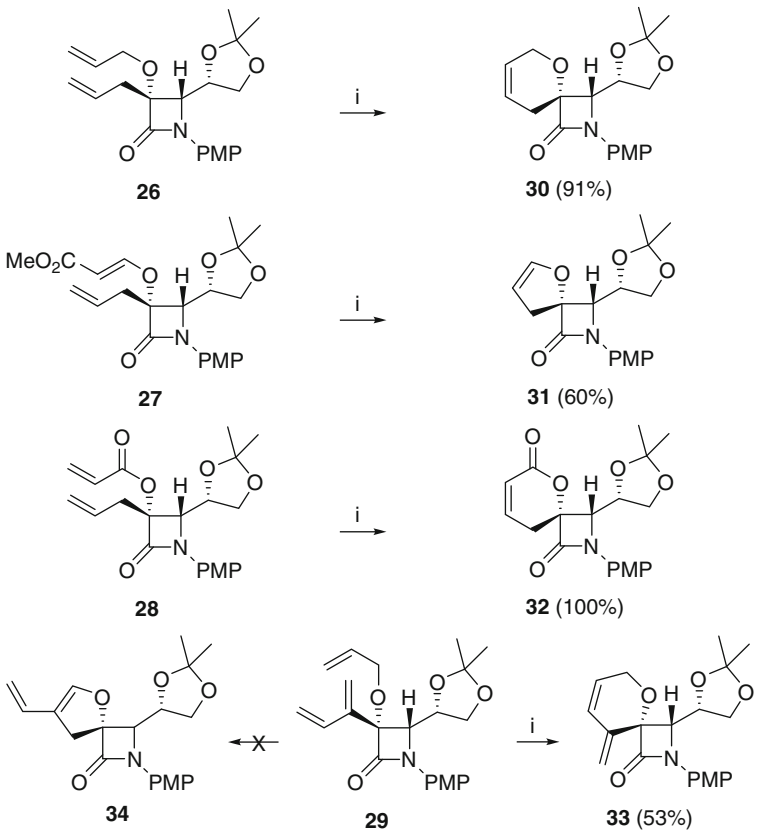
to furnish the 3-spirocyclopropanated 2-azetidinones related to **21** has also been developed. Microwave heating of mixtures of the three components in the presence of sodium acetate in ethanol for 15–120 min furnished the spirocyclic β-lactams in 49–78% yield (seven examples) [56].

Oxaciclopropane formation has been observed to give the highly strained oxiranyl-β-lactam **23**, possessing a spirocyclic structure by treatment of a 3-[bromo(nitro)methyl] 3-hydroxy-β-lactam **22** with bases (Scheme 8) [57]. The structure of the spirocycle **23** was proved by X-ray crystal structure analysis.

Treatment of bicyclic lactone **24** with benzylamine in dioxane afforded an open chain triflate amide, which was stirred in THF in the presence of potassium carbonate to cyclizate to the spirocyclic β-lactam **25** (Scheme 9) [58].

2.3 Using Metal-Mediated Reactions

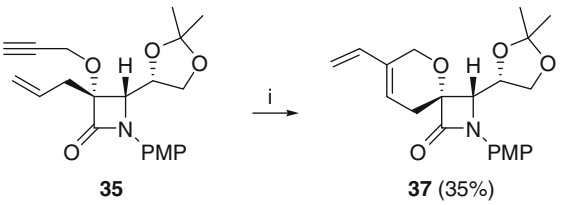
The synthesis of oxaspiro-β-lactam structures containing five- and six-membered rings was explored through RCM reaction. Unfortunately, dienes **26–29** having a



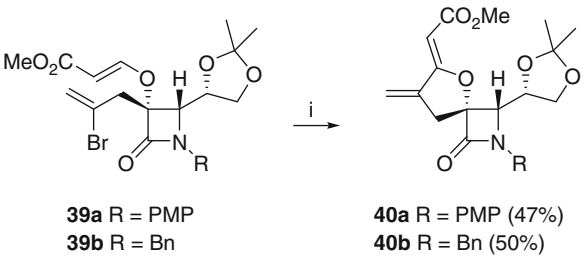
Scheme 10 Preparation of spirocyclic β-lactams using alkene methatesis (**i**) [$Cl_2(PCy_3)_2Ru$ = CHPh], toluene, reflux

quaternary center proved to be resistant to ring closure mediated by Ru-based first generation Grubbs' carbene under smooth reaction conditions (5 mol%, CH_2Cl_2, 25°C). The majority of the reaction mixture was composed of unreacted dienes. It was found that dienic substrates **26–29** require more vigorous conditions for ring closure. Spiro ring-closing metathesis was achieved upon heating at reflux temperature in a toluene solution. Under optimized conditions (5 mol% Grubbs' carbene, toluene 0.03M, 110°C), good yields of unusual β-lactams **30–32** containing dihydrofuran, dyhydropyran, and dyhydropyranone spiranic rings were obtained (Scheme 10). The six-membered spiro compound **33** which bears an exocyclic methylene was achieved when the spirocyclization took place on triene **29**. No traces of the five-membered regioisomer **34** could be detected, because only the least substituted double bond of the 1,3-diene system reacted (Scheme 10) [59].

Treatment of enynes **35** and **36** with first generation Grubbs' carbene under the above diene ring-closing metathesis conditions did not furnish the desired spirocycles. Next, trials of cyclization were attempted by using its imidazolidinylidene



Scheme 11 Preparation of spirocyclic β-lactams using alkyne methatesis (**i**) [Cl_2(Im)(Cy_3P)Ru = CHPh], toluene, reflux



Scheme 12 Preparation of spirocyclic β-lactams 40 using Heck reaction (**i**) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 105°C

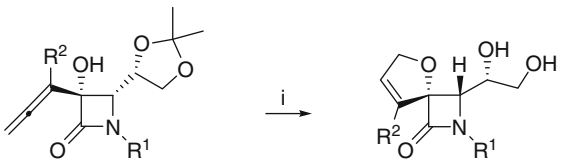
analog, the more active second generation Grubbs' carbene. In this way, the spirocyclization was effective on enyne-β-lactams **35** and **36** to afford the inner-outer-ring dienes (cyclic dienes in which one of the double bonds is *endo*-cyclic) **37** and **38** (Scheme 11) [60].

Palladium-catalyzed reaction of bromo dienes **39** was complete after a few hours, and afforded spirocycles **40a** and **40b** as single regio- and stereoisomers (Scheme 12). The Heck spirocyclization reaction is regioselective, giving five-membered heterocycles. In addition, it is stereoselective because the Heck adducts were obtained as single geometric isomers [60].

The $AgNO_3$-induced reaction of β-lactam-tethered α-allenic alcohols **41** gave, with concomitant acetonide cleavage, the spirocyclic dihydrofurans **42** in quantitative yields (Scheme 13) [59].

The palladium-catalyzed cyclizative coupling reaction of α-allenols **41** with alkenyl halides was also explored. The transformation of allenols **41** into spirocyclic disubstituted dihydrofuran β-lactams **43** was readily achieved in high yields, by treatment with allyl bromide or 2,3-dibromopropene in the presence of palladium (II) chloride (5 mol%) (Scheme 14) [60].

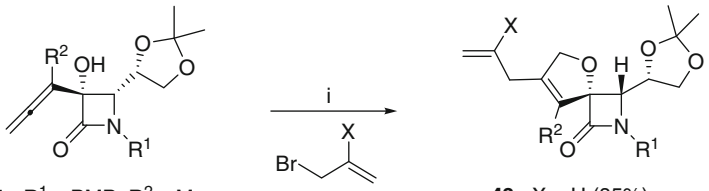
The formation of spirocyclic azetidinones **43** could be explained following a Pd (II)-catalyzed mechanism. Initial Pd(II)-coordination gave an allenepalladium



41a R^1 = PMP, R^2 = Me
41b R^1 = PMP, R^2 = Ph
41c R^1 = Bn, R^2 = Me
41d R^1 = Bn, R^2 = Ph

42a (100%)
42b (100%)
42c (100%)
42d (100%)

Scheme 13 Ag-promoted preparation of spirocyclic β-lactams **42** (**i**) $AgNO_3$ (1 equiv), acetone–H_2O (1:1), reflux



41a R^1 = PMP, R^2 = Me
41b R^1 = PMP, R^2 = Ph
41c R^1 = Bn, R^2 = Me
41d R^1 = Bn, R^2 = Ph
41d R^1 = Bn, R^2 = Ph

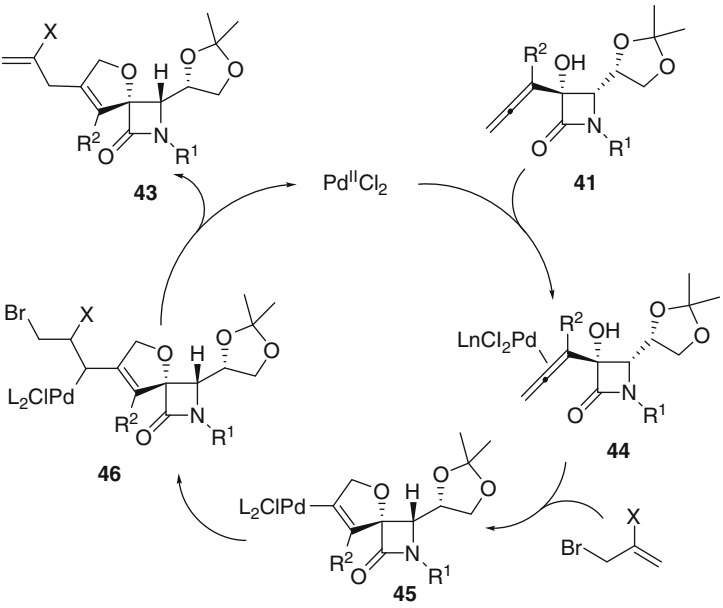
43a X = H (85%)
43b X = H (100%)
43c X = H (65%)
43d X = H (93%)
43e X = Br (95%)

Scheme 14 Pd-catalyzed preparation of spirocyclic β-lactams **43** (**i**) 5 mol% $PdCl_2$, DMF, RT

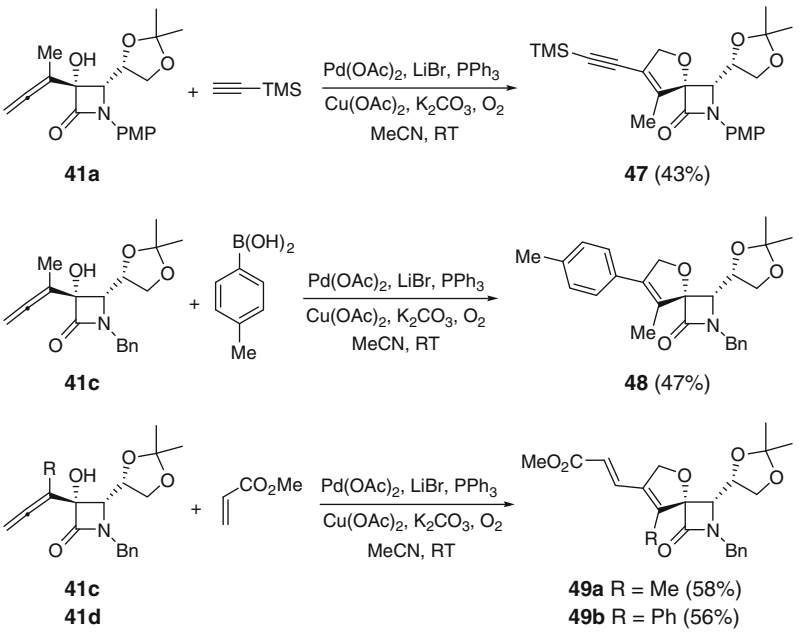
complex **44**. Species **44** suffered an intramolecular cycloetherification reaction to give the palladadihydrofuran **45**. Intermediate **45** reacted with the appropriate allyl bromide to form intermediates **46**, which after dehalopalladation generated spiro-β-lactams **43** with concomitant regeneration of the Pd(II) species (Scheme 15) [60].

Using a single catalytic system a domino cyclization of α-allenols-cross coupling (Heck, Sonogashira, and Suzuki) reaction sequence for the synthesis of spiro-β-lactams [61] has been successfully accomplished. Treatment of enantiopure α-allenols **41** with the appropriate coupling partner under optimized conditions, led to the formation of the desired products **47–49** as single isomers (Scheme 16). Similarly, the heterocyclizative cross-coupling between 2-azetidinone-tethered allenols and α-allenic acetates has resulted in the achievement of β-lactam-dihydrofuran hybrids in good yields [62].

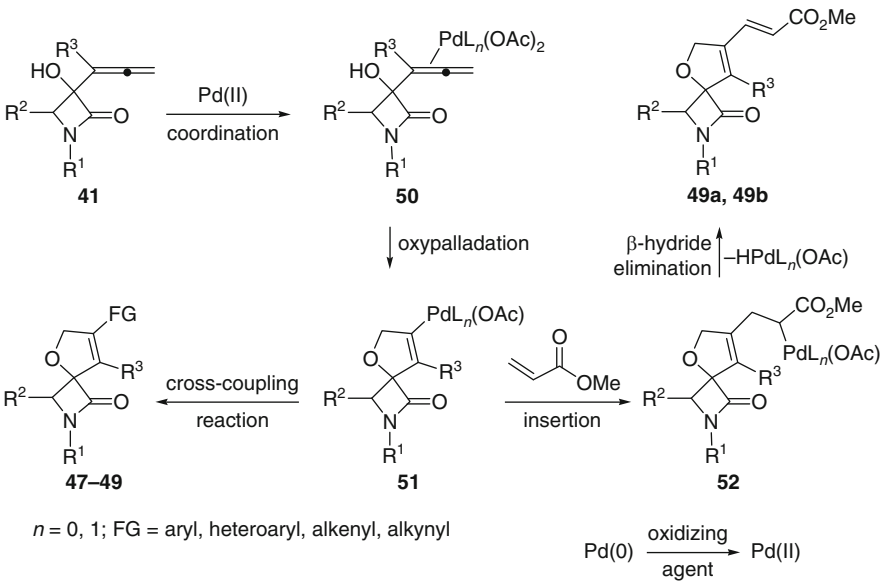
The formation of spirolactams **47–49** could be rationalized in terms of a sequence domino cyclization of α-allenols-cross coupling reactions. A palladium (II)-catalyzed mechanism for the domino sequence leading to spiranic adducts **47–49** is proposed in Scheme 17. It could be presumed that the initially formed allenepalladium complex **50** undergoes an intramolecular attack by the hydroxyl group (oxypalladation), giving rise to the spirocyclic vinylic palladium species **51**.



Scheme 15 Mechanistic explanation for the formation of spirocyclic β-lactam **43**



Scheme 16 Pd-catalyzed preparation of spirocyclic β-lactams **47–49**



Scheme 17 Mechanistic explanation for the formation of spirocyclic β-lactams **47–49**

Next, palladadihydrofuran intermediate **51** is trapped by the cross-coupling reagents leading to compounds **47–49**. For example, the palladium species **51** can then form the intermediate **52** in a subsequent Heck reaction with acrylate, which leads to the final spirocycles **49a** and **49b** and Pd(0) in a β-hydride elimination [61]. It is necessary for the catalytic cycle that Pd(0) is reoxidized to Pd(II); this is achieved by the addition of $Cu(OAc)_2$, which does not interfere with the course of the reaction.

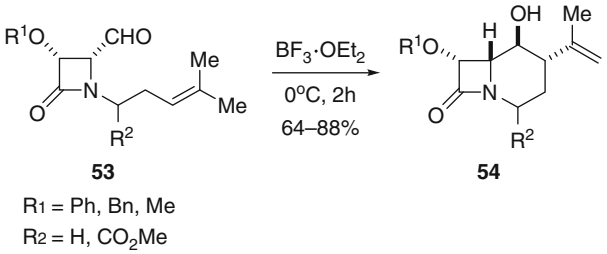
3 Preparation of Fused β-Lactams with Nonclassical Structure

3.1 Using Cycloaddition Reactions

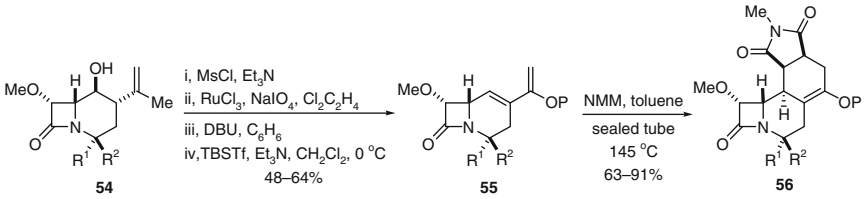
Enantiopure carbacepham derivatives **54** have been prepared in good yields via Lewis acid promoted carbonyl-ene cyclization of the corresponding 2-azetidinone-tethered alkenylaldehydes **53** (Scheme 18) [63].

Starting from some of the above 1-hydroxycarbacephams **54**, the synthesis of inner-outer-ring 2-[*tert*-butyldimethylsilyloxy]dienes **55** with a carbacepham structure and their totally π-facial *endo* selective Diels–Alder reactions to structurally novel polycyclic β-lactams **56** have been reported (Scheme 19) [64].

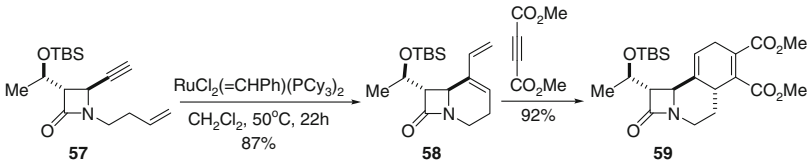
It has been shown that the combination of ring-closing metathesis and Diels–Alder reaction sequences is a useful synthetic tool for the asymmetric synthesis of



Scheme 18 Preparation of bicyclic β-lactam **54** using ene-reaction



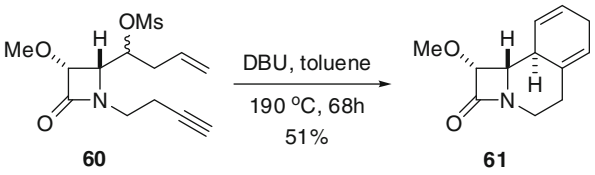
Scheme 19 Preparation of tetracyclic β-lactam **56** using Diels-Alder reaction



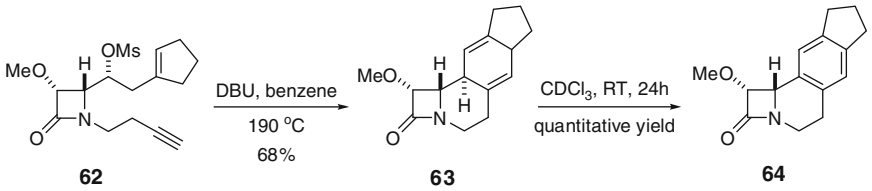
Scheme 20 Preparation of tricyclic β-lactam **59** using Diels-Alder reaction

novel polycyclic carbacephem derivatives [65–67]. Thus, enyne metathesis of monocyclic 2-azetidinone **57** afforded the bicyclic compound **58**. This diene was then engaged in a Diels–Alder reaction with dimethyl acetylenedicarboxylate as dienophile to obtain tricyclic β-lactam **59** in high yield (Scheme 20).

It has been demonstrated that the intramolecular Diels–Alder reaction is a simple and efficient entry to different tricyclic 2-azetidinones, with a six-membered ring fused to the β-lactam nucleus. Homoallylic mesylate **60** was used for the stereoselective preparation of fused tricyclic 2-azetidinone **61** through a tandem one-pot elimination-intramolecular Diels–Alder reaction (Scheme 21) [68, 69]. In a similar way, starting from mesylate **62**, elimination and intramolecular Diels–Alder reaction have allowed the preparation of enantiopure fused tetracyclic β-lactam **63** (Scheme 22) [70]. 1,4-Cyclohexadiene **63** is prone to undergo aromatization to afford the tetracyclic β-lactam **64** containing a benzene ring, as illustrated in Scheme 22.



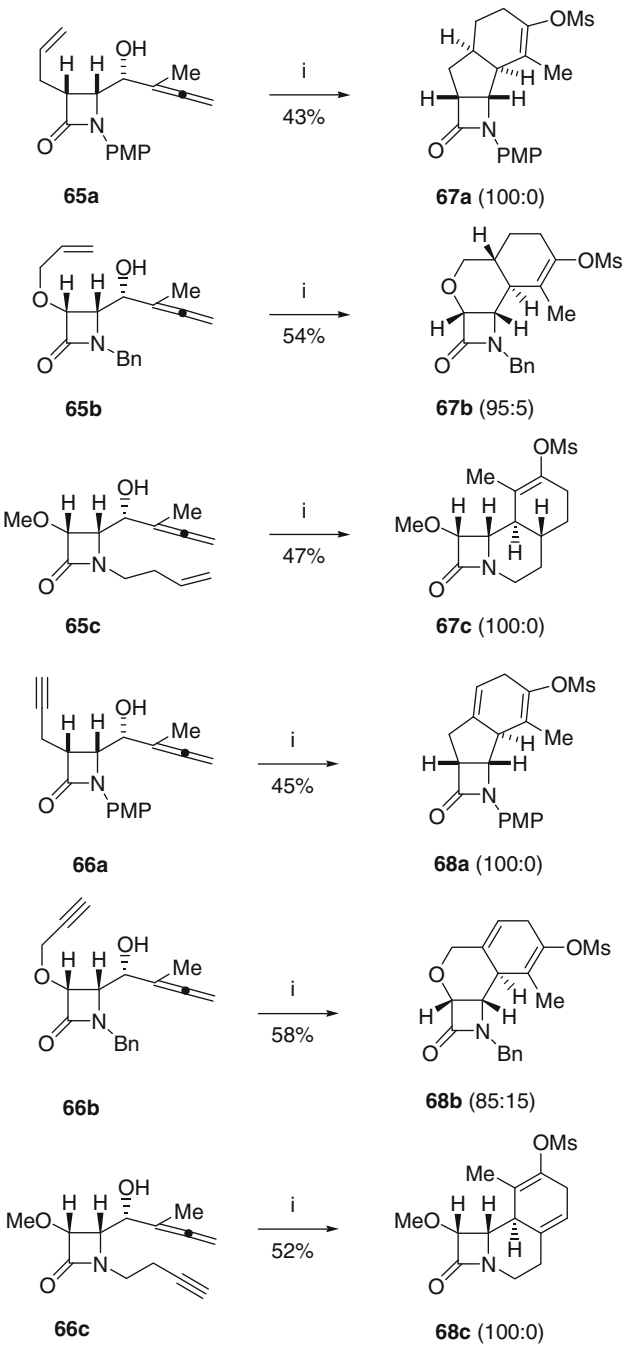
Scheme 21 Preparation of tricyclic β-lactam **61** using tandem elimination-intramolecular Diels-Alder (IMDA) reaction



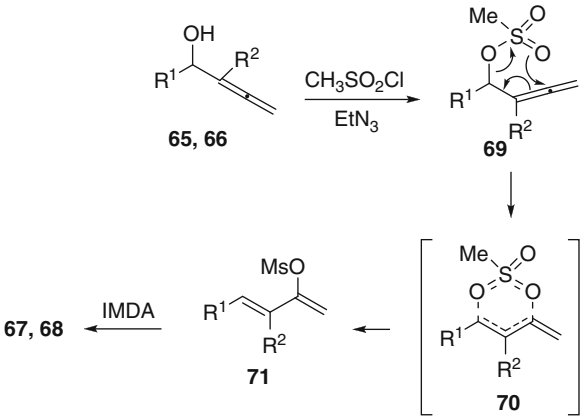
Scheme 22 Preparation of tetracyclic β-lactam **64** using tandem elimination-IMDA reaction

Reaction of enallenes **65** or allenynes **66** in the presence of methanesulfonyl chloride at 190°C provided tricyclic azetidinones **67** or **68**. These tricycles have been obtained from monocyclic allenols, masked functionalized dienes, via a domino allenol transposition/intramolecular Diels–Alder reaction process (Scheme 23) [71, 72]. The mechanism of the one-pot allenol-diene transformation is depicted in Scheme 24. The extremely high selectivity observed in the formation of dienes may point to a pericyclic reaction pathway. Accordingly, the allenol component reacts with methanesulfonyl chloride resulting in a methanesulfonate intermediate. Next, the in situ generated α-allenic methanesulfonate **69** suffers a [3,3]-sigmatropic rearrangement, involving the six-membered cyclic transition structure **70**, to give the corresponding mesyloxy-diene counterpart **71**.

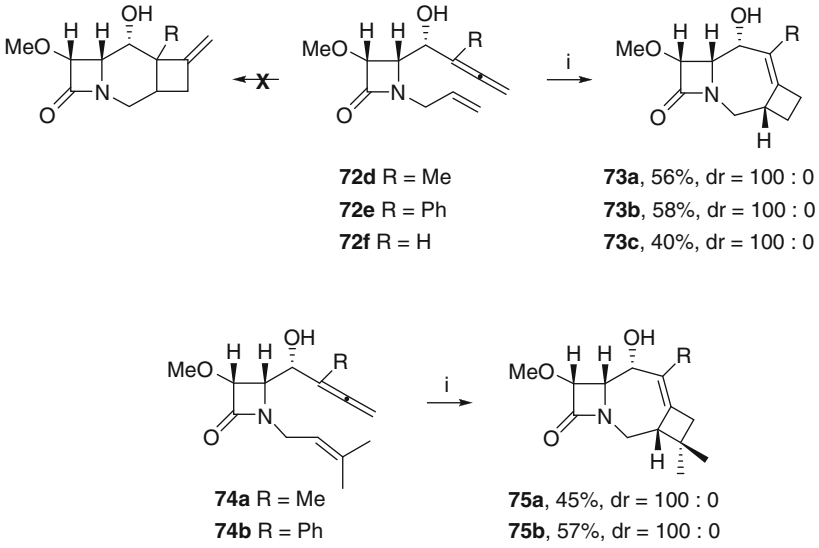
A convenient metal-free methodology for the preparation of structurally novel strained tricyclic β-lactams containing a cyclobutane ring has been developed. The first examples accounting for the intramolecular [2+2] cycloaddition reaction in β-lactams have been achieved via the thermolysis of 2-azetidinone-tethered enallenols **72** and **74** [73]. As shown in Scheme 25, enallenes **72** and **74** efficiently undergo [2+2] thermal cyclization to afford the corresponding strained tricycles **73** and **75**. The tricyclic ring structures **73** and **75** arise from a formal [2+2] cycloaddition of the alkene with the distal bond of the allene, most likely via a diradical intermediate. Exposure of *N*-methallyl allenols **76** to the above thermal treatment afforded methylenecyclobutane 2-azetidinones **77** as the only products (Scheme 26). Notably, the presence of an internal substituent on the alkene moiety switched the regioselectivity. The successful reversal of regioselectivity in the allene component by just a subtle variation in the substitution at the alkene moiety is an important development. In the current case, it allowed the preparation of a diverse array of structurally novel strained tricyclic β-lactams. For example,



Scheme 23 Preparation of tricyclic β-lactams **67–68** using allenol transposition-IMDA reaction (**i**) CH_3SO_2Cl, Et_3N, toluene, sealed tube, 190°C



Scheme 24 Mechanistic explanation for the allenol-1,3-diene transformation

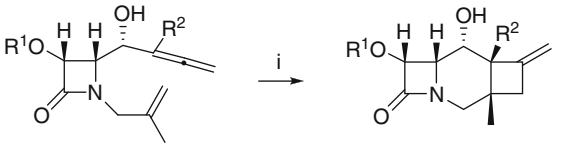


Scheme 25 Preparation of tricyclic β-lactams **73** and **75** using [2+2] cycloaddition (**i**) Toluene, sealed tube, 220°C

enantiopure compounds **77** are remarkable since they bear two quaternary stereogenic centers.

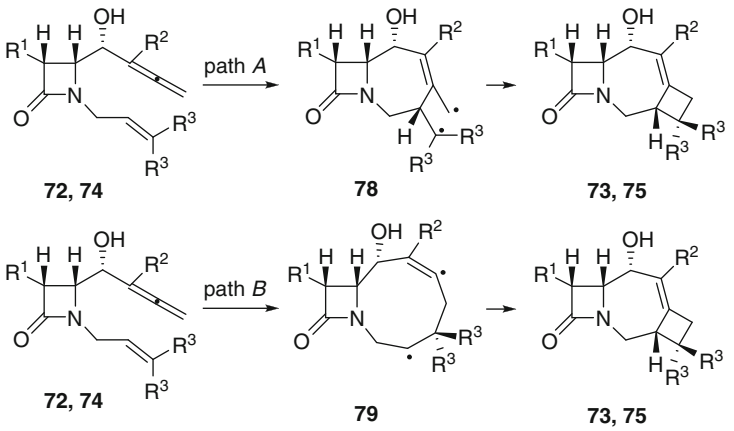
The formation of fused strained tricycles **73** and **75** can be rationalized by a mechanism which includes an exocyclic diradical intermediate **78** through an initial carbon–carbon bond formation, involving the central allene carbon and the proximal alkene carbon atom (path *A*, Scheme 27). An alternative mechanism for the

Scheme 26 Preparation of tricyclic β-lactams **77** using [2+2] cycloaddition (**i**) Toluene, sealed tube, 220°C



76a R^1 = Me, R^2 = Ph
76b R^1 = Ph, R^2 = Me
76c R^1 = Ph, R^2 = Ph

77a, 56%, dr = 100 : 0
77b, 52%, dr = 100 : 0
77c, 57%, dr = 100 : 0

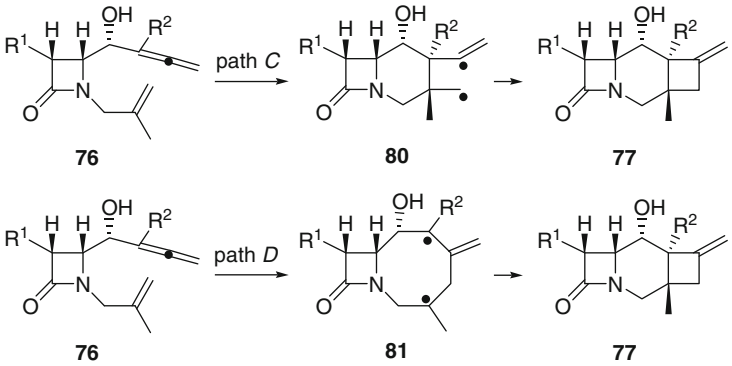


Scheme 27 Mechanistic explanation for the formation of tricyclic β-lactams **73** and **75**

thermal reaction leading to tricyclic 2-azetidinones **73** and **75** is proposed in path *B* (Scheme 27). This pathway involves an endocyclic diradical intermediate **79** arising from the initial attack of the terminal olefinic carbon onto the distal allene carbon. For both pathways, the final step must be a rapid ring-closure of the diradical intermediates which takes place before bond rotation can occur.

Analogously, the thermal formation of fused strained tricycles **77** can be rationalized by a mechanism which includes an exocyclic diradical intermediate **80** through an initial carbon–carbon bond formation, involving the proximal allene carbon and the internal alkene carbon atom (path *C*, Scheme 28). The alternative pathway leading to tricyclic 2-azetidinones **77** is proposed in path *D* (Scheme 28). This proposal involves an endocyclic diradical intermediate **81** arising from the initial attack of the terminal olefinic carbon onto the central allene carbon. The final ring-closure step of the diradical intermediates account for the cyclobutane formation.

It seems that the regioselectivity in this type of [2+2] cycloaddition reactions is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom, as the enallenes **72** and **74** lacking a methyl group exclusively gave addition at the β,γ-double bond, while the enallenes **76** bearing a methyl group at

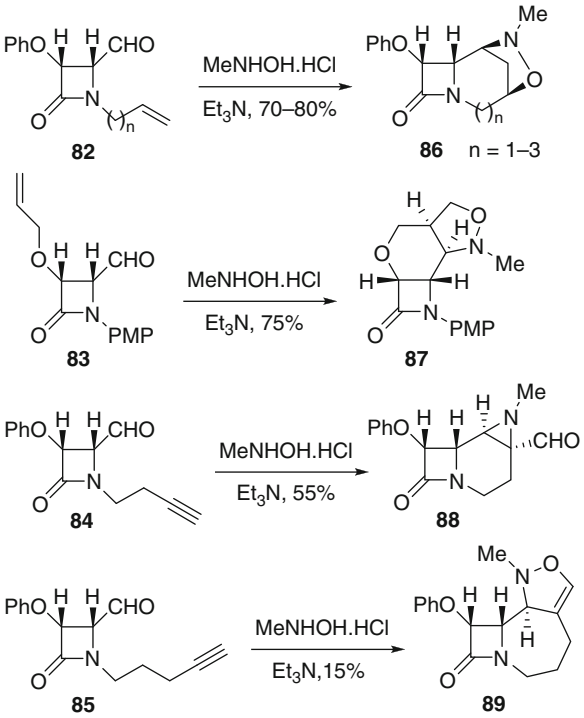


Scheme 28 Mechanistic explanation for the formation of tricyclic β-lactams **77**

the internal olefinic carbon underwent a formal [2+2] cycloaddition reaction at the α,β-double bond. The pathway *A* proposed in Scheme 27 looks valid for the formation of products **73** and **75**, where when R^3 = Me makes the exocyclic diradical most stable and the presence of the double bond makes the allylic radical **78** favored over the alternate endocyclic vinylic radical **79** in path *B*. However, it could be presumed that for the formation of compounds **77** the pathway *D* proposed in Scheme 28 is more reasonable. The simultaneous stabilization of the endocyclic diradical **81** in the presence of the methyl substituent as well as the allylic stabilization makes this radical favored over the exocyclic diradical **80**.

The intramolecular nitrone-alkene cycloaddition reaction using 2-azetidinone-tethered alkenyl(alkynyl)aldehydes **82**–**85** as starting materials has been introduced as an efficient route to prepare fused tricyclic aziridine-, isoxazoline-, and isoxazolidine-β-lactams **86**–**89** [74–76]. The regioselectivity of this cycloaddition deserves special mention, because depending on the alkene(alkyne) substituent position at the tethered alkenyl(alkynyl)aldehyde, the regioselectivity was tuned from bridged (**86**) to fused (**87**–**89**) tricyclic compounds (Scheme 29). When the alkene substituent was moved from C3 to N1 in the 1,4-tethered alkenylaldehyde, the bridged *N*,*O*-heterocycles **86** were formed as the exclusive products. Formation of the bridged-ring products **86** is worthy of note because only fused-ring products have been found in the intramolecular nitrone-alkene cycloaddition reactions of related *N*-alkenyl-2-prolinaldehyde and related cyclic-bridged alkenylaldehydes. It is possible that, because of the rigid angular disposition imparted by the planar lactam group, the fused-ring transition state increases in energy thereby becoming uncompetitive with the usually unfavored bridged-ring transition state. The aziridine carbaldehyde **88** may arise by thermal sigmatropic rearrangement.

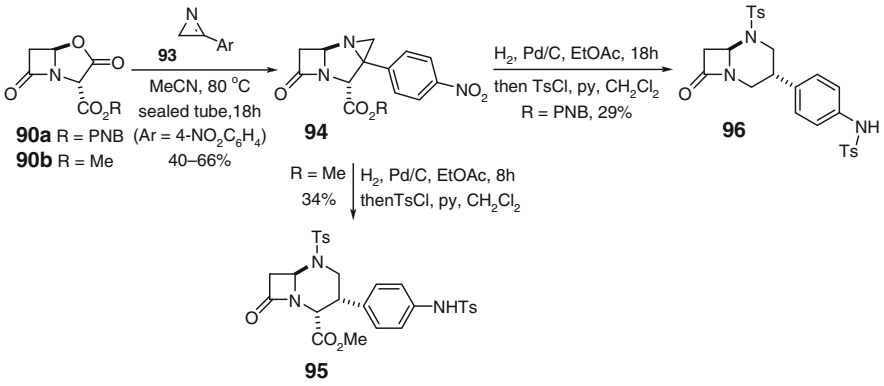
The reactivity of 2*H*-azirines **91** and **93** as 1,3-dipolarophiles towards β-lactam based azomethine ylides derived from oxazolidinones **90** has been investigated [77]. The reaction of 3-(4-methoxyphenyl)-2*H*-azirine **91** with oxazolidinone **90** did not afford the expected cycloadduct. However, compound **92** was isolated as the



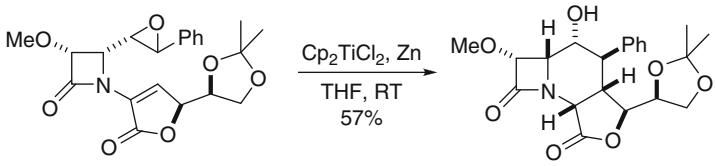
Scheme 29 Preparation of tricyclic β-lactams **86–89** using nitrone-alkene(alkyne) cycloadditions

Scheme 30 Preparation of tricyclic β-lactam **92** using azirine-azomethine cycloaddition

major product in 41% yield (Scheme 30). In contrast, by using a nitroaryl moiety at the 3-position of the azirine ring, the initial cycloadducts **94** were prevented from further fragmentation (Scheme 31). Subsequent release (by nitro group reduction and protection) of the corresponding anilide then triggers the desired C–N bond cleavage. It has also been demonstrated that depending on the nature of the ester-protecting group (**94a** vs. **94b**) these conditions lead to either **95** or **96**, both of which are novel azacepham derivatives.



Scheme 31 Preparation of bicyclic β-lactams **95** and **96** using azirine-azomethine cycloaddition

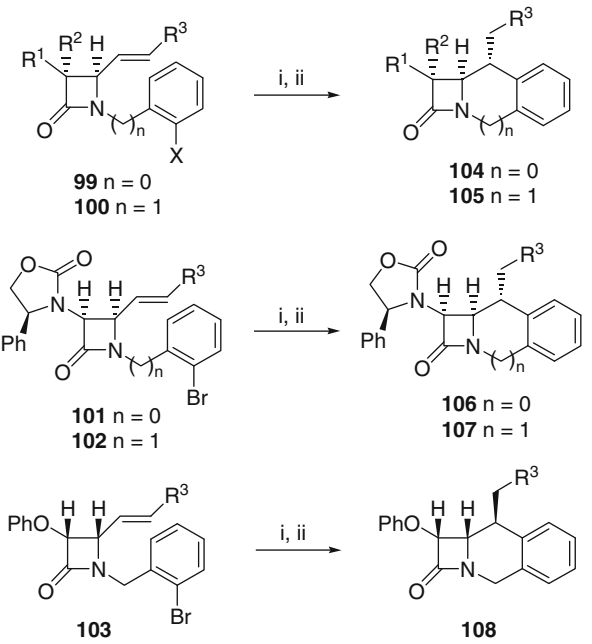


Scheme 32 Titanocene-promoted preparation of tricyclic β-lactam **98**

3.2 Using Radical Reactions

The reductive opening of epoxy-β-lactam **97** with titanocene(III) chloride gives rise to a benzyl radical that can be trapped by intramolecular π systems to give the tricyclic 2-azetidinone **98** (Scheme 32) [78].

An approach (racemic and asymmetric) to benzofused tricyclic β-lactams including benzocarbapenems as well as benzocarbacephems, through intramolecular aryl radical cyclization of 2-azetidinone-tethered haloarenes has been reported [79]. Haloaryl β-lactams **99–103** were reacted with tributyltin hydride and AIBN in benzene at reflux to give the expected benzocarbapenems **104** and **106** and benzocarbacephems **105**, **107,** and **108** in good yields as single diastereomers after chromatographic purification (Scheme 33, Table 1). These intramolecular radical reactions were carried out under standard dilution conditions, and did not require the use of high dilution techniques. Removal of the organotin halides by a solution of KF in water is essential for an appropriate chromatographic purification of compounds **104–108**. With the exception of the reaction of **101b**, neither cyclization products different from **104–108** nor reduction products were detected in the ^{1}H-NMR spectra of the crude reaction mixtures. The full stereoselectivity of the radical cyclization is particularly attractive, being independent of the substitution at



Scheme 33 Preparation of benzocarbacephems **104–108** using radical cyclization (**i**) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1–2 h; (**ii**) 10% aqueous KF, 30 min

Table 1 Preparation of fused tricyclic β-lactams **104–108**

Substrate[a]	R^1	R^2	R^3	X	n	Product[a]	Yield (%)[b]
99a	Me	Me	Ph	Br	0	**104a**	65
99b	PhO	H	Ph	Br	0	**104b**	66
cis-**99c**	BnO	H	Ph	I	0	*cis*-**104c**	60
trans-**99c**	BnO	H	Ph	I	0	*trans*-**104c**	65
100a	PhO	H	Ph	Br	1	**105a**	50
100b	BnO	H	Ph	Br	1	**105b**	61
101a			Ph		0	**106a**	70
101b			Me		0	**106b**	30
102			Ph		1	**107**	57
103a			CO_2Me			**108a**	64
103b			Me			**108b**	47

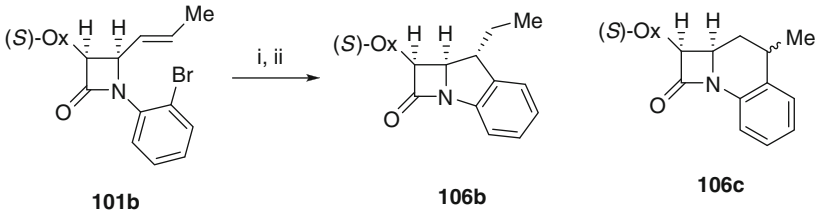
[a]Compounds **99**, **100**, **104** and **105** are racemic
[b]Yield of pure, isolated product with correct analytical and spectral data

C3 or N1 on the β-lactam ring. In addition, 2-azetidinones bearing styryl or carboxymethyl substituents at C4 underwent 5(or 6)-*exo-trig* radical cyclization to benzocarbapenems and benzocarbacephems **104–108** in a totally regioselective fashion, as expected when the radical acceptor has a radical-stabilizing moiety at the β-position. The radical reaction of the crotonaldehyde-imine derived β-lactam **101b**, lacking a radical-stabilizing moiety, deserves special mention. Haloalkenyl

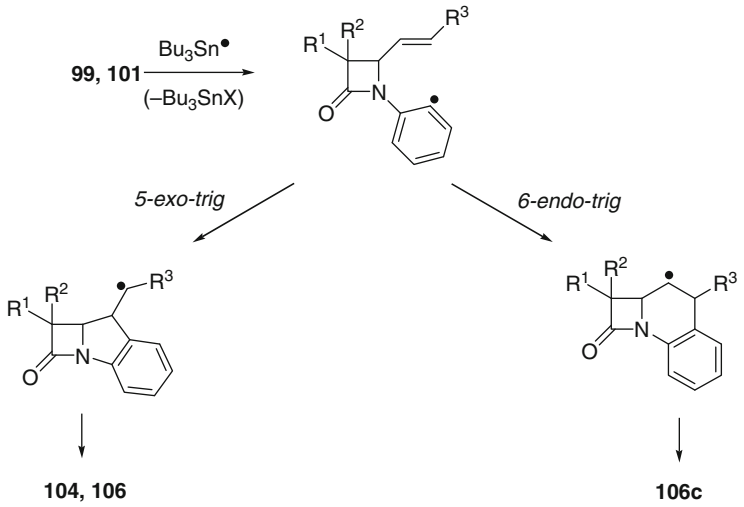
β-lactam **101b** formed, along with benzocarbapenem **106b** benzocarbacephem **106c** (Scheme 34).

A mechanistic explanation for tricyclic β-lactams **104** and **106** is depicted in Scheme 35. The complete selectivity observed in the formation of benzocarbapenems **104** and **106** and benzocarbacephems **105**, **107,** and **108** must be due to the preference of the radical intermediates for the conformation depicted in Scheme 36 for these cyclizations.

The extension of the above radical intramolecular cyclization of *N*-haloaryl-β-lactams to 2-azetidinones bearing the proradical center at C3 was also explored. The treatment of haloarenes **109a–c** under similar conditions for the preparation of benzocarbapenems and benzocarbacephems **104–108** gave the fused tricyclic β-lactams **110a–c** (Scheme 37, Table 2). Compounds **110a** and **110b** were obtained as mixtures of diastereomers, which are epimers at the newly formed C5 stereocenter, while the amino derivative **110c** could be prepared as a single isomer.

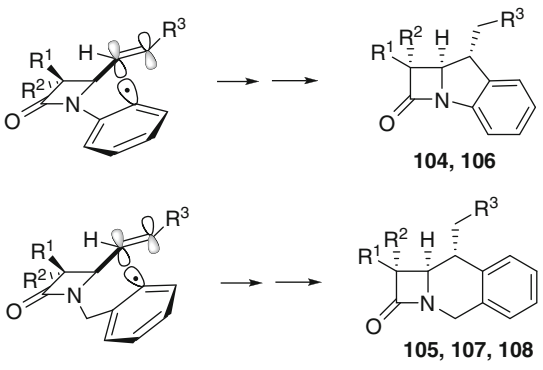


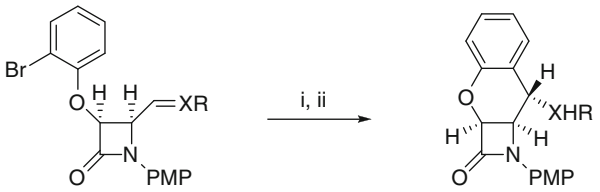
Scheme 34 Preparation of benzocarbapenem **106b** using radical cyclization (**i**) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1.5 h; (**ii**) 10% aqueous KF, 30 min



Scheme 35 Mechanistic explanation for the formation of compounds **104** and **106**

Scheme 36 Preferred conformations for the radical intermediates leading to compounds **104–108**





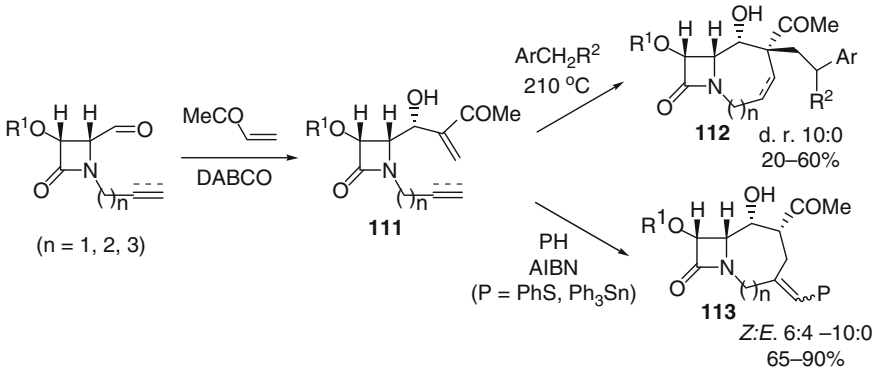
Scheme 37 Preparation of tricyclic β-lactams **110** using radical cyclization (**i**) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux, 1 h; (**ii**) 10% aqueous KF, 30 min

Table 2 Preparation of fused tricyclic β-lactams **110**

Substrate[a]	R	X	d.r.[c]	Product[a]	Yield (%)[b]
109a	Ph	CH	85:15	**110a**	69
109b	CO_2Me	CH	70:30	**110b**	56
109c	Bn	N	>95:5	**110c**	60

[a]PMP = 4-$MeOC_6H_4$
[b]Compounds **109** and **110** are racemic
[c]The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification
[d]Yield of pure product (mixture of isomers)

The formation of rings with more than seven atoms has unfavorable rates because the addition step is often too slow to allow it to compete successfully with other pathways open to the radical intermediate. In stannane based chemistry for example, premature hydrogen abstraction from the organotin hydride is difficult to avoid. However, Baylis-Hillman adducts **111** derived from enantiopure 1-alkenyl (or alkynyl)-4-azetidinone-2-carbaldehydes are used for the stereoselective and divergent preparation of highly functionalized bicycles **112** and **113** fused to medium-sized heterocycles (Scheme 38) [80, 81]. The Baylis-Hillman reaction using nonracemic protected α-amino aldehydes has been attempted with limited success due to partial racemization of the chiral aldehyde by DABCO after

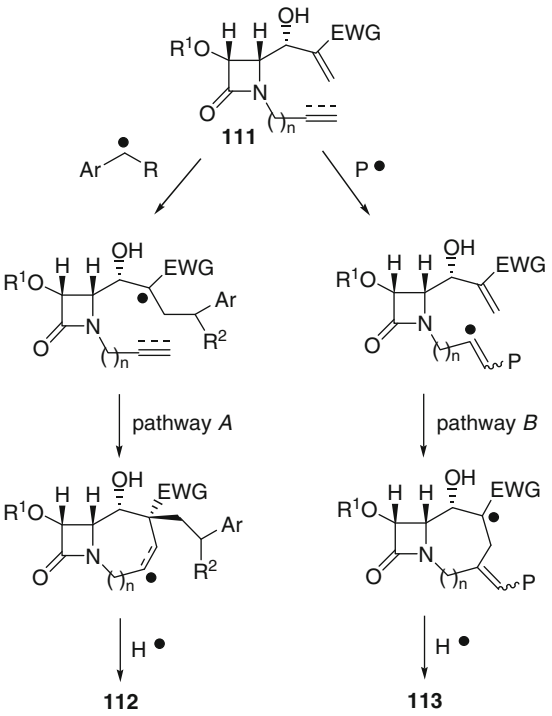


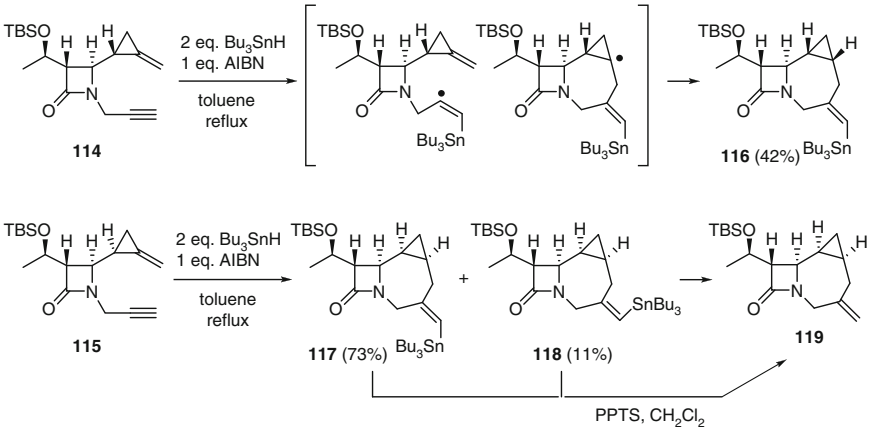
Scheme 38 Radical divergent preparation of bicyclic β-lactams **112** and **113**

prolongate exposure times. However, this is not the case of 4-oxoazetidine-2-carbaldehydes, because on reacting with various activated vinyl systems the corresponding adducts can be prepared almost as single diastereoisomers. The diastereofacial preference of this addition reaction for *syn*-addition to the aldehyde moiety was interpreted by the Felkin–Anh model. Formation of *N*-fused bicyclic β-lactams **112** and **113** can be explained in terms of a competition between a tandem radical Michael addition/*endo*-cyclization and a tandem radical addition/Michael addition, depending on the electronic nature of the radical promoter (Scheme 39). It is known that nucleophilic radicals react more rapidly with electron poor alkenes than with electron rich alkenes or alkynes, and conversely, electrophilic radicals react more rapidly with electron rich alkenes than electron poor alkenes. In the above case, Baylis-Hillman adducts may react through two different pathways to give the bicyclic systems. The more nucleophilic benzylic radical would favor formation of compounds **112**, while the more electrophilic radicals, such as $PhS^{\cdot}$ and $Ph_3Sn^{\cdot}$, should promote formation of compounds **113**. Alternatively, the differences in reactivity between the benzylic and the thiyl and stannyl radicals, respectively, could be explained by other considerations. Thus, for the thiyl and stannyl radicals the initial addition to the double bond is fast but reversible. Since the cyclization is a slow reaction, it cannot compete with fragmentation. However, the addition to the triple bond is irreversible and therefore only products deriving from addition to the triple bond are isolated. Addition of the benzylic radical to the double bond of course is not reversible.

The synthesis of *N*-fused tricyclic β-lactams involving a radical cascade sequence in enyne 2-azetidinones **114** and **115** bearing a methylenecyclopropane unit has been reported [82]. Slow addition of Bu_3SnH/AIBN to a refluxing solution of **114** gave tricyclic vinylstannane **116** as a single stereoisomer in 42% yield, whereas cyclization of **115** under identical conditions gave fused heterocycles **117** and **118** in 73 and 11% yield, respectively, in all three cases via a *7-endo* cyclization. Treatment of vinyl stannanes **117** and **118** with PPTS in dichloromethane yielded a common tricyclic product **119** (Scheme 40).

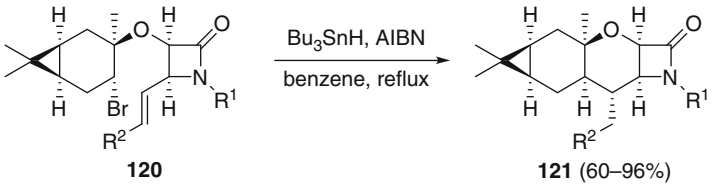
Scheme 39 Mechanistic explanation for the radical divergent formation of bicyclic β-lactams **112** and **113**





Scheme 40 Preparation of tricyclic β-lactams **116** and **119** using cascade radical cyclization

A different report provided the access to a highly strained tetracyclic [3.6.6.4] ring system containing a fused tetrahydropyran-β-lactam moiety [83]. The radical precursors **120** were easily accessible via cycloaddition reaction of the appropriate imines with a chiral chloride derived from enantiomerically pure (+)-3-carene.



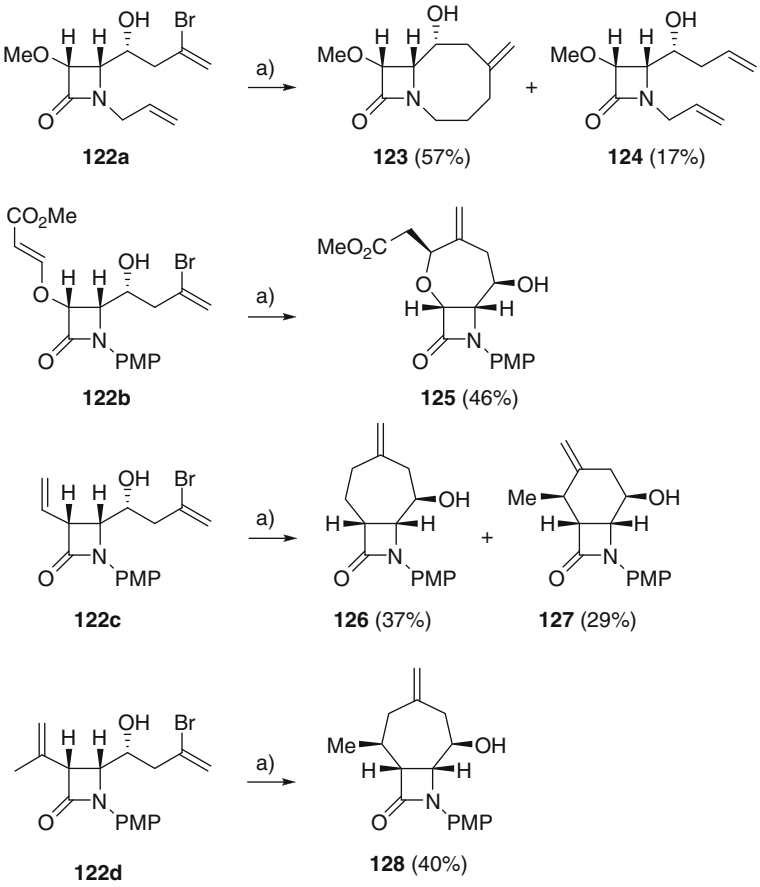
Scheme 41 Preparation of tetracyclic β-lactams **121** using radical cyclization

When compounds **120** were subjected to radical cyclization conditions, fused tetracyclic β-lactams **121** were achieved as a single diastereomer (Scheme 41). The high stereoselectivity in this 6-*exo-trig* cyclization was rationalized by invoking a six-membered transition state mode. The conformational constraint within the rigid bicyclic system and β-lactam framework with a flexible oxygen tether does not allow the system to go through the generally favored 6-*exo*-chair transition state, and now an energetically favored six-membered boat-like transition state seems to be involved.

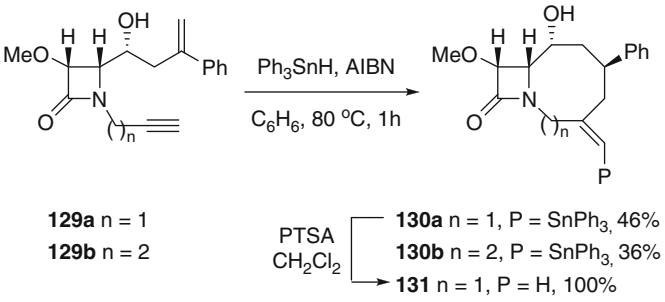
Six-, seven-, or eight-membered bicyclic 2-azetidinones have been prepared through triphenyltin hydride-promoted intramolecular free radical cyclization reaction of β-lactam-tethered bromodienes (Scheme 42) [84]. The tin-promoted radical reaction of bromodienic alcohol **122a** gave the eight-membered ring fused-β-lactam **123** together with the homoallylic alcohol **124**. The free radical cyclization proceeded elegantly in bromodiene **122b** to provide the desired nonconventional bicyclic β-lactam **125** as single isomer. The 1-vinyl-3-hydroxy-6-hexenyl radical (radical numbering) derived from bromide **122c** afforded the seven-membered ring fused bicycle **126** prevailing over the isomeric product **127** containing a six-membered ring. Triphenyltin hydride-promoted cyclization of bromodiene **122d** afforded the expected fused 2-azetidinone **128** as a single isomer in fair yield.

The synthesis of eight- and nine-membered rings fused to 2-azetidinones has been investigated using radical chemistry in β-lactam ene adducts bearing an extra alkyne tether [70]. The tin-promoted radical cyclization proceeded in enynes **129a** and **129b** to provide the desired nonconventional bicyclic β-lactams as single isomers in moderate yields (Scheme 43). Treatment of vinylic stannane **130a** with PTSA in CH_2Cl_2 yielded the destannilated eight-membered fused adduct **131**.

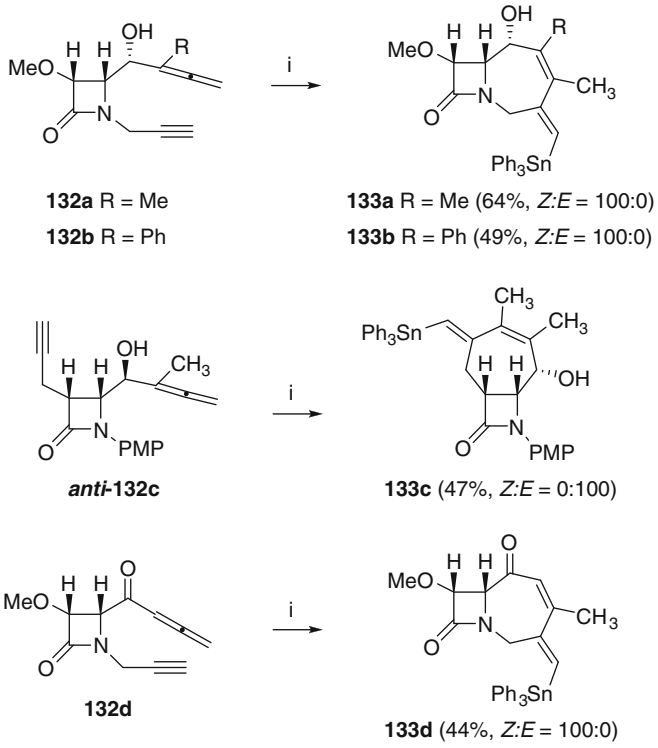
A novel approach to racemic and enantiopure nonconventional fused bi-and tricyclic β-lactams has been developed by using regio- and stereocontrolled intramolecular free radical reactions in monocyclic 2-azetidinone-tethered allenynes and haloallenes [85, 86]. In an initial study, we found that allenynol **132a** when heated in the presence of triphenyltin hydride and AIBN in benzene solution gave the bicyclic β-lactam **133a** in 64% yield as a single regio- and *Z*-isomer. Tin-promoted cyclization of allenynol **132b** afforded the expected 2-azetidinone **133b** containing a medium-sized ring. Allenynol *anti*-**132c** having the alkynyl side chain at C3 instead of N1 underwent cyclization to afford the C3–C4 fused β-lactam **133c**. Similar behavior was observed for the free radical cyclization of allenynone **132d**, which afforded the heterobicyclic ketone **133d**. Interestingly, only bicycles



Scheme 42 Preparation of bicyclic β-lactams **123** and **125–128** using radical cyclization (**a**) Ph_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux



Scheme 43 Tin-promoted radical preparation of bicyclic β-lactams **130**



132a R = Me
132b R = Ph

133a R = Me (64%, *Z:E* = 100:0)
133b R = Ph (49%, *Z:E* = 100:0)

***anti*-132c**

133c (47%, *Z:E* = 0:100)

132d

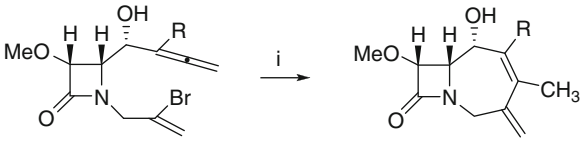
133d (44%, *Z:E* = 100:0)

Scheme 44 Tin-promoted radical preparation of bicyclic β-lactams **133** (**i**) Ph_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux

133 were found as a consequence of a totally regioselective radical cyclization onto the central carbon (Scheme 44). Neither the *endo*-cyclized product nor the *exo*-cyclized product was detected.

The extension of the above radical cyclization of 2-azetidinone-tethered allenynes to bromovinyl and haloaryl allenes bearing the proradical center at N1 was explored. The tin-promoted radical reaction was also useful in the conversion of the β-lactam allenes **134a** and **134b** with a bromopropenyl group substituted at the nitrogen atom, into the corresponding bicyclic systems **135a** and **135b** with similar efficiency and selectivity (Scheme 45). The treatment of β-lactam allenes **136a–d** having a bromo- or iodophenyl group (*N*-tethered) under similar conditions for the preparation of bicycles **133** and **135** gave the fused tricyclic β-lactams **137a–c** containing a central seven-membered ring (Scheme 46). Benzofused β-lactams **137** can be considered as superior cyclohomologous of benzocarbapenems and benzocarbacephems, which have been designed as suicide inactivators of β-lactamases.

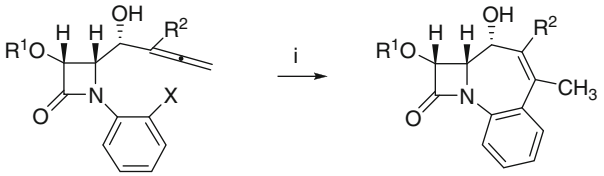
It is presumed that the stannyl radical, by addition to the terminal position of the triple bond in allenynes **132**, or through bromine abstraction in bromovinyl and haloaryl allenes **134** and **136** gives the vinylic radical intermediates **138** and **142** in the propagation step, followed by cyclization toward the central carbon bond of the



134a R = Me
134b R = Ph

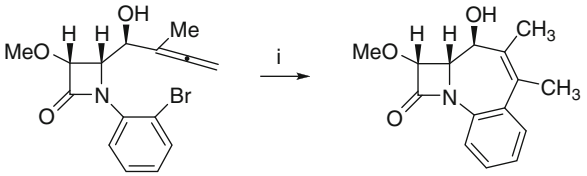
135a R = Me (67%)
135b R = Ph (61%)

Scheme 45 Preparation of bicyclic β-lactams **135** using radical cyclization (**i**) Ph_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux



136a R^1= Me, R^2 = Me,X = Br
136b R^1= Me, R^2 = Ph,X = Br
136c R^1= Me, R^2 = Me,X = I
136d R^1= Ph, R^2 = Me,X = I

137a (52%)
137b (46%)
137a (50%)
137c (41%)

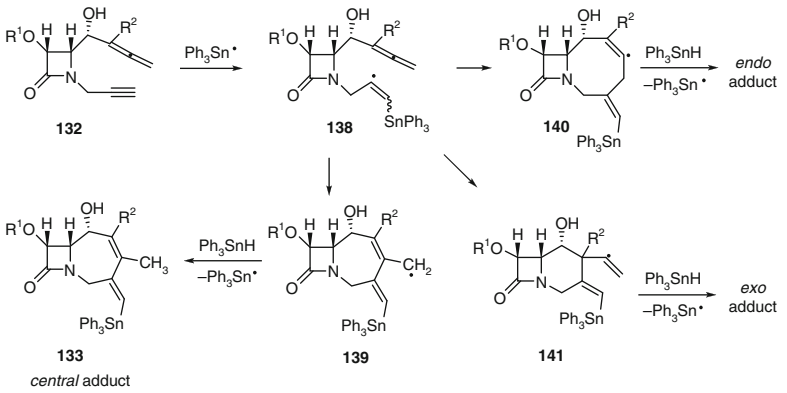


***anti*-136a** ***anti*-137a** (42%)

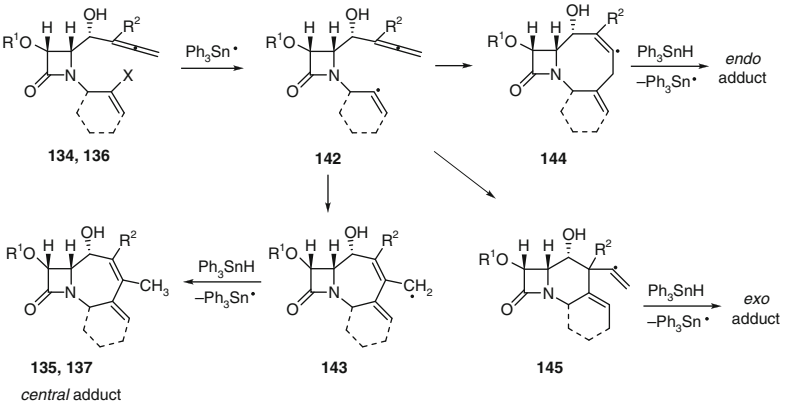
Scheme 46 Preparation of tricyclic β-lactams **137** using radical cyclization (**i**) Ph_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, reflux

allene moiety to give in a total regio- and stereoselective fashion fused cycles **133**, **135,** and **136** via allylic radical intermediates **139** and **143**. While both *endo*- and *exo*-cyclizations of radical intermediates **138** and **142** would give vinylic radicals **140**, **144** and **141**, **145**, respectively, *central*-cyclization would lead to the energetically more favored allylic radicals **139** and **143** (Schemes 47 and 48).

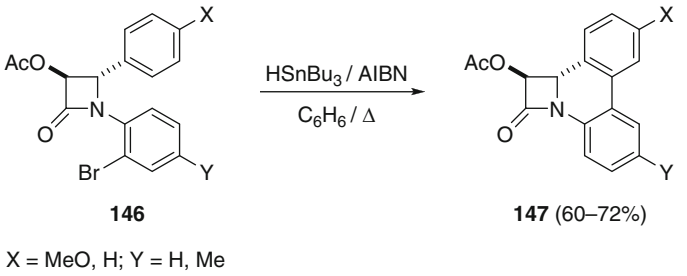
Aryl-2-azetidinone-tethered haloarenes were used for the regiocontrolled preparation of fused tetracyclic biaryl-2-azetidinones which can be considered as β-lactam-biaryl hybrids via aryl-aryl radical cyclization [87]. Treatment of *trans*-β-lactams **146** with tributyltin hydride and AIBN in benzene at reflux under high dilution conditions (215 mL per mmol of starting 2-azetidinone) smoothly formed the corresponding condensed tetracyclic biaryl-2-azetidinones **147** in good yields as single *trans*-diastereomers after chromatographic purification (Scheme 49) together with small amounts of reduced starting material.



Scheme 47 Mechanistic explanation for the formation of bicyclic β-lactams **133**



Scheme 48 Mechanistic explanation for the formation of tricyclic β-lactams **135** and **137**



Scheme 49 Preparation of tetracyclic β-lactams **147** using radical cyclization

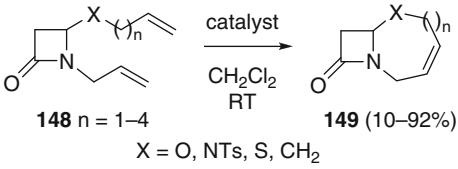
3.3 Using Metal-Mediated Reactions

It has been reported that the ring-closing metathesis (RCM) of 1,4-bis(ene)-substituted 2-azetidinones **148**, allowed synthetically rapid access to a wealth of novel, potentially biologically active, bicyclic β-lactam arrays, **149** (Scheme 50) [88–90]. The ring-closing metathesis runs were performed using either a molybdenum catalyst (Schrock catalyst) or a ruthenium catalyst (Grubbs' carbene), depending on the requirements of the reaction. Seven-membered ring closure to a homo-oxacephem derivative was achieved in an excellent isolated yield of 84%, clearly demonstrating the synthetic utility of this method in these systems. Closure of bicyclic β-lactams with increasing ring sizes was possible, albeit progressively less successful. The eight-membered ring system was produced in 52% yield using 5% mol of Schrock catalyst and in an improved 76% yield using 10% mol of the molybdenum catalyst. The nine-membered fused system was isolated in only 12% yield under the same conditions but could be optimized to 23% using 20% mol of Schrock catalyst. The ten-membered ring was produced in 3% yield using 5 mol % of the molybdenum catalyst and in 10% yield under high dilution and a higher catalyst loading.

While these results clearly established that polyfunctional β-lactam dienes were excellent substrates for metathesis, the reactions were not appropriate for the synthesis of bioactive β-lactam carboxylic acids. In order to find utility for this metathetic approach in the generation of novel drug candidates, a carboxylic acid motif adjacent to the lactam nitrogen was installed. The requisite framework was incorporated via Ireland–Claisen rearrangement of silyl ketene acetals derived from allyl ethers **150**. The silyl ketene acetals underwent smooth rearrangement affording the corresponding carboxylic acids in excellent yields, but as inseparable 1:1 mixtures of diastereoisomers. The above carboxylic acids had only limited solubility in the normal solvents for metathesis, and were directly converted into the corresponding ethyl or *p*-nitrobenzyl esters **151**. Treatment of monocyclic dienes **151** with Schrock or Grubbs carbenes resulted in cyclization to provide bicyclic β-lactams **152** (Scheme 51) [91].

The synthesis of bicyclic 2-azetidinones **154** has been accomplished by ring-closing metathesis reaction of monocyclic diene- and enyne-β-lactams. The enyne metathesis of compounds **153** afforded bicycles **154** in good yields (Scheme 52) [92].

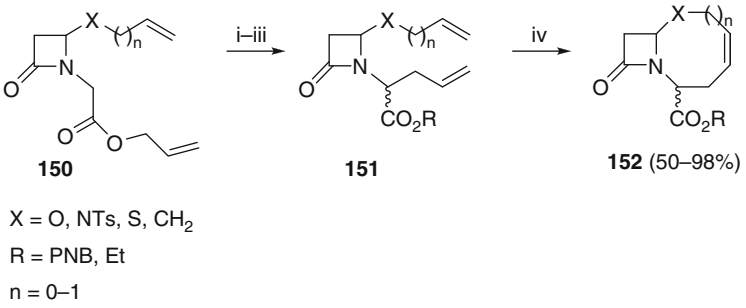
It has been reported that conveniently substituted bis-β-lactams, pyrrolidinyl-β-lactams, and piperidinyl-β-lactams undergo ring-closing methatesis using



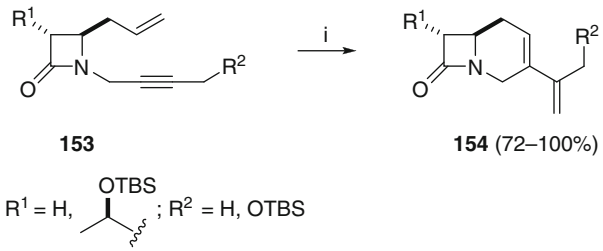
148 n = 1–4 **149** (10–92%)

X = O, NTs, S, CH_2

Scheme 50 Preparation of bicyclic β-lactams **149** using alkene-methatesis



Scheme 51 Preparation of bicyclic β-lactams **152** using alkene-methatesis (**i**) LiHMDS, THF; (**ii**) TMSCl, Δ; (**iii**) RBr, K_2CO_3, DMF; (**iv**) catalyst, CH_2Cl_2, RT

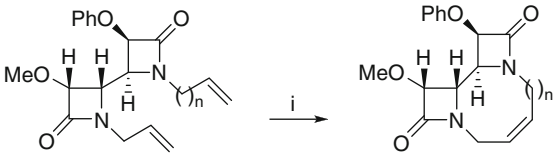


Scheme 52 Preparation of bicyclic β-lactams **154** using alkyne-methatesis (**i**) [$Cl_2(PCy_3)_2Ru$ = CHPh], CH_2Cl_2, RT

Grubbs' carbene, $Cl_2(Cy_3P)_2Ru$ = CHPh, to give medium-sized rings fused to bis-2-azetidinone, pyrrolidinyl-2-azetidinone, or piperidinyl-2-azetidinone systems [93]. The diolefinic cyclization precursors were obtained from optically pure 4-oxoazetidine-2-carbaldehydes bearing an extra alkene tether at position 1 or 3 of the β-lactam ring via [2+2] cycloaddition of imino 2-azetidinones, *N*-metalated azometine ylide [3+2] cycloaddition, and subsequent *N*-acylation of the pyrrolidinyl nitrogen atom, or through aza Diels–Alder of 2-azetidinone-tethered imines. Under standard reaction conditions, the combination of cycloaddition reactions of 2-azetidinone-tethered imines with ring-closing methatesis offers an asymmetric entry to a variety of unusual fused tricyclic 2-azetidinones bearing two bridgehead nitrogen atoms.

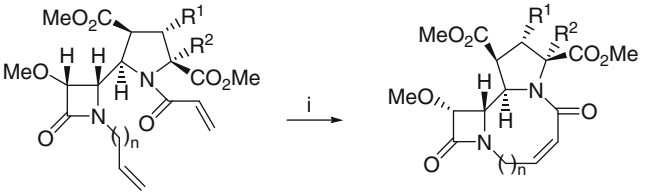
Treatment of dienes **155**, **157**, and **159** with Grubbs' catalyst under smooth ring-closing metathesis conditions (5 mol%, CH_2Cl_2, 25°C), analogous to those described for bicyclic β-lactams, did not furnish the desired tricycles. The majority of the reaction mixture was composed of unreacted dienes. It was found that dienic substrates **155**, **157**, and **159** require more vigorous conditions for ring closure. Among the various solvents and conditions tested, it was found that toluene at reflux temperature gave the best yields of tricyclic-β-lactams containing medium-sized central rings. Exposure of dienes **155**, **157**, and **159** to the ruthenium catalyst $Cl_2(Cy_3P)_2Ru$ = CHPh under optimized cyclization conditions (5 mol% catalyst,

Scheme 53 Preparation of tricyclic β-lactams **156** using alkene-methatesis (**i**) [$Cl_2(PCy_3)_2Ru$ = CHPh], toluene, reflux



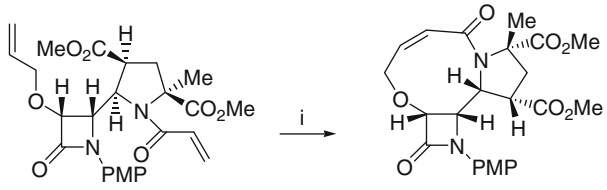
155a n = 1
155b n = 2

156a n = 1(69%)
156b n = 2(54%)



157a
157b
157c
157d
157e
157f

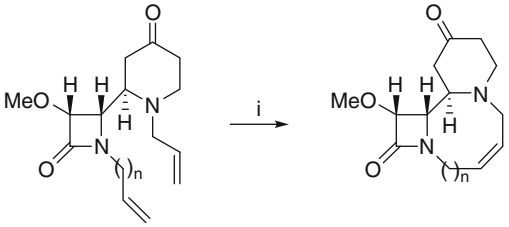
158a R^1 = H, R^2 = H, n = 1 (62%)
158b R^1 = H, R^2 = Me, n = 1 (67%)
158c R^1 = CO_2Me, R^2 = Me, n = 1 (57%)
158d R^1 = H, R^2 = H, n = 2 (58%)
158e R^1 = H, R^2 = Me, n = 2 (58%)
158f R^1 = H, R^2 = Me, n = 3 (35%)



157g

158g (35%)

Scheme 54 Preparation of tricyclic β-lactams **158** using alkene-methatesis (**i**) [$Cl_2(PCy_3)_2Ru$ = CHPh], toluene, reflux



159a
159b
159c

160a n = 1 (53%)
160b n = 2 (31%)
160c n = 3 (33%)

Scheme 55 Preparation of tricyclic β-lactams **160** using alkene-methatesis (**i**) [$Cl_2(PCy_3)_2Ru$ = CHPh], toluene, reflux

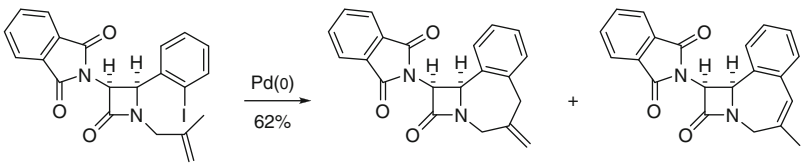
0.03M, toluene, 110°C) resulted in clean formation of tricycles **156**, **158**, and **160** in moderate to good yields (31–69%) (Schemes 53–55). It should be mentioned that for a successful RCM, a structural condition must be satisfied in the starting dienes, namely, a relative *anti*stereochemistry at the single bond connecting the two heterocyclic rings. Interestingly, in the Grubbs' carbene promoted reaction of compounds **159b** and **159c** together with the RCM products **160b** and **160c** *N*-deallylation products were also isolated.

The synthesis of tricyclic β-lactams via palladium-catalyzed cyclization of iodoaryl β-lactams using a catalyst system comprising 10 mol% $Pd(AcO)_2$, 20 mol% PPh_3, and Tl_2CO_3 (2 mol) has been afforded [94]. The methallyl β-lactam **161** underwent 7-*endo-trig* cyclization to give an 8:1 mixture of double bonds isomers **162** and **163** (Scheme 56).

It has been shown that combination of bromoallylation reaction and Heck cyclization is a useful methodology for the preparation of a variety of fused bicyclic β-lactams of nonconventional structure [95]. Starting from acetates **164** and using palladium acetate as the palladium source, DMF as solvent, potassium carbonate as base, and triphenylphosphine, the reaction occurred. The reaction conditions were further optimized and typical results for the preparation of bicyclic β-lactams **165–168** are summarized in Schemes 57.

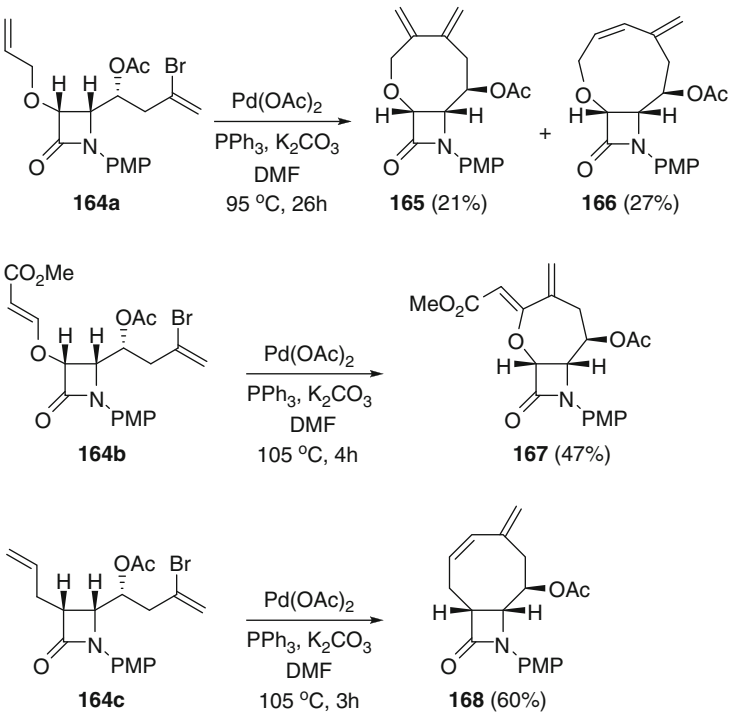
The Heck reaction of acetate **164d** deserves special mention. Substitution pattern on bromodiene **164d** should direct the regiochemical outcome of the cyclization to the six-membered or seven-membered ring formation. Interestingly, we found that the reaction produced the five-membered fused bicycle **169a** as the only isomer. As a result of steric congestion, the stereocontrolled construction of carbon atoms having four carbon ligands is a formidable challenge for chemical synthesis. Compound **169a** is remarkable since it bears a quaternary stereocenter. Adduct **169a** presumably arises from the Pd-catalyzed 5-*exo* cyclization of the initially formed α,β-unsaturated carbonyl compound **170a**. A similar reaction pattern was observed on reacting bromodienes *syn*-**164e** and *anti*-**164e**. Thus, bicyclic β-lactams **169b** and **169c** were also prepared through essentially the same procedure (Scheme 58).

The above hypothesis was probed showing that the intermediate **170** could be obtained from **164** and that this new bromodiene does give the corresponding fused β-lactam **169** under Heck conditions. This mechanistically informative result was provided by the treatment of the bromohomoallylic acetate **164d** with potassium carbonate in acetonitrile to give a separable mixture of isomeric bromodienes



161 **162** **163**

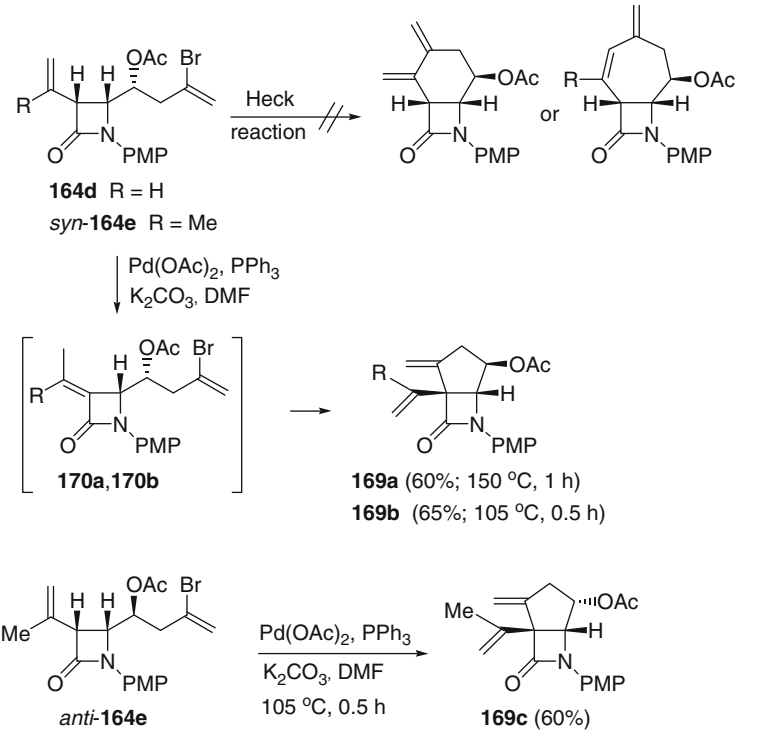
Scheme 56 Preparation of tricyclic β-lactams **162** and **163** using Heck reaction



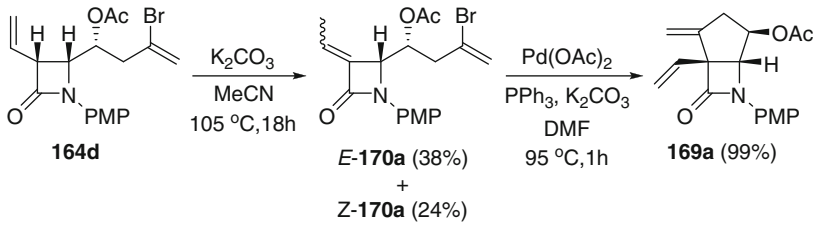
Scheme 57 Preparation of bicyclic β-lactams **165–168** and **163** using Heck reaction

E-**170a** and *Z*-**170a**, which under palladium catalysis afforded the expected bicycle **169a**. The two-step synthesis of compound **169a** from diene **164d** is depicted in Scheme 59.

The allene moiety represents a versatile and useful building block in organic synthesis. However, selectivity problems are significant. Intramolecularization of the reactions, usually by placing the group at a distance suitable for five- or six-membered rings to be formed, should automatically solve the positional selectivity problems because larger rings are unfavored. The less exploited allenic variant of the Pauson–Khand type cycloaddition was explored in allenynes **171** [96]. Substitution patterns on allenynes **171** were selected to direct the regiochemical outcome of the cycloaddition to the six-membered central ring formation because the intramolecular variant of the Pauson–Khand reaction has been largely restricted to the construction of bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones. However, it was found that the [2+2+1] cycloaddition produced tricycles **173** bearing a central seven-membered ring as the only isomer. Cycloadducts **173** presumably arises from the isomerization of the initially formed adducts **172** (Scheme 60). Conjugation of the dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of compounds **173**.

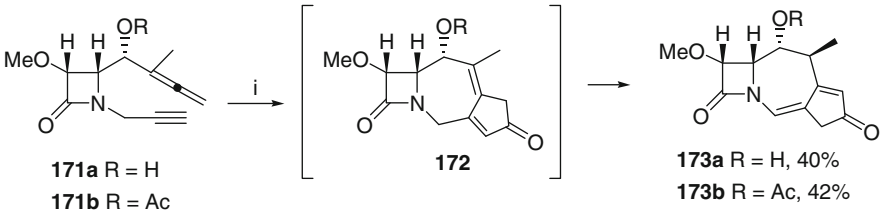


Scheme 58 Preparation of bicyclic β-lactams **169** using Heck reaction



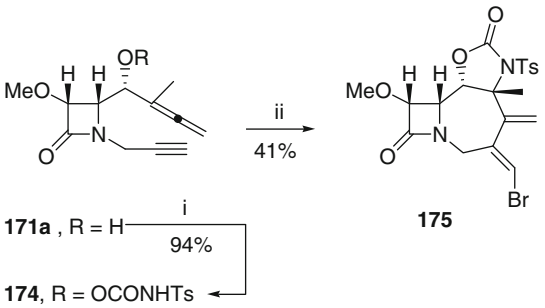
Scheme 59 Preparation of bicyclic β-lactam **169a** using Heck reaction

The 1,2-functionalization of the allene moiety in 2-azetidinone-tethered allenynol derivatives has also been explored [96]. Carbamate **174** was selected as the starting material for the palladium(II)-catalyzed reaction. The above carbamate was prepared from the α-allenic alcohol **171a** by treatment with tosyl isocyanate. Reaction of compound **174** was carried out at room temperature in acetonitrile in the presence of 10 mol% of $Pd(OAc)_2$, 5 equiv of LiBr, 2 equiv of $Cu(OAc)_2$ and 1.2 equiv of K_2CO_3 under an atmospheric pressure of oxygen. The ^{1}H-NMR spectrum of the crude material displayed neither signal corresponding to the allene



Scheme 60 Preparation of tricyclic β-lactams **173** using Pauson-Khand reaction (**i**) $Co_2(CO)_8$, Me_3NO, CH_2Cl_2, RT

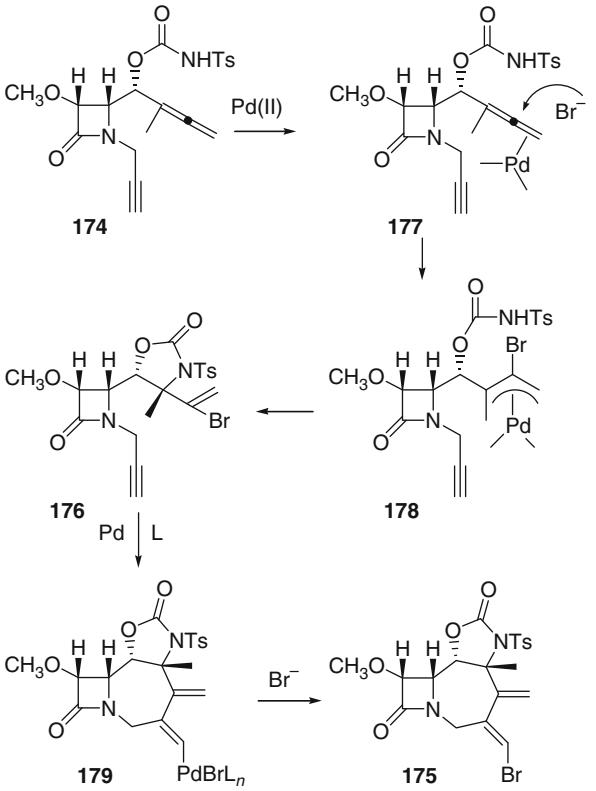
Scheme 61 Preparation of tricyclic β-lactam **175** using amino-allene cyclization (**i**) TsNCO, THF, RT; (**ii**) Pd $(OAc)_2$ 10 mol%, LiBr, Cu $(OAc)_2$, K_2CO_3, O_2, acetonitrile, RT



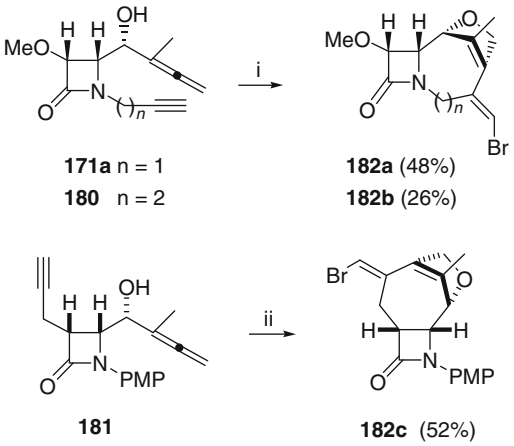
or alkyne moieties. To our delight, the resulting product was identified after purification as the tricycle **175** (Scheme 61). Compound **175** was isolated in moderate yield as the only isomer, indicating that both the regio- and stereoselectivity are extremely high.

The formation of compound **175** could be rationalized in terms of an unprecedented domino allene amidation/intramolecular Heck-type reaction. Compound **176** must be the nonisolable intermediate. A likely mechanism for **176** should involve a (π-allyl)palladium intermediate. The allene–palladium complex **177** is formed initially and suffers a nucleophilic attack by the bromide to produce a σ-allylpalladium intermediate, which rapidly equilibrates to the corresponding (π-allyl)palladium intermediate **178**. Then, an intramolecular amidation reaction on the (π-allyl)palladium complex must account for intermediate **176** formation. Compound **176** evolves to tricycle **175** via a Heck-type-coupling reaction. The alkenylpalladium intermediate **179**, generated in the *7-exo-dig* cyclization of bromoenyne **176**, was trapped by the bromide anion to yield the fused tricycle **175** (Scheme 62). Thus, the same catalytic system is able to promote two different, but sequential catalytic cycles.

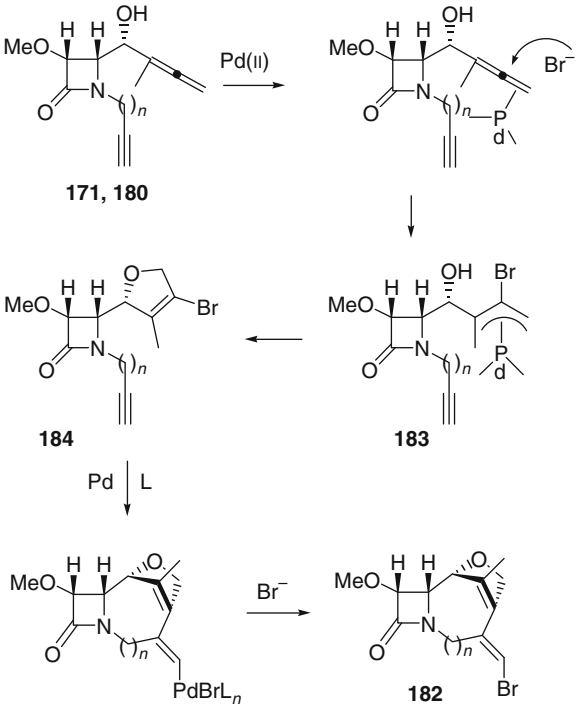
The reactivity of the allenynol moiety itself under these cascade conditions was also explored [96]. Interestingly, treatment of allenynols **171a**, **180,** and **181** under the above palladium-catalyzed domino reaction conditions afforded the bridged medium-sized ring tricycles **182** as single isomers albeit in moderate yields (Scheme 63). Although complete conversion was observed by TLC and ^{1}H NMR



Scheme 62 Mechanistic explanation for the formation of tricyclic β-lactam **175**



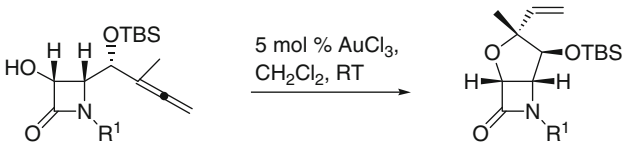
Scheme 63 Preparation of bridged tricyclic β-lactams **182** using oxy-allene cyclization (**i**) $Pd(OAc)_2$ 10 mol%, LiBr, $Cu(OAc)_2$, K_2CO_3, O_2, acetonitrile, RT; (**ii**) $Pd(OAc)_2$ 10 mol%, LiBr, $Cu(OAc)_2$, K_2CO_3, O_2, acetonitrile, reflux



Scheme 64 Mechanistic explanation for the formation of tricyclic β-lactams **182**

analysis of the crude reaction mixtures, the high polarity of adducts **182** may be responsible for the modest isolated yields. Compounds **182** are remarkable since they possess an unusual pyramidalized bridgehead structure. An analogous cascade process to compound **175** formation seems to be taking part in this transformation. However, a dramatic change in the regioselectivity of the nucleophilic insertion into the (π-allyl)palladium intermediate **183** was observed when the bridged dihydrofurans were formed as the exclusive products. The thermochemically more stable five-membered intermediate **184** must be involved in the reaction rather than the corresponding regioisomeric oxirane. Taking into account the precedent explanation for fused compound **175** formation, Scheme 64 outlines a mechanistic hypothesis for the achievement of bridged compounds **182**.

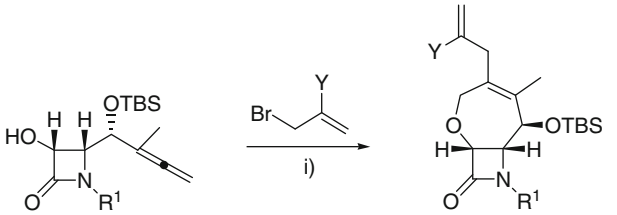
γ-Allenol **185a** was used as initial substrate in a screen to identify regioselective hydroalkoxylation catalysts for the preparation of bicyclic β-lactams [97]. Thus, $[PtCl_2(CH_2{=}CH_2)]_2$ and $AgNO_3$ afforded rather low yield or disappointing diastereomeric mixture of bicycle **186a**. Although $AgNO_3$ was less diastereoselective than $[PtCl_2(CH_2{=}CH_2)]_2$ (60:40 vs. 100:0), it was a more efficient catalyst affording adduct **186a** in reasonable yield (54% vs. 12%). Gratifyingly, it was found that Au^{I} or Au^{III} salts were effective as 5-*exo* selective hydroalkoxylation catalysts. $AuCl_3$ was selected as catalyst of choice because of its superior performance.



185a R^1 = Bn
185b R^1 = allyl

186a R^1 = Bn (57%)
186b R^1 = allyl (58%)

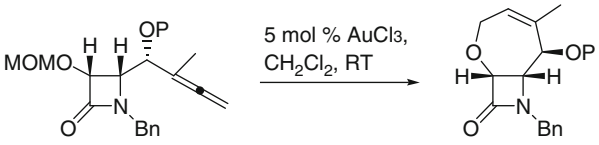
Scheme 65 Preparation of bicyclic β-lactams **186** using Au-catalyzed oxy-allene cyclization



185a R^1 = Bn
185a R^1 = Bn
185a R^1 = Bn
185b R^1 = allyl

187a R^1 = Bn, Y = H (83%)
187b R^1 = Bn, Y = Me (67%)
187c R^1 = Bn, Y = Br (63%)
187d R^1 = allyl, Y = H (94%)

Scheme 66 Preparation of bicyclic β-lactams **187** using Pd-catalyzed oxy-allene cyclization (**i**) 5 mol% $PdCl_2$, DMF, RT



188a P = 4-BrC_6H_4CO
188b P = PMPCO

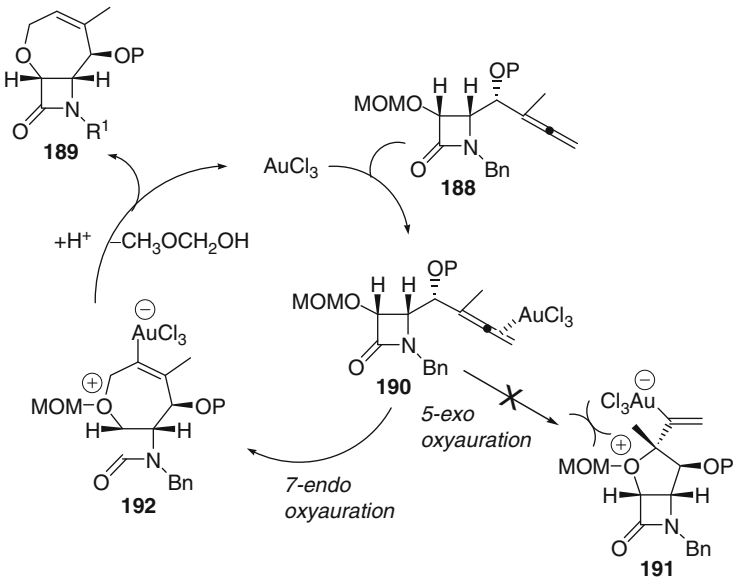
189a P = 4-BrC_6H_4CO (58%)
189b P = PMPCO (45%)

Scheme 67 Preparation of bicyclic β-lactams **189** using Au-catalyzed oxy-allene cyclization

No diastereo- or regioisomeric products were detected, giving exclusively the fused five-membered oxacycles **186** (Scheme 65). Tetrahydrofuran-fused 2-azetidinones **186** are remarkable since they bear a quaternary stereocenter.

A solution for the 5-*exo* selective hydroalkoxylation having been found, the more intricate heterocyclizative problem associated with tuning the regioselectivity of γ-allenols was next examined. Worthy of note, the Pd^{II}-catalyzed cyclizative coupling reaction of γ-allenols **185a** and **185b** with allyl halides gave impressive yields (up to 94%) of the desired seven-membered adducts **187a–d** (Scheme 66), resulting from a 7-*endo* oxycyclization [98].

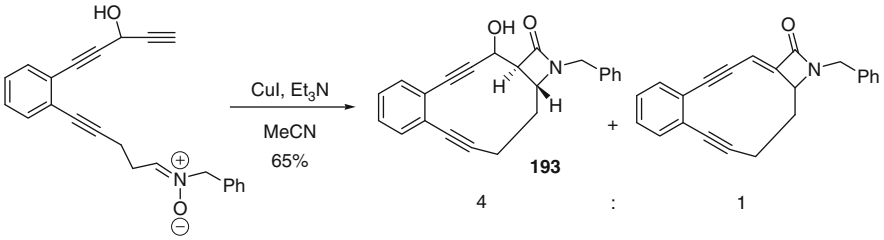
When MOM protected γ-allenol derivatives **188a** and **188b** were used as starting materials for the Au^{III}-catalyzed cycloisomerization, the 5-*exo* mode was



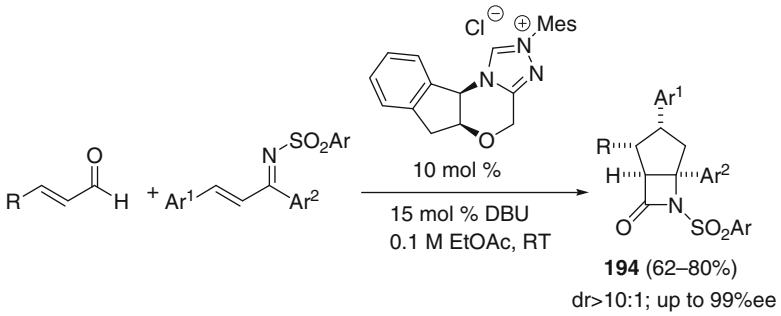
Scheme 68 Mechanistic explanation for the formation of bicyclic β-lactams **189**

completely reverted to a 7-*endo* cyclization to afford bicycles **189** in fair yields (Scheme 67). It seems that the reactivity in this type of Au^{III}-catalyzed reactions is determined by the presence or absence of a methoxymethyl protecting group at the γ-allenol oxygen atom, as the free γ-allenols **185a** and **185b** gave 5-*exo* hydroalkoxylation, while MOM protected γ-allenol derivatives **188a** and **188b** exclusively underwent a 7-*endo* oxycyclization [98]. No other isomers or side products were detected.

The pathway proposed in Scheme 68 looks valid for the formation of products **189**. It could be presumed that the initially formed allenegold complex **190** undergoes an intramolecular attack (7-*endo* vs. 5-*exo* oxyauration) by the (methoxymethyl)oxy group, giving rise not to species **191** but to the tetrahydrooxepine intermediate **192**. Protonolysis of the carbon–gold bond linked to an elimination of methoxymethanol would then liberate the bicycle **189** with concomitant regeneration of the Au^{III} species. Probably, the proton in the last step of the catalysis cycle comes from the trace amount of water present in the solvent or in the catalyst. In order to confirm the mechanistic proposal of Scheme 68, labeling studies with deuterium oxide were performed. Thus, the addition of two equivalents of D_2O to the solution of MOM protected γ-allenol **188b** and $AuCl_3$ in dichloromethane caused the disappearance of the peak at 6.35 ppm, which is a signal of the proton H4, on the 2-oxa-8-azabicyclo[5.2.0]non-4-en-9-one **189b**. The fact that the $AuCl_3$-catalyzed conversion of allenol **188b** into bicycle **189b** in the presence of 2 equiv of D_2O afforded 4-[D]-**189b** as judge by ^1H NMR spectroscopy, suggests that a deuterolysis of the carbon–gold in species **192** has occurred. It may be inferred



Scheme 69 Preparation of tricyclic β-lactams **193** using Kinugasa reaction



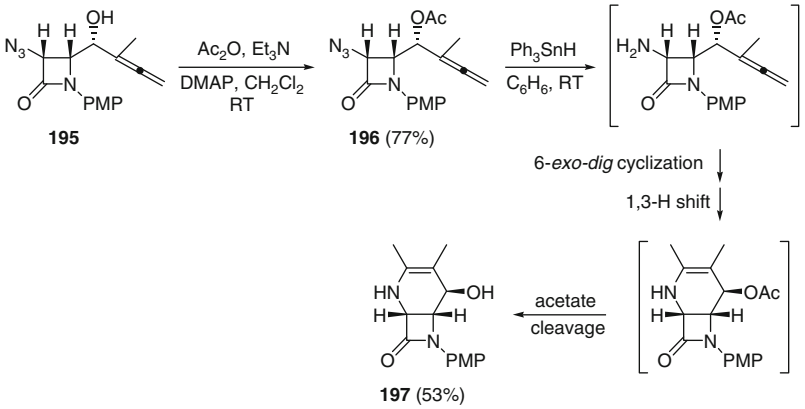
Scheme 70 Preparation of bicyclic β-lactams **194** catalyzed by NHC

that different steric effects in the organometallic species **191** and **192** may be responsible for the different reactivity preference, stabilizing one of the intermediates rather than the other. In the presence of MOM group, 5-*exo* cyclization falters. Probably, 5-*exo* oxyauration via **191** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter [99].

A synthetic route to β-lactam-fused enediynes by intramolecular Kinugasa reaction has been successfully developed. The method has widened the scope of the Kinugasa reaction in the synthesis of sensitive systems like tricycle **193** (Scheme 69) [100].

3.4 Using Cyclization Reactions

A wide range of α,β-unsaturated aldehydes, including 3-alkyl derivatives, undergo *N*-heterocyclic carbene (NHC)-catalyzed annulations with *N*-sulfonyl ketimines under mild conditions to provide bicyclo[3.2.0]lactams **194** with outstanding diastereo- and enantioselectivity (Scheme 70) [101]. This concise route to β-lactams

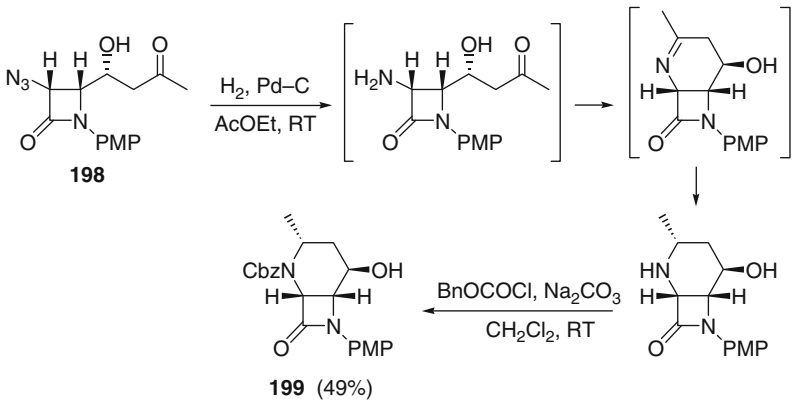


Scheme 71 Preparation of bicyclic β-lactam **197** using azido-allene cyclization

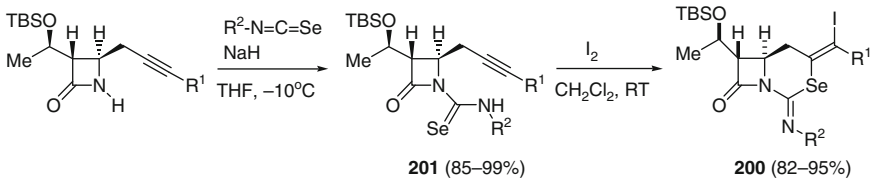
established four new chiral centers in a single operation. Although this process could occur via the intermediacy of a catalytically generated homoenolate equivalent, the stereochemical outcome supports a tandem or concerted aza-benzoin/oxy-Cope reaction as the key bond-forming step.

Two different stereocontrolled accesses to new 4-hydroxypipecolic acid analogs with a bicyclic β-lactam structure have been developed by using intramolecular reductive amination or allenic hydroamination reactions in 2-azetidinone-tethered azides [102]. When attempts were made to reduce azide **195** using the triphenylphosphine method, a complex reaction mixture was observed. Fortunately, it was found that 2-azetidinone-tethered azidoallenic acetate **196** when treated at room temperature with triphenyltin hydride in benzene solution, gave in a totally regioselective fashion, the bicyclic 4-hydroxypipecolic acid analog **197** through a 6-*exo-dig* aminocyclization with concomitant acetate cleavage (Scheme 71). Exposure of aldol adduct **198** to the $Ph_3P–H_2O$ reductive system did afford a mixture of highly polar compounds, which could not be characterized. The hydrogenation reaction of azidoaldol **198** performed in the presence of Boc_2O revealed through ^1H NMR monitoring the formation of little cyclization product, while the major components in the mixture were side-products. Then, it was decided to carry out reduction of the azide and in situ cyclization and protection of the resultant secondary amine as the benzylcarbamate. Interestingly, exposure of compound **198** to H_2 (1 atm) in ethyl acetate at room temperature in the presence of a catalytic amount of Pd (10% on C) followed by the addition of benzyl chloroformate, provided the 4-hydroxypipecolic acid analog **199** with a bicyclic β-lactam structure (Scheme 72).

A convenient approach to synthesize novel selenium-β-lactams, namely 3-selena-1-dethiacephems **200**, was accomplished via the regioselective iodocyclization reaction (Scheme 73) [103]. The key starting materials, alkyne-selenoureas **201**, for this approach were readily prepared by the *N*-alkylation reaction of the corresponding previously known propargyl-azetidinones with a wide variety of isoselenocyanates under basic conditions. First, the reaction of β-alkyne-selenourea



Scheme 72 Preparation of bicyclic β-lactam **199** using azido-ketone cyclization



Scheme 73 Preparation of bicyclic β-lactam **200** using selenacyclization

201a (R^2 = 4-ClC_6H_4) with 1.05 equiv of iodine or NIS in THF at room temperature was examined. It was found that the reaction was highly dependent on the type of electrophile used. With NIS, the desired 3-selena-1-dethiacephem **200a** (R^1 = H, R^2 = 4-ClC_6H) along with 3-aza-4-selenoxo-1-dethiacephem and 3-aza-4-oxo-1-dethiacephem was obtained. The 3-aza-4-oxo-1-dethiacephem was probably formed by the decomposition of 3-aza-4-selenoxo-1-dethiacephem. However, when the reaction was carried out using 1.05 equiv of iodine, the desired product **200a** was exclusively produced in good isolated yield (84%) with only trace amount of byproducts (as indicated by TLC). To improve the yield of cyclization, different reaction conditions were then screened. CH_2Cl_2 was found to be the best solvent for the cyclization reaction. Furthermore, the reaction was heavily influenced by the amount of iodine added, and the best result was obtained when 1.25 equiv of iodine was used (92% yield). On the basis of the above results, the iodocyclization of other alkyne-selenoureas **201** with 1.25 equiv of iodine was conducted in CH_2Cl_2 at room temperature. A variety of 3-selena-1-dethiacephems **200** were obtained in good to excellent yields. The nature of the R^2 group on the selenourea had very little effect on the reaction rate or product yields. Aryl-substituted selenoureas gave slightly higher yield than alkyl-substituted selenoureas. The aryl substitution at alkynes was also well accommodated and afforded the cyclized products in excellent yields. The reaction shows high regioselectivity for six-membered ring selenacephems **200**. Seven-membered ring products were never detected under these reaction conditions.

4 Conclusion

The synthesis of spirocyclic and fused unusual β-lactam derivatives has been discussed. The 2-azetidinone skeleton has been extensively used as a template on which to build the carbo(hetero)cyclic structure joined to the four-membered ring, using the chirality and functionalization of the β-lactam ring as a stereocontrolling element. In many cases the compounds described in this chapter were included because of an interesting synthesis or structure, although limited biological data were found.

References

1. Singh GS (2004) Mini-Rev Med Chem 4:69
2. Singh GS (2004) Mini-Rev Med Chem 4:93
3. Niccolai D, Tarsi L, Thomas RJ (1997) Chem Commun 2333
4. Southgate R (1994) Contemp Org Synth 1:417
5. Southgate R, Branch C, Coulton S, Hunt E (1993) Recent progress in the chemical synthesis of antibiotics and related microbial products. In: Lukacs G (ed) Springer, Berlin, 2:621
6. Page I (ed) (1992) The Chemistry of β-Lactams. Chapman and Hall, London
7. Morin RB, Gorman M (eds) (1982) Chemistry and biology of β-lactam antibiotics. Academic, New York
8. Cabri W, Di Fabio R (2000) Sanfetrinems from bench to market: the evolution of chemical synthesis. Oxford University Press, Oxford, 72
9. Kanno O, Kawamoto I (2000) Tetrahedron 56:5639
10. Hanessian S, Reddy B (1999) Tetrahedron 55:3427
11. Biondi S, Pecunioso A, Busi F, Contini SA, Donati D, Maffeis M, Pizzi DA, Rossi L, Rossi T, Sabbatine FM (2000) Tetrahedron 56:5649
12. Ghiron C, Rossi T (1997) The chemistry of Trinems in targets in heterocyclic systems-chemistry and properties. In: Attanasi OA, Spinelli D (eds) Societa Chimica Italiana, Rome, 1:161
13. Ngo J, Castañer J (1996) Drugs of the future 21:1238
14. Brown AG, Butterworth D, Cole M, Hanscomb G, Hood JD, Reading C (1976) J Antibiot 29:668
15. Veinberg G, Vorona M, Shestakova I, Kanepe I, Lukevics E (2003) Some of the more notable advances concern the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus protease, thrombin, prostate specific antigen, and cell metastasis and as inhibitors of acyl-CoA cholesterol acyl transferase. Curr Med Chem 10:1741
16. Hogan PC, Corey EJ (2005) J Am Chem Soc 127:15386
17. Clader JW (2004) J Med Chem 47:1
18. Kvaerno L, Ritter T, Werder M, Hauser H, Carreira EM (2004) Ang Chem Int Ed 43:4653
19. Burnett DA (2004) Curr Med Chem 11:1873
20. Page MI, Laws AP (2000) Tetrahedron 56:5631
21. Haley TM, Angier SJ, Borthwick AD, Singh R, Micetich RG (2000) Drugs 3:512
22. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Hoberg MD, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su Zz, Gupta P, Fisher PB (2005) Nature 433:73 It has been reported that β-lactams act to modulate the expression of glutamate neurotransmitter transporters via gene activation
23. Macías A, Morán Ramallal A, Alonso E, del Pozo C, González J. (2006) J Org Chem 71:7721

24. Bittermann H, Gmeiner P (2006) J Org Chem 71:97
25. Bittermann H, Böckler F, Einsiedel J, Gmeiner P (2006) Chem Eur J 12:6315
26. Alonso E, López-Ortiz F, del Pozo C, Peralta E, Macías A, González J. (2001) J Org Chem 66:6333
27. Kambara T, Tomioka K (1999) J Org Chem 64:9282 For their evaluation as cholesterol absorption inhibitors, see
28. Skiles JW, McNeil D (1990) Tetrahedron Lett 31:7277 For their evaluation as inhibitors of poliovirus and rhinovirus 3C-proteinases, see
29. Macías A, Alonso E, del Pozo C, Venturini A, González J (2004) J Org Chem 69:7004
30. Macías A, Alonso E, del Pozo C, González J (2004) Tetrahedron Lett 45:4657
31. Alonso E, del Pozo C, González J (2002) Synlett 69
32. Dolle RE, Li CS, Novelli R, Kruse LI, Eggleston D (1992) J Org Chem 57:128
33. Baran PS, Shenvi RA (2006) J Am Chem Soc 128:14028
34. Sun C, Lin X, Weinreb SM (2006) J Org Chem 71:3159
35. Baran PS, Shenvi RA, Mitsos CA (2005) Ang Chem Int Ed 44:3714
36. Nishikawa T, Kajii S, Isobe M (2004) Synlett 2025
37. Pinder JL, Weinreb SM (2003) Tetrahedron Lett 44:4141
38. Kajii S, Nishikawa T, Isobe M (2008) Chem Commun 3121, Synthetic studies and biosynthetic speculation inspired by an unexpected reaction on the marine alkaloid chartelline C have been described
39. Alcaide B, Almendros P, Aragoncillo C (2007) Chem Rev 107:4437
40. Alcaide B, Almendros P (2004) Curr Med Chem 11:1921
41. Deshmukh ARAS, Bhawal BM, Krishnaswamy D, Govande VV, Shinkre BA, Jayanthi A (2004) Curr Med Chem 11:1889
42. Alcaide B, Almendros P (2002) Synlett 381
43. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2001) Synlett 1813
44. Alcaide B, Almendros P (2001) Chem Soc Rev 30:226
45. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (1999) Amino-acids 16:321
46. Ojima I, Delaloge F (1997) Chem Soc Rev 26:377
47. Wagle MMS, DR CJ, Bose AK (1988) Heterocycles 27:1755
48. Alonso E, del Pozo C, González J (2002) J Chem Soc Perkin Trans 1:571
49. del Pozo C, Macías A, López-Ortiz F, Maestro MA, Alonso E, González J (2004) Eur J Org Chem 535
50. Arjona O, Murcia MC, Plumet J (2002) Tetrahedron Lett 34:6405
51. Anklam S, Liebscher J (1998) Tetrahedron 54:6369
52. Nishikawa T, Kajii S, Isobe M (2004) Chemistry Lett 33:440
53. Chowdari NS, Suri JT, Barbas CF III (2004) Org Lett 6:2507
54. Clayden J, Hamilton SD, Mohammed RT (2005) Org Lett 7:3673
55. Zanobini A, Gensini M, Magull J, Vidović D, Kozhushkov SI, Brandi A, de Meijere A (2004) Eur J Org Chem 4158
56. Zanobini A, Brandi A, de Meijere A (2006) Eur J Org Chem 1251
57. Alcaide B, Almendros P, Luna A, Torres MR (2008) Org Biomol Chem 6:1635
58. Simone MI, Edwards AA, Tranter GE, Fleet GWJ (2008) Tetrahedron: Asymmetry 19:2887
59. Alcaide B, Almendros P, Martínez del Campo T, Rodríguez-Acebes R (2004) Tetrahedron Lett 45:6429
60. Alcaide B, Almendros P, Martínez del Campo T, Rodríguez-Acebes R (2007) Adv. Synth Catal 349:749
61. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) Chem Eur J 11:5708
62. Alcaide B, Almendros P, Martínez del Campo T, Carrascosa R (2008) Chem Asian J 3:1140
63. Alcaide B, Pardo C, Rodríguez-Ranera C, Rodríguez-Vicente A (2001) Org Lett 3:4205
64. Alcaide B, de Murga RM, Pardo C, Rodríguez-Ranera C (2004) Tetrahedron Lett 45:7255
65. Desroy N, Robert-Peillard F, Toueg J, Duboc R, Hénaut C, Rager MN, Savignac M, Genêt JP (2004) Eur J Org Chem 4840

66. Desroy N, Robert-Peillard F, Toueg J, Hénaut C, Duboc R, Rager MN, Savignac M, Genêt JP (2004) Synthesis 2665
67. Duboc R, Hénaut C, Savignac M, Genêt JP, Bhatnagar N (2001) Tetrahedron Lett 42:2461
68. Alcaide B, Almendros P (1999) Tetrahedron Lett 40:1015
69. Alcaide B, Almendros P, Salgado NR (2000) J Org Chem 65:3310
70. Alcaide B, Almendros P, Pardo C, Rodríguez-Ranera C, Rodríguez-Vicente A (2003) J Org Chem 68:3106
71. Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2005) Eur J Org Chem 98
72. Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2002) Chem Commun 1472
73. Alcaide B, Almendros P, Aragoncillo C, Redondo MC, Torres MR (2006) Chem Eur J 12:1539
74. Alcaide B, Sáez E (2005) Eur J Org Chem 1680
75. Alcaide B, Alonso JM, Aly MF, Sáez E, Martínez-Alcázar MP, Hernández-Cano F (1999) Tetrahedron Lett 40:5391
76. Alcaide B, Sáez E (2000) Tetrahedron Lett 41:1647
77. Brown D, Brown GA, Andrews M, Large JM, Urban D, Butts CP, Hales NJ, Gallagher T (2002) J Chem Soc Perkin Trans 1:2014
78. Ruano G, Grande M, Anaya J (2002) J Org Chem 67:8243
79. Alcaide B, Almendros P, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:2767
80. Alcaide B, Almendros P, Aragoncillo C (2001) J Org Chem 66:1612
81. Alcaide B, Almendros P, Aragoncillo C (1999) Chem Commun 1913
82. Penfold DJ, Pike K, Genge A, Anson M, Kitteringham J, Kilburn JD (2000) Tetrahedron Lett 41:10347
83. Joshi SN, Puranik VG, Deshmukh ARAS, Bhawal BM (2001) Tetrahedron: Asymmetry 12:3073
84. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) Synthesis 2335
85. Alcaide B, Almendros P, Aragoncillo C (2003) Org Lett 5:3795
86. Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2007) J Org Chem 72:1604
87. Alcaide B, Almendros P, Pardo C, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:7894
88. Barrett AGM, Baugh SPD, Braddock DC, Flack K, Gibson VC, Procopiou PA (1997) Chem Commun 1375
89. Barrett AGM, Baugh SPD, Gibson VC, Giles MR, Marshall EL, Procopiou PA (1997) Chem Commun 155
90. Barrett AGM, Baugh SPD, Braddock DC, Flack K, Gibson VC, Giles MR, Marshall EL, Procopiou PA, White AJP, Willians DJ (1998) J Org Chem 63:7893
91. Barrett AGM, Ahmed M, Baker SP, Baugh SPD, Braddock DC, Procopiou PA, White AJP, Willians DJ (2000) J Org Chem 65:3716
92. Tarling CA, Holmes AB, Markwell RE, Pearson ND (1999) J Chem Soc Perkin Trans 1:1695
93. Alcaide B, Almendros P, Alonso JM, Redondo MC (2003) J Org Chem 68:1426
94. Burwood M, Davies B, Díaz I, Grigg R, Molina P, Sridharan V, Hughes M (1995) Tetrahedron Lett 36:9053
95. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) J Org Chem 70:2713
96. Alcaide B, Almendros P, Aragoncillo C (2002) Chem Eur J 8:1719
97. Alcaide B, Almendros P, Martínez del Campo T (2007) Angew Chem Int Ed 46:6684
98. Alcaide B, Almendros P, Martínez del Campo T, Soriano E, Marco-Contelles, JL (2009) Chem Eur J 15:1901
99. Alcaide B, Almendros P, Martínez del Campo T, Soriano E, Marco-Contelles, JL (2009) Chem Eur J 15:1909
100. Pal R, Basak A (2006) Chem Commun 2992
101. He M, Bode JW (2008) J Am Chem Soc 130:418
102. Alcaide B, Almendros P, Luna A, Martínez del Campo T (2008) J Org Chem 73:1635
103. Garud DR, Koketsu M (2008) Org Lett 10:3319

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Spirocyclic β-Lactams: Synthesis and Biological Evaluation of Novel Heterocycles

Shamsher S. Bari and Aman Bhalla

Abstract β-Lactam rings containing compounds are a group of antibiotics of unparalleled importance in chemotherapy. Considerable effort has been reported in the development of novel, more effective β-lactam compounds as well as their biological evaluation. This article reviews the progress made in the stereoselective synthesis of spiro-β-lactams, a unique class of heterocycles, their biological evaluation, and their applications in various related fields. The introductory paragraph highlights the significance of the β-lactam chemistry and is followed by an overview of monocyclic-, bicyclic-, and tricyclic-β-lactams. The other sections of the article deal with the stereoselective synthesis and biological evaluation of spiro-β-lactams, including their use as synthetic intermediates for β-turn mimics and β-turn nucleators. The potential of spiro-β-lactams as cholesterol absorption inhibitors, β-lactamase inhibitors, and antiviral, antibacterial, and antimicrobial agents has also been described.

Keywords Biological activity · Cholesterol absorption inhibitors · Ketene-imine cycloaddition · Spiroazetidin-2-ones · Spiro-β-lactams · Synthetic intermediates · β-Lactamase inhibitors

Contents

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Abbreviations

Ac	Acetyl
AIBN	2,2′-Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
Bu	Butyl
t-Bu	*tert*-Butyl
Cbz	Benzyloxycarbonyl
d	Day(s)
DCC	*N*,*N*-Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DIBALH	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
h	Hour(s)
HATU	*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluranium tetrafluroborate
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
MCPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
MIC	Minimal inhibitory concentration
min	Minute(s)
mL	Milliliter(s)
Ms	Mesityl
NCS	*N*-Chlorosuccinimide

NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
i-Pr	Isopropyl
PTC	Phase transfer catalyst
p-TSA	*p*-Toluenesulfonic acid
f	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TCNE	Tetracyanoethylene
TEA	Triethylamine
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts	Tosyl

1 Introduction

β-Lactam antibiotics have proved to be chemotherapeutics of incomparable effectiveness, possessing a broad spectrum of biological activities with low host toxicity [1]. First synthesized in 1907 by Staudinger, [2] the four membered cyclic amide derivatives of 3-aminopropionic acids known as β-lactams, did not come to the forefront in organic chemistry until Fleming's landmark discovery of penicillin in 1929 [3]. The resulting recognition of the β-lactam moiety as the key pharmacophoric component of the penam antibiotics initiated a flurry of synthetic activity. Today, thousands of compounds containing β-lactam rings are known. Whether isolated from natural sources or synthesized chemically, penicillins and cephalosporins are marked by high efficacy and safe toxicological profiles and are still the most commonly used antibiotics the world over [4].

Further, the discovery of 7-α-methoxycephalosporins [5] from "*Streptomyces*" in 1971, carbapenems [6], thienamycin [7], clavulanic acid [8], sulbactum [9] as well as the totally synthetic oxapenems [10], oxacephams [11], and other bicyclic β-lactams stimulated the search for novel antibiotics. More recent dedicated efforts to find new active molecules and modify the penicillin and cephalosporin structure have resulted in the discovery of simple monocyclic β-lactams such as norcardicins and monobactams [12, 13]. Yet another dimension has been added to the β-lactam research with the recent discovery of tricyclic β-lactam antibiotics called trinems [14]. Thus, β-lactam antibiotics in general can be classified into several groups based on their structures (Fig. 1).

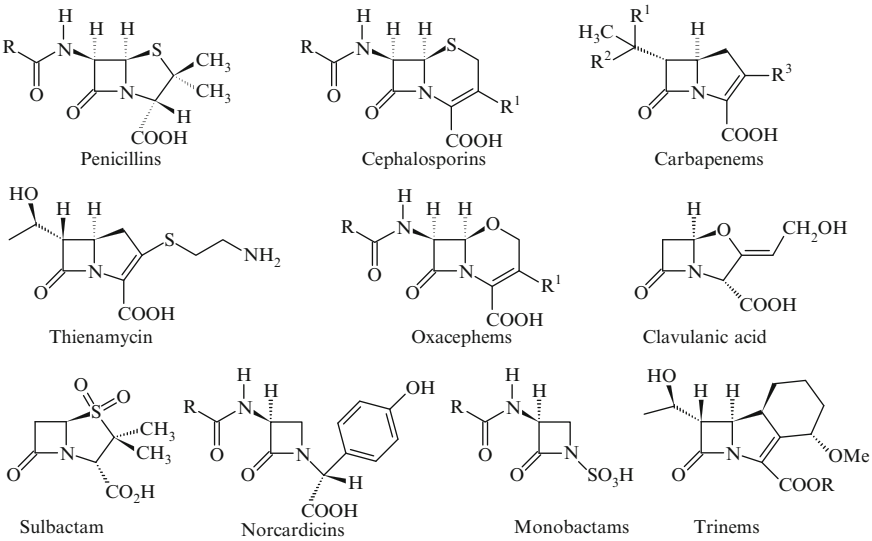


Fig. 1 β-Lactam antibiotics

Very recently, β-lactam antibiotics have been shown to offer neuroprotection by increasing glutamate transporters expression via gene activation [15]; in addition, the discoveries of new biologically active β-lactams such as cholesterol acyl transferase inhibitors [16–18], thrombin inhibitors [19], human cytomegalovirus protease inhibitors [20], matrix-metallo protease inhibitors [21], inhibitors of human leukocyte elastase (HLE) [22, 23] and cysteine protease [24, 25], and apoptosis inductors [26, 27] have provided much needed motivation for continuous development of new β-lactam systems.

Besides this, the utility of β-lactams as intermediates for α- and β-amino acids, alkaloids, other heterocycles, taxoids, and other important compounds of biological and medicinal interest [28–34] has given impetus to research leading to the synthesis of novel bioactive β-lactam compounds. Enthused by their pharmacological applications besides the limitation associated with their biosynthesis, organic chemists were challenged with the task of synthesizing the strained four-membered ring (azetidin-2-one), with a variety of appendages like side chains, unsaturations, heteroatoms, and, in many cases, another ring system.

The vast work reported on the chemistry of β-lactams has demonstrated that β-lactam systems are quite readily accessible through a number of different approaches, with newer versions still being reported. These molecules possess enough stability as to be suitable for the standard isolation, separation, and purification processes at both the laboratory and the industrial scales [35–37]. Recently, several review articles have highlighted the different methodologies for the steroselective syntheses of mono-, bi-, tri-, and polycyclic β-lactams with associated biological activities [38–43].

The Alcaide and Almendros group [38] have reviewed the synthesis of fused and nonfused bi-, tri-, and polycyclic β-lactams of biological interest, while Singh [39] has reviewed recent developments in synthetic and biological studies of monobactams and carbapenems. In addition to this, Palomo and coworkers [40] have described the recent progress made in the asymmetric synthesis of β-lactams and their use as building blocks of natural and non-natural products. Besides this, Deshmukh et al. [41] have made efforts to explore new aspects of azetidin-2-ones as synthons for biologically important compounds in their latest review on β-lactams. Chmielewaski et al. [42] have focused attention on explaining strategies for the stereocontrolled formation of oxygen analogs of penicillins and cephalosporins, while Buynak has reviewed the detailed research directed toward the development of useful broad-spectrum β-lactamase inhibitors [43].

The resistance of pathogenic bacteria to β-lactam antibiotics has an important incidence in human infections. As a consequence, in the last few years many research groups have been actively involved in improving the microbiological activity of antibacterial agents, as well as finding β-lactamase inhibitors [44], and exploring new β-lactam containing ring systems. In particular, spirocyclic β-lactams have, at present, become the center of attraction as they exhibit cholesterol absorption inhibiting (CAI) activity [45, 46], antiviral [47] and antibacterial properties [48], serve as efficient β-turn nucleators [49], behave as β-turn mimetics [50] and precursors of α,α-disubstituted β-amino acids [51].

This article aims to review the development in stereoselective synthesis of spiro-β-lactams and their biological evaluation as well as applications in various fields.

2 Monocyclic, Bicyclic and Tricyclic β-Lactams: An Overview

2.1 Monocyclic β-Lactams

Synthesis of unusual amino acids, peptidomimetics, synthetic enzymes, and new drugs containing β-lactam rings as an integral part of their structure, has currently renewed interest worldwide in this four-membered heterocycle [52–54]. Furthermore, the appropriately substituted and configuredβ-lactam frameworks now constitute effective tools for the incorporation of a wide variety of both β- and α-amino acids in short peptide segments of various biologically active molecules.

The discovery of the norcardicins and monobactams demonstrated for the first time that a conformationally constrained bicyclic structure was not necessary for antibacterial activity of β-lactams [12, 13]. In recent years, various natural and unnatural monocyclic-β-lactams have been shown to exhibit high biological activity, suggesting that the biological activity of the particular ring is influenced by the type of substitution attached to the azetidin-2-one ring (Fig. 2).

Burnett et al. [16] have reported monocyclic β-lactam **I** as a potent cholesterol absorption inhibitor in vivo, and this can inhibit the absorption of dietary

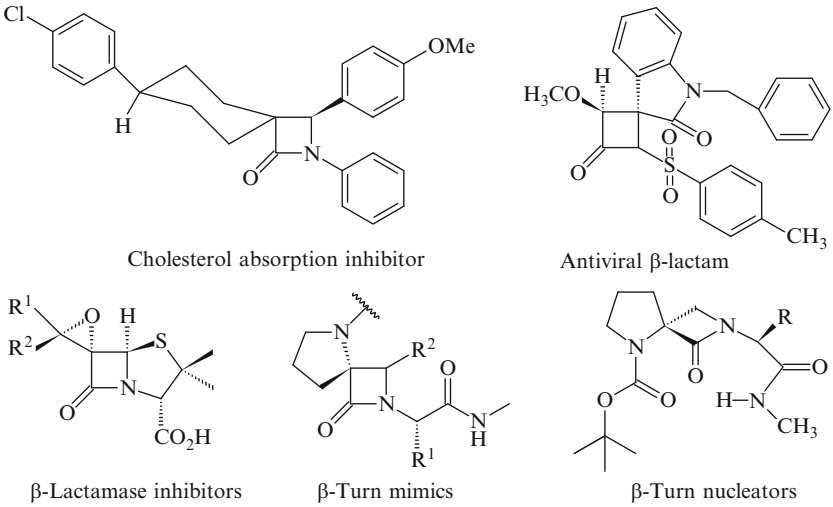
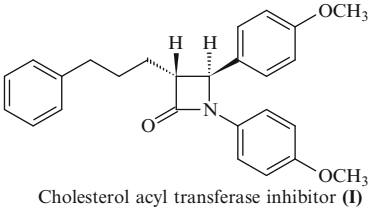


Fig. 2 Biologically active spirocyclic β-lactams

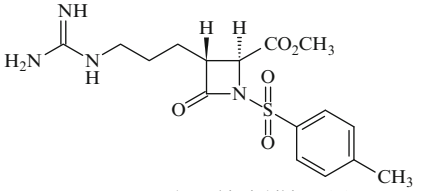
cholesterol by inhibiting the enzyme acyl-CoA: *cholesterol acyl transferase* (ACAT), which is associated with cholesterol esterification. The potential use of monocyclic β-lactam **II** as thrombin inhibitor [19] and **III** as prostate specific antigen inhibitor [55] has been documented well. Many of the anticancer drugs in current use are toxic and thus, limited in their efficacy. Recently, Smith et al. [26, 27] have discovered and characterized the apoptosis inducing properties of a family of novel monocyclic *cis*-3-methoxy-β-lactam **IV** antibiotics against leukemia, breast, prostate, and head-and-neck cancer cells.

The clinical demand for newer, more specific and potent inhibitors of proteases is growing continuously, especially for enzymes such as HLE whose activity has proven to be instrumental in a number of cases of severe, acute, and chronic pathology. Garbisa et al. [21] have reported that monocyclic β-lactam **V** exhibits activity against HLE at micromolar concentrations. Monocyclic azetidin-2-ones have been assessed for enzyme inhibiting and antitubercular activity as well. Georg and Schloss [56] revealed that 3-amino β-lactam **VI** is a time-independent inhibitor of α-*chymotrypsin*, *carboxypeptidase Y,* and *cathepsin G*. *N*-Substituted azetidin-2-one **VII**, which was screened in vitro and has been found to exhibit antitubercular activity against *Mycobacterium tuberculosis H37Rn* strain [57]. The discovery of β-lactams likes **VIII**, **IX**, **X**, which find use as hypocholesterolemic, anti-inflammatory, antidegenerative, and antileukemic, respectively, has added another distinct dimension in the search for biologically active novel monocyclic β-lactams [58–60].

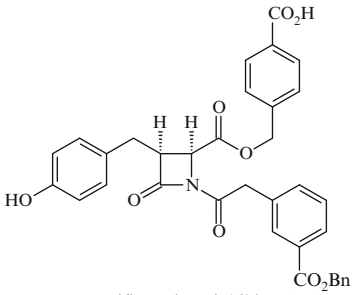
Recently, Banik et al. [61, 62] have explored the anticancer activity of monocyclic β-lactam **XI** against leukemia and colon carcinoma cell lines and very recently, Imbach et al. [63] reported the monocyclic β-lactam **XII** as the selective inhibitor of the chymotrypsin-like activity of the human 20 S proteasome (Fig. 3).



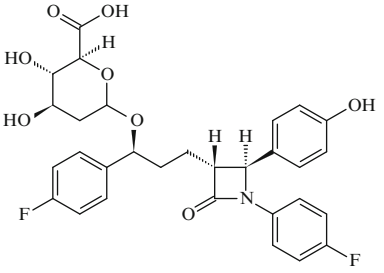
Cholesterol acyl transferase inhibitor **(I)**



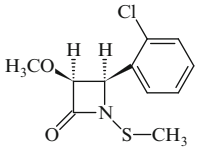
Thrombin inhibitor **(II)**



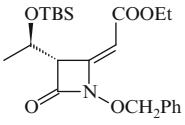
Prostate specific antigen inhibitor **(III)**



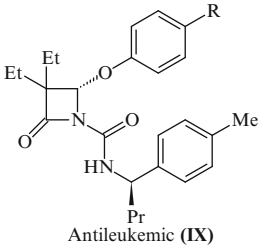
Hypocholesterolemic **(VIII)**



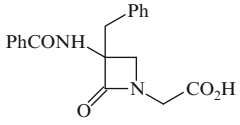
Antitumor **(IV)**



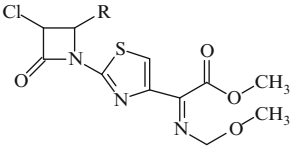
Human leukocyte elastase inhibitor **(V)**



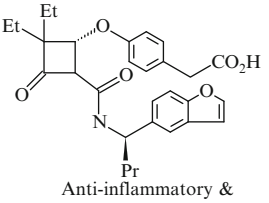
Antileukemic **(IX)**



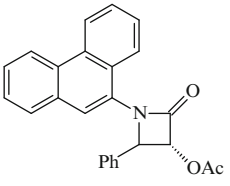
Enzymatic inhibitor **(VI)**



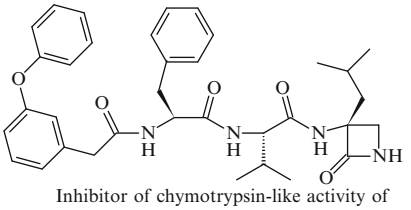
Antituberculic **(VII)**



Anti-inflammatory & antidegenerative **(X)**



Anticancer **(XI)**



Inhibitor of chymotrypsin-like activity of human 20S proteasome **(XII)**

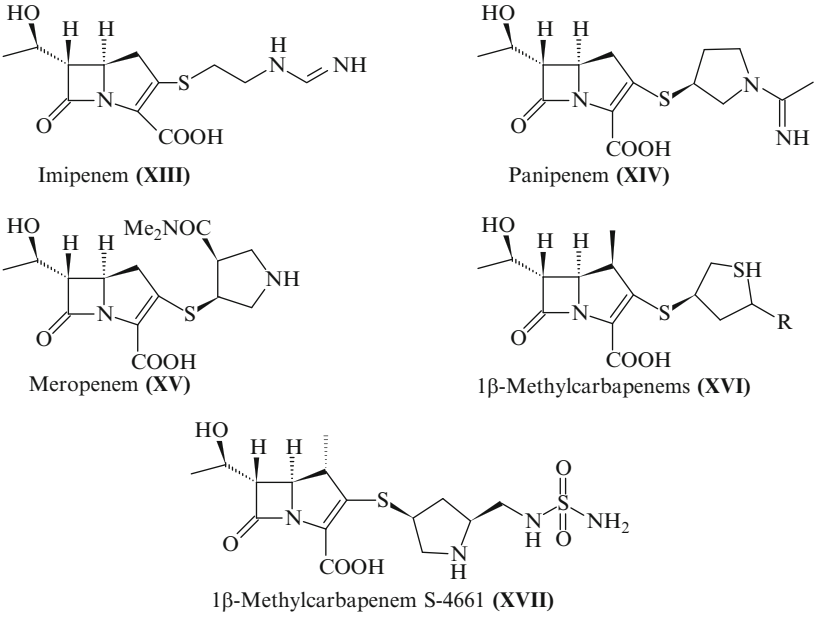
Fig. 3 Biologically active monocyclic β-lactams

2.2 Bicyclic β-Lactams

The development of antibacterial chemotherapy during the past 75 years has spearheaded the successful use of today's drugs to combat bacterial infections. Studies in β-lactam chemistry were stimulated when β-lactam ring, the four membered heterocycle, was recognized as a key structural feature as well as a key therapeutic feature of the bicyclic β-lactam antibiotics such as penicillins, cephalosporins, and other classical antibiotics. The last two decades have registered the discovery of several nonclassical bicyclic β-lactam antibiotics, e.g., thienamycin and carbapenems of natural origin like olivanic acids, carpetimycin, pluracidomycin, and aspareomycins.

Currently, bicyclic β-lactams such as, imipenem (**XIII**), panipenem (**XIV**), and meropenem (**XV**) have been shown to exhibit broad antimicrobial spectrum and potent bactericidal activity [64–66].

Recently, Kang et al. [67] have found that the bicyclic β-lactams (**XVI**) exhibit potent antibacterial activities against a wide range of Gram-(+) and Gram-(−) bacteria and high stability to the *renal dehydropeptidase-I* (DHP-I). Mikamo et al. [68] have reported in vitro and in vivo antibacterial activity of bicyclic β-lactam S-4661 (**XVII**) against *S. agalactiae, E. coli, P. magnus, B. fragilis,* and *P. bivia*, the major pathogens in the fields of obstetrics and gynecology [69] (Fig. 4).



Bicyclic-β-lactams: Antibacterial and highly stable to *porcine renal dehydropeptidase-I* (DHP-I)

Fig. 4 Biologically active bicyclic β-lactams

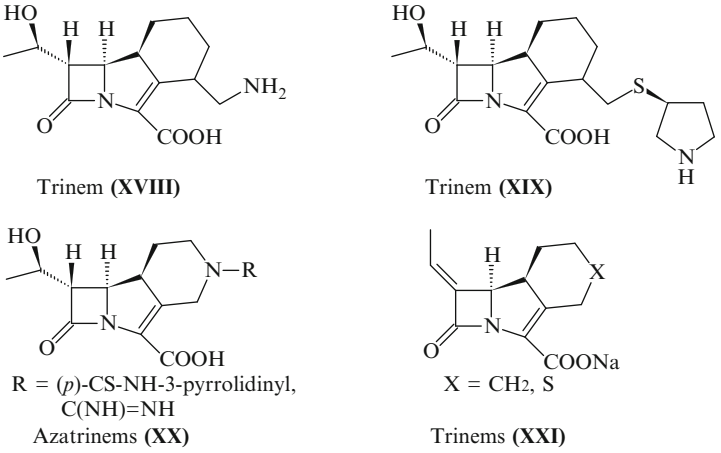


Fig. 5 Biologically active tricyclic β-lactams

2.3 Tricyclic β-Lactams

Trinems are a class of fused tricyclic totally synthetic antibiotics. These are potent antibacterial agents with broad spectrum of activity against both aerobic and anaerobic Gram-(+) and Gram-(−) bacteria. Kanno et al. [70] have reported that tricyclic β-lactam **XVIII** showed antibacterial activity against both Gram-(+) and Gram-(−) bacteria (MIC = 0.01–6.2 μg mL^{-1}). However, tricyclic β-lactam **XIX** having pyrrolidinylthiomethyl moiety exhibit the most potent anti-MRSA activity (MIC = 1.5 μg mL^{-1}) against Gram-(+) bacteria *S. aureus 209P* [71].

Recently, Mori et al. [72] have reported the stereoselective synthesis and antibacterial activity of tricyclic β-lactams with azacyclohexane ring (**XX**). These 5-azatrinems (**XX**) showed high potency and well-balanced spectrum against Gram-(+) and Gram-(−) bacteria. In continuation to this study, Copar et al. [73] have designed biologically active tricyclic β-lactams **XXI** using theoretical computation and molecular modeling. These trinems have been shown to possess inhibitory activity against Class C β-lactamase (Fig. 5).

3 Spirocyclic β-Lactams: Synthesis and Biological Evaluation

Although, considerable synthetic progress has been made in the area of mono and bicyclic β-lactam antibiotics in recent years, the discovery and development of new antibacterial agents with enhanced bioactivity and greater stability toward β-lactamases still remains an important endeavor for medicinal chemists. Also, the widespread incidence of antibacterial resistance to β-lactam antibiotics caused by

β-lactamase formation has provoked a growing interest in the development of effective β-lactamase inhibitors. In addition, the search for novel candidates with different biological activities still remains a field of much interest.

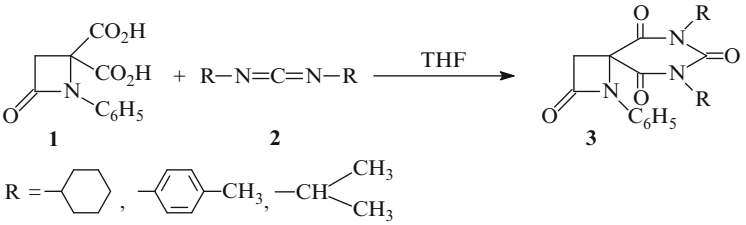
The synthesis of β-lactams having a small fused ring is of interest since the large strain of the ring should substantially alter the reactivity of β-lactams. Several approaches for the synthesis of spiro-β-lactams have been described in literature.

3.1 Synthesis

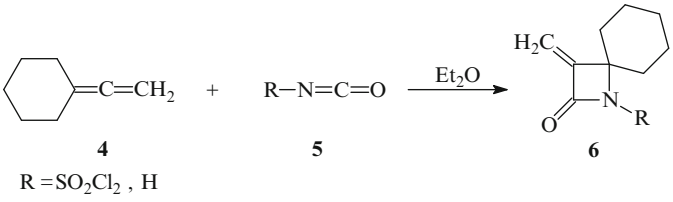
Bose et al. [74] have investigated the novel synthetic route for the preparation of spirobarbiturates–a class of compounds known for their interesting physiological activity. The synthesis of spiro-β-lactams **3** (Scheme 1) was achieved by the reaction of 4,4-dicarboxy-*N*-phenylazetidin-2-one **1** with carbodiimides **2** in tetrahydrofuran.

Moricini and Kelly [75] have reported the synthesis of spiro-β-lactams **6** containing an exocyclic double bond (Scheme 2) by the 1,2-dipolar cycloaddition of symmetrically/unsymmetrically substituted allene **4** with chlorosulfonyl isocyanate **5** in ether.

In the course of their studies on the synthesis of α-amido-spiro-β-lactams as analogs of penicillin and cephalosporin, Manhas et al. [76] have prepared 1-phenyl-3-phenoxy-4,4-spirocyclohexylazetidin-2-ones by the reaction of phenoxyacetyl chloride **7** and cyclohexylidenephenylamine **8** in the presence of triethylamine and dichloromethane. Azidoacetyl chloride was found to be even more reactive

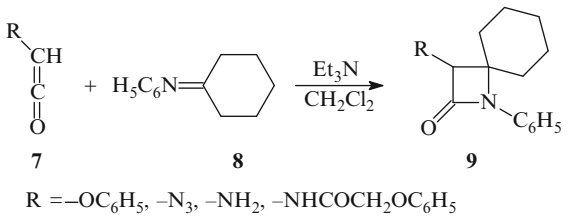


Scheme 1 Preparation of spirobarbiturates using 4,4-dicarboxy-*N*-phenylazetidin-2-one and carbodiimides

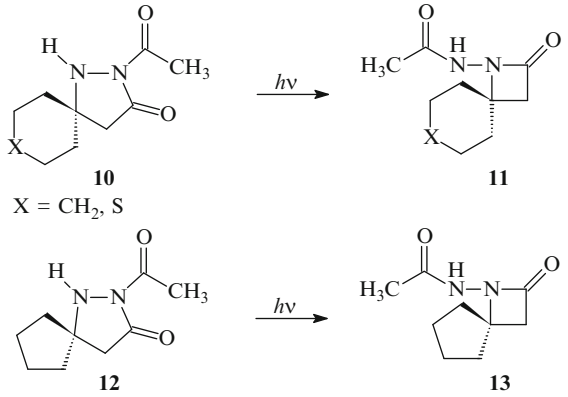


Scheme 2 Synthesis of spiro-β-lactams by 1,2-dipolar cycloaddition

Scheme 3 Preparation of spiro-β-lactams using of phenoxyacetyl chloride and cyclohexylidenephenylamine



Scheme 4 Photochemical synthesis of spirocyclic-β-lactams



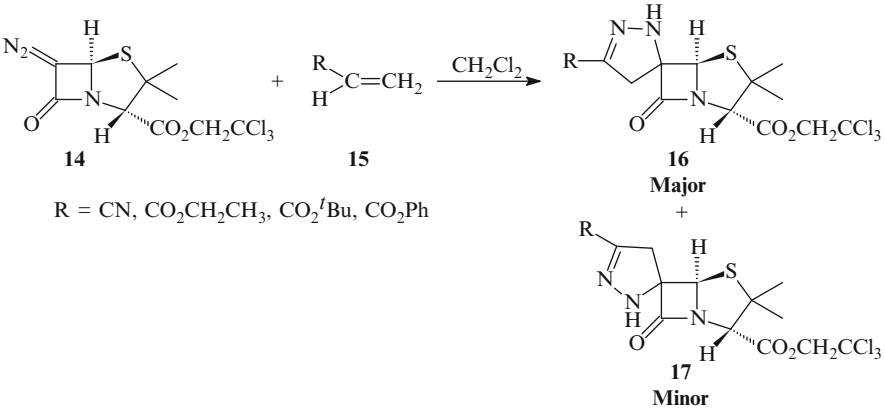
than phenoxyacetyl chloride in the cycloaddition reaction, giving azido β-lactam in 54% yield. The azide group was easily reduced by catalytic hydrogenation in the presence of Adam's catalyst. Acylation with phenoxyacetyl chloride of the amine group readily transformed it into α-amido-spiro-β-lactam **9** (Scheme 3) in a quantitative yield.

Johnson et al. [77] have prepared spiro-1-acylaminoazetidin-2-ones **11, 13** (Scheme 4) by photolysis of spiro-2-acylpyrazolidin-3-ones **10, 12**, respectively. The *N*-acylaminoazetidin-2-one moiety has been found to be the dominant feature of 6-azapenicillins and 7-azacephalosporins.

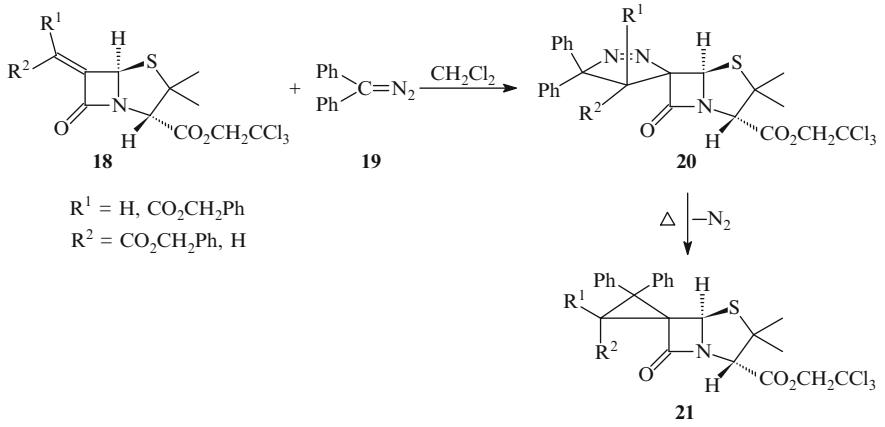
Novel spiropenicillins (Scheme 5) have also been prepared by Sheehan et al. [78]. β,β,β-Trichloroethyl-6-diazopenicillanate **14** reacts with acrylonitrile, ethyl acrylate, and *t*-butyl acrylate to give isomeric compounds **16** and **17**. The preferred mode of addition is from the sterically less hindered α-side.

This study has further been extended by carrying out the reaction of dipolarophile penicillin molecule **18** with diphenyldiazomethane **19** and this reaction resulted in the formation of single isolable spiro-β-lactams **20**. Further pyrolysis of **20** gave spiro-β-lactams **21** (Scheme 6). Addition is expected to occur from the α-side.

Singh and Mehrotra [79] have published the synthesis of spiro-β-lactams **24** (Scheme 7) by the reaction of 2-diazo-1,2-diphenylethanone **22** with 2-phenyliminoacenaphthenone **23** in refluxing benzene. These compounds were further subjected to reduction with sodium borohydride which afforded spiro-β-lactams **25**. This study has also revealed that the carbonyl group in the spiro-β-lactams **24** have



Scheme 5 Divergent synthesis of spiropenicillians

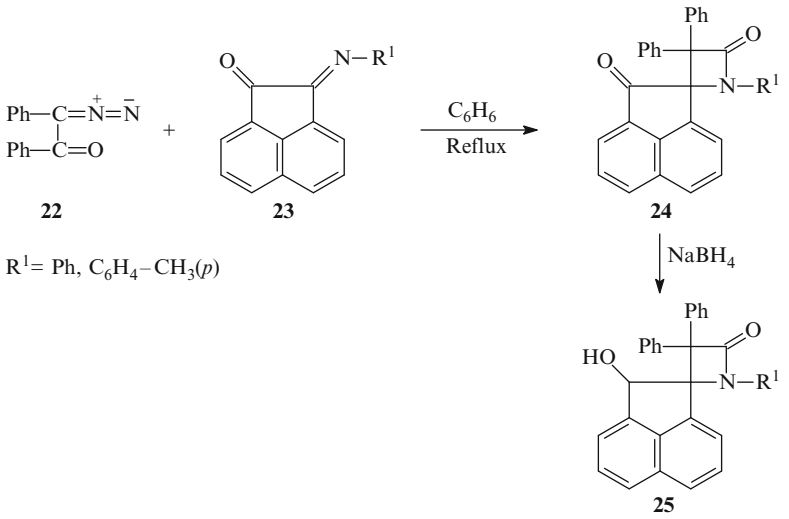


Scheme 6 Use of diphenyldiazomethane in preparation of spiropenicillians

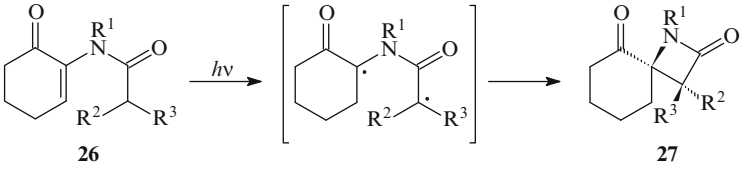
been found to be unaffected either by hydrolysis or treatment with sodium borohydride and could be used as precursors for the introduction of other desired functionalities.

Ikeda et al. [80] have reported a photochemical entry to spiro-β-lactams **27** (Scheme 8) by the irradiation of a solution of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enone **26** in acetone with a 300 W high pressure mercury lamp in a pyrex vessel under nitrogen. The reaction occurred with the intervention of the 1,4-diradical intermediate formed via abstraction of a hydrogen on the *N*-acyl group by the β-carbon atom of the α,β-enone system.

Joshi et al. [81] have incorporated azetidin-2-one moiety into indole nucleus and synthesized several fluorine containing spiro-β-lactams (Scheme 9). The synthesis involved the condensation of primary amines with an appropriate indole-2,3-dione



Scheme 7 Preparation of spiro-β-lactams using 2-diazo-1,2-diphenylethanone and 2-phenyliminoacenaphthenone



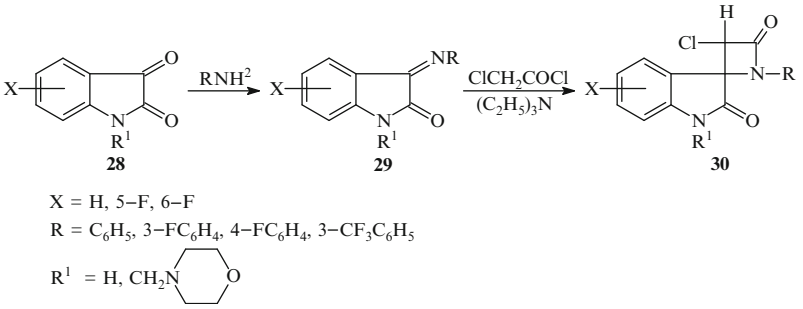
$R^1 = CH_3$, ^{i}Pr, CH_2Ph
$R^2 = CH_3$, SCH_3, Ph, $-[CH_2]_5-$
$R^3 = CH_3$, H, $-[CH_2]_5-$

Scheme 8 Photochemical entry to spiro-β-lactams

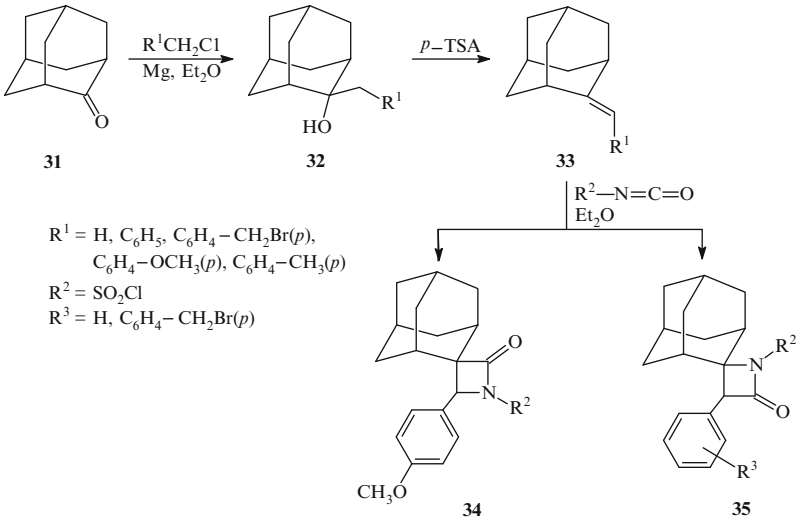
28 resulting in the formation of the intermediate Schiff's bases **29** which on cycloaddition with chloroacetyl chloride gave the spiro-β-lactams **30**.

Georgiev et al. [82] have described the preparation of novel adamantine-spiro-heterocyclic β-lactams **34, 35,** and **40**. Grignard reaction of 2-adamantanone **31** with benzylmagnesium halide provided the compound **32**, which on further dehydration afforded corresponding analogs **33**. Condensation reaction of compound **33** with chlorosulfonyl isocyanate in ether afforded spiro-β-lactams **34** and cycloaddition with chlorosulfonyl isocyanate resulted in the formation of spiro product **35** (Scheme 10).

In another synthetic approach for the preparation of spiro-β-lactams, treatment of *N*-methyladamantanyl nitrone **36** with methyl crotonate **37** gave rise to the spiro esters **38**, which on further catalytic hydrogenation resulted in the ring opening to



Scheme 9 Synthesis of fluorine substituted spiro-β-lactams

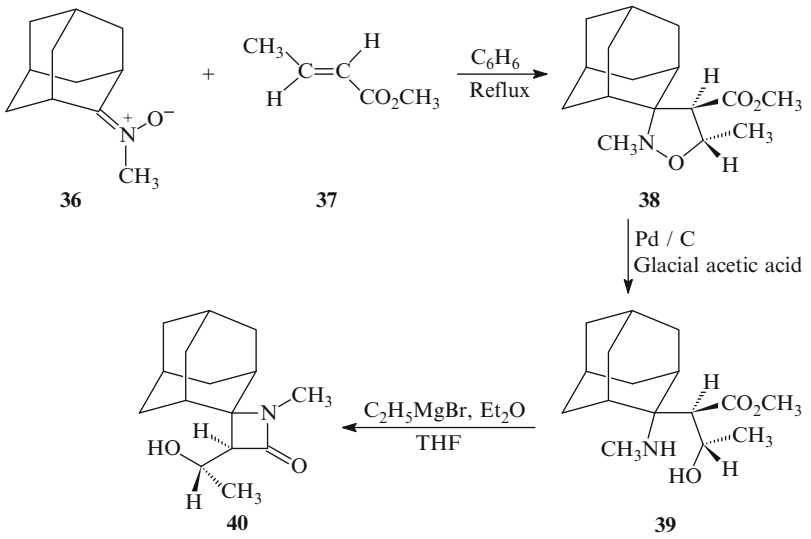


Scheme 10 Preparation of adamantine-spiroheterocyclic β-lactams

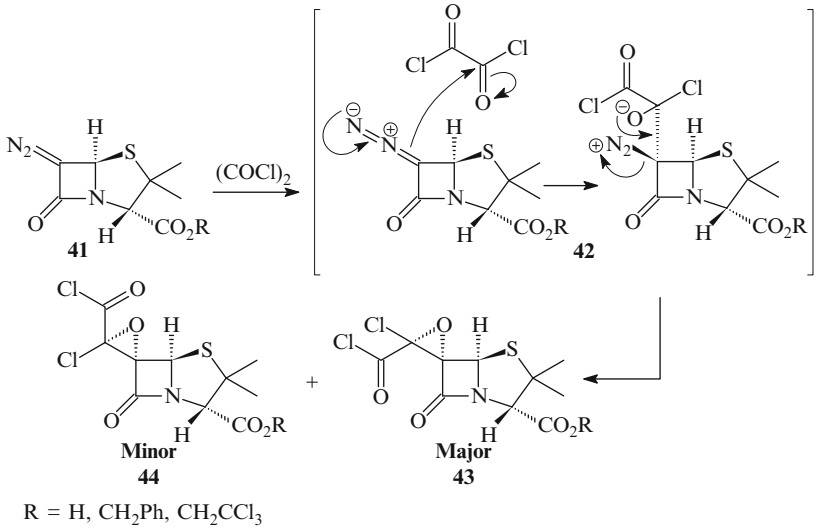
provide the aminoalcohol ester **39**. Subsequent treatment of compound **39** with ethyl magnesium bromide furnished spiro-β-lactam **40** (Scheme 11).

Bycroft et al. [83] have prepared a series of novel 6-spiro-epoxypenicillins **43**, **44** (Scheme 12) by the reaction of diazopenicillanate **41** with oxalyl chloride followed by reactions with various nucleophiles. These compounds notably exhibit β-lactam inhibitory and antibacterial properties [84] depending on substituents and stereochemistry of epoxides. These inhibitors possess side-chains, which are highly conformationally restricted but structurally similar to those of some active penicillins.

The reaction sequence proposed in Scheme 12 is consistent with the approach of the reagent from the least hindered α-face of the penicillanate and interaction of the diazo-group predominantly with the *re*-face of one of the carbonyl groups of the oxalyl chloride thus, resulting in the formation of spiro product **43, 44** by displacement of nitrogen.

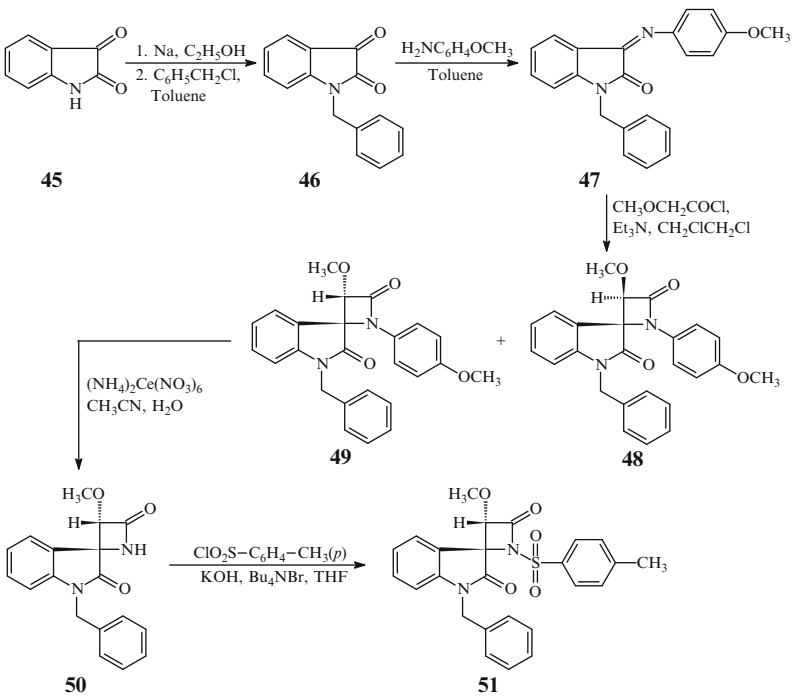


Scheme 11 Parallel synthesis of spiro-β-lactams using *N*-methyladamantanyl nitrone



Scheme 12 Synthesis of series of 6-spiro-epoxypenicillins by use of diazopenicillanate and oxalyl chloride

In the year 1990, Skiles and McNeil [47] synthesized novel spiro-β-lactam **51**, making it a successful entry into the class of antiviral β-lactams. This β-lactam has been found to be a good inhibitor of both *poliovirus* and *human rhinovirus 3C-proteniases* ($IC_{50} = 20$ μg mL^{-1}). All picornaviruses studied produced a 3C-proteinase, which is required for the virus to undergo maturation.

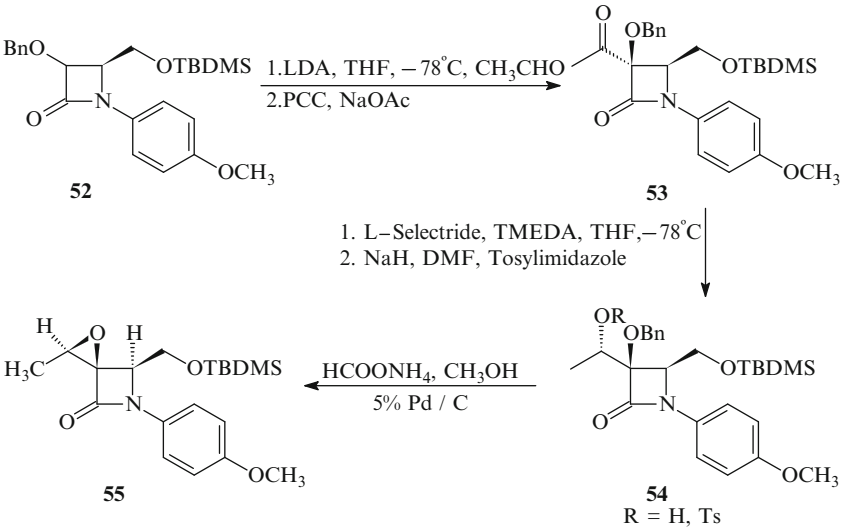


Scheme 13 Synthesis of antiviral spiroindolinone-β-lactams

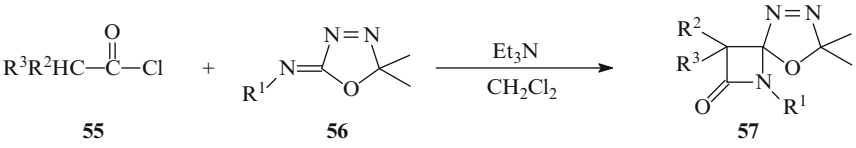
The synthesis of antiviral spiro-β-lactam **51** begins with the benzylation of isatin **45** to give 1-benzylisatin **46**, which affords Schiff's base **47** on reaction with anisidine in ethanol. The Schiff's base **47** on treatment with methoxyacetyl chloride by the chloride–imidate cycloaddition [85] route afforded a mixture of spiro *E*- and *Z*-azetidin-2-ones **48** and **49**, which were separated by chromatography. The (Z)-*N*-arylazetidin-2-one **49** was further converted to desired 4-spiro-β-lactam **51** by treatment with ceric ammonium nitrate and subsequently with tetrabutylammonium bromide in THF in the presence of pulverized KOH (Scheme 13).

Durst and Sharma [86] have reported the stereospecific synthesis of 3-spiro-epoxyazetidin-2-ones **55** (Scheme 14). The oxidation of the diastereoisomers of compound **52** with PCC provided a single acetyl compound 3-acetyl-3-benzyloxy-azetidin-2-one **53**. Nonchelation controlled L-Selectride reduction of **53** gave the isomerically pure 3-hydroxyethylazetidin-2-one as the sole reduced product, which was further converted to tosylate **54** using NaH/tosylimidazole. The debenzylation-oxirane formation sequence was conveniently performed as a single pot operation with ammonium formate, 5% Pd/C in refluxing methanol as the hydrogen transfer reagent combination.

This study shows that by combining the diastereospecific reduction of acylazetidin-2-ones and the suitable functional group manipulations, it has been possible to synthesize the 3-spiro-epoxyazetidin-2-ones in a diastereospecific manner.



Scheme 14 Stereospecific synthesis of 3-spiro-epoxyazetidin-2-ones



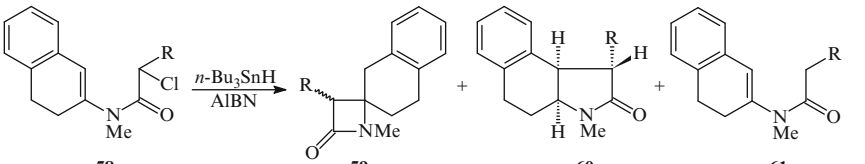
R^1 = Ph, CH_3, CH_2Ph, $CH_2CH_2OSi(CH_3)_2C(CH_3)_3$, CH_2CH_2OH, $C_6H_4-OCH_3(p)$

$R^2 = R^3$ = Ph, Me, Cl, OPh

Scheme 15 General strategy for the synthesis of spiro-β-lactam oxadiazolines

Warkentin and Zoghbi [87] have demonstrated the synthesis of novel spiro-β-lactam oxadiazolines **57** (Scheme 15) by the reaction of differently substituted acid chloride **55** and 2-amino-Δ^3-1,3,4 oxadiazolines **56** using triethylamine in dichloromethane.

Ishibashi et al. [88] have studied the radical cyclization of *N*-vinylic-α-chloro-acetamide. They found that *n*-Bu_3SnH mediated cyclization of α-chloroacetamide **58** gives spiro-β-lactams **59** (Scheme 16). The difference in the mode of cyclization among various substrates **58** may be explained in terms of the electronic stability and/or the steric conjestion between radical intermediates generated by ring closure of **58**. The exclusive formation of the β-lactam **59** when R = H suggests that the benzylic radical generated by 4-*exo*-ring closure is more stable than the acylamino radical, led to the formation of **60**. However, substitutents like Me and Ph undergo steric repulsion with the neighboring gem-dialkyl groups, which leads to the predominant formation of α-acylamino radical thus, resulting in an increase in the amount of the γ-lactam **60**.



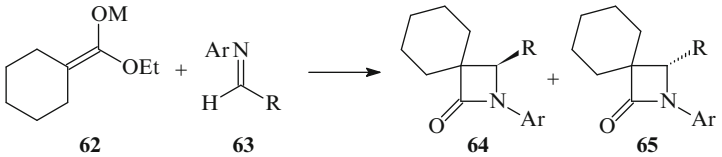
58
R = H, Me, Ph

59
50 % (R = H)
42 % (R = Me)
0 % (R = Ph)

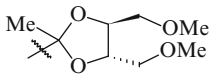
60
0 % (R = H)
35 % (R = Me)
76 % (R = Ph)

61
32 % (R = H)
19 % (R = Me)
0 % (R = Ph)

Scheme 16 Preparation of spiroazetidin-2-ones through n-Bu_3SnH mediated cyclization of α-chloroacetamide



62 **63** **64** **65**

R = 

Ar = $C_6H_4-OCH_3(p)$

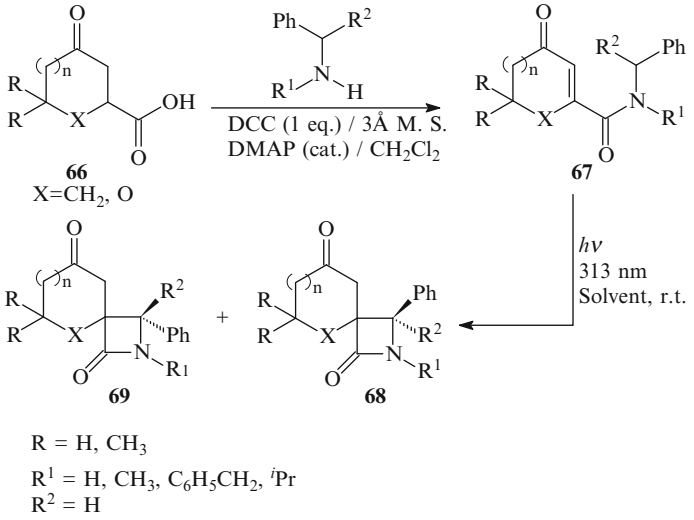
M = Li, $Ti(O^iPr)_3$

Scheme 17 Stereodivergent synthesis of spiro-β-lactams using ester enolates and chiral imines

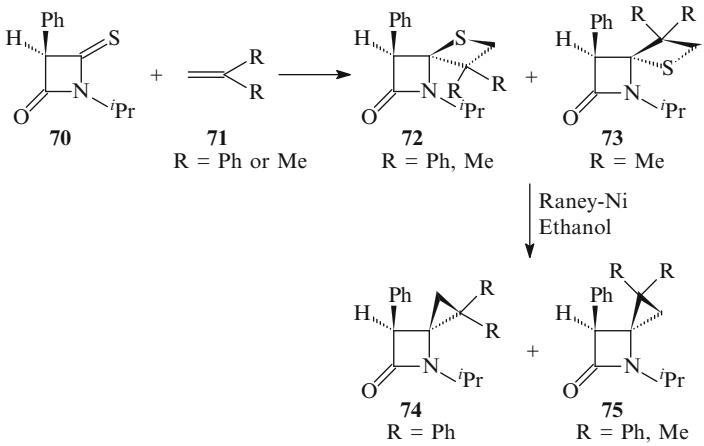
Fujisawa et al. [89] have reported the stereodivergent synthesis of spiro-β-lactams **64**, **65** (Scheme 17) by reaction of lithium or titanium ester enolates **62** with single chiral imines **63** by taking advantage of different coordination states of the enolate metals. Almost complete reversal of the diastereofacial-discrimination with respect to the C-4 of the β-lactam skeleton has been attained in this reaction coupled with flexibility in the selection of the enolates and ready removal of the chiral auxiliary.

Pavia et al. [90] have developed a new, efficient, and diastereoselective method to synthesize spiro-β-lactams (Scheme 18). The strategy involves the direct conversion of unsaturated *N*-benzyl-α,β-unsaturated cyclic oxomides **67** to spiranic β-lactams **68**, **69** by intramolecular hydrogen abstraction under photochemical activation. Starting oxomides **67** were synthesized from the corresponding known unsaturated oxoacids or commercially available oxoacid **66** and primary or secondary benzylamines.

Aoyama et al. in relation to their studies on photochemical synthesis of β-lactams [91] reported the synthesis of 4-spirocyclopropylazetidin-2-one [92] via photocycloaddition of 4-thioxoazetidin-2-one to alkenes followed by subsequent desulfurization. A solution of 1-isopropyl-3-phenyl-4-thioxoazetidin-2-one **70** and 1,1-diphenylethylene in benzene on irradiation with a high pressure mercury lamp afforded a [2 + 2] adduct **72** (R = Ph), in 67% yield which, on desulfurization with Raney-nickel [93] in anhydrous ethanol gave two isomeric



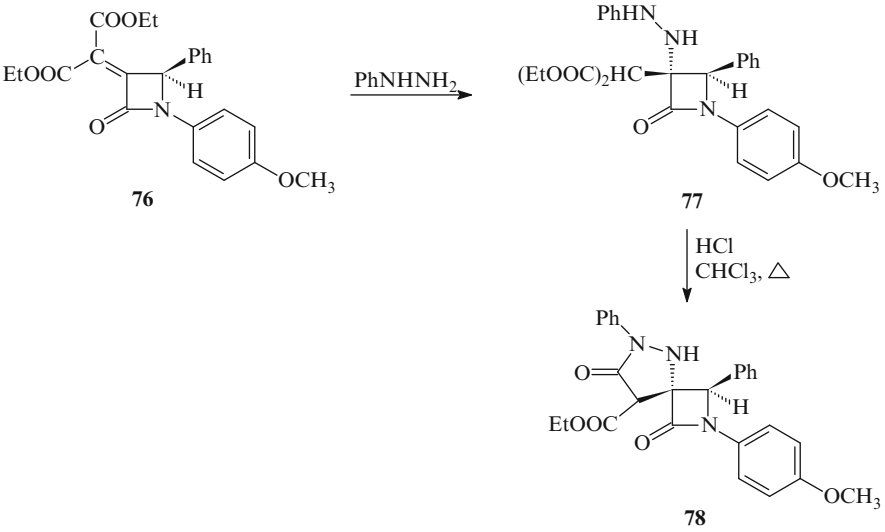
Scheme 18 Photochemically induced diastereoselective route to spiro-β-lactams



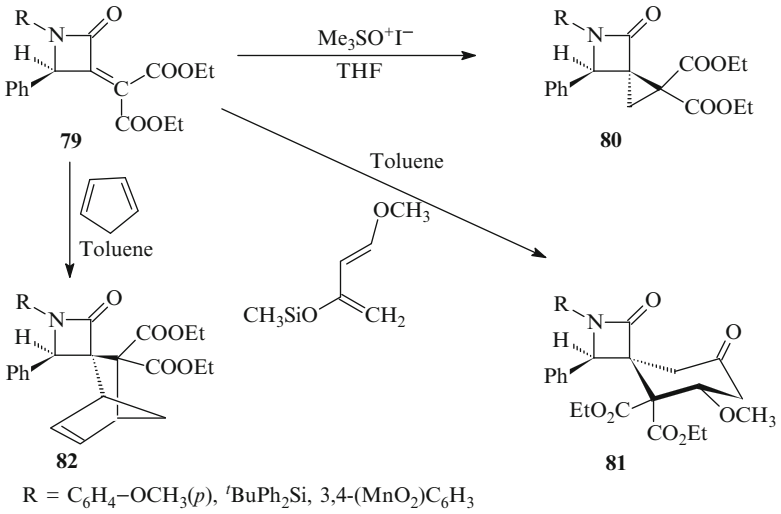
Scheme 19 Synthesis of 4-spirocyclopropylazetidin-2-one via photocycloaddition

4-spirocyclopropylazetidin-2-ones **74**, **75** (R = Ph). However, photochemical reaction of **70** with 2-methylpropene yielded two isomeric thietanes **72** (R = Me) and **73** both of which produced the spiro-β-lactam **75** (R = Me) on desulfurization with Raney-nickel (Scheme 19).

Otto et al. [94] have described the synthesis of spiro-β-lactam **78** (Scheme 20) by the addition reaction of nucleophile to the exocyclic double bond of dicarboxylates of 3-methylene β-lactams **76**.



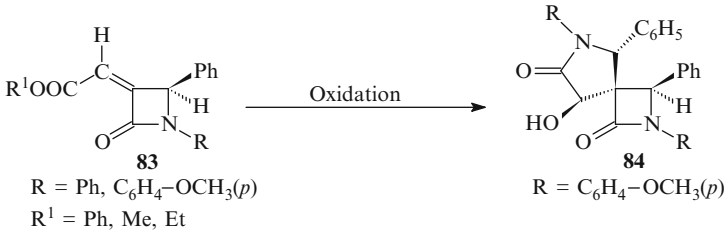
Scheme 20 Preparation of spiro-β-lactams using addition reactions to exocyclic double bond



Scheme 21 Use of *Diels-Alder* reaction in synthesis of spiro-β-lactams

The addition of the hydrazine derivative to **76** at room temperature resulted in the hydrazine adduct **77**. When phenyl hydrazines adduct **77** was heated in $CHCl_3$ solution with conc. HCl solution, the *N*-atom and one COOEt group underwent thermally reversible reaction to afford spiro-β-lactam **78**.

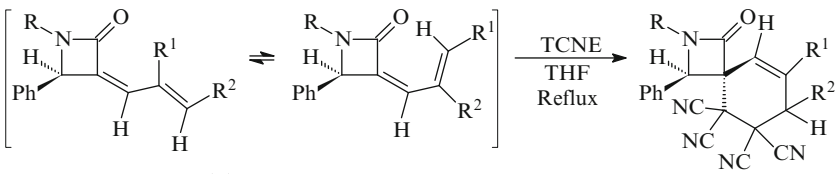
In continuation to this, they used α,β-unsaturated β-lactams **79** for the construction of spirocyclic compounds **80–82** (Scheme 21) by the addition of a methylene



83
R = Ph, C_6H_4–OCH_3(*p*)
R^1 = Ph, Me, Et

84
R = C_6H_4–OCH_3(*p*)

Scheme 22 Unusual rearrangement of monocarboxylates of 3-methylidene-β-lactams to spiro-β-lactams



(*Z*)-**85**
R = Ph, C_6H_4–OCH_3(*p*)
R^1 = H, Me
R^2 = H, Me, Ph

86

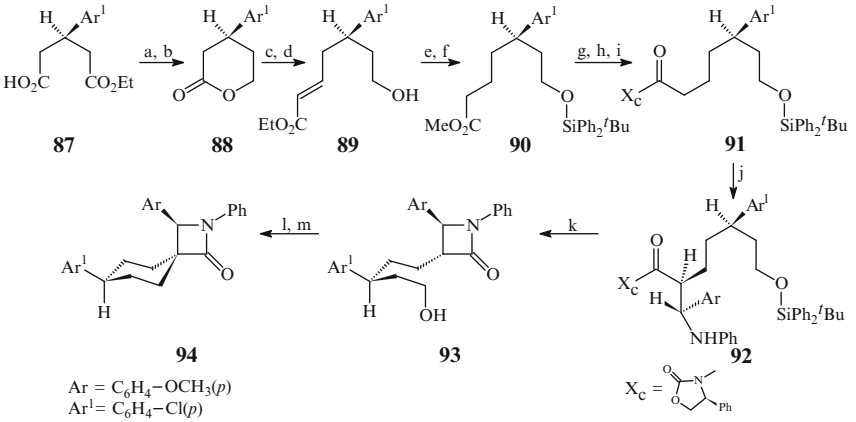
Scheme 23 Incorporation of 3-(prop-2-enylidene)azetidin-2-one for the synthesis of spiro-β-lactams via *Diels-Alder* reactions

group forming cyclopropane derivatives and the use of the electron-poor double bond as a dienophile in *Diels-Alder* reactions. The spiro-β-lactams **80** were prepared by the addition of the ylide from trimethylsulfoxonium iodide and **79**, whereas the use of *Diels-Alder* reactions in the synthesis of spiro-β-lactams **81–82** was demonstrated by carrying out the reactions of **79** with cyclopentadiene and *Danishefsky's* diene in toluene, respectively.

The structures of these compounds were supported by their NMR (NOE and 2D-NOESY) spectra and it established that these isomers are not *endo*/*exo*-isomers but *cis*/*trans* isomers. They could not detect any other isomer but believed the main products formed are *cis* isomers, as reaction was believed to proceed by *trans*-addition, meaning that the *Diels-Alder* reactions at the side opposite to the bulkier constituent at C-4 is favored.

In their further studies [95], the synthesis of spiro-β-lactams **84** (Scheme 22) were carried out by unusual oxidative rearrangement of monocarboxylates of 3-methylidene-β-lactams **83** with different oxidizing reagents such as H_2O_2 in alkali, *t*-BuOOH, or KOCl. The reaction always resulted in the single isolated crystalline spiro-β-lactam **84** whose stereochemistry was established by single X-ray crystallography.

Otto and Ruf [96] have incorporated the 3-(prop-2-enylidene)azetidin-2-one derivatives **85** for the synthesis of spiro-β-lactams **86** via *Diels-Alder* reactions (Scheme 23). The reaction of (*Z*)-**85** with highly reactive tetracyanoethylene (TCNE) was performed in THF at refluxing temperature, which afforded spiro-β-lactams **86**.



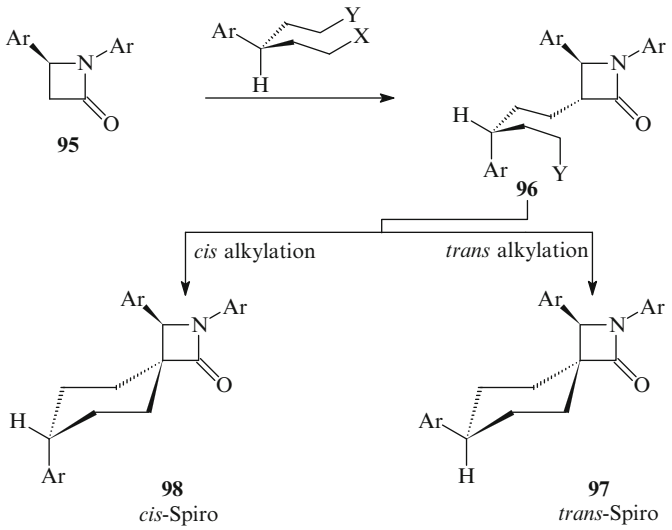
Scheme 24 Enantioselective synthetic route to cholesterol absorption inhibitor spiro-β-lactams

Out of (*E*, *E*)-, (*Z*, *E*)-, or (*Z*)-isomers, the (*Z*)-isomers are the favorable substrates for *Diels-Alder* reactions as calculated by preferred conformations and minimum energies, which is also in agreement with the performed experiments.

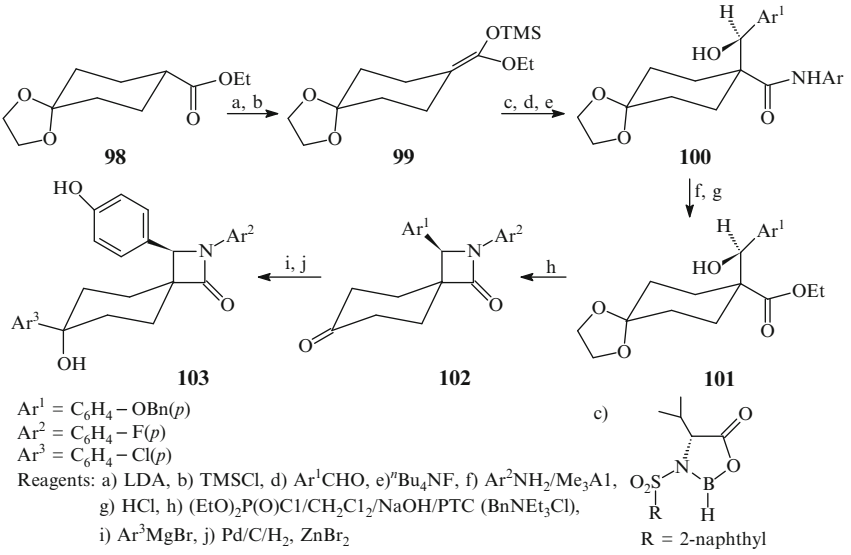
Spiro-β-lactams (+)-SCH 54016 **94** have been found to exhibit CAI activity, therefore an efficient synthetic route for these spiro-β-lactams for continuing biological evaluation was of great interest. Chen et al. [45] have reported an efficient and highly enantioselective synthetic route to spiro-β-lactam (+)-SCH 54016 (Scheme 24).

(*R*)-3-(4-Chlorophenyl)glutarate monoethyl ester **87** was reduced to hydroxy acid and subsequently cyclized to afford lactone **88**. This was further submitted to reduction with diisobutylaluminium hydride to provide lactol followed by Horner-Emmons reaction, which resulted in the formation of hydroxy ester product **89** in good yield. The alcohol was protected as silyl ether and the double bond in **89** was reduced with magnesium powder in methanol to provide methyl ester **90**. The hydrolysis to the acid and condensation of the acid chloride with Evans's chiral auxiliary provided product **91**, which was further converted to titanium enolate on reaction with $TiCl_4$. This was submitted to enolate-imine condensation in the presence of amine to afford **92**. The silylation of the **92** with *N*, *O*-bis(trimethylsilyl) acetamide followed by treatment with tetrabutylammonium fluoride resulted in cyclization to form the azetidin-2-one ring and subsequently hydrolysis provided **93**. This product was converted to bromide analog, which on treatment with LDA underwent intramolecular cyclization to afford the cholesterol absorption inhibitor spiro-β-lactam (+)-SCH 54016 **94**.

They have employed the strategy of intramolecular *trans* alkylation of azetidin-2-ones since C–4 substituted azetidin-2-one enolates, predominantly yield the C–3, 4-*trans*-diastereomer upon reaction with electrophiles, [45] thus, providing control of stereochemistry of substituents at the cyclohexyl ring (Scheme 25).



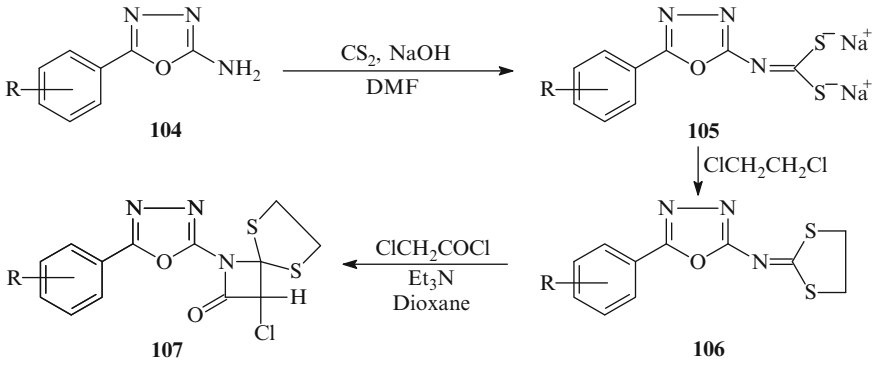
Scheme 25 Intramolecular alkylation of azetidin-2-ones to access spiro-β-lactams



Scheme 26 Catalytic enantio- and diastereoselective synthesis of spiro-β-lactam (+)-SCH 58053

Similarly, Guangzhong Wu et al. [46] have published the catalytic enantio- and diastereoselective synthesis of another spiro-β-lactam (+)-SCH 58053 **103** (Scheme 26) which has been shown to exhibit CAI activity.

Treatment of the starting ester **98** with LDA and subsequent trapping with TMSCl provided the silyl ester enol ether **99**. The desired chiral center via an



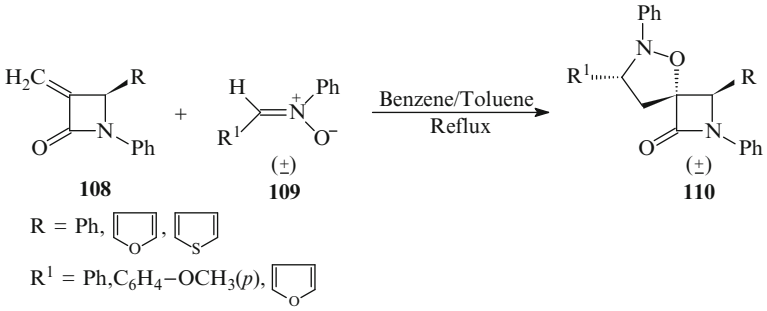
Scheme 27 Efficient synthetic route to antimicrobial spiroazetidin-2-ones

aldol condensation was constructed and followed by *n*-Bu_4NF deprotection to furnish the hydroxy ester **100** in 95% ee. The hydroxy ester **100** was reacted with amine in the presence of Me_3Al to achieve aminated compound **101**, which was further cyclized to generate the β-lactam ring **102** by using $(EtO)_2P(O)Cl$ and subsequently NaOH/PTC. Addition of Grignard reagent to this compound **102**, followed by selective debenzylation produced spiro-β-lactam (+)-SCH 58053 **103** in 99.5% chemical purity and 99.5% ee.

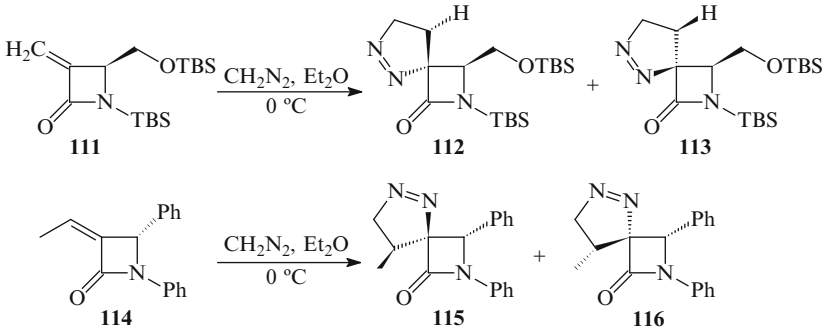
Hussain and Nizamuddin have synthesized 1, 3-dithiolane substituted spiro-β-lactams (Scheme 27) since 1, 3-dithiolane derivatives exhibit various biological activities like fungicidal, bactericidal, and insecticidal [97]. The starting thiadiazoles **104** were treated with sodium hydroxide and carbon disulfide to get the corresponding disodium dithiocarbamate **105**, which were stirred with 1,2-dichloroethane to obtain **106**. Cyclocondensation of **106** with chloroacetyl chloride in dry dioxane in the presence of triethylamine gave the spiro-β-lactams **107**. These spiro-β-lactams were found to exhibit antifungal activity 75–85% at 100-ppm concentration against *P. oryzae* and *F. oxysporum*.

Basak et al. [98] have reported the synthesis of spiro-β-lactams **110** (Scheme 28), which serve as the synthetic intermediates for preparation of 3-hydroxyazetidin-2-ones following Baldwin [99] strategy, which deals with regiospecific nitrone cycloaddition. Keeping this in mind, Basak et al. have carried an enatiospecific cycloaddition route keeping a substituent at C-4. The alkenyl β-lactams **108** were subjected to cycloaddition conditions along with various nitrones **109** to provide spiroazetidin-2-ones **110**.

Liebscher and Anklam [100] have introduced a facile access to novel optically active spiro-β-lactams **112–113, 115–116** through cycloaddition reaction of diazomethane to α-alkylidene-β-lactams (Scheme 29). Diazomethane gave a clean reaction to α-methylene-β-lactam **111** affording spiroazetidin-2-ones **112**, **113** (d.r. 87:13, 93%) with preference of anti-addition with respect to the CH_2OTBS substituent. The α-ethylene-β-lactam **114** reacted slowly with diazomethane and



Scheme 28 Preparation of spiro-β-lactams using regiospecific nitrone cycloaddition

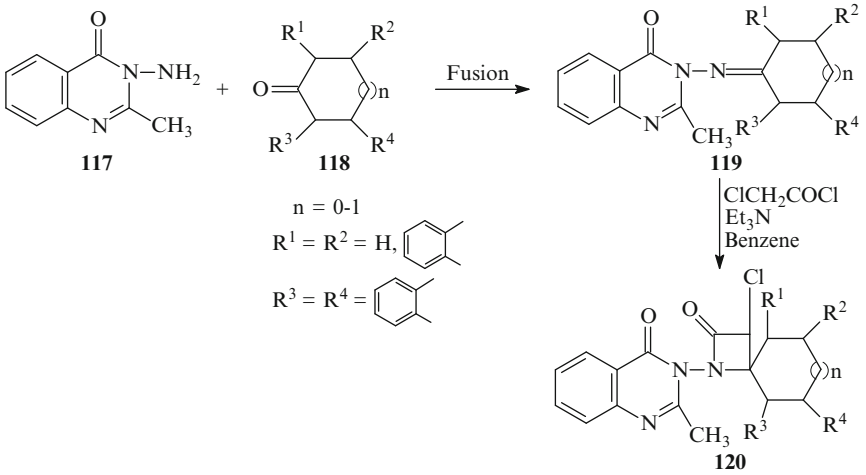


Scheme 29 Synthesis of optically active spiro-β-lactams using α-alkylidene-β-lactams

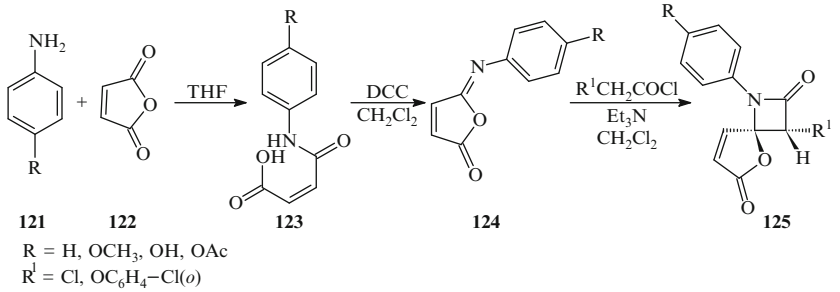
resulted into spiro products **115, 116** (d.r. 82:18, 97%). The diastereomers were obtained in pure form by column chromatography. The CH_2OTBS moiety found in the spiro-β-lactams **112, 113** offers the possibility of establishing tricyclic system related to the carbapenam series [6].

Al-Thebeiti and El-Zohary [101] have reported an efficient synthesis of a new series of spiroazetidin-2-one derivatives incorporated with quinazoline (Scheme 30). 3-Amino-2-methyl-3*H*-quinazolin-4-one **117** was treated with cyclic ketones **118** to afford the corresponding cycloalkylidene-3-aminoquinazolinone derivatives **119** in good yields. The reaction of the compounds **119** with chloroacetyl chloride in the presence of triethylamine as a catalyst yielded the spiroazetidin-2-ones **120**.

Santillian et al. [102] have investigated the synthesis of *N*-aryl substituted spiro-β-lactams **125** (Scheme 31) using [2 + 2] cycloaddition of isomaleimides to acid chlorides. The arylamines **121** were treated with maleic anhydride **122** to afford arylmaleamic acids **123** in excellent yields, which on reaction with dicyclohexylcarbodiimide provided isomaleimides **124**. Further these underwent [2 + 2] cycloaddition reaction with acid chlorides in the presence of triethylamine and resulted in the regioselective formation of spiro-β-lactams **125**. The *trans* stereochemistry of



Scheme 30 Competent synthetic route to quinazoline substituted spiro-β-lactams

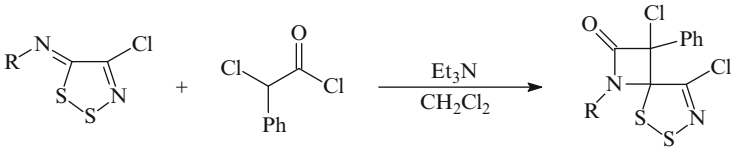


Scheme 31 Preparation of *N*-aryl-substituted spiro-β-lactams via Studinger cycloaddition

these spiro-β-lactams **125** was established by NOE experiments and X-ray diffraction analysis. The molecular perspective of these compounds nearly show a planner arrangement for the β-lactam ring and the *N*-phenyl group.

Kim et al. [103] have shown that spiro-β-lactams **128** (Scheme 32) obtained by a facile synthesis, serves as a precursor for the synthesis of hitherto unknown β-lactams undergoing cleavage of the bond between S-1 and S-2 with nucleophiles. Treatment of 5-substitutedimino-4-chloro-5*H*-1,2,3-dithiazoles **126** with 2-chloro-2-phenylacetyl chloride **127** in the presence of triethylamine afforded spiro-β-lactams **128**.

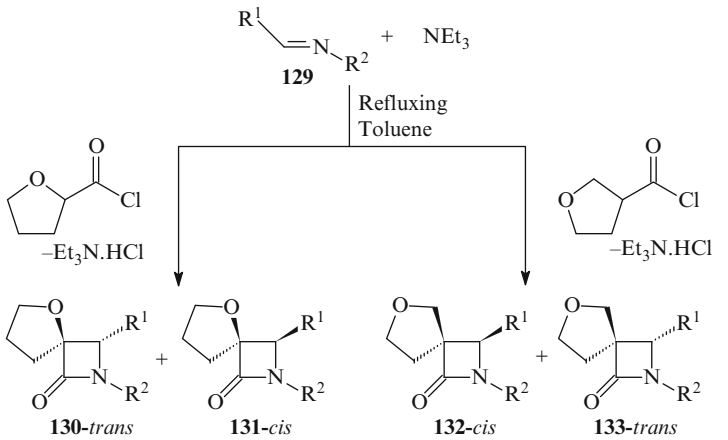
Gonzalez et al. [104] have synthesized spiro-β-lactams directly by employing Staudinger reaction using unsymmetrical ketenes. The β-lactams **130–133** were prepared by reaction of either 2-tetrahydrofuroyl chloride or 3-tetrahydrofuroyl chloride with imines **129** resulting in the generation of a mixture of *cis*- and *trans*-spiro-β-lactams (Scheme 33).



126 **127** **128**

R = $C_6H_4-OCH_3(p)$, $C_6H_4-CH_3(p)$, $C_6H_4-Cl(p)$, $C_6H_4-NO_2(p)$, $C_6H_4-COCH_3(p)$

Scheme 32 Synthesis of spiro-β-lactams using 5-substitutedimino-4-chloro-5*H*-1,2,3-dithiazoles and 2-chloro-2-phenylacetyl chloride



130-*trans* **131-***cis* **132-***cis* **133-***trans*

R^1 = C_6H_5, $C_6H_4-OCH_3(p)$, $C_6H_4-NO2(p)$, $C_6H_5CH=CH$, 2-Furyl, 3-Pyridyl

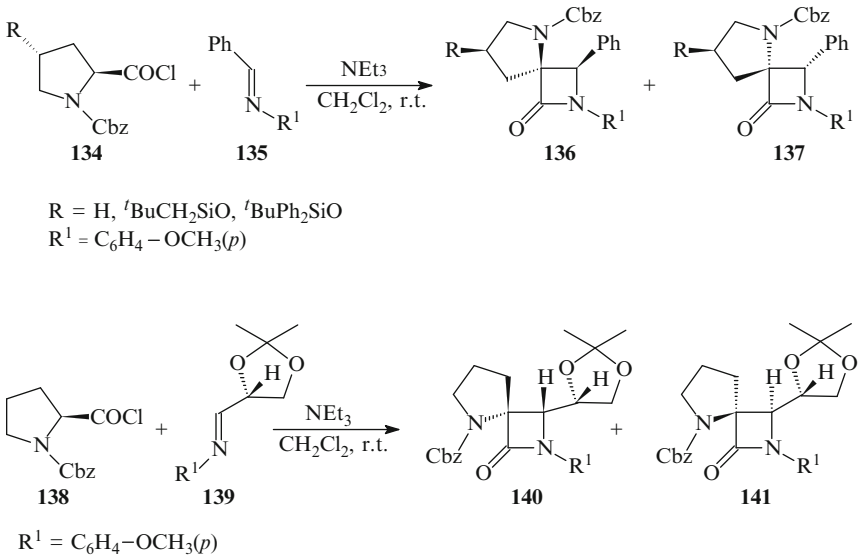
R^2 = CH_3, C_6H_5, $C_6H_4-OCH_3(p)$, $C_6H_4-NO_2(p)$

Scheme 33 Synthesis of *cis*- and *trans*-spiro-β-lactams using unsymmetrical ketenes

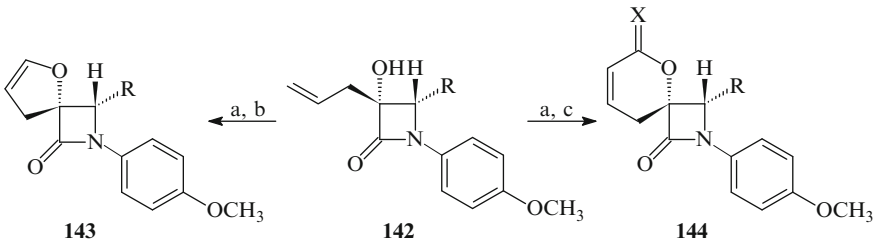
The ratio of *cis*/*trans* reported, is to be strongly influenced by two factors: the position of oxygen on acyl chloride precursor and the electronic nature of substituents R^1 and R^2 on the imine. Thus, the reaction of 2-tetrahydrofuroyl chloride with imine is more stereoselective than that of 3-tetrahydrofuroyl chloride. The presence of electron withdrawing group decreases the stereoselectivity of reaction while the presence of electron releasing group on imine increases stereoselectivity.

Gonzalez et al. [105] have further investigated the diastereoselective [2+2] cycloaddition reaction of unsymmetrical cyclic ketenes with imines for the synthesis of a variety of spiro-β-lactams (Scheme 34).

The reaction of *N*-benzyloxycarbonyl L-proline acid chlorides **134** with imine **135** in the presence of triethylamine, at room temperature, gave the corresponding spiro-β-lactams **136, 137** as a 1:1 mixture of diastereoisomers, which were separated by column chromatography. The Staudinger reaction proceeds with complete stereoselectivity with a *cis* relative disposition of the pyrrolidine nitrogen and the phenyl group, but no asymmetric induction was observed. However, very



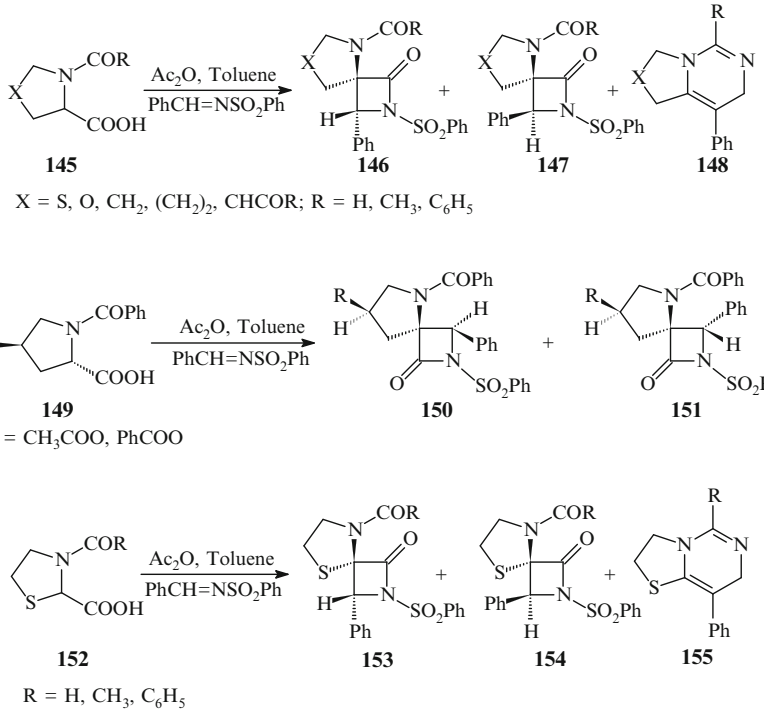
Scheme 34 Preparation of spiro-β-lactams using unsymmetrical cyclic ketenes



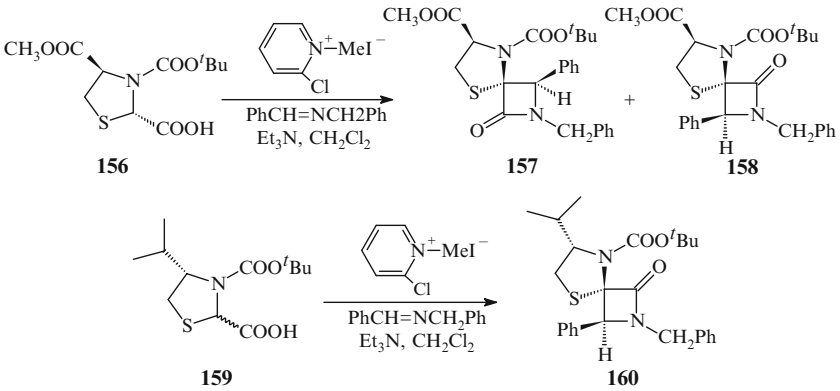
Scheme 35 Metal catalyzed intramolecular cyclization accessing enantiopure spirocyclic β-lactams

good levels of asymmetric induction were achieved in the Staudinger reaction of *N*-benzyloxycarbonyl L-proline acid chlorides **138** with optically active imine **139**. The reaction afforded the diastereomeric spiro-β-lactams **140, 141** (d.r. 95:5), separable by column chromatography.

A novel approach to enantiopure spirocyclic β-lactams has been developed by Alcaide et al. [106] using different intramolecular metal catalyzed cyclization reactions with monocyclic unsaturated alcohols **142** (Scheme 35). Ring-closing metathesis is one of the most powerful and reliable methods to construct a ring system. Transformation of alcohols in diolefin precursors followed by ring-closing



Scheme 36 Stereoselective synthesis of *N*-phenylsulfonyl-spiro-β-lactams



Scheme 37 Diastereoselective preparation of spiro-β-lactams using Mukaiyama's reagent

metathesis proved to be a straightforward access to spirocyclic β-lactams containing five or six-membered oxacycles **143** and **144**, respectively.

Rosa et al. [107–111] have been actively engaged in developing new stereoselective routes to the spiro-β-lactams (Schemes 36 and 37). They have reported on the reactivity of bicyclic mesoionic compounds derived from cyclic *N*-acyl-α-amino

acids **145** [107, 108]. The method involves a convenient and simple synthesis of a mixture of two diastereoisomeric spiro-β-lactams **146, 147** (Scheme 36) by the reaction of *N*-acyl-α-amino acids **145** with *N*-(phenylmethylene)benzene sulfonamide in toluene using acetic anhydride as the dehydrating agent.

These results prompted them to attempt the stereoselective synthesis of the *N*-phenylsulfonyl substituted spiro-β-lactams **150, 151** (Scheme 36) from the *N*-(phenylmethylene)benzenesulfonamide and the ketene valence tautomer of the bicyclic mesoionic compounds such as (2 *S*,4*R*)-4-acetyloxy or benzoyloxy-*N*-acyl-prolines **149** in the presence of acetic anhydride [109]. The presence of the stereocenter in position 4 of the cyclic amino acid **149** was found to be sufficient to ensure complete stereoselectivity on the spiranic C-4.

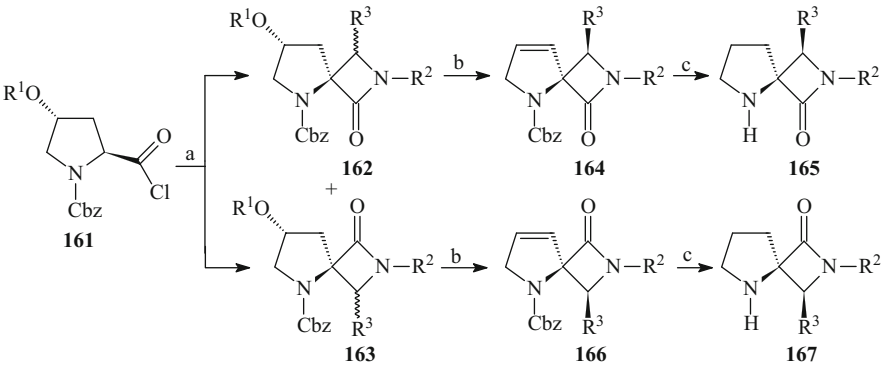
In connection with these results, and as an extension of their studies toward the reactivity of new bicyclic mesoionic compounds and their usefulness in the synthesis of condensed heterocycles, they further reported the stereoselective synthesis of spiro-β-lactams **153, 154** (Scheme 36) by reactions of imines with mesoionic compounds or ketenes generated from *N*-acyl-thiozolidine-2-carboxylic acids **152** [110].

Recently, they have synthesized enantiomerically pure 1,3-thiazolidine-derived spiro-β-lactams [111] (Scheme 37) using Staudinger ketene-imine reaction starting from optically active *N*-boc-1,3- thiazolidine-2-carboxylic acid derivatives and imines, thus confirming the generality of the earlier reported 1,3-thiazolidine-derived spiro-β-lactams.

Treatment of amino acid **156**, imine and 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) in the presence of triethylamine in refluxing dichloromethane afforded spiro-β-lactams **157, 158**. These were obtained as a 1.8:1 mixture of diastereoisomers and separated by column chromatography. The reaction of **159** and imine under the usual experimental conditions resulted in the formation of a single diastereoisomer **160**. The absolute (3 *S*, 4 *S*, 7 *S*)-configuration was assigned on the basis of mechanistic considerations and ^{1}H NMR spectra. The presence of the stereocenter affords complete diastereoselectivity (only *trans* diastereoisomers **157**, **158**) and enantioselectivity (**160**).

Thiruvazhi et al. [112] have shown interest in the area of β-turn mimetics and the synthetic application of D- and L-proline for asymmetric synthesis of proline-derived spiro-β-lactams. It has been shown that the asymmetric Staudinger reaction of optically active acid chloride of D- and L-proline with achiral imines is impossible due to the loss of stereochemistry at C-2. The authors have developed a strategy in which a chiral group at C-4 of the acid chloride of proline directs the stereoselectivity of the reaction and is sacrificed later to obtain optically active spiro-β-lactams (Scheme 38).

The Staudinger reaction between optically active acid chloride **161** and *N*-benzyl-*N*-[(1*E*)-phenylmethylene]amine in the presence of triethylamine in dichloromethane resulted in the formation of two diastereomerically pure spiro-β-lactams **162** (51%), **163** (20%) as single enantiomers in each case. The spiro-β-lactams **162**, **163** were further transformed to proline-derived spiro-β-lactams **165**, **167** via elimination of methanesulfonic acid using K_2CO_3/MeOH and



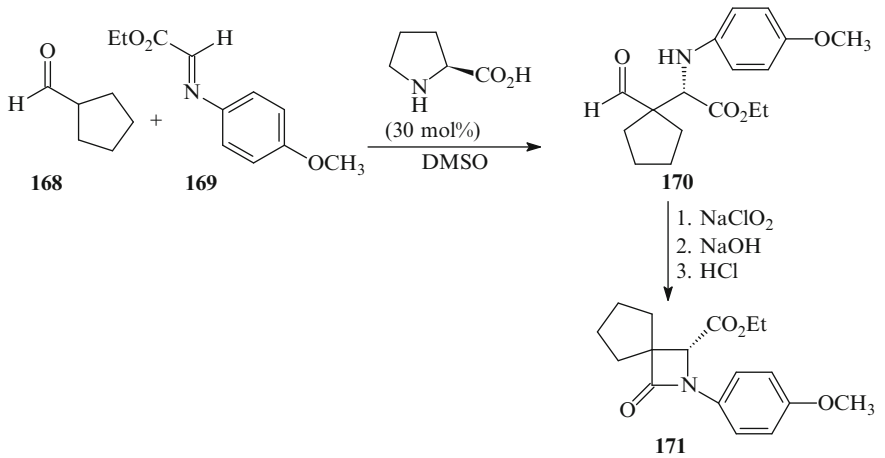
Reagents: a) *E*-R^3 CH=NR^2, Et_3N, CH_2Cl_2 b) K_2CO_3, MeOH, c) H_2,10% Pd/C, EtOH

R^1 = Ms, Ts, Ns

R^2 = $CH_2C_6H_5$, $CH_2C_6H_5$—OCH_3(*p*), C_3H_5

R^3 = C_6H_5, CH_3, C_3H_5, C_6H_{11}, C_6H_5—OCH_3(*p*), C_6H_5—F(*p*)

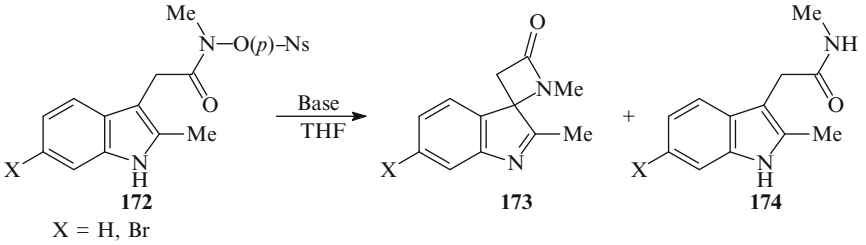
Scheme 38 Asymmetric synthesis of proline-derived spiro-β-lactams



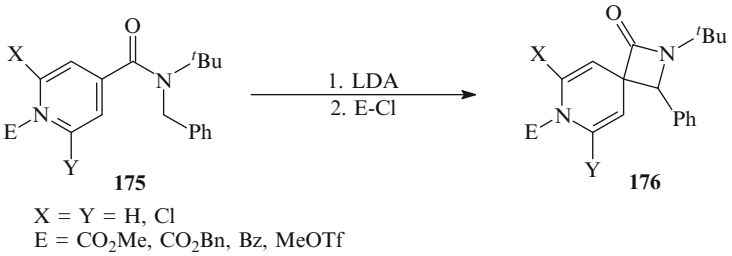
Scheme 39 Proline-catalyzed Mannich reaction furnishing spiro-β-lactams

deprotection along with hydrogenation. The proposed mechanism of Staudinger reaction on proline-derived ketenes demonstrated that for the achievement of excellent stereoselectivity in the synthesis of these types of spiro-β-lactams, R^1 substitutent of proline should be aliphatic, R^2 of the imine could be either aliphatic or aromatic and R^3 should be aromatic.

Barbas et al. [113] have published the asymmetric synthesis of spiro-β-lactams **171** (Scheme 39) using proline-catalyzed Mannich reaction with branched aldehyde donors. The Mannich reactions of α,α-disubstituted aldehydes **168** with



Scheme 40 Efficient synthesis of indolenine spiro-β-lactams in Chartelline



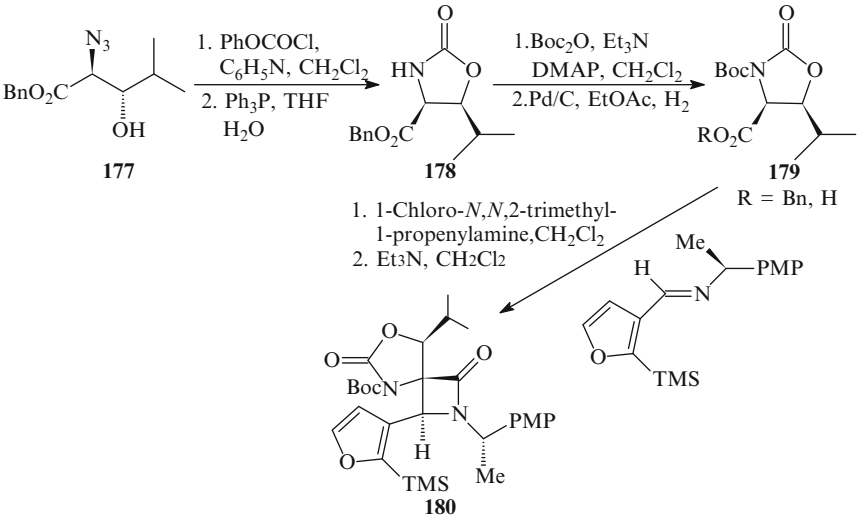
Scheme 41 Synthesis of spiro-β-lactams via cyclization of lithiated pyridine and quinoline carboxamides

N-*p*-methoxyphenyl protected α-imino ethyl glyoxalate **169** in the presence of L-proline as catalyst resulted in the formation of enantioselective β-formyl α-aminoacid derivatives **170** in excellent yields.

The authors have demonstrated for the first time the use of α,α-disubstituted aldehydes in the Mannich reaction to generate all-carbon quaternary stereocenters. The enantioselective β-formyl α-aminoacid derivatives **170** were further transformed to spiro-β-lactams **171** using oxidation followed by basic hydrolysis and acidification.

Isobe et al. [114] have revealed the novel synthesis of indolenine spiro-β-lactams **173** (Scheme 40) in Chartelline, which belongs to the family of marine natural products. The starting precursors **172** were submitted to cyclization by employing a variety of bases such as EtMgBr, *n*-BuLi, *t*-BuOK, LDA, KHMDS, NaHMDS, and LiHMDS in THF at different reaction temperatures. Out of all these bases, LiHMDS at –78°C was found to be the best which provided the exclusive formation of spiro-β-lactams **173** without *N*-methylamide **174** as a side product.

Clayden et al. [115] have reported the synthesis of spirocyclic β-lactams **176** (Scheme 41) by exo-cyclization of lithiated pyridine and quinoline carboxamides. The reaction of isonicotinamide or chlorinated isonicotinamide **175** with LDA at –40°C with addition of methyl chloroformate led to the formation of spirocyclic β-lactams **176** in good yields. Benzyl chloroformate, benzoyl chloride, methyl triflate can also be used as the effective acylating agents. In these type of reactions, lithiation of *N*-benzyl pyridine and quinoline carboxamides to nitrogen provided



Scheme 42 Preparation of spiro-β-lactams, synthons for proteasome inhibitors

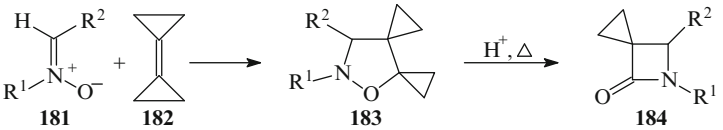
anions, which underwent intramolecular attack on the pyridine or quinoline ring either directly or on activation of the ring by *N*-acylation.

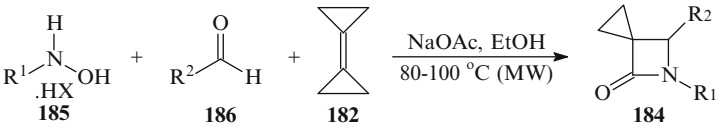
Corey et al. [116] have published the synthesis of spiro-β-lactam **180** (Scheme 42), which is a synthetic intermediate for other β-lactams, which are able to inhibit proteasome. Proteasome inhibition helps in the therapy of cancer and has been evaluated for multiple myeloma [104].

The alcohol **177** was converted to starting substrates oxazolidinone **178** by acylation followed by reduction of the azide function along with cyclization. Oxazolidinone **178** was protected with *t*-butylpyrocarbonate-4-(dimethylamino) pyridine (DMAP) and triethylamine, which was further subjected to reductive cleavage of the benzyl ester unit to afford carboxylic acid **179**. The treatment of **179** with solution of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine resulted in the easy formation of the corresponding acid chloride which on reaction with imine in the presence of triethylamine provided the stereoselective formation of spiro-β-lactam **180**.

Meijere et al. [117] group have investigated the direct synthesis of 3-spiro-cyclopropanated β-lactams **184** (Scheme 43) using novel three-component cascade reaction. Earlier, Alberto Brandi and coworkers [118–120] have applied nitrones **181** and bicyclopropylidene **182** to obtain cylcoadducts **183**, which were further fragmented under acidic conditions to afford spiro-β-lactams **184**. However, this reaction required longer reaction time for the formation of cycloadducts **183**.

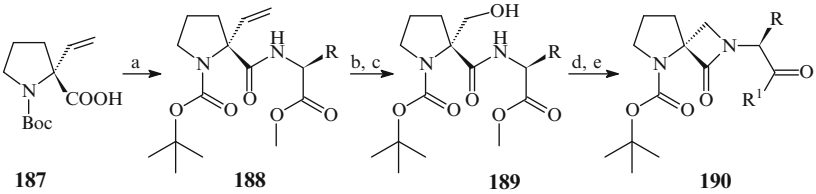
Taking this into account, Meijere and Brandi [117] together explored the effect of microwave heating during the 1,3-dipolar cycloaddition of nitrones, generated in situ and bicyclopropylidene **182** for the synthesis of these spiro-β-lactams **184** (Scheme 43). The reaction of *N*-substituted hydroxylamine hydrochlorides **185**,





R^1 = Bn, Me, $CHPh_2$, ^{t}Bu, $CH_2C_6H_4$–$OCH_3(p)$
R^2 = H, CO_2Et, CO_2Me
X = Cl, $(COOH)_2$

Scheme 43 Three-component cascade reaction to afford 3-spirocyclopropanated β-lactams



R = H, DCCB DCCB:
R^1= $NHCH_3$, OH

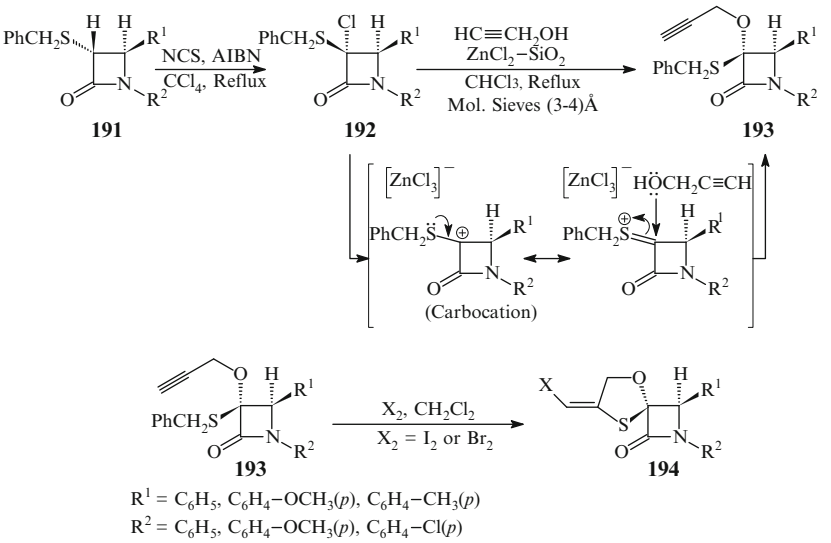
Reagents: a) HATU, DIPEA, NMP, GlyOMe.HCl (R = H)/O-(2,6-dichlorobenzyl)tyrosine methyl ester hydrochloride (R = DCCB), b) O_3, CH_2Cl_2, c) $Na[BH(OAc)_3]$ d) DEAD, PPh_3, THF, e) CH_3NH_2, EtOH / LiOH, THF, H_2O

Scheme 44 Chirospecific synthesis of spiro-β-lactams serving as efficient β-turn nucleators

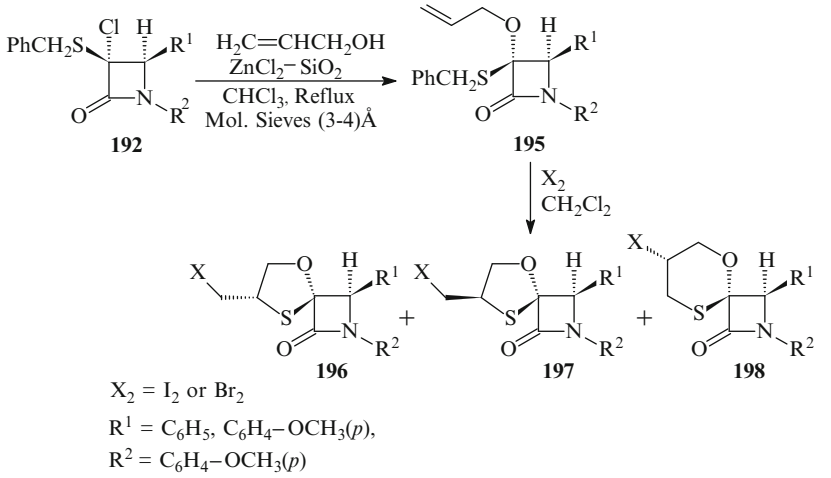
aldehydes **186,** and bicyclopropylidene **182** in the presence of sodium acetate and ethanol under microwave irradiation furnished the desired spiro-β-lactams **184** after 30–120 min in single operation. The time required for the completion of this reaction was never more than 2 h, whereas, with traditional heating at 45°C reaction completed in 16 d and at higher temperatures, only the corresponding spirocyclopropanated piperidone derivative was formed.

Recently, Bittermann and Gmeiner [49] have provided a novel protocol for the synthesis of enantiomerically pure spiro-β-lactams **190** and characterized them as efficient β-turn nucleators (Scheme 44).

The starting substrate, protected α-vinylproline **187** was activated by HATU and coupled with glycine methyl ester hydrochloride to give protected peptide derivatives **188**. Further, ozonolysis of these derivatives and subsequent reduction with excess of $Na[BH(OAc)_3]$ provided the hydroxymethyl-substituted derivative **189** in



Scheme 45 Novel synthetic approach to spiro-β-lactams via halogen-mediated intrasulfenyl cyclization



Scheme 46 Extended halogen-mediated intrasulfenyl cyclization using allyl alcohol

excellent yields. The derivatives **189** were introduced to intramolecular Mitsunobu reaction using DEAD with PPh_3, which on subsequent aminolysis or LiOH-promoted hydrolysis afforded spiro-β-lactams **190**.

In connection with these studies, recently, we have reported from our laboratory a novel, operationally simple and efficient approach for the synthesis of spiro-β-lactams **194**, **196–198** (Schemes 45 and 46) [121]. In our earlier publications, we have demonstrated well the synthetic potential of cationic β-lactam equivalents

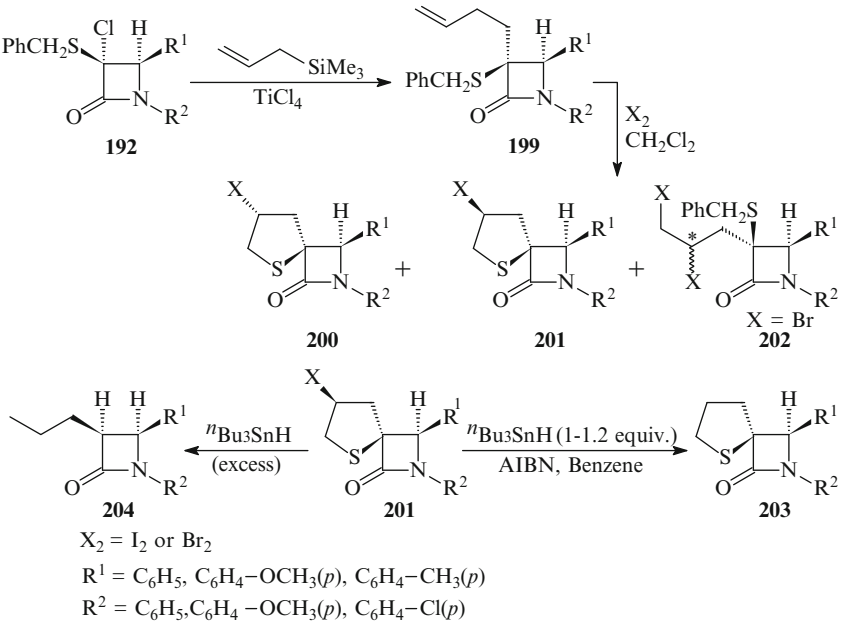
192 for the synthesis of novel azetidin-2-ones and their C-3 functionalizations [122–127].

The *trans*-3-benzylthio-3-chloro-β-lactams **192**, the appropriate β-lactam carbocation equivalents, were prepared by stereospecific chlorination of their corresponding *trans*-3-benzylthio-β-lactams **191** using *N*-chlorosuccinimide and catalytical amount of AIBN [125]. These β-lactam carbocation equivalents **192** on treatment with propargyl alcohol or allyl alcohol in the presence of $ZnCl_2/SiO_2$ were further transformed to suitable substrates, such as, *cis*-3-benzylthio-3-(prop-2-ynyloxy/enyloxy)-β-lactams **193** and **195** respectively [126].

Initially, the substrates **193** were subjected to halogen-mediated intrasulfenyl cyclization reactions with iodine or bromine in the presence of dichloromethane. The reaction afforded the exclusive formation of the five membered ring spiro-β-lactams **194** (Scheme 45). To probe further into the underlying features governing the selectivity in 5-exo versus 6-endo additions, we set out to examine the halogen mediated cyclization reactions of 3-alkenyloxy-β-lactams **195** (Scheme 46). The treatment of **195** with iodine or bromine under similar reaction conditions resulted in the formation of a mixture of two diastereomeric five-membered ring spiro-β-lactams **196** and **197** as the major products along with a single isomer of six-membered ring spiro-β-lactams **198** as the minor one. Further, the major isomeric cyclized 5-membered ring adducts **196** and **197** were formed in 1:1 ratio as evident from ^{1}H NMR and one of the isomer **196** crystallized in pure form, whereas, the other isomer **197** remained an oily product. The exclusive formation of five membered ring cycloadducts and the stereochemistry at spiro-junction C-3 of **194**, **196** was established through single crystal X-ray crystallographic analysis.

These studies have revealed interesting features of the halocyclization of *cis*-3-alkoxy-β-lactams **193** and **195**. The regio- and stereochemistries of the products, formed after the intramolecular addition of heteronucleophile depends on the type of unsaturation within the substrate. Further, the alkynyloxy sulfide ring closures led to the exclusive formation of five-membered ring spiro-β-lactams **194**, whereas, alkenyloxy sulfide ring closures led to the formation of a mixture of five-membered ring spiro-β-lactams **196, 197** as the major products along with six-membered ring spiro-β-lactams **198** as the minor products. The regiospecificities of these ring closures may in part, be due to a kinetic preference for formation of the five-membered rings.

Further, we have investigated [128] the synthesis of spiro-β-lactams **200, 201** (Scheme 47) using a similar strategy i.e. through halogen-mediated intrasulfenyl cyclization reactions of 3-allyl-3-benzylthio-β-lactams procured through a Lewis acid mediated C-3 alkylation of the *trans*-3-benzylthio-3-chloro-β-lactams **192** [112]. $TiCl_4$ promoted allylation of β-lactams **192** with allylsilane provided the suitable substrates **199**, which were further subjected to halogen-mediated intrasulfenyl cyclization reactions with iodine or bromine under similar reaction conditions. The reaction produced a mixture of two isomers of five membered ring spiro-β-lactams **200, 201**, which were separable by column chromatography. However, a small amount of an additional product **202** was obtained, when bromine was used as a halogenating reagent.



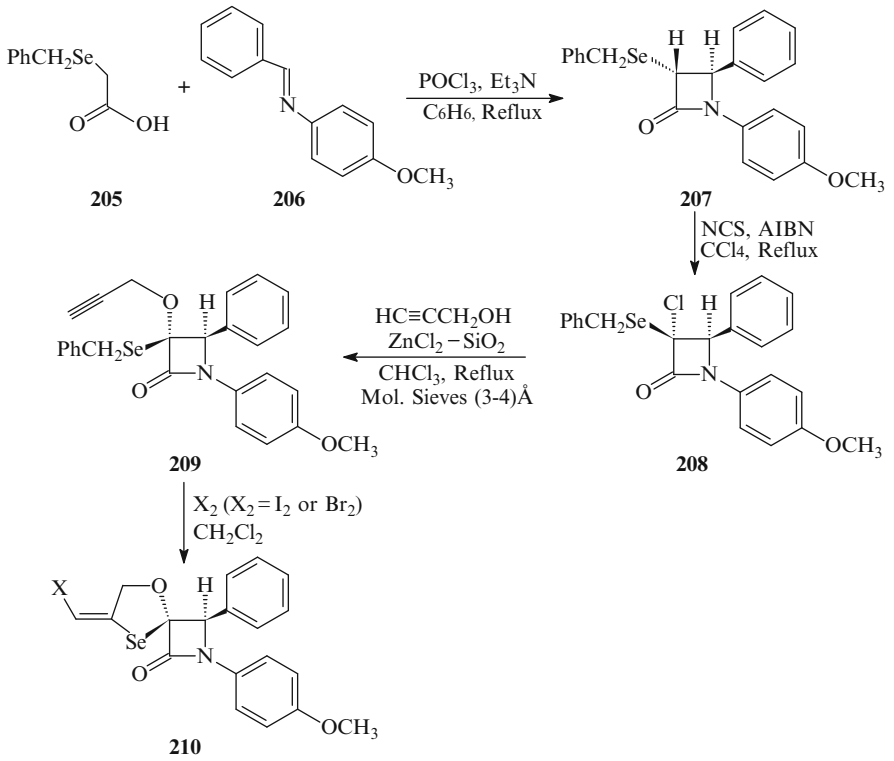
Scheme 47 Synthesis of spiro-β-lactams using 3-allyl-3-benzylthio-β-lactams

These halospiro-β-lactams **201** were further subjected to dehalogenation reactions using tri-*n*-butyltinhydride in the presence of catalytic amount of AIBN and gave the clean dehalogenated spiro-β-lactams **203**. However, it was observed that increasing the amount of tri-*n*-butyltinhydride led to desulfurization also along with dehalogenation leading to ring opening and formation of *cis*-3-propyl-β-lactams **204**.

The construction of naturally occurring or unnatural β-lactams with attendant control of functional groups and stereochemistry has been the goal of the synthetic organic chemists for the past few decades. In addition, the ever-increasing bacterial resistance to β-lactam antibiotics presents a very serious concern and efforts have been made to meet this challenge by exploring new β-lactam chemistry by the skeletal modification of naturally occurring β-lactam antibiotics. The sulfur atom of penicillins and cephalosporins has been replaced by selenium and its chemophysical and microbiological effects have also been investigated.

Very recently, in continuation to our studies directed toward the synthesis of spiro-β-lactams, we have reported the synthesis of a new class of spiro seleno-β-lactams [129] (Scheme 48). No report on the synthesis of spiro seleno-β-lactams has appeared in literature so far.

The seleno-β-lactam **207**, required for this study, was prepared from 2-benzylselenoethanoic acid [130] **205** and appropriate imine **206** in the presence of phosphorus oxychloride as the condensing reagent and triethylamine as the base. This was further transformed to appropriate β-lactam carbocation equivalent,

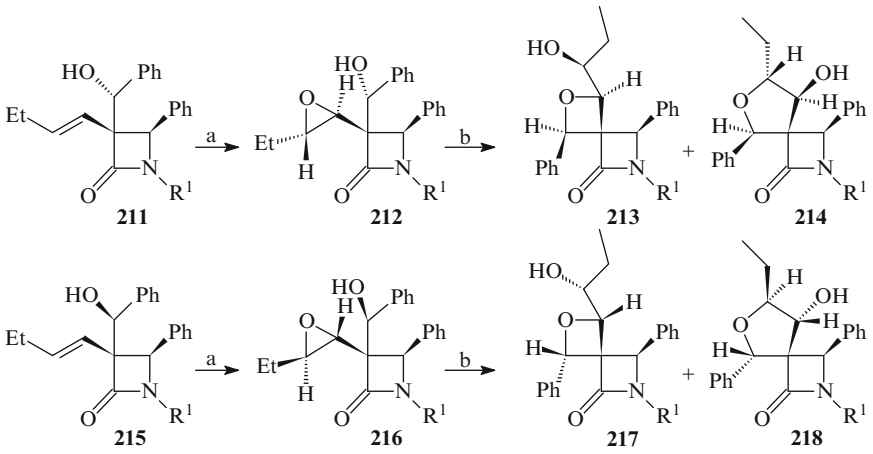


Scheme 48 Facile synthesis of new class of spiro seleno-β-lactams

cis-3-chloro-3-benzylseleno-β-lactam **208** using *N*-chlorosuccinimde and AIBN. The *cis*-3-chloroseleno-β-lactam **208** was successfully converted to *cis*-3-benzyl-seleno-3-(prop-2-ynyloxy)-β-lactam **209**, which served as potential substrate for undergoing halogen-mediated intraselenyl cyclization reaction. Exposure of 3-alkoxyseleno-β-lactam **209** to iodine or bromine in dry dichloromethane at room temperature afforded the exclusive formation of five-membered ring spiro seleno-β-lactams **210** in quantitative yields.

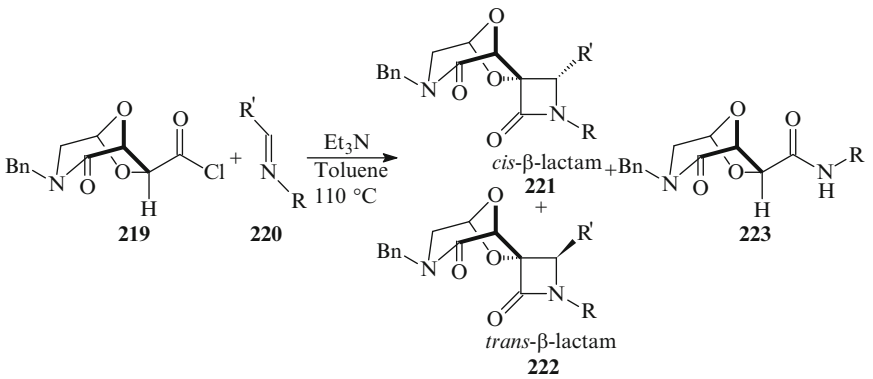
Tolomeli et al. [131, 132] have reported novel classes of four- and five-membered hydroxyl-spiro-β-lactams **213, 217** and **214, 218** via regioselective ring opening of hydroxyl-epoxides **212, 216**, respectively (Scheme 49). Treatment of hydroxyl-alkenyl-β-lactams **211, 215** with meta-chloroperoxybenzoic acid in dichloromethane led to the formation of *trans*-epoxides **212, 216** in high diastereomeric ratio, which were further subjected to intramolecular ring opening using $BF_3{\cdot}Et_2O$ in dichloromethane affording spiro-β-lactams **213–214**, **217–218** in highly regio- and stereoselective fashion. These spiro-β-lactams have been found to exhibit CAI activity and confirmed through ACAT inhibition assays.

Guarna et al. [133] have employed unsymmetrical bicyclic ketene in the Staudinger reaction for diastereoselective synthesis of highly constrained



Reagents: a) MCPBA, CH_2Cl_2, r.t., overnight, b) $BF_3.Et_2O$, CH_2Cl_2, r.t.
R^1 = $CH_2C_6H_5$, CH_2CH_2COOEt, (*S*)-$CH(CH_3)Ph$

Scheme 49 A synthetic route to four- and five-membered hydroxyl-spiro-β-lactams

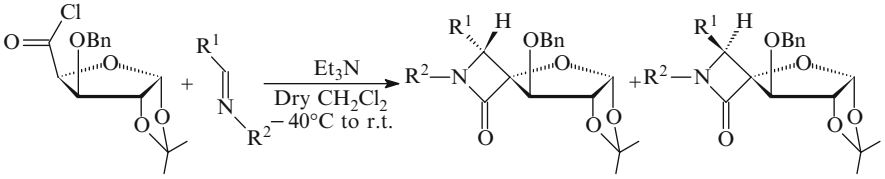


R' = C_6H_5, $C_6H_4-NO_2(p)$, $C_6H_4-OCH_3(p)$, $C_6H_4-Br(p)$
R = $CH_2C_6H_4$, $C_6H_4-NO_2(p)$, $C_6H_4-OCH_3(p)$, $C_6H_4-CH_3(p)$, $CH(CH_2C_6H_5)COOCH_3$

Scheme 50 Diastereoselective synthesis of spiro-β-lactams using unsymmetrical bicyclic ketene

spiro-β-lactams **221–222** (Scheme 50). The reaction of unsymmetrical bicyclic acyl chloride **219** with appropriate imines **220** in triethylamine and toluene proceeded with high stereoselectivity to produce the *cis*-spiro-β-lactams **221** as the major compounds accompanying with *trans*-spiro-β-lactams **222** as the minor compounds.

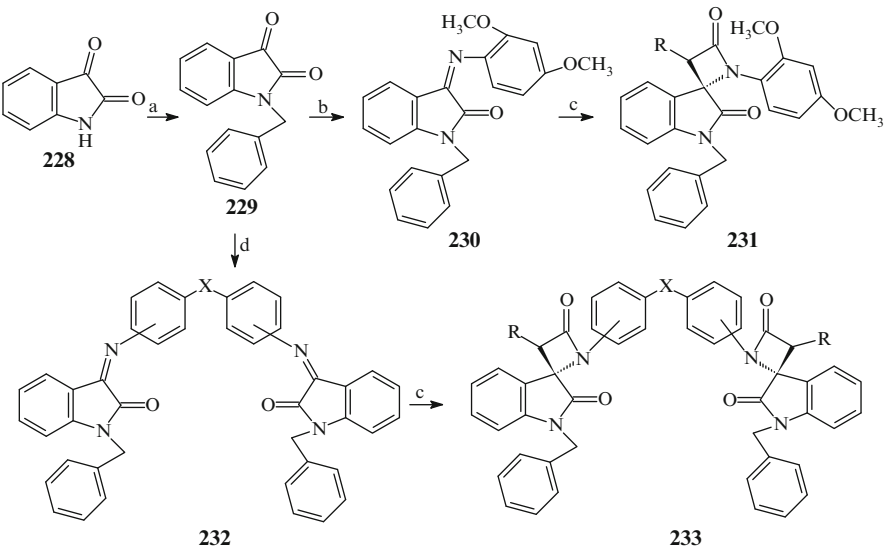
The *cis* stereochemistry of spiro-β-lactams **221** was established by NOE experiments and X-ray diffraction analysis. These spiro-β-lactams would serve as important heterocyclic compounds possessing diverse scaffolds to which different functional groups could be fixed in a stereodefined 3D topological arrangement.



224 225 226 227

R^1 = C_6H_5, C_6H_4–CH_3(*p*), C_6H_4–OCH_3(*p*), Styryl
R^2 = C_6H_5, C_6H_4–OCH_3(*p*), C_6H_4–Cl(*p*), C_6H_4–CH_3(*p*)

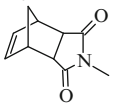
Scheme 51 Stereoselective synthesis of spiro-β-lactams using $_D$-(+)–glucose derived chiral ketenes



228 229 230 231 232 233

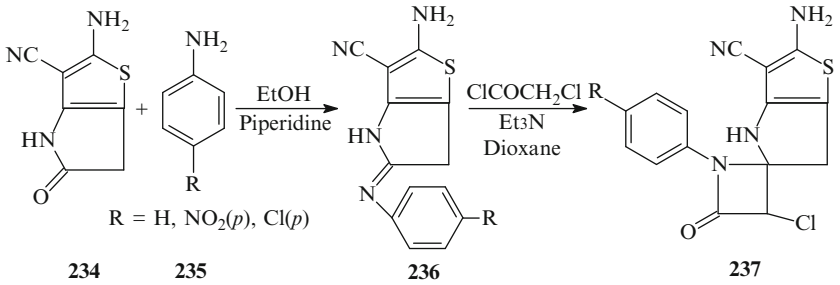
Reagents: a) Benzyl bromide, CaH_2, DMF, 50° C, b) 2,4-Dimethoxyaniline, EtOH, Reflux
c) RCH_2COCl, Et_3N, CH_2Cl_2,–10 °C to r.t. d) Diamine, EtOH, Reflux

R = OCH_3. OC_6H_5, PhthN,
X = CH_2, O



Scheme 52 Synthesis of mono- and bis-spiro-β-lactams from benzylisatin

Deshmukh et al. [134] have investigated the use of $_D$-(+)–glucose derived chiral ketenes in the stereoselective synthesis of spiro-β-lactams **226–227**. The $_D$-(+)–glucose acid chloride **224**, serving as a ketene precursor, in the Staudinger cycloaddition reaction with appropriate imines **225** afforded the diastereomeric mixture of spirocyclic-β-lactams **226–227** in 70:30 ratio, respectively. This reaction has cleanly produced only two diastereoisomers instead of theoretically possible four



Scheme 53 Synthesis of spiro-β-lactams using chloroacetylchloride and Schiff bases

diastereomers and this outcome was in accordance with the remarkable influence of the toroquoelectronic effect (Scheme 51).

Jarrahpour et al. [135] have described the synthesis of novel mono- and bis-spiro-β-lactams **231** and **233**, respectively, from benzylisatin **229** (Scheme 52). The starting substrate, benzylisatin **229** was prepared by reaction of isatin **228** with benzyl bromide and calcium chloride in DMF. The benzylisatin substituted imines **230** and di-imines **232** were further subjected to Staudinger reaction with ketenes derived from methoxy, phenoxy, and phthaloglycyl chlorides to afford novel mono- and bis-spiro-β-lactams **231** and **233**, respectively. The configuration of benzylisatin **229** and monocyclic spiro-β-lactams **231** was established by X-ray crystallographic studies. These spiro-β-lactams will be studied as precursors of modified β-amino acids, β-peptides and monobactam analogues.

Recently, Soleiman et al. [136] have published the synthesis of novel class of spiro-β-lactams **237** using chloroacetylchloride and Schiff bases **236** in the presence of triethylamine and dioxane (Scheme 53). The new Schiff bases **236** were prepared by reaction of **234** with different aromatic amines using ethanol and piperidine as catalysts.

3.2 Biological Evaluation

For over 75 years, the β-lactam antibiotics have provided a powerful line of defence against a wide variety of bacterial infections. These potent antibacterial agents have helped in controlling not only the spread of life-threatening diseases, but also prevented the onset of opportunistic infections in immune-deficient patients. The agility with which these four-membered heterocycles can undergo ring scission and rearrangements has provided an easy access to get many other heterocycles and acyclic compounds of interest. The widespread incidence of antibacterial resistance to β-lactam antibiotics caused by β-lactamase formation and the use of β-lactams as important synthons for a variety of natural products has provoked renewed interest in the building of spiro-β-lactam systems. Recently, spiro-β-lactams have become centers of attraction due to their diverse biological applications.

3.2.1 Cholesterol Absorption Inhibitors

Atherosclerotic coronary heart disease (CHD) is a significant disease around the globe and is one of the major causes of death and cardiovascular morbidity in humans. Risk factors for CHD include hypertension, diabetes mellitus, male gender, cigarette smoking etc. but the most dominating risk factor is the serum cholesterol.

The two significant sources of cholesterol in body are endogenously synthesized cholesterol and exogenous or dietary cholesterol. Efforts to inhibit the absorption of dietary cholesterol have primarily focused on the inhibition of ACAT, a major enzyme associated with cholesterol esterification. Inhibition of this enzyme blocks the absorption of intestinal cholesterol and may also inhibit cholesteryl ester deposition in the vascular wall in the form of fatty streaks associated with atherosclerotic plaque.

Structure-activity relation studies have revealed that 3-spiro-β-lactams SCH 54016 **A** [45] and SCH 58053 **B** [46] (Fig. 6) exhibit CAI activity, making them potentially useful compounds for development of drugs for lowering the high level of cholesterol. Besides that, it has recently been shown that cholesterol regulation [137] is also coupled to the activity of an enzyme, which is responsible for the cleavage of the amyloid precursor protein, which is thought to be involved in the pathogenesis of Alzheimer's disease.

The dissymmetric spiroannulation at C-3 provided the *trans* relationship between lactam carbonyl and 4-chlorophenyl functionality, which imparts the

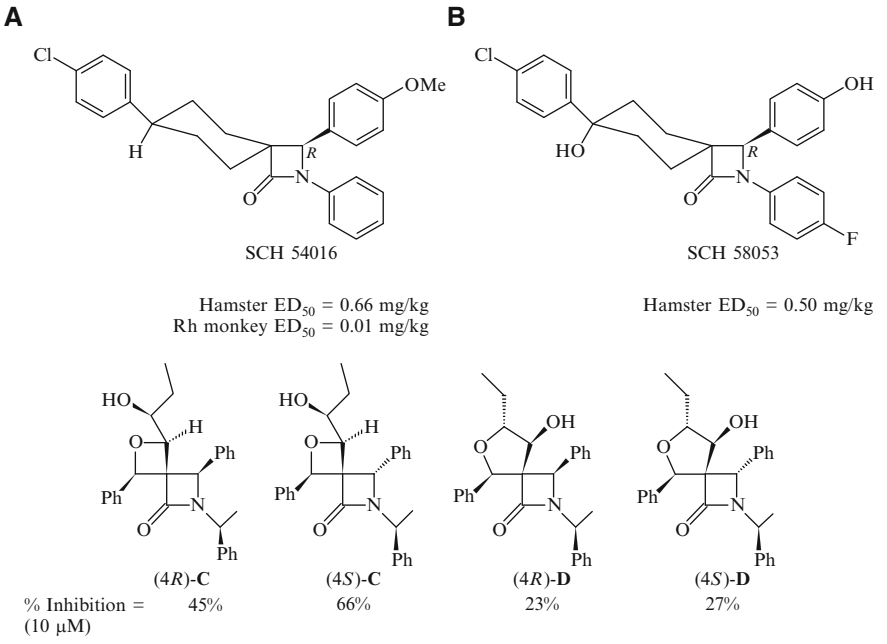


Fig. 6 Potent cholesterol absorption inhibiting spiro-β-lactams

CAI activity with an $ED_{50} = 0.66$ mg kg^{-1} in cholesterol-fed hamster assay [138]. In addition, this spiro-β-lactam (**A**) has been found to be an active compound in inhibiting cholesterol absorption ($ED_{50} = 0.01$ mg kg^{-1}) in rhesus monkeys, a primate species which shows similarity to the lipid profile of humans. The spiro-β-lactam **B** has also been found to show activity in the seven-day hamster cholesterol absorption assay with ED_{50} of 0.50 mg kg^{-1}. The axial benzylic hydroxyl group in the 4-position of cyclohexyl ring imparts about a favorable 10-fold shift in the potency as compared with similar analogs lacking this substitution. Recently, the enantiopure spiro-β-lactams **C** and **D** were reported to be ACAT inhibitors [131, 132]. These spiro-β-lactams were tested using Lovastatin as reference standard ($IC_{50} = 12$ μM from the literature data, $IC_{50} = 16.8$ μM when concurrently tested) with enzymatic assays performation and measured by quantitation of [^{14}C]–Cholesterol esterification using palmitoyl-CoA. The biological evaluation displayed results that four membered ring spiro-β-lactams are more active than five-membered ones; further, the (4 *S*)- spiro derivatives are showing enhanced activity with respect to the (4*R*)- derivatives. Thus, ACAT inhibitor contains spiroazetidin-2-one ring system that provides sufficient ring scaffold upon which the substitution pattern and their orientation in three dimensions can be varied.

3.2.2 Antiviral Agents

The replication of many plant and animal viruses has been found to be entirely dependent on proteolytic processing [139]. The proteolytic enzymes are involved in a variety of functions, such as, separation of structural and nonstructural proteins, generation of specific enzymes (RNA polypeptides), coordinated assembly of the virion, and maturation. The evidence suggests that the processing of viral precursor polypeptide involves virus-encodea *proteinases*. All picornaviruses produce a polypeptide 3C-proteinase, which carried out the most cleavages of the polyprotein occurring between glutamine and glycine, thus, enabling the virus to undergo maturation.

From the class of 4-spiro-β-lactams, β-lactam **E** (Fig. 7) has been found to be a good inhibitor of both *poliovirus* and *human rhinovirus 3C-proteinases* ($IC_{50} = 20$ μg mL^{-1}) [47]. Besides this, it also inhibited HLE ($IC_{50} = 0.4$ μg mL^{-1}) as well as Cathepsin G ($IC_{50} = 4.0$ μg mL^{-1}).

E

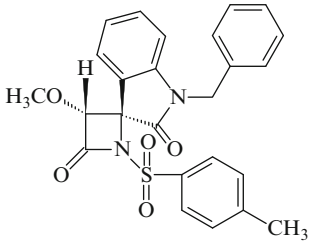
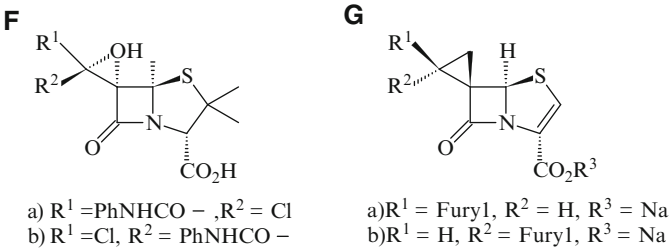


Fig. 7 Antiviral spiro-β-lactam

3.2.3 β-Lactamase Inhibitors and Antibacterial Agents

Bycroft et al. [83] have reported a series of semisynthetic penicillin derivatives such as, 6-spiro-epoxypenicillins **F, G** (Fig. 8) possessing both β-lactamase inhibitory and antibacterial activity (Fig. 8). It has been found that novel chlorinated 6-spiro-epoxypenicillins **F** are potent in vitro inhibitors of a range of chemically important β-lactamases [84], whereas, 6-spirocyclopropylpenems, **G**, show a reduced level of β-lactamase inhibitory activity. The significance of the five fold difference between the turnover numbers for **F(a)** and **G(b)** (differ only in their stereochemistry at one center) was found to be in close comparison with the turnover number of 20,000, reported for the established β-lactamase inhibitor, sulbactam [140]. Thus, the notable β-lactamase inhibitory and antibacterial properties of these spiro-β-lactams depend upon the substituents and the stereochemistry of the epoxide.

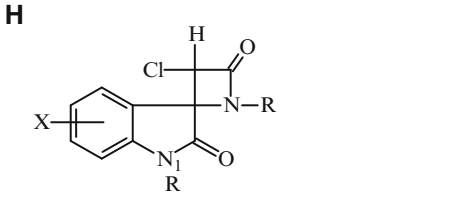
A class of Fridricamycins having indoles with C-3 spiro atoms has shown pronounced biological activities such as antitumor and antibiotic. Taking a clue from this, Joshi et al. [81] have investigated the synthesis of spiro-β-lactams **H** (Fig. 9) by incorporation of fluorine substituted indole nucleus and screened them for antibacterial activity. The compounds were tested for antibacterial activity against gram-positive bacteria, such as, *S. coagulase, S. viridaus, S. hemollyticus,* and gram-negative bacteria such as, *E. coli, P. pyocyneus,* and *C. frundii* by disc method, in the presence of ethanol, at a concentration of 10 mg ml^{-1}. The study revealed that all the compounds are moderately active against gram-positive



a) R^1 =PhNHCO − ,R^2 = Cl
b) R^1 =Cl, R^2 = PhNHCO −

a)R^1 = Fury1, R^2 = H, R^3 = Na
b)R^1 = H, R^2 = Fury1, R^3 = Na

Fig. 8 β-Lactamase inhibiting and antibacterial spiro-β-lactams

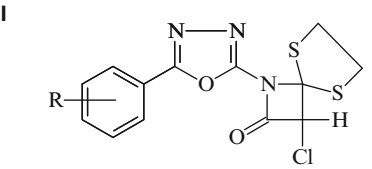


X = H, 5−F, 6−F
R = C_6H_5, 3−FC_6H_4, 4−FC_6H_4, 3−$CF_3C_6H_5$

R^1 = H, CH_2N O

Fig. 9 Antibacterial spiro-β-lactams

Fig. 10 Antimicrobial spiro-β-lactams



R = H, $OCH_3(p)$, Cl(*p*), $CH_3(p)$, $NO_2(p)$

bacteria (zone of inhibition between 10–17 mm in diameter), maximum against *S. hemollyticus*. However, these spiro-β-lactams have been found to be inactive against gram-negative bacteria except against *E. coli*, where slight activity has been observed (zone of inhibition between 7–10 mm).

3.2.4 Antimicrobial Agents

Hussain and Nizamuddin [97] combined the 1,3-dithiolane moieties with azetidin-2-ones for the study of different biological activities. The spiro-β-lactams **I** (Fig. 10) have been screened against *A. niger, P. oryzae, F. oxysporum,* and *C. sacchari* using agar growth technique at 100 and 10 ppm concentrations. The standard fungicide carbendazim was chosen to be the reference compound for studying the antifungal activities of these spiro-β-lactams **I**.

The observed data reveals that these spiro-β-lactams are antifungal in nature and the introduction of chloro, methyl and methoxy group further enhances the antifungal activity whereas, nitro group reduces it. The spiro-β-lactams **I** were also found to exhibit strong antibacterial activity against *E. coli*, *S. typhi*, and *B. aureus*.

3.2.5 Precursors for Tabtoxinine-β-Lactams

Tabtoxin **J** is a dipeptide exotoxin produced by *Pseudomonas tabaci*, the organism responsible for the wildfire disease of tobacco plants [141]. When hydrolyzed by *peptidase,* in vivo, this exotoxin releases tabtoxinine-β-lactam **K**, which inhibits *Glutamine synthetase* of the photorespiratory nitrogen cycle, causing chlorosis and death of tobacco plants [142].

As the dipeptide **J** itself does not inhibit purified *Glutamine synthetase* in vitro [143], the amino acid **K** is considered to be the active form of **J** and hence, the actual toxin of wildfire disease. Since, the detailed mechanism of *Glutamine synthetase* inhibition by tabtoxinine-β-lactam attracts chemical interest, a synthetic approach to the toxin **K** and its analogs, is of increasing importance. Spiro-β-lactam L (Fig. 11) has been found to be an efficient precursor of toxin **K**.

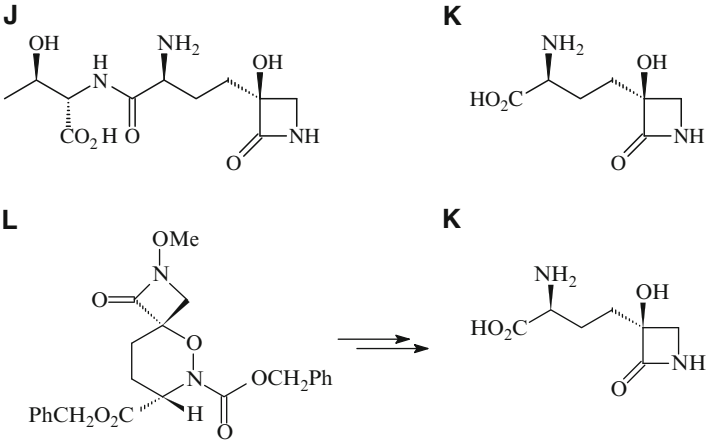


Fig. 11 Spiro-β-lactam: precursor for tabtoxin

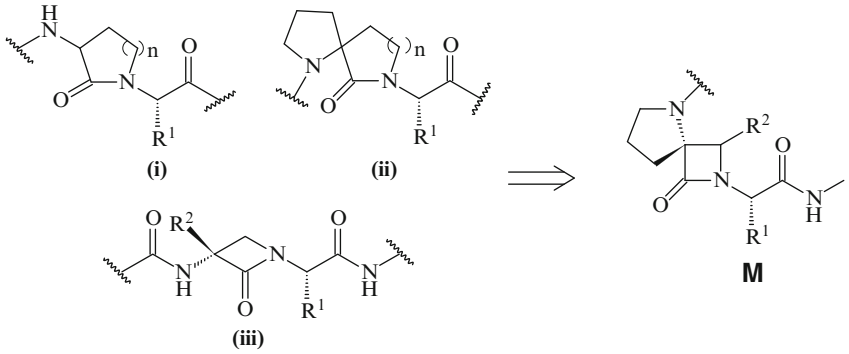


Fig. 12 Spiro-β-lactams as β-turn mimics

3.2.6 β-Turn Mimics

Recently, much attention has been directed toward the synthesis of peptidomimetics. These compounds can replace native peptides in the interaction with receptors. They showed increased metabolic stability, better bioavailability, and longer duration of action than native peptides, thus displaying favorable pharmacological properties [52–54]. In this sense, the design and synthesis of conformationally restricted peptidomimetics is an important approach toward improving the potency, selectivity, and metabolic stability of peptide based drugs.

Among the various strategies available for β-turn mimics, the Freidinger γ-lactam structure (1), or a spiro system [144] (2),has been found suitable for the design of a variety of medicinally relevant targets. In addition, it has been recently reported that use of α,α-disubstituted β-lactam (3) could also be a good approach to promote a β-turn folding in a peptide chain [145] (Fig. 12).

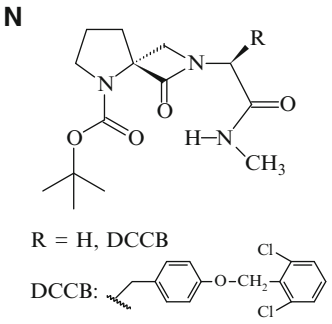


Fig. 13 Spiro-β-lactams as β-turn nucleators

Molecular modeling calculations using ab initio methods (MP2/6-31+G*) predict that spiro-β-lactam of type **M** adopt a β-turn secondary structure [50] which is very close to the ideal type-III β-turns. Thus, these spiro-β-lactams are the important members of the core for the preparation of different types of peptidomimetics using well-established chemistry. They combine the structural features required for inducing β-turn motif.

3.2.7 β-Turn Nucleators

Bittermann and Gmenier [49] have reported the chirospecific synthesis of proline-derived spirocyclic β-lactams **N** (Fig. 13) and investigated their utilization as reverse turn nucleators. These spiro-β-lactams possess valuable conformational properties as established from NMR and IR spectroscopic studies. Interestingly, the combination of both the spirocyclic structure and further conformational constraints by a four-membered lactam, enables a more ideal calibration of the geometrical properties required for adoption of a canonical type-II β-turn leading to a coplanar spatial arrangement and thus, promising antiparallel pleated β-sheet nucleators.

4 Concluding Remarks

In conclusion, the CAI activity of spiro-β-lactams, their antiviral and antibacterial properties, their potential as efficient β-turn nucleators and β-turn mimetics, and their application as synthons for α,α-disubstituted β-amino acids motivated synthetic and medicinal chemists to design novel spirocyclic β-lactams. Several approaches to the stereoselective synthesis of spiro-β-lactams have been described in this review. However, ketene-imine cycloaddition (Staudinger Reaction) shows much versatility for the access to diversely functionalized spiro-β-lactams. In addition, we have developed a facile route to novel spiro-β-lactams by using

intramolecular halogen-mediated cyclization reactions of *cis*-3-prop-2-ynyloxy/enyloxy- or 3-allyl-3-benzylthioazetidin-2-ones.

We would like to apologize to those scientists whose work may not have appeared in this review either due to the limited scope of the review or oversight. We gratefully acknowledge the financial support for our spiro-β-lactam research programme from Council of Scientific and Industrial Research, New Delhi and Department of Science and Technology (DST), New Delhi, Government of India (Project No. SP/S1/G-50/99 and SR/FTP/CS-135/2006).

References

1. Wright AJ (1999) The penicillins. Mayo Clin Proc 74:290
2. Staudinger H (1907) Annalen 356:51
3. Fleming AJ (1929) Exp Pathol 10:226
4. Nathwani D, Wood MJ (1993) Drugs 45:866
5. Morin RB, Gorman M (eds) (1982) Chemistry and biology of β-lactam antibiotics. Academic Press, New York
6. Kahan JS, Kahan FM, Goegelman R, Currie SA, Jackson M, Stapley EO, Miller TW, Miller AK, Hendlin D, Mochales S, Hernandez S, Woodruff HB, Birnbaum J (1979) J Antibiotics 32:1
7. Kahan JS, Kahan FM, Stapley EO, Goegelman R, Hernandez S (1976) U S Patent 3950357
8. Brown AG, Goodacre J, Harbidge JB, Howarth TT, Ponsford RJ, Stirling I, King TJ (1976) J Antibiotics 29:295
9. Yang Y, Rasmussen BA, Shales DM (1999) Pharmacol Ther 83:141
10. Cherry PC, Newall CE (1980) In: Morin RB, Gorman M (eds) Chemistry and biology of β-lactam antibiotics. Academic Press, New York
11. Yamamoto S, Aoki T, Nishitani Y, Mori S, Satoh H, Hamada Y, Ishitobi H, Nagata W (1980) Tetrahedron Lett 21:351
12. Imada A, Kitano K, Kintaka K, Muroi M, Asai M (1981) Nature 289:590
13. Sykes RB, Cimarusti CM, Bonner DP, Floyd DM, Georgopapadakou NH, Koster WH, Liu WC, Bush K, Trejo WH, Wells JS (1981) Nature 291:48
14. Tsuji N, Nagashima K, Kobayashi M, Terui Y, Matsumoto K, Kondo E (1982) J Antibiotics 35:536
15. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Hoberg MD, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su Z-z, Gupta P, Fisher PB (2005) Nature 433:73
16. Burnett DA, Caplen MA, HRJr D, Burrie RE, Clader JW (1994) J Med Chem 37:1733
17. Dugar S, Yumibe N, Clader JW, Vizziano M, Huie K, van Heek M, Compton DS, HR D Jr (1996) Bioorg Med Chem Lett 6:1271
18. Wu GG (2004) Org Process Res Det 4:298
19. Han WT, Trehan AK, Wright JJK, Federici ME, Seiler SM, Meanwell NA (1995) Bioorg Med Chem 3:1123
20. Borthwick AD, Weingarte G, Haley TM, Tomaszewski TM, Wang W, Hu Z, Bedard J, Jin H, Yuen L, Mansour TS (1998) Bioorg Med Chem Lett 8:365
21. Cainelli G, Galletti P, Garbisa S, Giacomini D, Sartor L, Quintavalla A (2003) Bioorg Med Chem 11:5391
22. Doherty JB, Ashe BM, Agrenbright LW, Baker PL, Bonney RJ, Chandler GO, Dahlgren MEJr, Dorn CP, Finke PE, Firestone RA, Fletcher D, Hagemann WK, Munford R, O'Grady L, Maycock AL, Pisano JM, Shah SK, Thompson KR, Zimmerman M (1986) Nature 322:192

23. Cvetovich RJ, Chartran M, Hartner FW, Roberge C, Amato JS, Grabowski E J (1996) J Org Chem 61:6575
24. Zhou NE, Guo D, Thomas G, Reddy AVN, Kaleta J, Purisima E, Menard R, Micetich RG, Singh R (2003) Bioorg Med Chem Lett 13:139
25. Setti EL, Davis D, Chung T, McCarter J (2003) Bioorg Med Chem Lett 13:2051
26. Smith DM, Kazi A, Smith L, Long TE, Heldreth B, Turos E, Dou QP (2002) Mol Pharmacol 61:1348
27. Kazi A, Hill R, Long TE, Kuhn DJ, Turos E, Dou QP (2004) Biochem Pharmacol 67:365
28. Ojima I (1995) Acc Chem Res 28:383
29. Banik BK, Manhas MS, Bose AK (1994) J Org Chem 59:4714
30. Alcaide B, Almendros P (2002) Synlett 381
31. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2001) Synlett 1813
32. Alcaide B, Almendros P (2001) Chem Soc Rev 30:226
33. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (1999) Amino Acids 16:321
34. Manhas MS, Wagle DR, Chiang J, Bose AK (1998) Heterocycles 27:1755
35. Page MI (ed) (1992) The chemistry of β-lactams. Chapman and Hall, London
36. Georg GT (ed) (1993) The organic chemistry of β-lactams. VCH, New York
37. Kidwai M, Sapra P, Bhushan KR (1996) Curr Med Chem 6:195
38. Alcaide B, Almendros P (2004) Curr Med Chem 11:1929
39. Singh GS (2004) Curr Med Chem 4:69
40. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2004) Curr Med Chem 11:1837
41. Deshmukh ARAS, Bhawal BM, Krishnaswamy D, Govande VV, Shinkre BA, Jayanthi A (2004) Curr Med Chem 11:1889
42. Lysek R, Borsuk K, Furman B, Kaluza Z, Kazimierski A, Chmielewski M (2004) Curr Med Chem 11:1813
43. Buynak JD (2004) Curr Med Chem 11:1951
44. Niccolai D, Tarsi L, Thomas RJ (1997) Chem Commun 2333
45. Chen LY, Zaks A, Chackalamannil S, Dugar S (1996) J Org Chem 61:8341
46. Guangzhong Wu, Toruos W (1997) J Org Chem 62:6412
47. Skiles JW, McNeil D (1990) Tetrahedron Lett 31:7277
48. Sheehan JC, Chacko E, Lo YS, Ponzi DR, Sato E (1978) J Org Chem 43:4856
49. Bittermann H, Gmeiner P (2006) J Org Chem 71:97
50. Alonso E, Lopez-Ortiz F, del-Pozo C, Peralta E, Macia A, Gonzalez J (2001) J Org Chem 66:6333
51. Alonso E, del-Pozo C, Gonzalez J (2002) Synlett 69
52. Gante J (1994) Angew Chem Int Ed Engl 33:1699
53. Giannis A, Kolter T (1993) Angew Chem Int Ed Engl 32:1244
54. Robinson JA (1999) Synlett 429
55. Adlington RM, Baldwin JE, Chen BN, Cooper SL, McCoull W, Pritchard GJ, Howe TJ (1997) Bioorg Med Chem Lett 7:1689
56. Wu Z, Georg GI, Cathers BE, Schloss JV (1996) Bioorg Med Chem Lett 6:893
57. Parikh K, Oza P, Bhatt SB, Parikh AR (2000) Indian J Chem 39B:716
58. Ghosal A, Zbaida S, Chowdhury SK, Iannucci RM, Feng W, Alton KB, Patrick JE, Davis HR (2003) US Patent 6982251
59. Doherty J, Dorn C, Durette P, Finke P, McCoss M, Mills S, Shrenik S, Sahoo S, Hagmann W, Polo S US Patent 5952321
60. Goel RK, Singh A, Naidu PS, Mahajan MP, Kulkarni SK (2005) J Pharm Pharmacent Sci 8:182
61. Banik BK, Banik I, Becker FF (2005) Bioorg Med Chem 13:3611
62. Banik BK, Becker FF, Banik I (2004) Bioorg Med Chem 12:2523
63. Imbach P, Lang M, Gracia-Echeverria C, Guagnano V, Noorani M, Roesel J, Bitsch F, Rihs G, Furet P (2007) Bioorg Med Chem Lett 17:358
64. Leanza WJ, Wildonger KJ, Miller TW, Christensen BG (1979) J Med Chem 22:1435

65. Sunagawa M, Matsumura H, Inoue T, Fukasawa M, Kato M (1990) J Antibiotics 43:519
66. Miyadera T, Sugimura T, Hashimoto T, Tanaka K, Lino K, Shibata T, Sugawara S (1983) J Antibiotics 36:1034
67. Kang YK, Shin KJ, Yoo KH, Seo KJ, Hong CY, Lee CS, Park SY, Kim DJ, Park SW (2000) Bioorg Med Chem Lett 10:95
68. Iso Y, Irie T, Nishino Y, Motokawa K, Nishitani Y (1996) J Antibiotics 49:199
69. Mikamo H, Izumi K, Hua YX, Hayasaki Y, Sato Y, Tamaya T (2000) J Antimicrob Chemother 46:471
70. Kanno O, Kawamoto I (2000) Tetrahedron 56:5639
71. Kanno O, Shimoji Y, Ohya S, Kawamoto I (2000) J Antibiotics 53:404
72. Mori M, Somada A, Oida S (2000) Chem Pharm Bull 48:716
73. Copar A, Prevee T, Borut A, Mesar TZ, Seli L, Vilar M, Solmajer T (2007) Bioorg Med Chem Lett 12:971
74. Bose AK, Garratt S, Perlosi JJ (1963) J Org Chem 28:730
75. Moriconi EJ, Kelly JF (1966) J Am Chem Soc 88:3657
76. Manhas MS, Chib JS, Chiang YH, Bose AK (1969) Tetrahedron 25:4421
77. Johnson PY, Hatch CE (1975) J Org Chem 40:3502
78. Sheehan JC, Lo YS, Loliger J, Podewell C (1974) J Org Chem 39:1444
79. Singh SB, Mehrotra KN (1982) Can J Chem 60:1901
80. Ikeda M, Uchino T, Ishibashi H, Tamura Y, Kido M (1984) J Chem Soc Chem Commun 758
81. Joshi KC, Jain R, Sharma V (1986) J Indian Chem Soc LXIII:430
82. George B, Mullen, Georgiev V (1986) Heterocycles 24:3441
83. Bycroft BW, Shute RE, Begley MJ (1988) J Chem Soc Chem Commun 274
84. Bycroft BW, Gledhill L, Shute RE, Williams P (1988) J Chem Soc Chem Commun 1610
85. Bose AK, Chiang YH, Manhas MS (1972) Tetrahedron Lett 13:4091
86. Sharma MK, Durst T (1990) Tetrahedron Lett 31:3249
87. Zoghbi M, Warkentin J (1991) J Org Chem 56:3214
88. Ishibashi H, Nakamura N, Sato T, Takeuchi M, Ikeda M (1991) Tetrahedron Lett 32:1725
89. Fujisawa T, Ukai Y, Noro T, Date K, Shimizu M (1992) Tetrahedron 48:5629
90. Blanc SPL, Pete J-P, Piva O (1992) Tetrahedron Lett 33:1993
91. Aoyama H, Sakamoto M, Kuwabara K, Yoshida K, Omote Y (1983) J Am Chem Soc 105:1958
92. Aoyama H, Sagae H, Hosomi A (1993) Tetrahedron Lett 34:5951
93. Machida M, Oda K, Yoshida E, Kanaoka Y (1986) Tetrahedron 42:4691
94. Gurtler S, Johner M, Ruf S, Otto HH (1993) Helv Chim Acta 76:2958
95. Johner M, Rihs G, Gurtler S, Otto HH (1994) Helv Chim Acta 77:2147
96. Ruf S, Otto HH (1995) Helv Chim Acta 78:629
97. Khan MH, Nizamuddin (1997) Indian J Chem 36B:625
98. Basak A, Bdour HMM, Bhattacharya G (1997) Tetrahedron Lett 38:2535
99. Baldwin JE, Otsuka M, Wallace PM (1986) Tetrahedron 42:3097
100. Anklam S, Liebscher J (1998) Tetrahedron 54:6369
101. Al-Thebeiti MS, El-Zhory MF (1998) Indian J Chem 37B:804
102. Barba V, Hernandez C, Rojas-Lima S, Farfan N, Santillan (1999) Can J Chem 77:2025
103. Jeon MK, Kim K, Parl YJ (2001) Chem Commun 1412
104. Alonso E, del Pozo C, Gonzalez J (2002) J Chem Soc Perkin Trans 1:571
105. Macias A, Alonso E, Pozo CD, Venturini A, Gonzalez J (2004) J Org Chem 69:7004
106. Alcaide B, Almendros P, Campo TM, Rodriquez-Acebes R (2004) Tetrahedron 45:6429
107. Croce PD, Ferraccioli R, Rosa CL (1995) Tetrahedron 51:9385
108. Croce PD, Ferraccioli R, Rosa CL (1999) Tetrahedron 55:201
109. Croce PD, Rosa CL (1999) Tetrahedron: Assymetry 10:1193
110. Cremonesi G, Croce PD, Rosa CL (2004) Tetrahedron 60:93
111. Cremonesi G, Croce PD, Fontana F, Forni A, Rosa CL (2005) Tetrahedron: Assymetry 16:3371

112. Khasanov AB, Ramirez-Weinhouse MM, Webb TR, Thiruvazhi M (2004) J Org Chem 69:5766
113. Chowdari NS, Suri JT, Barbas CF III (2004) Org Lett 6:2507
114. Nishikawa T, Kajii S, Isobe M (2004) Synlett 2025
115. Clayden J, Hamilton SD, Mohammed RT (2005) Org Lett 7:3673
116. Hogan PC, Corey EJ (2005) J Am Chem Soc 127:15386
117. Zanobini A, Brandi A, de Meijere A (2006) Eur J Org Chem 1251
118. Zanobini A, Gensini M, Magull J, Vidovic D, Kozhushkov SI, Brandi A, de Meijere A (2006) Eur J Org Chem 1251
119. Salvati M, Pisaneschi F, Brandi A, (2004) Eur J Org Chem 2205
120. Brandi A, Cicchi S, Cordero FM, Goti A (2003) Chem Rev 103:1213
121. Bhalla A, Venugopalan P, Bari SS (2006) Eur J Org Chem 4943
122. Madan S, Arora R, Venugopalan P, Bari SS (2000) Tetrahedron Lett 41:5577
123. Bari SS, Venugopalan P, Arora R (2003) Tetrahedron Lett 44:895
124. Bari SS, Venugopalan P, Arora R, Modi G, Madan S (2006) Heterocycles 68:749
125. Bhalla A, Madan S, Venugopalan P, Bari SS (2006) Tetrahedron 62:5054
126. Bhalla A, Venugopalan P, Bari SS (2006) Tetrahedron 62:8291
127. Bhalla A, Rathee S, Madan S, Venugopalan P, Bari SS (2006) Tetrahedron Lett 47:5255
128. Bari et al., unpublished work
129. Bhalla A, Venugopalan P, Bhasin KK, Bari SS (2007) Tetrahedron 63:3195
130. Bhalla A, Sharma S, Bhasin KK, Bari SS (2007) Synth Commun 37:783
131. Benfatt F, Cardillo G, Gentilucci L, Tolomelli A (2007) Eur J Org Chem 3199
132. Benfatt F, Cardillo G, Gentilucci L, Tolomelli A (2007) Bioorg Med Chem Lett 17:1946
133. Trabocchi A, Lalli C, Guarna F, Guarna A (2007) Eur J Org Chem 4594
134. Chincholkar PM, Puranik VG, Deshmukh ARAS (2007) Tetrahedron 63:9179
135. Jarrahpour A, Khalili D (2007) Tetrahedron Lett 48:7140
136. Soleiman HA, Elkanzi NAA (2008) Phosphorus, Sulfur and Silicon 183:1679
137. Austen BM, Frears ER, Davies H (2000) In: International Symposium on Proteinase Inhibitors and Activators. University of Oxford, UK 6
138. Burnett DA (2004) Curr Med Chem 11:1873
139. Wimmer E, Kuhn RJ, Pincus S, Nicklin MJH, Takeda NJ (1987) Cell Sci Suppl 7:251
140. Mezes PSF, Clarke AJ, Dmitrienko GI, Viswanatha T (1982) FEBS Lett 143:265
141. Stewart WW (1971) Nature 229:174
142. Uchytil TF, Durbin RD (1980) Experientia 36:301
143. Thomas MD, Langston-Unkefer PJ, Uchytil TF, Durbin RD (1983) Plant Physiol 71:912
144. Ward P, Ewan GB, Jordon CC, Ireland SJ, Hagan RM, Brown JR (1990) J Med Chem 33:1848
145. Palomo C, Aizpurua JM, Benito A, Galarza R, Khamrai UK, Vazquez J, de Pasual-Teresa B, Nieto PM, Linden A (1999) Angew Chem Int Ed Engl 38:3056

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Novel and Recent Synthesis and Applications of β-Lactams

Luigino Troisi, Catia Granito, and Emanuela Pindinelli

Abstract In this chapter, a comprehensive overview of the most significant and interesting contributions published from 2000 until now, concerning the preparation of novel β-lactam structures is presented. Among the different synthetic strategies available, either novel or already known but efficient and versatile methodologies are covered. The simple modifications of one or more substituents linked to the nitrogen N-1, the C-3, and the C-4 carbon atoms of the β-lactam nucleus were considered as an alternative synthetic protocol of more complex and polyfunctionalized molecules. Indeed, it is well known and extensively reviewed that the biological activity of this strained four-membered heterocycle is strictly dependent on the nature of the substituent groups that affect the reactivity towards the molecular active sites, increasing or lowering the possibility of interaction with the substrates. Finally, a synthetic survey of the most significant biological and pharmacological applications of the 2-azetidinones is reported.

Keywords Beta-lactam · Cyclization reaction · Enzyme inhibitor

Contents

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Abbreviations

ACAT	Acyl coenzyme A cholesterol transferases
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
bpy	2,2′-bipyridyl
BQ	Benzoylquinine
BSA	Bis-trimethylsilylacetamide
BTPP	*tert*-butylimino-tri(pyrrolidino)phosphorane
n-BuLi	*normal*-butyllithium
s-BuLi	*sec*-butyllithium
CAD	Coronary artery disease
CAI	Cholesterol absorption inhibitor
CAIBP	Cholesterol absorption inhibitor binding protein
Cbz	Benzyloxycarbonyl
CH_3OTf	Methyl triflate
CNS	Central nervous system
CSI	Chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
ECM	Extracellular matrix
EDG	Electron-donating group
EWG	Electron-withdrawing group
Fmoc	9-fluorenylmethoxycarbonyl
GPCR	G protein-coupled receptor
HCMV	Human cytomegalovirus
HIU	High intensity ultrasound
HLE	Human leukocyte elastase
HMDA	Hexamethylendiamine
LDA	Lithium diisopropylamide

LE	Leukocyte elastase
LHMDS	Lithium bis(trimethylsilyl)amide
MCBA	*meta*-chloroperbenzoic acid
MMP	Matrix metalloproteinase
MMPP	Magnesium monoperoxyphthalate
MRSA	Methicillin-resistant *Staphylococcus aureus*
MW	Microwave
NMP	*N*-methylpyrrolidone
NMR	Nuclear magnetic resonance
OMP	*ortho*-methoxyphenyl
PBP	Penicillin-binding proteins
Pmb	*para*-methoxybenzaldehyde
PMN	Polymorphonuclear
PMP	*para*-methoxyphenyl
PPE	Porcine pancreatic elastase
PPY	4-(pyrrolidino)pyridine
SAR	Structure-activity relationship
SET	Single-electron-transfer
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-butyl dimethylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMSCl	Trimethylsilyl chloride
TPA	Tripyridylamine
TS	Transition state
Ts	Tosyl, 4-toluenesulfonyl

1 Introduction

β-Lactam nucleus is the core of the biological activity of a large class of antibiotics characterized by the presence of this four-membered ring and differentiated by side chains, unsaturations, heteroatoms, and, in many cases, by the presence of five-or six-membered rings.

After the discovery of penicillins and cephalosporins as classical β-lactam antibiotics and clinically useful active agents, the past few decades have witnessed a remarkable growth in the field of β-lactam chemistry [1, 2]. The need for potentially effective β-lactam antibiotics as well as more effective β-lactamase inhibitors has motivated synthetic organic and medicinal chemists to design new functionalized 2-azetidinones. Besides their clinical use as antibacterial agents, these compounds have also been used as synthons in the preparation of various heterocyclic compounds of biological significance [3–7]. The potential use of some

β-lactams as therapeutic agents for lowering plasma cholesterol levels has been documented as well [8, 9]. Extensive studies of the human leukocyte elastase (HLE) inhibitory mechanism and the biological activity of this class of compounds have also been published [10].

As a result, considerable attention is paid by the synthetic organic and medicinal chemists to continue updating their knowledge about novel β-lactam synthesis, based either on new or well established methodologies, or on the modification of preexisting groups linked to the four-membered ring.

In this chapter, we present a comprehensive overview of the most significant and interesting contributions on the preparation of the β-lactam structures published in various journals since 2000. The synthetic methodologies covered are based either on new or well established methodologies. As an alternative protocol, the simple structural modification of preexisting groups linked to the nitrogen N-1, the C-3, or the C-4 carbon atoms was also examined. Moreover, a synthetic survey of the literature on the biological and pharmacological applications of the 2-azetidinone compounds is included, focusing attention on the structure-activity relationships (SARs) studies, which can be employed to design new and more efficient molecules.

2 Biological Activity

In this paragraph, a synthetic survey of the most significant biological and pharmacological applications of β-lactam derivatives is reported. A more detailed survey of the current literature in this field is given in Sect. 4.3

2.1 Antibacterial Activity: Inhibitors of β-Lactamases

The emergence of pathogenic microorganisms resistant to multiple classes of antibiotics is a serious clinical challenge [11–16]. Among these classes of antibacterials, β-lactam antibiotics are still the most commonly used, over 50 years after their initial introduction. The most common mechanism for resistance to β-lactam antibiotics is the ability of bacteria to produce β-lactamases [17–21]. These enzymes hydrolyze the β-lactam moiety in the drugs, inactivating the antibiotics. Studies of amino acid sequence homology have identified four distinct classes of β-lactamase: A, B, C, and D [22]. Among these, classes A and C are currently the most important in human disease [21]. A successful approach to overcoming the adverse action of these enzymes has been the coadministration of β-lactamase inhibitors together with the typical β-lactam antibiotics, such as pennicillins [21–24]. Unfortunately, this approach has been compromised by the discovery of new variants of β-lactamases, resistant to the inhibition afforded by known inhibitors [25–30]. Therefore, the development of novel β-lactam inhibitors

to withstand inactivation by the ever-increasing diversity of β-lactamases has thus been a continuous and still on-going battle.

Several monocyclic β-lactams variously substituted have also been reported to have antibacterial activity against different strains of bacteria and with different mechanisms of action.

2.2 Inhibitors of Various Enzymes

Leukocyte elastase (LE) is a serine protease, expressed by polymorphonuclear (PMN) leukocytes, mainly neutrophils, which acts both intracellularly to kill engulfed pathogens and extracellularly to mediate coagulation, immune responses, and wound debridement [31]. Because LE has the potential to degrade some structural proteins of the extracellular matrix (ECM) such as elastin, fibronectin, and collagens, excess of LE activity has been involved in a number of pathological conditions that lead to the impairment of ECM organization, including rheumatoid arthritis, emphysema, cystic fibrosis, and tumor progression [32]. LE also activates the proenzymatic form of matrix metalloproteinase (MMP)-9 [31], massively released by the PMN leukocytes and instrumental to their extravasation [33, 34]. A number of β-lactams, compounds widely used as antimicrobial drugs, have been identified as inhibitors of these serine enzymes, in particular LE [35]. Inhibitors of LE, and in particular of HLE, have a core structure of a four-membered β-lactam ring. Most of them are based on the cephem nucleus or are bicyclic compounds, such as clavams and cephalosporins. More recently, monocyclic β-lactams variously substituted have also been studied.

Among the inhibition of other types of enzymes, several representatives of the class of β-lactams have been found to effectively inhibit proteases. 2-Azetidinones tetrasubstituted have also been identified as powerful and selective inhibitors of thrombin, a serine protease involved in both venous and arterial thrombotic episodes. Analogous compounds have also been found to display inhibition towards tryptase.

2.3 Azetidin-2-Ones as Vasopressin V1a Antagonists

The neurohypophysical hormones vasopressin and oxytocin exert a wide range of physiological effects through binding to specific membrane receptors belonging to the G protein-coupled receptor superfamily [36]. To date, three vasopressin receptor subtypes and one oxytocin receptor have been pharmacologically and functionally described [36]. Although vasopressin is perhaps best-known for its role in the cardiovascular system, it also has actions in the central nervous system (CNS). Arginine vasopressin functions as a neurochemical signal in the brain to affect social behavior. There is an expanding literature from animal and human studies

showing that vasopressin, through the vasopressin 1A receptor (V1a), can stimulate aggressive behavior. The β-lactam structure, prepared by different research groups, is the essential scaffold of several antagonists directed to the vasopressin V1a receptor.

2.4 Hypocholesterolemic and Antihyperglycemic Activity

Atherosclerotic coronary artery disease (CAD) is one of the major causes of death. Although reducing dietary fat and cholesterol is still considered the appropriate first-line therapy, the advent of more effective pharmacological agents has led to an increased use of drug therapy to control serum cholesterol [37, 38]. Serum cholesterol can be reduced by inhibiting endogenous cholesterol biosynthesis, promoting hepatic cholesterol clearance from the plasma, and inhibiting the absorption of dietary and biliary cholesterol from the intestines (for a review of pharmacological approaches to the treatment of atherosclerosis see [39]). 2-Azetidinones with various substituents have been studied as effective inhibitors of cholesterol absorption.

Monocyclic β-lactams tetrasubstituted have been reported for antidiabetic activity, as they are able to control diabetic hypercholesterolemia. Induction of diabetes was confirmed by a significant rise in serum glucose and a depression in hepatic glycogen contents that control the cholesterol metabolism.

2.5 Anticancer Activity

Recently discovered antitumor monocyclic and bicyclic β-lactam systems [40–42] are, in general, in good agreement with the phenomenon of azetidin-2-one pharmacophore of inexhaustible pharmacological potential on account of the specific ability of its numerous derivatives to inhibit not only bacterial transpeptidase, but also mammalian serin and cystein proteases [43]. As a measure of cytotoxicity, some compounds have been assayed against nine human cancer cell lines.

A family of novel β-lactam antibiotics based on *N*-methyltio substituted 2-azetidinones have also shown the apoptosis-inducing properties against human solid tumor cell lines such as breast, prostate, and head-and-neck [44].

2.6 Antiviral Activity

Human cytomegalovirus (HCMV) is a ubiquitous member of the herpes virus family. Although most infections are asymptomatic, severe manifestations of HCMV can be seen in individuals whose immune system has been weakened by

disease such as late-stage cancers and AIDS, or by immunosuppressive therapy following organ transplantation [45–47]. Due to its critical role in capsid assembly and viral maturation, HCMV serine protease has become an attractive target for the development of anti-HMCV drugs [48]. Among the latter, a series of monocyclic β-lactams have resulted in highly potent inhibitors.

3 General Synthetic Methodologies of β-Lactam's Preparation

Considering the large pharmacological potential and use of the β-lactam systems, intensive research has generated numerous methods for synthesizing this skeleton, and the topic has been amply documented and reviewed several times [49, 50]. Moreover, as documented in the subsequent Sect. 4, the chemical reactivity of the β-lactam ring depends strongly on the substitution at the N-1, the C-3, and the C-4 positions.

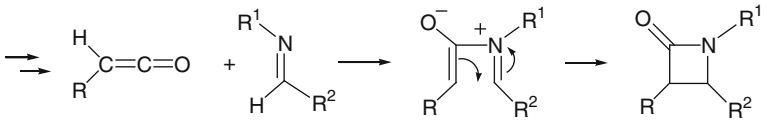
The synthetic methodologies covered are either new or already known and they are classified, in this paragraph, by the kind of reaction. The most efficient and used class of synthetic reactions for preparing the β-lactam ring are reported as follows:

Staudinger-reaction. The Staudinger reaction consists in the coupling of ketenes with imines. The ketene could be also prepared in situ in different ways (Scheme 1).

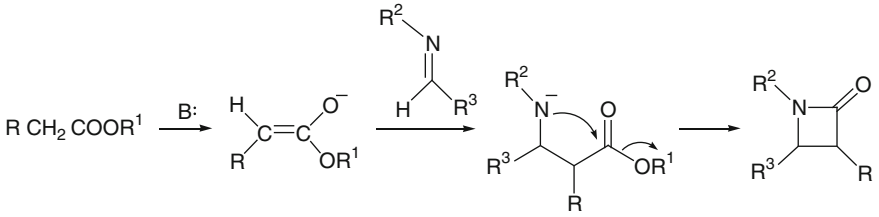
Gilman–Speeter reaction. The Gilman–Speeter reaction is the coupling of anion enolates with imines (Scheme 2).

Alper reaction. The Alper reaction corresponds to the ring expansion of aziridines by metal-catalyzed CO insertion (Scheme 3).

Mitsunobu reaction. The Mitsunobu reaction is an intramolecular cyclization of suitable amides (Scheme 4).

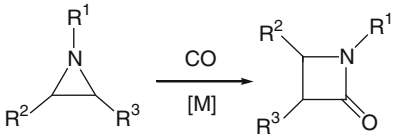


Scheme 1

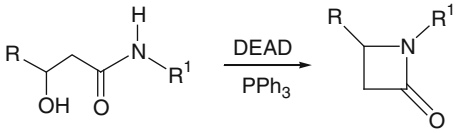


Scheme 2

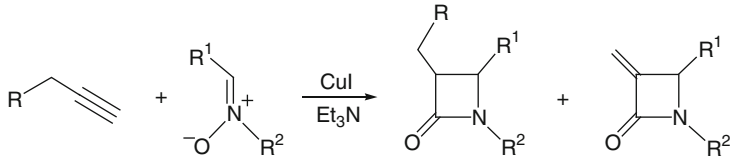
Scheme 3



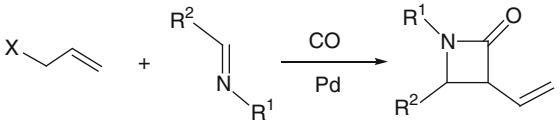
Scheme 4



Scheme 5



Scheme 6



Kinugasa reaction. The Kinugasa reaction consists in the coupling of nitrones with propargyl moieties catalyzed by copper salts (Scheme 5).

Torii Reaction. The Torii reaction is a metal-catalyzed cyclocarbonylation of allyl derivatives with imines (Scheme 6).

Intramolecular cyclization. The intramolecular cyclization of suitable substrates can afford 2-azetidinones under the following conditions:

(a) Electrochemical induction
(b) Photo-irradiation
(c) Ultra-sound irradiation
(d) Lewis-acid catalysis
(e) Base catalysis

Heterocyclic rearrangement. Suitable heterocycles can rearrange to 2-azetidinones.

Other reactions. In this paragraph, the reactions not included above are reported.

4 Literature Survey

4.1 Synthesis of Novel Substituted β-Lactams

4.1.1 Staudinger Reaction

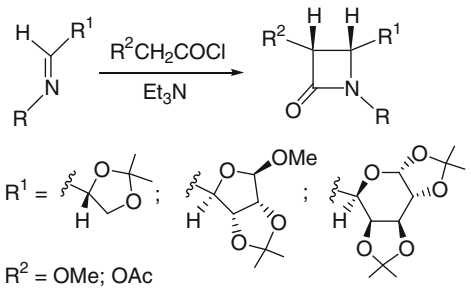
In 2000, the group of Banik et al. reported the enantiospecific synthesis of 3-hydroxy-2-azetidinones by microwave assisted Staudinger reaction [51]. Chiral imines, derived from chiral aldehydes and achiral amines, reacted with methoxy- or acetoxy-acetyl chloride to afford a single, optically pure *cis*-β-lactam, (Scheme 7).

3-Unsubstituted β-lactams have instead been obtained, by the same authors, through indium-mediated reaction of imines with alkyl bromoacetates [52]. β-Lactams having a wide range of substituents linked to the nitrogen atom, such as aryl, aryl alkyl, or allyl groups, could be prepared by this pathway.

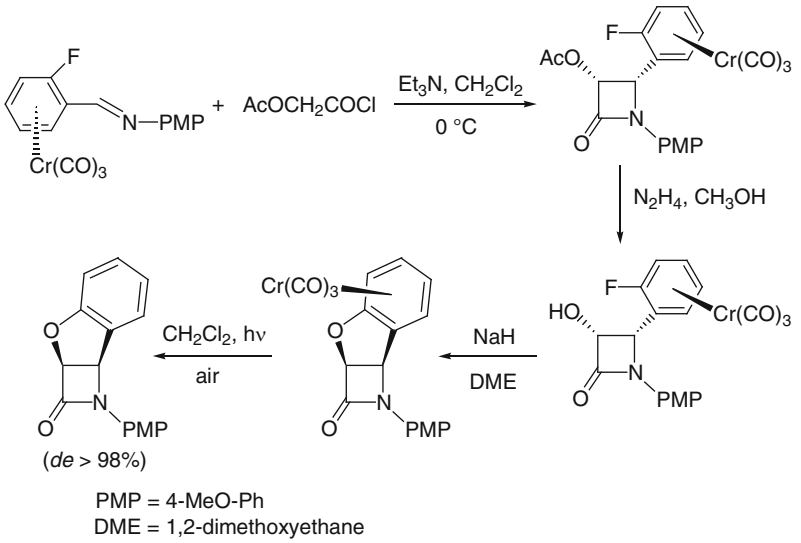
Microwave-induced organic reaction enhancement chemistry techniques have been reported to allow highly accelerated synthesis of variously substituted vinyl-β-lactams, using limited amounts of solvents and with efficient stereocontrol [3].

Enantiopure tricyclic β-lactams have been prepared by a stereoselective synthesis. The [2+2] cycloaddition of imine, obtained from the corresponding tricarbonyl chromium(0) 2-fluoro benzaldehyde and *para*-methoxyaniline [53], with acetoxy-acetyl chloride at 0°C and Et_3N in CH_2Cl_2 afforded the *cis* β-lactam as a single diastereoisomer in 94% yield (*de*>98%). Subsequent treatment of the *cis* β-lactam with hydrazine in CH_3OH gave, in 85% yield, the corresponding *cis* 3-hydroxy β-lactam. The intramolecular displacement of the fluorine atom, with an equimolar amount of NaH at room temperature, produced the tricyclic β-lactam. Finally, the uncomplexed compound was obtained quantitatively by exposure of the complex to air and sunlight in CH_2Cl_2 solution (Scheme 8), [54]. This latter product was also synthesized in racemic and enantiopure form starting from the enantiomerically pure tricarbonyl chromium(0) complex.

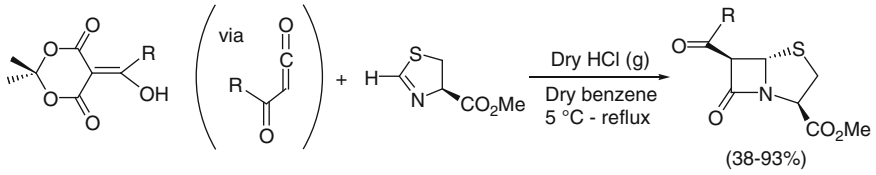
The synthesis of penams has been reported to be conveniently prepared from Meldrum's acid [55] and thiazoline [56]. The substrates were reacted in dry benzene containing dry HCl (gas) at reflux to afford a series of penam derivatives with aryl, *n*-hexyl, and cyclohexyl substituents (Scheme 9), [57].



Scheme 7 Synthesis of optically pure *cis*-β-lactams



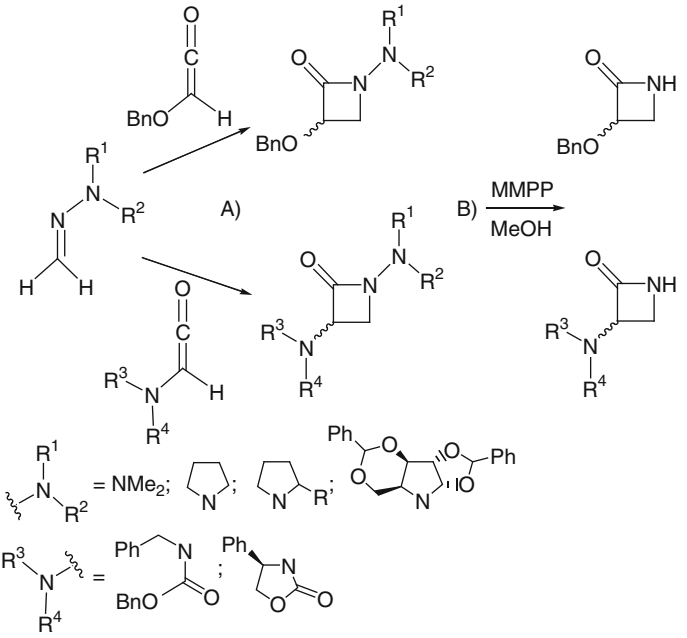
Scheme 8 Stereoselective synthesis of tricyclic β-lactams



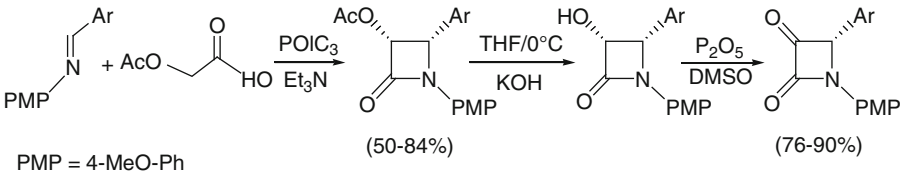
Scheme 9 Stereoselective synthesis of penam derivatives

The synthesis of enantiopure 4-unsubstituted 3-alkoxy- and 3-amino β-lactams has been reported to be performed in two steps: (a) and (b). (a) The [2+2] cycloaddition reaction of chiral formaldehyde *N*, *N*-dialkylhydrazones to alkoxy or aminoketenes. (b) The magnesium monoperoxyphthalate (MMPP)-promoted oxidative N–N bond cleavage of the resulting hydrazides (Scheme 10), [58].

A protocol has been reported based on a cyclization procedure followed by hydrolysis and oxidation, which allowed the preparation of α-keto-β-lactams (Scheme 11), [59]. The cyclization of imines with acetylglyoxylic acid, in the presence of $POCl_3$ and Et_3N, gave 3-acetoxy-β-lactams in good yields as *cis*-isomers, prevalently. These latter were hydrolyzed to alcohols in excellent yields under very mild conditions. Subsequent oxidations were performed by treatment with dimethyl sulfoxide (DMSO) in the presence of phosphorous pentoxide to give α-keto-β-lactams. More 2-azetidinones were synthesized varying the substituent of the acetyl moiety.



Scheme 10 Synthesis of 4-unsubstituted 3-alkoxy- and 3-amino-β-lactams from formaldehyde *N*, *N*-dialkylhydrazones

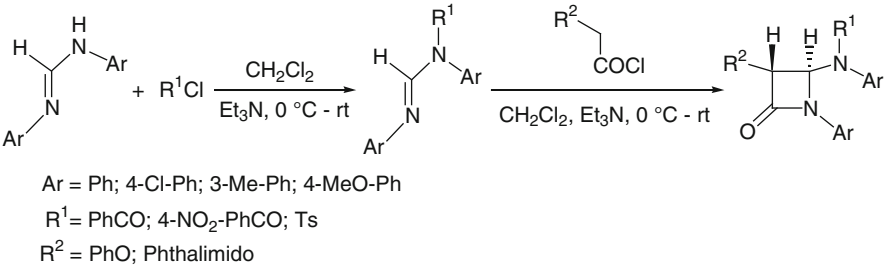


Scheme 11 Synthesis of α-keto-β-lactams

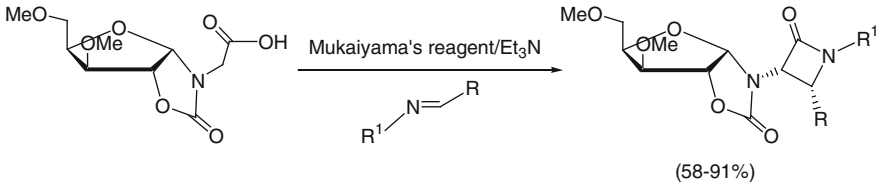
4-acylamino and 4-sulphonamido-*trans*-β-lactams have been reported to be synthesized from trisubstituted amidines via cycloaddition reaction with ketenes (Scheme 12), [60]. Amidines bearing an electron-withdrawing substituent on enamine nitrogen could increase the β-lactam stability. The starting trisubstituted amidines were prepared by reacting *N′*,*N′*-diarylamidines with aryloyl chloride in the presence of triethylamine.

D-xylose derivative has been reported to be an excellent chiral auxiliary in the Staudinger reaction for the construction of β-lactams (Scheme 13), [61].

Cyclic imines furnished *trans* products whereas acyclic imines possessing *trans* geometry gave *cis* products.



Scheme 12 Synthesis of 4-substituted amino-*trans*-β-lactams by cycloaddition reaction



Scheme 13 Asymmetric synthesis of β-lactams by chiral auxiliary based on D-xylose derivative

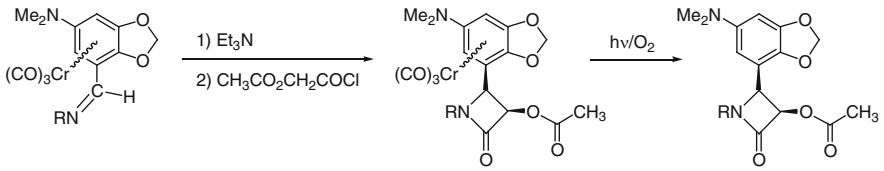
N-Ts-imines have been reported to react with ketenes in the presence of suitable nucleophilic catalysts to give *rac*-β-lactams in good chemical yields at room temperature [62]. The diastereomeric ratios were highly influenced by the kind of nucleophile involved. For instance, using chiral nucleophiles such as benzoylquinine (BQ) the synthesis became highly diastereo- and enantioselective (*dr, cis/trans* = 99:1; *ee*>95%).

In 2001, β-lactams have been reported to be obtained via Staudinger reaction with complete *cis*-diastereoselection starting from prochiral imine chromium complexes (Scheme 14), [63].

Enantioselective synthesis of analogous β-lactams has been also reported [63]. If the starting imine complex was prepared from the corresponding chiral amine in enantiomerically pure form (Fig. 1), two separable diastereomers were obtained. Using, then, one of the two diastereomers, *cis*-β-lactams were isolated as single enantiomers.

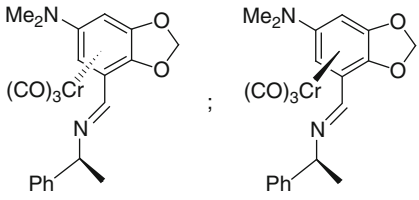
In 2002, the asymmetric synthesis of 3-substituted 3-hydroxy-β-lactams has been reported to be realized by metal-mediated 1,3-butadien-2-ylation reactions between 1,4-dibromo-2-butyne and optically pure azetidine-2,3-diones [64]. This latter starting material was prepared via Staudinger reaction followed by sequential transesterification and Swern oxidation (Scheme 15), [65].

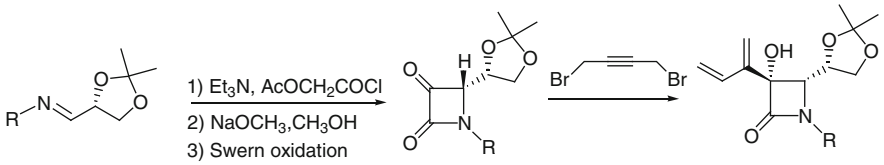
An efficient synthesis of tetrahydrofuran-derived spiro-β-lactams has been reported to be performed by a Staudinger-type reaction of either 2- or 3-tetrahydrofuroyl chloride with imines [66]. The reaction was carried out by adding Et_3N



Scheme 14 *cis*-Diastereoselective synthesis of β-lactams using prochiral imine chromium complexes

Fig. 1





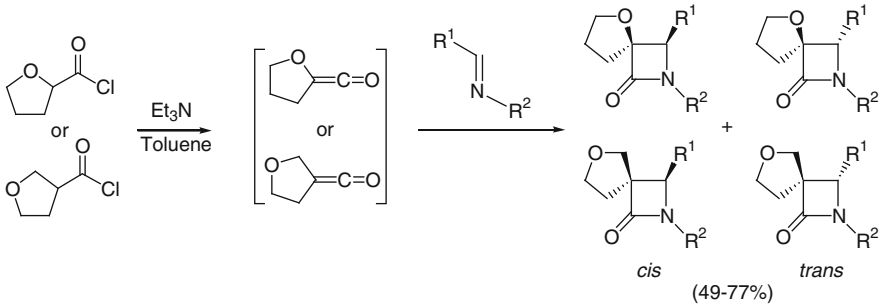
Scheme 15 Asymmetric synthesis of 3-substituted 3-hydroxy-β-lactams

to the acyl chloride in refluxing toluene and adding then the imine. A mixture of *cis*- and *trans*-spiro-β-lactams in good to moderate yield was obtained (Scheme 16).

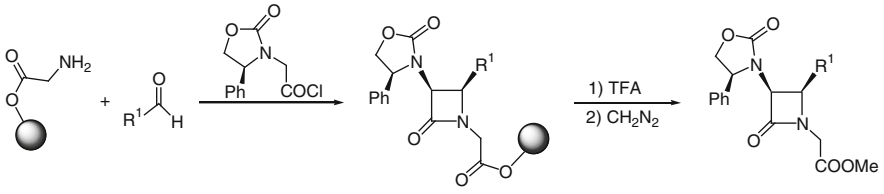
The Staudinger reaction of imines derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides has been reported to afford spiro-β-lactams with an unexpected *exo* stereochemistry [67].

The chiral glycine derivatives, having the oxazolidinone moiety as a chiral auxiliary [68], have been reported to give the asymmetric Staudinger reaction on solid support with different resin bound aldimines in the presence of triethylamine [69]. Optically active substituted β-lactams were obtained, after cleaving from the resin, in good to high overall yields with high diastereoselectivity (Scheme 17).

Rink resin derived imines have been reported to give cycloaddition reactions with acetyl chlorides (or equivalent) using triethylamine as the base and dichloromethane as the solvent at temperature ranging from 0°C to room temperature [70]. The resin-bound β-lactam could be cleaved by using 50% trifluoroacetic acid (TFA) in dichloromethane, to afford the *N*-unsubstituted β-lactam.



Scheme 16 Synthesis of tetrahydrofuran-derived spiro-β-lactams



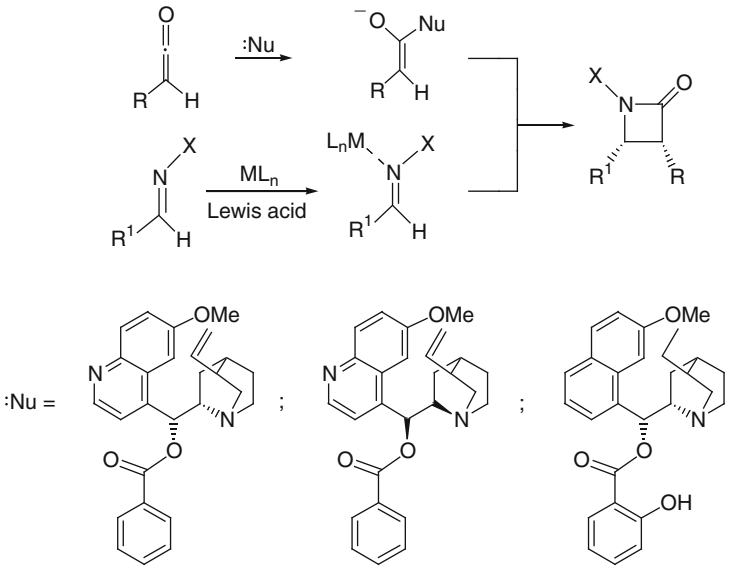
Scheme 17 Solid phase synyhesis of 3,4-substituted azetidinones

N,*N*-Dialkylhydrazones as the imine component in the Staudinger-like [2+2] cycloaddition to benzyloxyketene have been reported [71, 72]. The reaction led to the desired β-lactams in excellent yields (84–98%), moderate to good selectivities (3*R*,4*S* > 3*S*,4*R*), and only traces of *trans* isomers (3*R*, 4*R*) were detected in some cases.

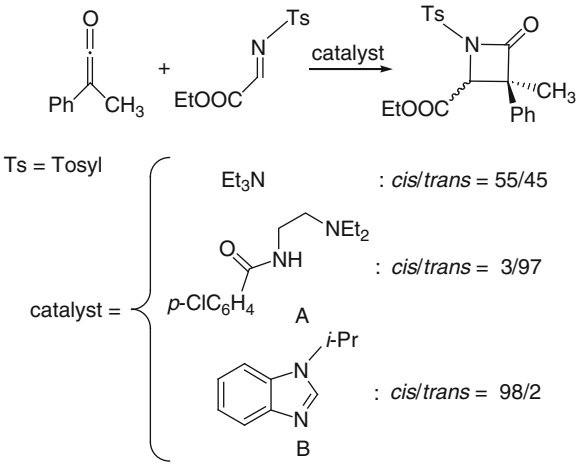
The coupling of ketenes and imines has been reported to be catalyzed by a bifunctional system in which a chiral nucleophile was paired with an achiral Lewis acid metal salt [73, 74]. Optically enriched β-lactam products were isolated in high yields, (Scheme 18). Among the various Lewis acids studied, such as $Mg(OTf)_2$, $Cu(MeCN)_4ClO_4$, $YbCl_3$, $La(OTf)_3$, AgOTf, $Al(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_2$,and $In(OTf)_3$, this latter was the best overall cocatalyst for promoting the reaction. The best chiral nucleophiles used are reported in Scheme 18.

Planar-chiral derivatives of 4-(pyrrolidino)pyridine (PPY) have been reported as efficient catalysts for enantioselective Staudinger reactions [75]. These chiral derivatives catalyzed the reactions between a range of symmetrical and unsymmetrical disubstituted ketenes and a wide imine array leading to β-lactams with good stereoselections and yields.

A methodology for the catalytic asymmetric synthesis of β-lactams has also been reported, resulting from the development of a catalyzed reaction of ketenes (or their derived zwitterionic enolates) and imines [76]. Despite the fact that simple tertiary



Scheme 18 Bifunctional Lewis acid/nucleophile catalyzed synthesis of β-lactams



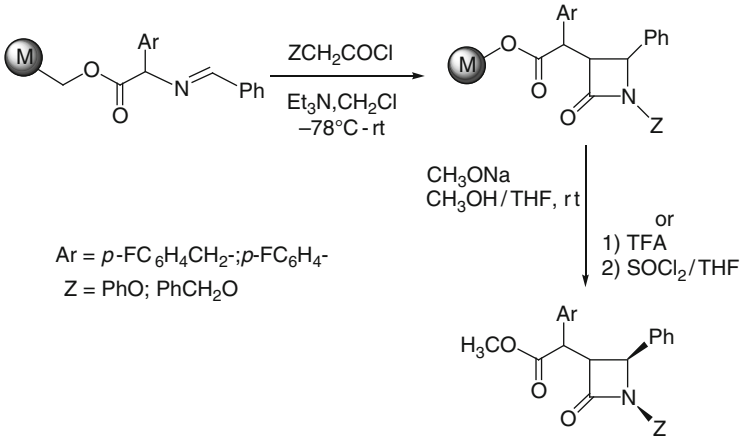
Scheme 19 Diastereoselectivity in the nucleophile-catalyzed reaction of methylphenylketene and imine

amines such as triethylamine usually catalyzed the reaction in a nonselective fashion, bifunctional catalyst, such as A and B (Scheme 19), may lead to a potentially rigid activated complex affording products in a *cis*/*trans* ratios of 3/97 and 98/2, respectively.

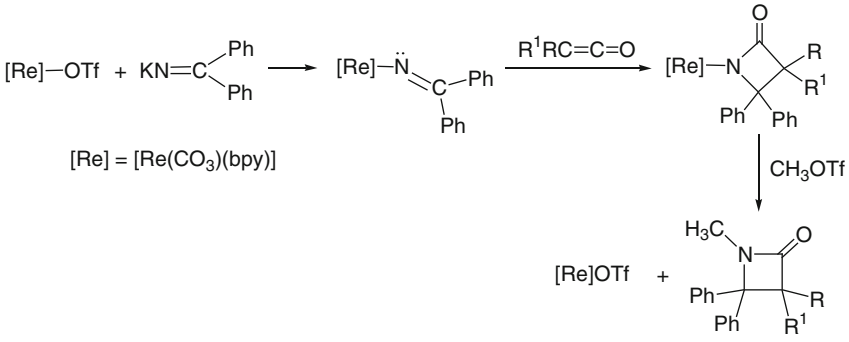
The use of a chiral catalyst such as benzoylquinine in this reaction allowed the obtaining of a high enantioselectivity with ee > 95%.

A multistep solid phase synthesis of β-lactams with imines of benzaldehyde coming out from commercially available fluorinated α-amino acids has been reported in 2003 [77]. Using the Merrifield resin-bound imine [78, 79] in dichloromethane, the cycloaddition was carried out between –78°C and rt by addition of benzyloxyacetyl chloride in the presence of triethylamine. The resin cleavage using sodium methylate resulted in the two *cis* β-lactam derivatives (Scheme 20).

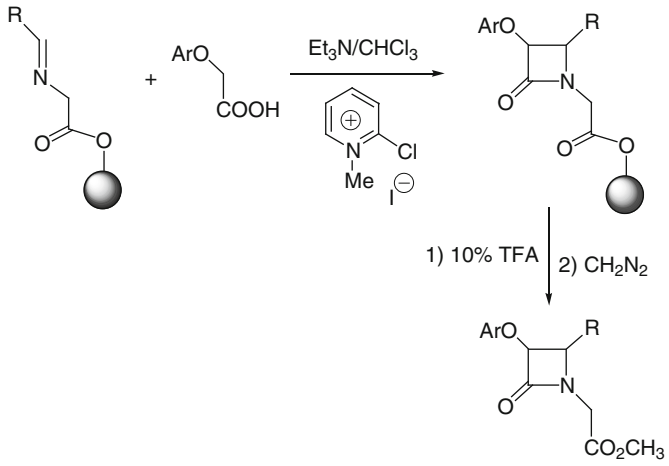
Alkylideneamido complex $[Re(N{=}CPh_2)(CO)_3(bpy)]$ [80] has been reported to react with ketene to afford, via Staudinger reaction, a single β-lactam complex whose structure was determined by X-ray diffraction [75]. The β-lactam complex reacted with methyl triflate (CH_3OTf), affording the free *N*-methyl-β-lactam and the complex used as precursor (Scheme 21), [81].



Scheme 20 Solid phase synthesis of *cis* β-lactams



Scheme 21 Synthesis of β-lactams from *N*-rhenaimine



Scheme 22 Stereoselective synthesis of β-lactams using Mukaiyama's salt

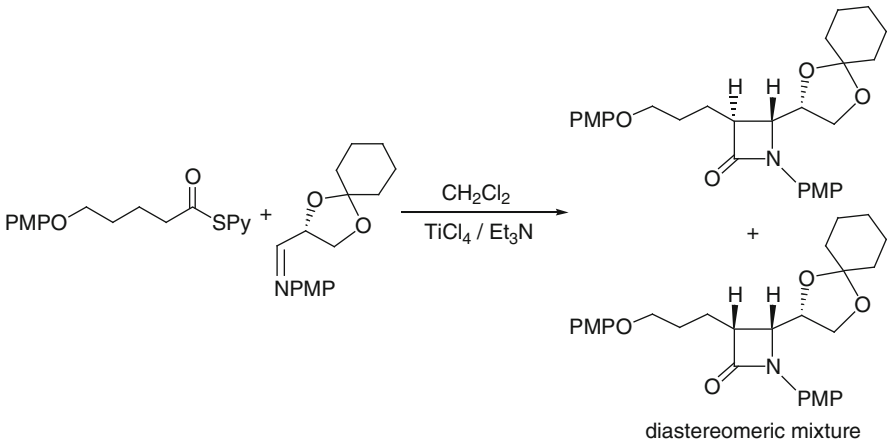
Instead, complexes with chiral chelates of the 2,2′-bipyridine (bpy) ligand could lead to asymmetric induction in the synthesis of chiral β-lactams.

The use of Mukaiyama's salt for the Staudinger reaction in a solid-phase synthesis of β-lactams has been reported to produce the ring construction in a stereoselective manner [82, 83]. The cycloaddition reaction was carried out adding 2,5 equiv. of aryloxylacetic acid and 6 equiv. of triethylamine to a suspension of the resin-bound aldimine in chloroform, followed by 3 equiv. of Mukaiyama's salt and stirring at reflux temperature for 2 h. After cleavage and esterification, β-lactam was obtained in good yield (50–85%), and fairly good stereoselectivity (*cis* > *trans*), (Scheme 22).

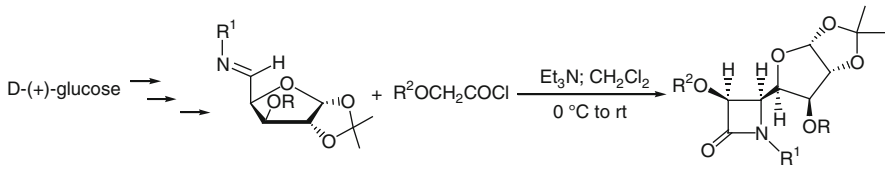
The synthesis of an enantiopure β-lactam as advanced precursor of thrombin and tryptase inhibitor, has been centered on the condensation between *S*-2-pyridylthio 5-(4-methoxyphenoxy)pentanoate and the *N*-4-methoxyphenylimine derived from *O*,*O*-cyclohexylidene D-glyceraldehyde (Scheme 23), [84].

Chiral imines derived from D-(+)-glucose have allowed an asymmetric synthesis of β-lactams by the [2+2] cycloaddition with ketenes [85]. *cis*-β-Lactams were formed with very high diastereoselectivity and the stereochemistry at the C-3 and the C-4 was established as *3S* and *4R* from the known absolute configuration of the sugar moiety (Scheme 24).

The stereochemistry of the Staudinger reaction was highlighted [86] using as substrates polyaromatic imines and acetoxy, phenoxy, or phthalimido acid chloride. The stereochemistry of the resulting β-lactams seemed to vary depending on the substituents present in the imines and the acid chlorides. For instance, if the polyaromatic moiety was linked to the iminic nitrogen, the reaction produced *trans*-β-lactams; if the same moiety was linked to the iminic carbon, *cis*-β-lactams were isolated.



Scheme 23 Synthesis of an enantiopure β-lactam as precursor of thrombin and tryptase inhibitor

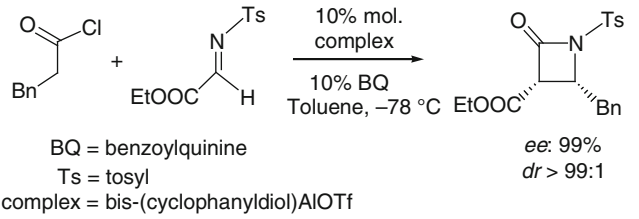


Scheme 24 Asymmetric synthesis of *cis*-β-lactams starting from chiral imines derived from D-(+)-glucose

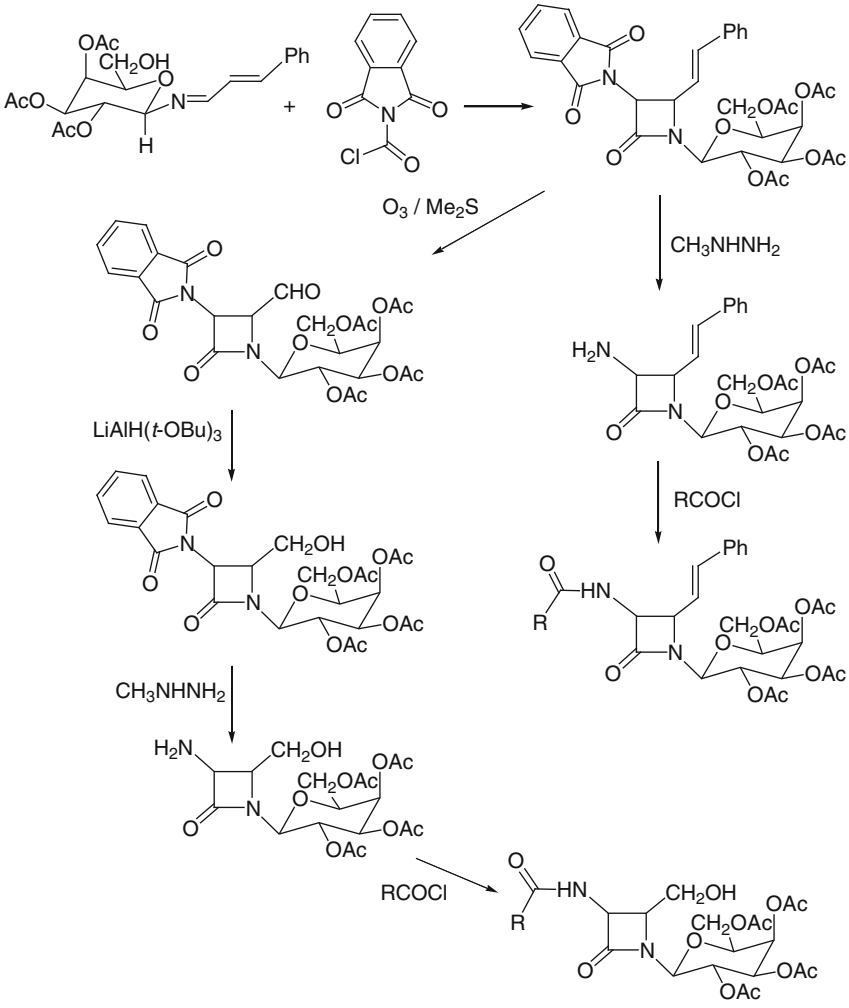
In 2004, bis-(cyclophanyldiol)AlOTf complex has been reported to catalyze the enantio- and diastereoselective synthesis of β-lactams via Staudinger reaction (Scheme 25), [87].

The Staudinger [2+2] cycloaddition of chiral carbohydrate Schiff base with phthalimidoacetyl chloride has yielded the sugar-based monocyclic β-lactam as a single isomer [88]. This latter could be transformed in several β-lactams variously functionalized through ozonolysis, reduction, hydrolysis, and acetylation reactions, (Scheme 26).

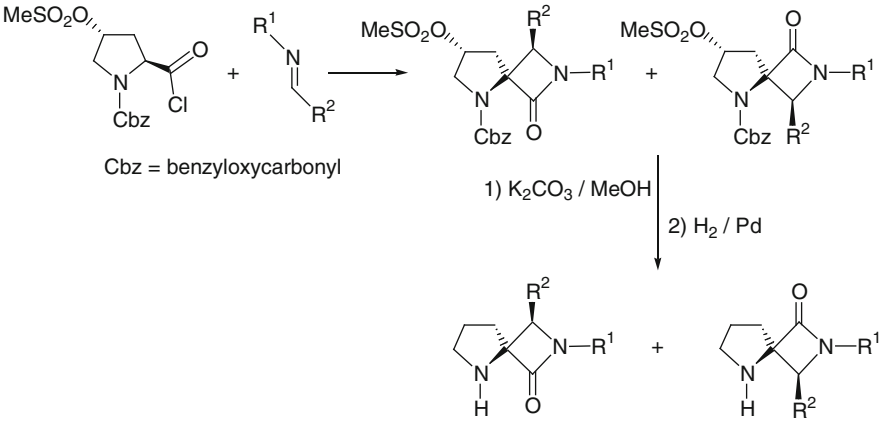
A chiral group at the C-4 of the acid chloride of proline directed the stereoselectivity of Staudinger reaction and later was sacrified to obtain optically active 5,4-spiro-β-lactams [89]. The Staudinger reaction between an in-situ generated ketene, derived from optically active acid chloride, and imines was conducted in CH_2Cl_2 using Et_3N as base at rt (Scheme 27). The chromatography purification of the crude products afforded two diastereomerically pure β-lactams (single enantiomers in each case) in good yields. Proline-derived spiro-β-lactams were obtained eliminating the methansulfonic acid and the *N*-Cbz-group (with K_2CO_3/MeOH), and hydrogenating by Pd.



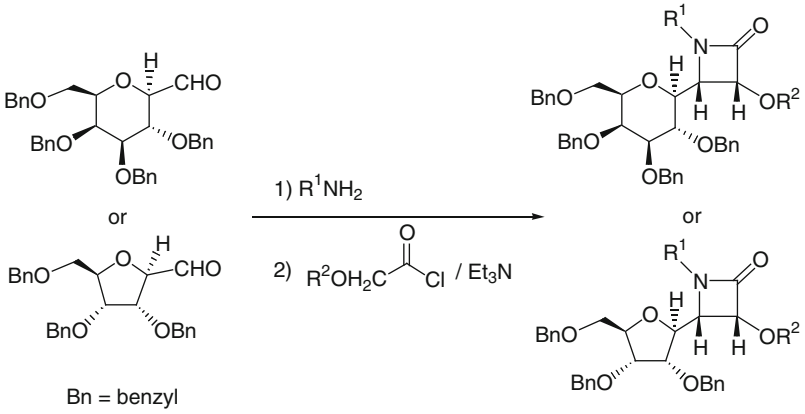
Scheme 25 Catalytic synthesis of β-lactams by a dimeric cyclophane ligand



Scheme 26 Synthesis of sugar-based monocyclic β-lactams by Staudinger [2+2] cycloaddition reaction



Scheme 27 Synthesis of 5,4-spiro-β-lactams by Staudinger reaction

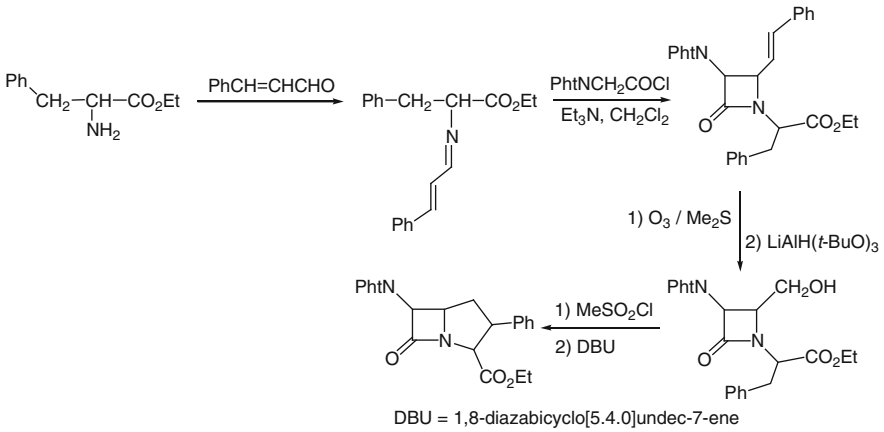


Scheme 28 Synthesis of 4-(*C*-galactosyl)- and 4-(*C*-ribosyl)-β-lactams

A collection of 4-(*C*-galactosyl)- and 4-(*C*-ribosyl)-β-lactams featuring different substituents at C-3 and N-1 has been prepared by combining in a one-pot procedure a formyl *C*-glycoside, a primary amine, and a substituted acetyl chloride in the presence of a base (Scheme 28), [90].

The synthesis of 1,3-disubstituted-4-trichloromethyl azetidin-2-ones by the Staudinger cycloaddition of ketenes with imines derived from chloral has been described to occur with high stereoselectivity [91]. The *cis*-isomer was obtained almost always as the major or the single product.

Reaction of D-phenylalanine ethyl ester with cinnamaldehyde has been reported to give a chiral Schiff base, that underwent an asymmetric Staudinger [2+2] cycloaddition reaction with phthalimidoacetyl chloride to give the monocyclic



Scheme 29 Synthesis of mono- and bicyclic β-lactams starting from D-phenylalanine ethyl ester

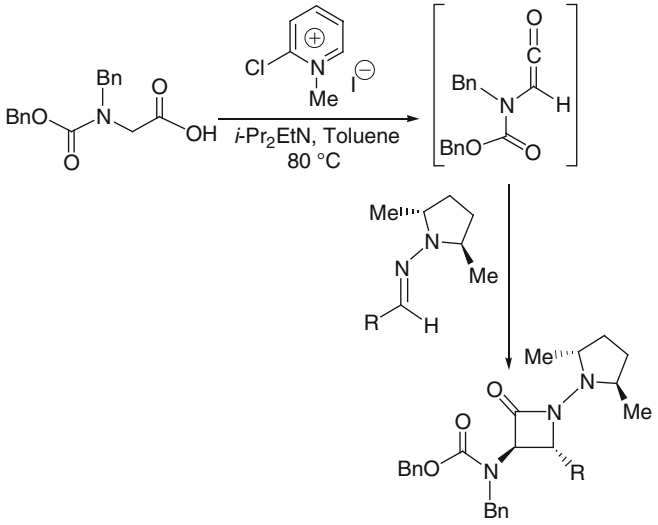
β-lactam as a single stereoisomer. Ozonolysis of this latter followed by reduction with lithium aluminum tri(*tert*-butoxy)hydride has produced the hydroxymethyl-β-lactam, that was converted to the bicyclic β-lactam upon treatment with metansulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), (Scheme 29), [92].

α-Amino-β-lactams have been reported to be prepared via Staudinger-like [2+2] cycloaddition of *N*,*N*-dialkylhydrazones to α-aminoketenes [93]. The reaction was stereoselective leading to *trans*-3-amino-4-alkylazetidin-2-ones as single diastereomers (Scheme 30).

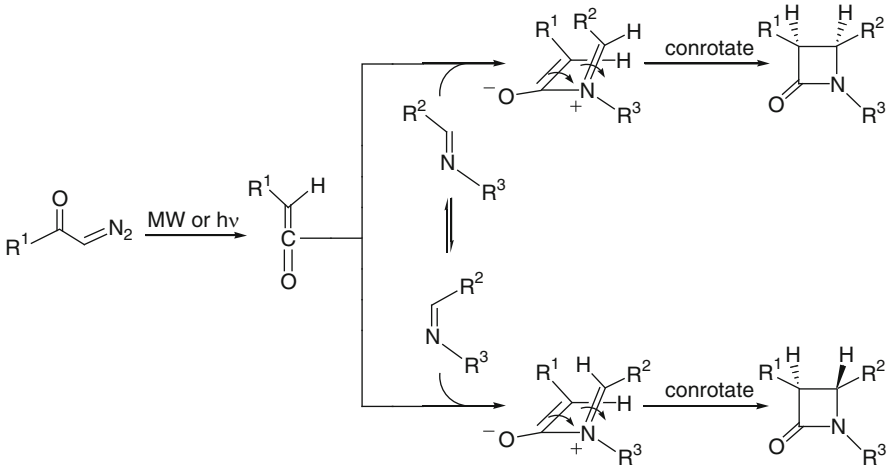
A solid-phase strategy for the synthesis of *trans* 3-alkyl β-lactams has been reported to start from 9-fluorenylmethoxycarbonyl(Fmoc)-glycine thethered to Wang resin [94]. The amine group was deprotected by treatment with 30% piperidine in *N*,*N*-dimethylformamide (DMF) and condensed with *p*-anisaldehyde in 1% acetic acid in DMF to give the corresponding aldimine. The subsequent [2+2] cycloaddition between the in situ generated ketene and the imine has produced the β-lactamic product. The resin cleavage followed by the esterification afforded the β-lactam as a single product with excellent *trans* selectivity.

Benzodiazepines [95, 96] and triethylamine in CH_2Cl_2 treated with acetoxyacetyl chloride or phthalimidoacetyl chloride at 0°C afforded exclusively the β-lactam-fused 1,4-benzodiazepines [97]. In all the cases studied, the reaction provided the final tricyclic systems in very good yields. A high level of diastereoselectivity was achieved and the final products were isolated as single diastereomers, with a *cis* relationship between the aryl group from the benzodiazepine and the substituent of the ketene.

In 2005, reactions of ketenes generated from α-diazoketones with acyclic and cyclic imines have been investigated under both microwave and photoirradiation conditions [98]. The reported results indicated that the zwitterionic



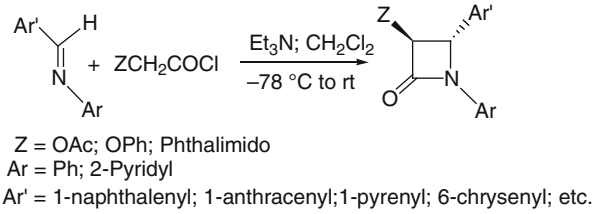
Scheme 30 Stereoselective synthesis of *trans* 3-amino-4-alkylazetidin-2-ones



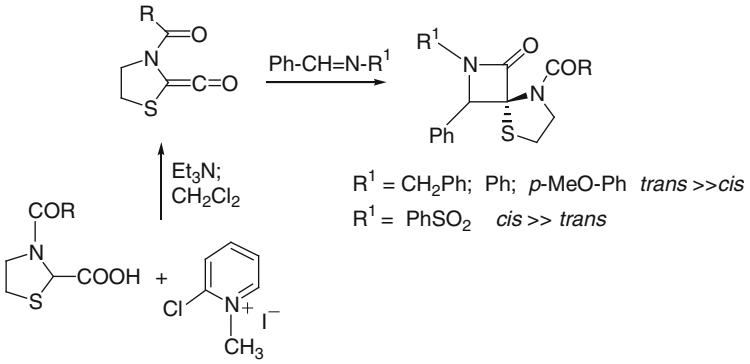
Scheme 31 Mechanism of the Staudinger reaction starting from ketenes generated from α-diazoketones under microwave and photoirradiation conditions

azabutadiene-type intermediates yielded from imines and ketenes underwent a conrotatory ring closure to produce exclusively β-lactams (Scheme 31).

β-Lactams with polyaromatic substituents at C-4 have been reported to be synthesized, via Staudinger reaction [99]. The reaction of polyaromatic imines with acetoxy, phenoxy and phthalimido acid chloride in the presence of triethylamine at



Scheme 32 Synthesis by microwave irradiation of β-lactams having polyaromatic substituents at the C-4 position



Scheme 33 Synthesis of spiro-β-lactams by [2+2] cycloaddition reaction

–78°C to rt produced exclusively *trans*-β-lactams in good yields, (Scheme 32). The domestic microwave irradiation on this type of substrates was utilized with good success. The effect of a *peri* hydrogen was found to be significant in controlling the stereochemistry of the resulting β-lactams.

Spiro-β-lactams have been synthesized via [2+2] cycloaddition of cyclic ketenes with imines [100]. Opposite *trans* or *cis* diastereoselectivity was obtained using different imines with electron-donating or electron-withdrawing (R^1) substituents at the N-atom, (Scheme 33).

The cyclic ketenes were generated from *N*-acyl-1,3-thiazolidine-2-carboxylic acids by means of Mukaiyama's reagent. The same reaction generated enantiomerically pure 1,3-thiazolidine-derived spiro-β-lactams, using optically active *N-tert*-butoxycarbonyl-1,3-thiazolidine-2-carboxylic acid derivatives as precursors of the asymmetrical chiral cyclic ketenes (*tert*-butoxycarbonyl: Boc) [101].

A comprehensive study on the solid-phase synthesis of β-lactam compounds has been reported [102]. In situ generated ketenes reacted with aldimines, immobilized on commercially available solid supports, under mild conditions to generate libraries of β-lactams in good to very good overall isolated yields. Different β-lactam derivatives with various substituents at the C-3 and the C-4 position

were obtained. The utility of this protocol was also demonstrated by highlighting efficient asymmetric versions when homochiral ketenes or homochiral aldimines were used.

The Staudinger reaction, catalyzed by 4-(pyrrolidino)pyridine derivative, could be controlled through the appropriate choice of the *N*-protecting group of the imine [103]. Thus, ketenes coupled with *N*-tosyl imines predominantly generated *cis*-β-lactams, whereas reactions with *N*-triflyl imines preferentially furnished *trans* isomers.

A combined theoretical and experimental study has been reported for the formation of silylated β-lactams, via Staudinger [2+2] cycloaddition reaction from silylketenes and imines, in the presence or in the absence of a Lewis acid [104].

The experimental study was carried out with two different imines: a standard one, *n*-hesanaldimine, and an electron-poor one, *n*-butyl glyoxylate imine. The Scheme 34 shows that the formation of the β-lactam occurred only when the glyoxylate imime and BF_3-Et_2O reacted with (trimethylsilyl)ketene.

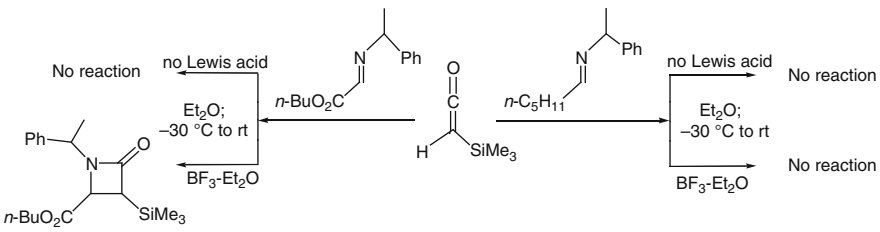
The β-lactam was formed in fair yield and in a 60:15:15:10 (*cis:cis:trans:trans*) mixture of four diastereoisomers.

In order to investigate the mechanism of the Staudinger reactions studied experimentally, the energy profiles for the formation of the *cis* and *trans* β-lactams were calculated. Theoretical results suggested that the reaction would proceed most favorably with the BF_3 catalyst coordinated to the ketene.

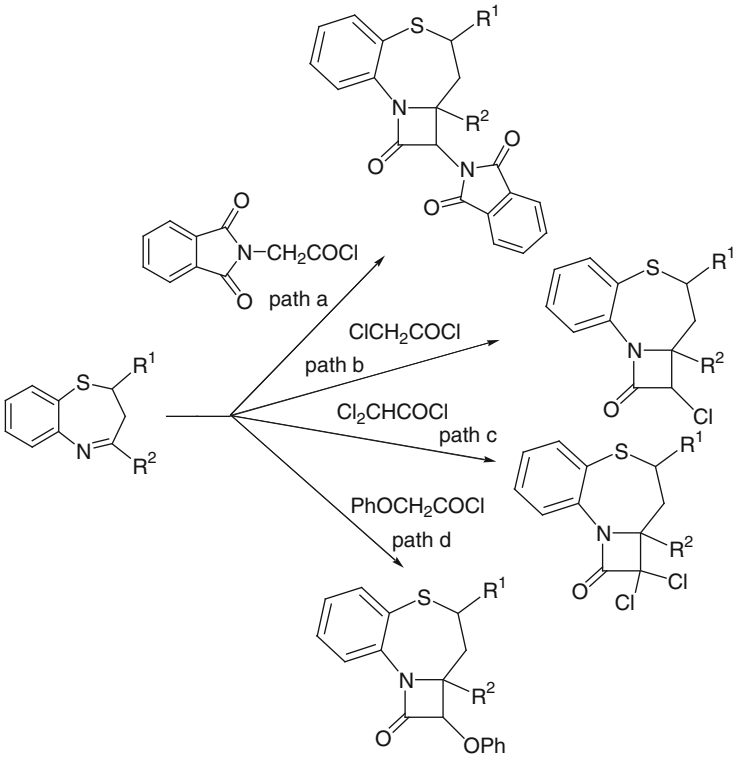
Treatment of imines with ethyl bromodifluoroacetate and Et_2Zn, in the presence of $RhCl(PPh_3)_3$ in anhydrous medium, has been reported to give via Reformasky-type reaction difluoro-β-lactams and 3-amino-2,2-difluorocarboxylic esters, [105]. Different product ratios were observed changing the reaction conditions (solvent, reaction time, addition of $MgSO_4$).

A benzothiazepine-fused β-lactam library has been reported to be obtained [106] via Staudinger cycloaddition of 2,3- dihydro-1,5-benzothiazepines and various acyl chlorides such as phthalimidoacetyl chloride (path a, Scheme 35), chloroacetyl chloride (path b, Scheme 35), dichloroacetyl chloride (path c, Scheme 35), and phenoxyacetyl chloride (path d, Scheme 35).

The Schiff base obtained by (*S*)-(−)-tyrosine ethyl ester hydrochloride with 2-hydroxybenzaldehyde has been reported to be transformed, via Staudinger



Scheme 34 Synthesis of silylated-β-lactams via Staudinger [2+2] cycloaddition reaction



Scheme 35 Synthesis of benzodiazepine-fused β-lactam library

reaction, into the chiral monocyclic β-lactam by treatment with achiral ketene prepared in situ from phthaloylglycyl chloride and triethylamine [107].

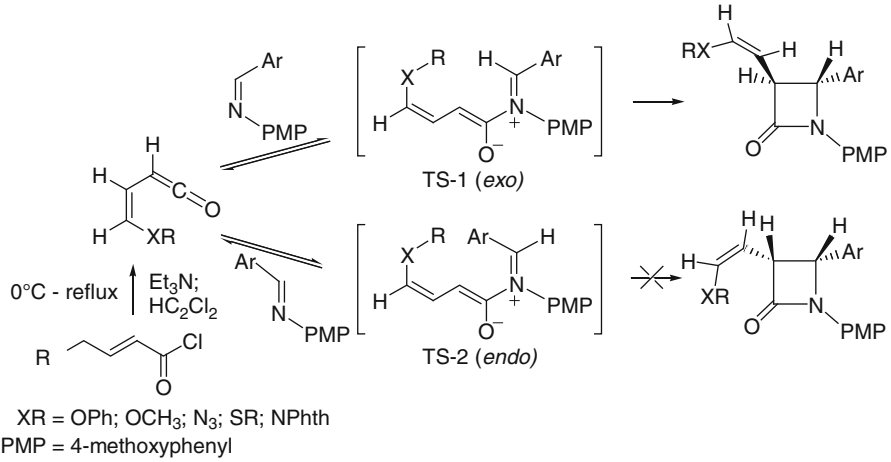
Ketene-imine cycloaddition reactions of ethoxycarbonyl(phenylthio)ketene with various imines and subsequent desulfurization reactions have been reported in 2006 to synthesize 3-ethoxycarbonyl β-lactam derivatives [108].

The stereoselective synthesis of bis-β-lactams grafted macrocycles has been described [109]. Macrocyclic imine and phenoxy acetyl chloride in the presence of triethylamine produced a diastereomeric mixture of *cis* macrocyclic bis-β-lactams (Scheme 36) by the Staudinger reaction.

trans-β-Lactams have been reported to be regioselectively synthesized by [2+2] Staudinger cycloaddition reactions of imine such as (3,4-dimethoxybenzylidene)-(4-methoxyphenyl)-amine and ketenes derived from different acyl chlorides and triethylamine [110].

trans-β-Lactams have also been obtained by the Staudinger reaction carried out between divinylimine and *N*-acylimidazoles possessing an electron-withdrawing group (EWG) in α position [111]. This latter were prepared by treatment of α-EWG substituted carboxylic acids with 1,1-carbonyldiimidazole.

Scheme 36 Stereoselective synthesis of *cis* macrocyclic bis-β-lactams



Scheme 37 Plausible mechanism for the formation of *trans*-β-lactams

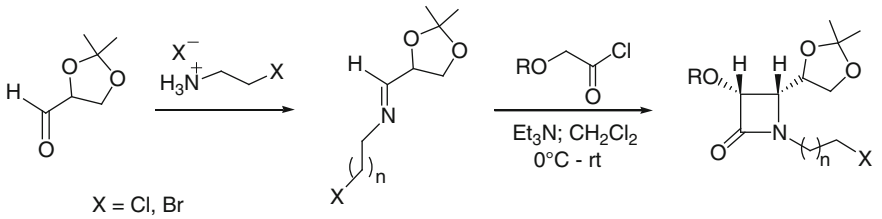
A stereocontrolled Staudinger cycloaddition reaction has been reported to be performed on vinylketenes, possessing a γ-heteroatom, and imines to produce *trans*-vinyl-β-lactams [112]. The vinyl side chain adopted stereoselectively the *(Z)* configuration in the transition state, stabilizing the vinyl ketene and leading, exclusively, to the *trans*-3-vinyl-β-lactam (Scheme 37).

The *(Z)* configuration, adopted by the RX-vinyl groups, was explained by the authors via participation of the γ-heteroatom ion pair of electrons. Although, the *(E)*-imine is more stable compared to the corresponding *(Z)*-imine, it is less reactive due to the severe steric interaction between the RX group and the aryl group of the imine in the transition state TS-2. This steric interaction is absent in TS-1 that arose from the *exo* attack of the *(Z)*-imine on the vinylketene. Therefore, TS-1 was preferentially formed, which by conrotatory ring closure gave *trans*-β-lactams.

Chiral imines have been prepared by reacting *(R)*-glyceraldehyde acetonide with different ω-haloalkylammonium halides. Treatment of the latter with 1.3 equiv. of benzyloxy-, phenoxy- or methoxy acetyl chloride in dichloromethane, in the presence of triethylamine afforded the optically active corresponding β-lactams (Scheme 38) in high yield and high diastereomeric excess [113].

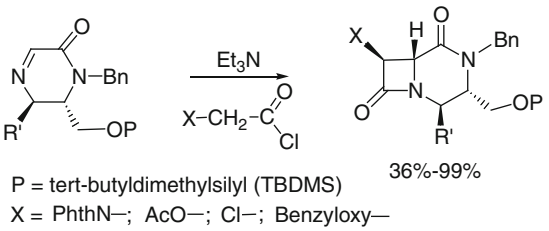
The Staudinger reaction between enantiopure 5,6-dihydropyrazin-2-(*1H*)-ones and an excess of 2-heterosubstituted acetylchloride in the presence of triethylamine in dichloromethane at room temperature has been reported to produce in excellent yield and high diastereoselectivity fused oxopiperazino-β-lactams (Scheme 39), [114].

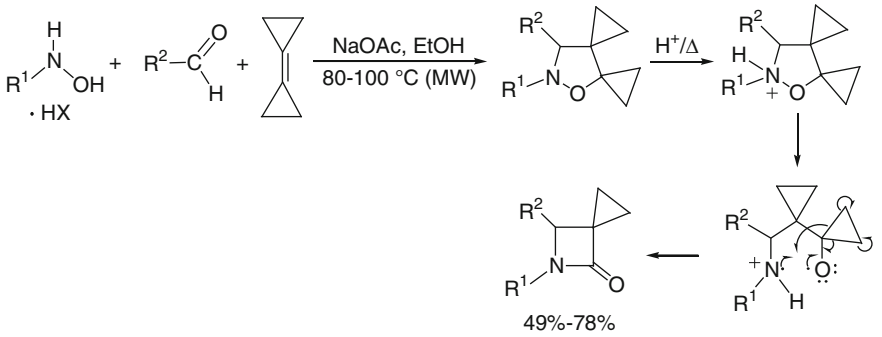
3-Spirocyclopropanated β-lactams have been prepared by a three-component cascade reaction [115]. A mixture of alkylhydroxylamine hydrochlorides, aldehydes, and bicyclopropylidene, under microwave heating in ethanol as solvent, furnished 3-spirocyclopropanated 2-azetidinones with good yields (Scheme 40).



Scheme 38 Preparation of optically active β-lactams by the Staudinger reaction

Scheme 39 Synthesis of fused oxopiperazino-β-lactams by the Staudinger reaction

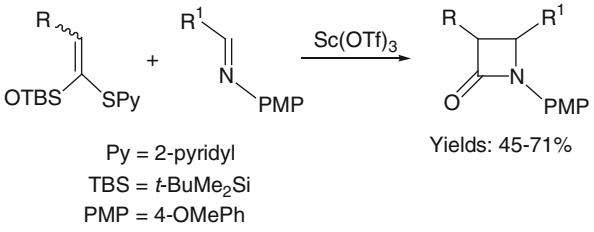




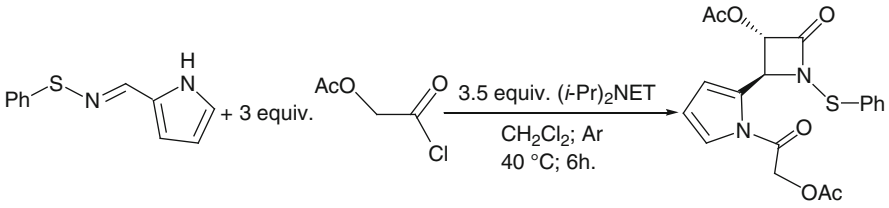
Scheme 40 Synthesis of 3-spirocyclopropanated 2-azetidinones by a cascade three-component reaction

cis/*trans* Mixture of β-lactams have been obtained in 2007, by a new protocol involving a catalytic, one-pot reaction carried out in the absence of solvent [115, 116]. The Scandium (III) triflate catalyzed, at room temperature the condensation between silyl ketene thioacetals, readily obtained from 2-pyridyl thioesters, and imines in fair to good yields (45–71%), (Scheme 41). This procedure could be applied also to the stereoselective synthesis of enantiomerically pure azetidinones.

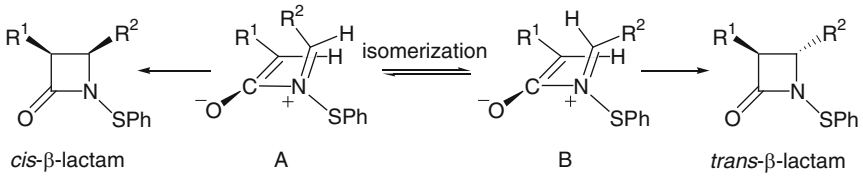
Disubstituted β-lactams have been obtained with high *trans* diastereoselection in the reaction between *N*-phenylsulfenylimines, as nucleophilic partners in the Staudinger reaction, and acetoxyacetyl chloride (Scheme 42), [117].



Scheme 41 Synthesis of β-lactams by catalytic one-pot reaction



Scheme 42 Reaction between *N*-sulfenylimine and acetoxyacetyl chloride affording disubstituted β-lactams



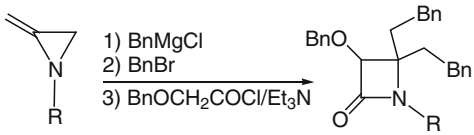
Scheme 43 Model for the relative stereoselectivity in the Staudinger reaction

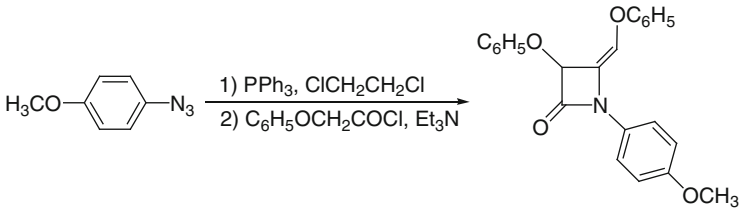
The comparison of these results with those observed for the cycloaddition of alkoxyketene [118] suggested an *exo* approach of the ketene for the formation of the zwitterionic intermediate A (Scheme 43), that might directly affect ring closing to afford *cis* products. Alternatively, A might undergo a C=N bond isomerization to B prior to ring closing thus affording *trans* products.

The use of less electron-releasing acetoxy substituent reduced the direct ring closure rate sufficiently to allow a complete C=N isomerization, thus affording pure *trans* products.

β-Lactams have been obtained in 2008, by treatment of methyleneaziridines in THF with BnMgCl and CuI inducing ring opening of the aziridine at the C-3 to generate the metalloenamine, which was alkylated with BnBr. Subsequent addition of glacial acetic acid and then (benzyloxy)ketene (generated from $BnOCH_2COCl$ and Et_3N) yielded β-lactam (Scheme 44), [119].

Scheme 44 Synthesis of substituted β-lactams by four-component reaction





Scheme 45 Synthesis of 4-phenoxymethylene-β-lactam from (4-methyloxyphenyl)azides and phenoxyacetyl chloride

1-nosyl 3,3-dichloro-β-lactams were reported to be prepared using the Staudinger reaction between *N*-nosyl imines and dichloroketene [120].

N-Heterocyclic carbenes were demonstrated to be efficient catalysts for the Staudinger reaction of ketenes with *N*-aryl-, *N*-alkylcarbonyl imines [121]. Chiral *N*-heterocyclic carbenes gave the corresponding *cis*-β-lactams in good yields with good diastereoselectivities and excellent enantioselectivities (*ee*>99%).

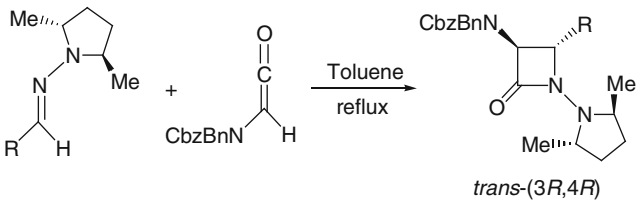
A one-pot cascade approach to 4-alkylidene-β-lactams from aryl azides and aryloxyacetyl chlorides has been reported. (4-Methyloxyphenyl)azides reacted with triphenylphosphine in 1,2-dichloroethane to form triphenylphosphazene, which was treated with phenoxyacetyl chloride and Et_3N to afford 4-phenoxymethylene-β-lactam (Scheme 45), [122].

The synthesis of 4-aryl-3-(3-chloropropyl)azetidin-2-ones was reported to be performed by means of a Staudinger reaction between arylmethylideneamines and 5-chloropentanoyl chloride in the presence of 2,6-lutidine [123].

The [2+2] cycloaddition of aliphatic hydrazones derived from (2*R*,5*R*)-1-amino-2,5-dimethylpyrrolidine to *N*-benzyl-*N*-(benzyloxycarbonyl)aminoketene was reported to take place affording the corresponding β-lactams in good yields when $i\text{Pr}_2\text{EtN}$ was used as the base (Scheme 46), [124].

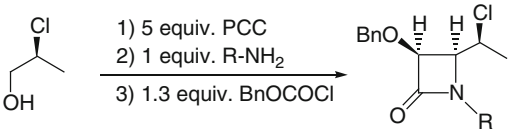
The reaction proceeded in all cases with excellent stereocontrol to afford exclusively products having the (3*R*) configuration. Temperature was observed to exert a strong influence on the *cis*/*trans* selectivity, allowing the obtention of single *trans* or *cis* cycloadducts in most cases, simply by performing the reactions at 80°C or room temperature, respectively.

A new and efficient one-pot approach towards chiral 2-azetidinones has been reported to start from (2*S*)-chloro-1-propanol. The treatment of this latter with 5 equivalents of pyridinium chlorochromate in dichloromethane at room temperature afforded the (2*S*)-chloropropanal which treated with 1 equivalent of amine and 1.5 equivalents of $MgSO_4$ yielded the (*S*)-*N*-(2-chloropropylidene)amines. Finally,



Scheme 46 Synthesis of 3-amino-4-alkyl-2-azetidinones by [2+2] cycloaddion of aliphatic hydrazones to *N*-benzyl-*N*-(benzyloxycarbonyl)aminoketene

Scheme 47 One-pot synthesis of chiral 4-(1-chloroethyl)-β-lactams from (2 *S*)-chloro-1-propanol

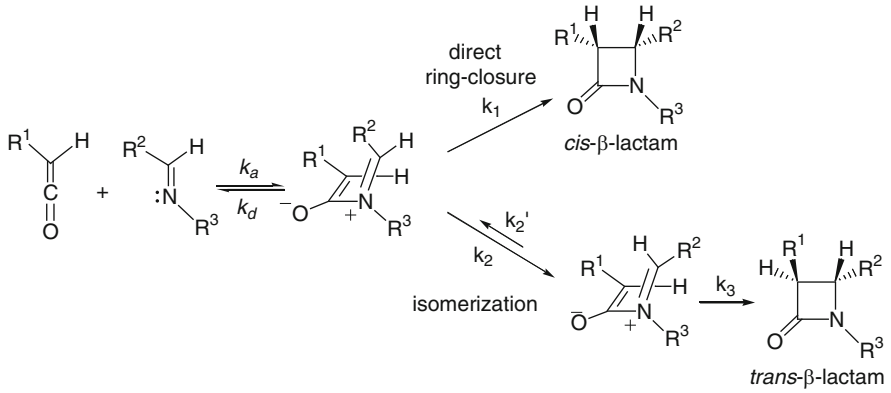


treating the chloropropylideneamines with 1.3 equivalents of benzyloxyacetyl chloride, under Staudinger conditions, gave the corresponding β-lactams (Scheme 47), [125].

Although many attempts have been made to explain the Staudinger reaction, the nature of the relative stereoselectivity remains obscure. Several investigators have suggested different models to predict the stereoselectivity, but their proposals were in conflict to some extent [126–131]. An interesting contribution to the interpretation of the stereoselectivity in the β-lactam formation was done by Xu and coworkers [118]. They proposed a model based on a kinetic analysis of the *cis*/*trans* ratios of reaction product. Based on their results the origin of the relative stereoselectivity can be described as follows: a) the stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerization of the imine moiety in the zwitterionic intermediate; b) the ring closure step is most likely an intramolecular nucleophilic addition of the enolate to the imine moiety, that is obviously affected by the electronic effect of the ketene and the imine substituents; c) electron-donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ring closure, leading to a preference for *cis*-β-lactam formation, while electron-withdrawing ketene substituents and electron-donating imine substituents (EDG) slow the direct ring closure, leading to a preference for *trans*-β-lactam formation; d) the electronic effects of the substituents on the isomerization is a minor factor influencing the stereoselectivity (Scheme 48 and Fig. 2).

4.1.2 Gilman–Speeter Reaction

In a micro-review the group of Benaglia [132] reported in 2000 that *S*-thioesters could be used as versatile reagents for the efficient preparation of a variety of



Scheme 48 Suggested model for the relative stereoselectivity in the Staudinger reaction

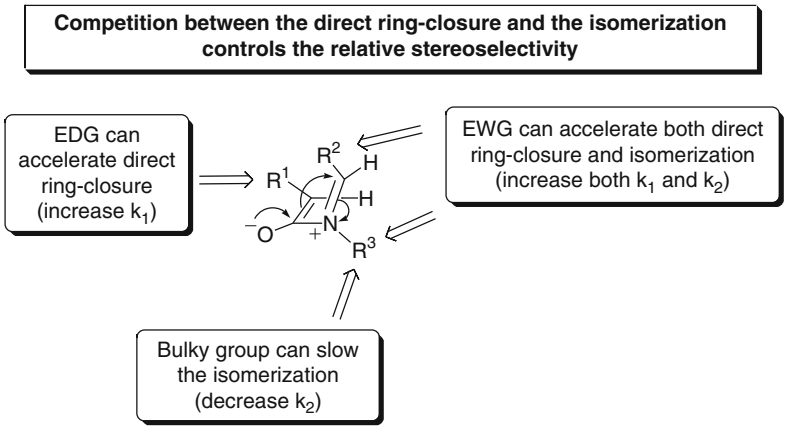
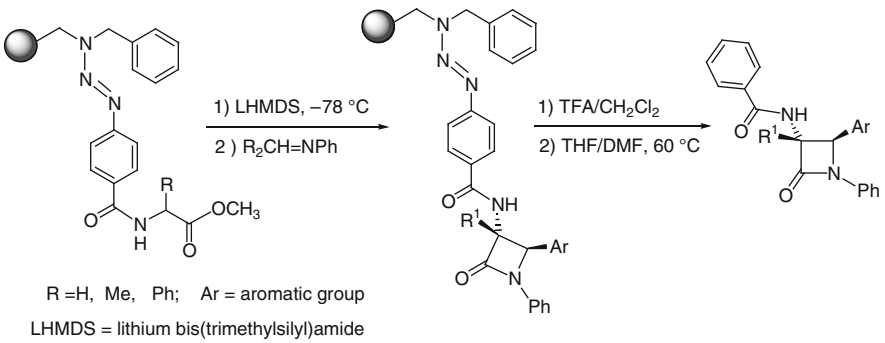


Fig. 2

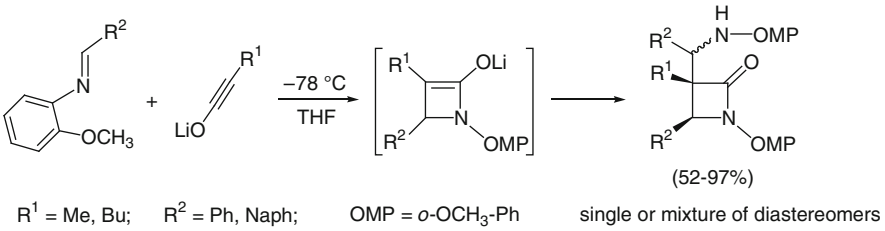
β-lactams by the enolate/imine condensation reaction. The stereocontrol was provided by the stereocenter on the *S*-thioester or by the one on the imine nitrogen. Notwithstanding the numerous attempts made, varying also the cyclization conditions, it appeared very difficult to predict the *trans/cis* stereoselectivity as many different factors could concur in determining the stereochemical results.

The condensation reaction of immobilized ester enolates with imines has been reported to give β-lactam resins in good yields and high diastereomeric excess (Scheme 49), [133]. Traceless cleavage from the linker system yielded the desired β-lactams.

The cycloaddition of the *N*-2-methoxyphenyl aldimines with lithium ynolates (for a review see [134]) has been reported to give β-lactams enolates, that



Scheme 49 Solid-phase synthesis of β-lactams via ester enolate-imine condensation



Scheme 50 Cycloaddition of ynolates with *N*-2-methoxyphenyl imines affording β-lactams

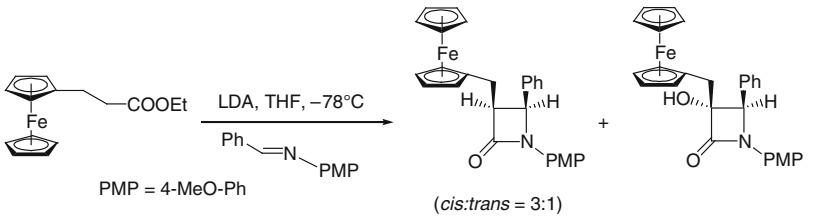
reacted with one more equivalent of the imine to give β-lactams in good yields (Scheme 50), [135].

For activating the cyclization reaction a strategic role was played by the 2-position of the methoxy group linked to the imine and the R^2 substituent should not be bulky. For instance, when the methoxy moiety was in 4-position and R^2 = *tert*-butyl, the reaction proceeded very slowly or did not afford the desired product.

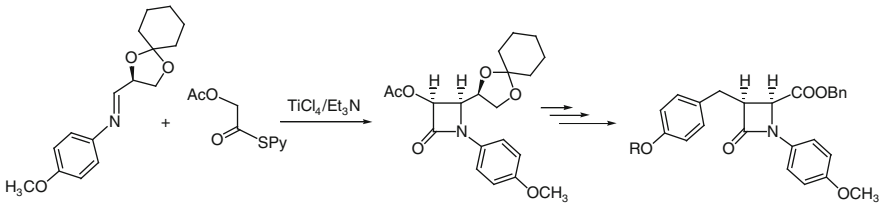
In 2001, Sierra and coworkers have reported that ethyl 3-ferrocenylpropanoate reacting with an excess of lithium diisopropylamide (LDA) afforded an enolate that condensed with imine: the resulting reaction mixture contained the expected 2-azetidinone as a *cis*/*trans* mixture (3:1), and the unexpected 3-hydroxy β-lactam [136]. The ferrocene moiety was linked to the β-lactam ring at the C-3 position, (Scheme 51).

In 2002, the condensation of the titanium enolate derived from 2-pyridylthio acetoxyacetate with *N*-4-methoxyphenylimine of (*S*)-*O*,*O*-cyclohexylidene protected glyceraldehyde has been reported to give (3*S*,4*R*,4′*R*)-β-lactam as a single product in 65% isolated yield (Scheme 52), [137]. A reactions sequence at C-3 and C-4 led in good yield to the β-lactam inhibitor of the serine protease prostate-specific antigen.

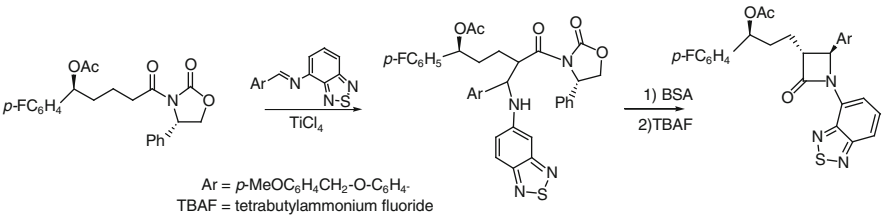
The condensation of chiral furaldimines with lithium esther enolates has been reported as an efficient route to chiral furyl β-lactams [138]. The (4*R*)-β-lactam was formed with high diastereoselectivity.



Scheme 51 Synthesis of C-3 ferrocene-substituted 2-azetidinones



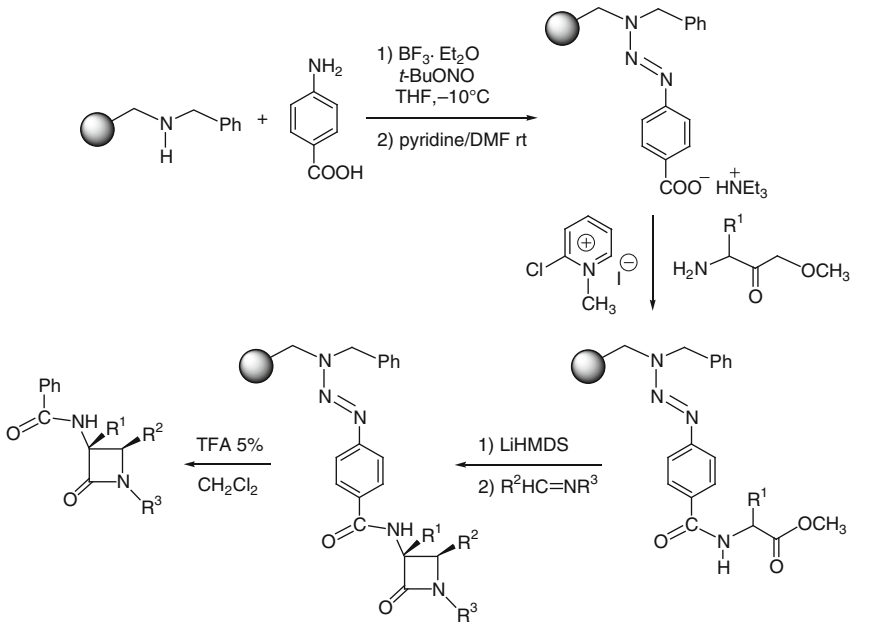
Scheme 52 Stereoselective synthesis of β-lactam inhibitor of the serine protease prostate-specific antigen



Scheme 53 Synthesis of enantiomerically pure β-lactams

The synthesis of β-lactams enantiomerically pure, via a multistep Gilman-Speeter type reaction [139] has been reported to be carried out with chiral oxazolidinones [140]. Titanium tetrachloride mediated condensation with imine gave an intermediate β-amino acyloxazolidinone, the major diastereomer of which could readily be purified by SiO_2 chromatography. Silylation and fluoride catalyzed cyclization gave the final β-lactam (Scheme 53).

The synthesis of monocyclic β-lactams via the ester-enolate imine condensation route has been reported to be carried out utilizing triazene esters (Scheme 54), [141]. Esters were attached to benzylamine resin by a triazene linker employing the respective diazonium salts. Immobilized ester-enolates were reacted with various imines to give polymer-bound β-lactams in different substitution patterns. Traceless cleavage from the triazene linker yielded the desired β-lactams.



Scheme 54 Solid phase synthesis of monocyclic β-lactam derivatives

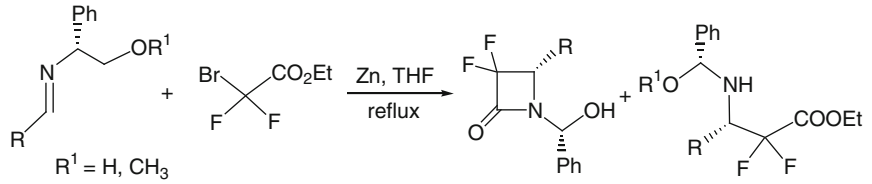
Iridium-catalyzed reductive coupling of acrilates and imines has been reported to provide *trans* β-lactams with high diastereoselection [142]. The use of electron-deficient aryl acrylates resulted in improved product yields. The mechanism, proposed by the authors, started from an in situ generated iridium hydride reacting with the acrilate to provide an iridium enolate that, then, reacted with the imine to give a β-amido ester. Subsequent cyclization furnished the β-lactam and an iridium alcoxide.

In 2007, Boyer and coworkers developed a complete study of the parameters that can influence the selective synthesis of β-lactam or β-aminoester during Reformatsky reaction between ethyl bromodifluoroacetate and various imines. It clearly appeared that by modifying the nature of the amine or the reaction conditions, it was always possible to inverse the β-aminoester/β-lactam ratio (Scheme 55).

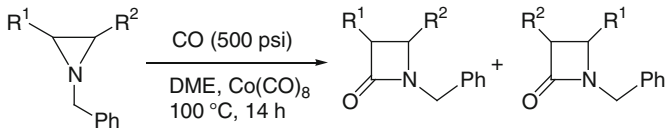
Moreover, high levels of stereoselectivity were obtained for *gem*-difluoro-β-aminoesters and *gem*-difluoro-β-lactams using either (*R*)-phenylglycinol or (*R*)-methoxyphenylglycinol [143].

4.1.3 Alper Reaction

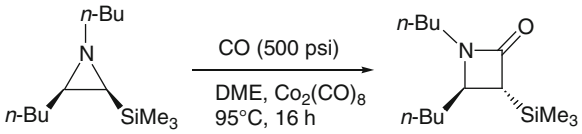
The ring expansion of aziridines has been reported in 2001 as a well established protocol [144] for preparing β-lactams in a regioselective manner [145]. A variety of aziridines with different substituents and stereochemistry was subjected to cobalt carbonyl-catalyzed carbonylation to give β-lactams. The ring expansion to



Scheme 55 Synthesis of *gem*-difluoro-β-aminoesters and *gem*-difluoro-β-lactams from ethyl bromodifluoroacetate



Scheme 56 Regioselective synthesis of β-lactams by cobalt-catalyzed ring expansion of aziridines



Scheme 57 Conversion of *cis* aziridines to *trans* β-lactams

β-lactams took place in the absence of an electron-withdrawing substituent and higher yields were always obtained for *cis*-aziridines, (Scheme 56). The regioselectivity of the reaction and then the β-lactam ratios, were affected by the nature of the substituents at the ring carbon atoms.

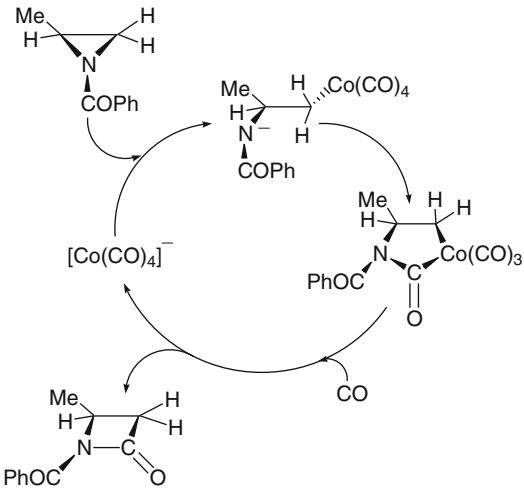
A complete regioselectivity has been observed in 2002 in the carbonylative ring expansion of aziridines trimethylsilylsubstituted, using $Co_2(CO)_8$ as catalyst to give β-lactams (Scheme 57), [146].

[Lewis acid]$^+$[$Co(CO)_4$]$^-$ complexes have been reported as a versatile class of catalysts for carbonylative ring expansion of aziridines to β-lactams [147]. For instance, catalysts such as [$C_5H_5Ti(thf)_2$][$Co(CO)_4$] and [(salph)$Al(thf)_2$][$Co(CO)_4$][1] [148] have been shown to efficiently carbonylate a variety of aziridines under mild conditions. Further, the authors proposed a mechanism for the CO insertion into aziridines. A theoretical investigation has been also reported for the [$Co(CO)_4$]$^-$-catalyzed carbonylative ring expansion of *N*-benzoyl-2-methylaziridine to β-lactams (Scheme 58), [149].

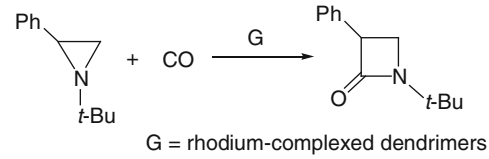
Rhodium-complexed dendrimers, supported on a resin, have been reported to show high activity for the carbonylative ring expansion of aziridines with carbon monoxide to give β-lactams (Scheme 59), [150].

[1] Salph = *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)phenylenediamine.

Scheme 58 Proposed catalytic cycle for aziridine carbonylation



Scheme 59 Carbonylative ring expansion of aziridines with rhodium-complexed dendrimers



Theoretical studies have also been reported on the catalytic activity of the rhodium (I) in the carbonylative ring expansion of aziridines to β-lactams [151].

4.1.4 Mitsunobu Reaction

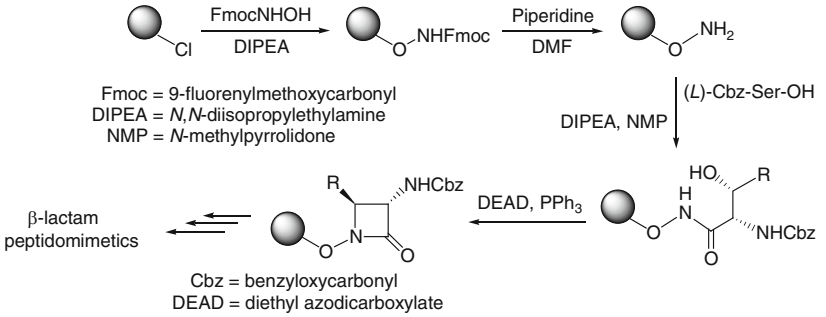
β-Lactams have been reported in 2001 to be prepared on solid phase starting from serine, threonine, or other β-hydroxyacids derived from naturally occurring amino acids and a resin bound hydroxylamine [152]. The ring closure was carried out under Mitsunobu conditions, (Scheme 60).

In 2005, α-benzylserine derivative [153] was reported to be converted into the β-lactone using PPh_3 and diethyl azodicarboxylate, giving an aza-peptide, which was then subjected to Mitsunobu conditions to afford the 3-benzyl-β-lactam azapeptidomimetic (Scheme 61), [154].

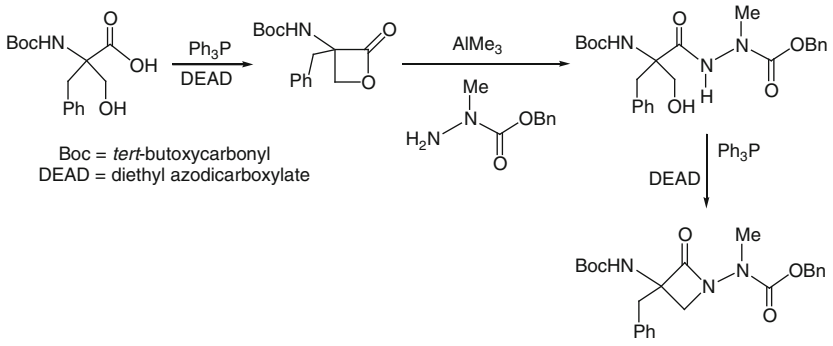
N-Benzyloxy-4-aryl-3-*(S)*-hydroxybutanamide gave ring closure to β-lactam, via Mitsunobu reaction [155].

4.1.5 Kinugasa Reaction

In 2002, the coupling of alkynes with nitrones catalyzed by Cu(I)/bis(aza-ferrocene) has been reported to produce β-lactams enantioselectively [156]. The generation of



Scheme 60 Solid phase synthesis of β-lactams under Mitsunobu conditions



Scheme 61 Synthesis of 3-benzyl-β-lactam azapeptidomimetic

the β-lactam proceeded with excellent *cis* diastereoselectivity irrespective of the nature of the substituents linked to the alkynes or the nitrones (Scheme 62).

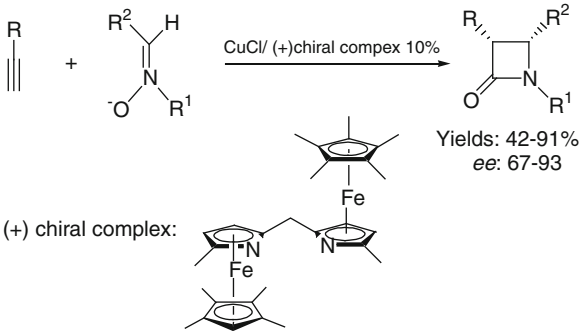
In 2005, the Kinugasa reaction performed on *N*-propargyl nucleobases, such as adenine, uracil, and thymine derivatives, with diphenyl nitrone has been reported to produce *cis*- and *trans*-β-lactam nucleosides (Scheme 63), [157].

The 3-*exo*-methylene β-lactam was isolated only using the di-Boc protected adenine as substrate.

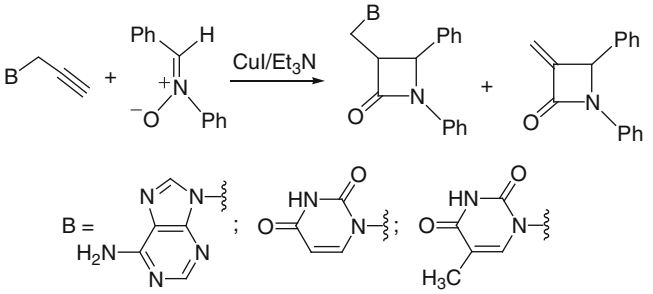
The ynamide-Kinugasa reaction has been used for the highly stereoselective synthesis of chiral α-amino-β-lactams. The application of this reaction consists in the preparation of chiral α-amino-2-azetidinones starting from chiral ynamide (Scheme 64), [158].

4.1.6 Torii Reaction

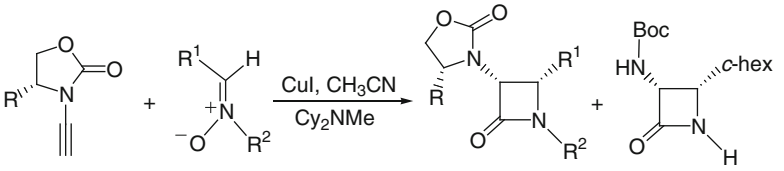
In 2004, Troisi and coworkers have reported the palladium-catalyzed [2+2] carbonylative cycloaddition of imines to allyl halides of different structures to give β-lactams (Scheme 65), [159].



Scheme 62 Enantioselective catalyzed synthesis of *cis* β-lactams



Scheme 63 Synthesis of β-lactam nucleosides via Kinugasa reaction

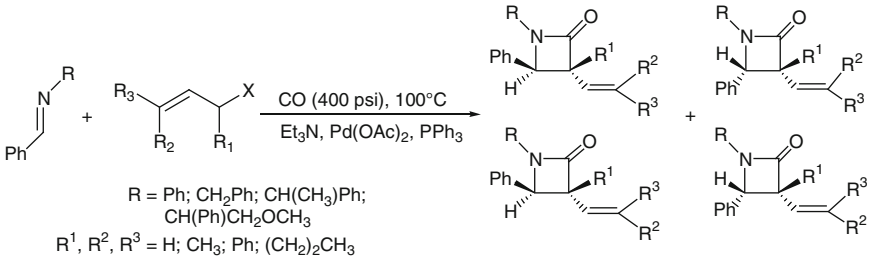


Scheme 64 Synthesis of α-amino-β-lactams via ynamide-Kinugasa reaction

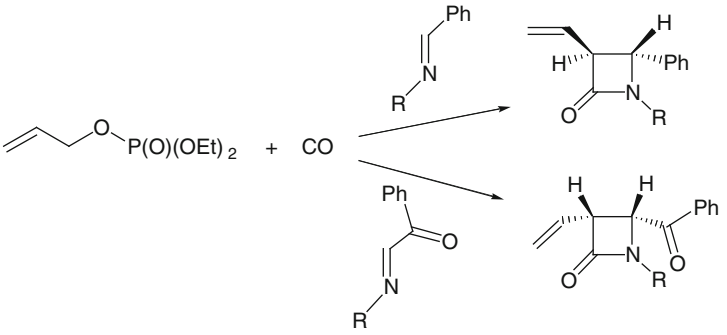
The carbonylative [2+2] cycloaddition was performed also on chiral imines with allyl halides affording β-lactams with good stereoselectivity [160].

These results were obtained by performing the reactions in slightly different conditions than those used by Torii and coworkers. For instance, they reported the palladium-catalyzed cyclocarbonylation of allyl phosphate with imines in a stereoselective manner, depending on the imine used for the coupling, (Scheme 66), but they could not obtain any reaction product starting from allyl halides [161].

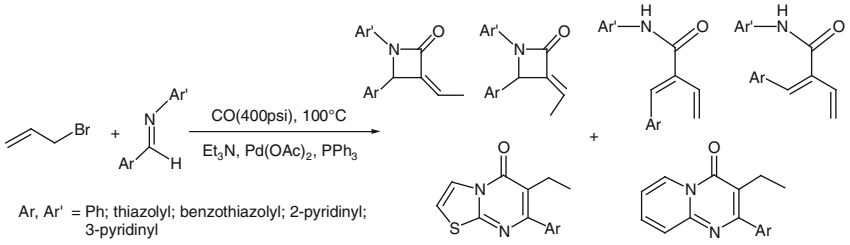
In 2006, the palladium-catalyzed carbonylative [2+2] cycloaddition of allyl bromide with heteroaryliden anilines was reported to afford 2-azetidinones



Scheme 65 Stereoselective synthesis of allyl β-lactams



Scheme 66 Palladium-catalyzed cyclocarbonylation of allyl phosphate with imines



Scheme 67 [2+2] Cyclocarbonylation of allyl bromide with *N*-α-aza-heteroaryl substituted imines

N-phenyl substituted, with a heteroaryl moiety linked to the C-4 carbon, and an alkenyl group at the C-3 carbon [162]. The reaction proceeded with high stereoselectivity.

A similar reaction performed with allyl bromide and *N*-α-aza-heteroaryl substituted imines has been reported to give partially β-lactams. This latter, for instance, underwent isomerization to the more stable α,β-unsaturated carbonyl compounds, and variously substituted pyrimidinones were also isolated (Scheme 67), [163].

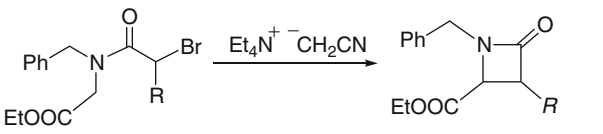
In 2008, the same authors reported the synthesis of polyfunctionalized *N*-alkyl-β-lactams with high stereoselectivity in an efficient manner performing the same reaction with allyl bromide and heteroarylidene *N*-alkyl-amines. Interestingly, by modulating the type of alkyl group linked to the nitrogen atom, it is possible to influence the reaction stereoselectivity [164].

4.1.7 Intramolecular Cyclization

Electrochemical Induction

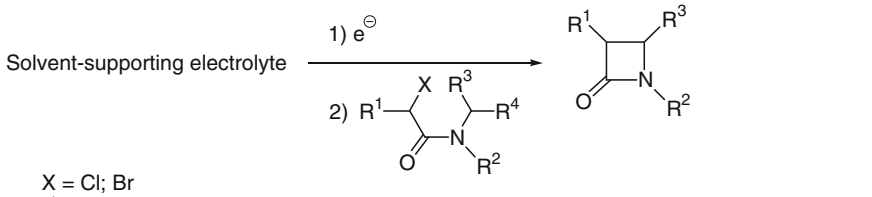
In 2005, a diastereoselective synthesis of *cis*-3-alkyl-1-benzyl-4-ethoxycarbonyl-β-lactams has been reported to be developed by galvanostatic electrolysis of a solution of acetonitrile containing a tetraalkylammonium salt, as supporting electrolyte and *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamides [165]. The electrogenerated cyanomethyl anion, at room temperature and under a nitrogen atmosphere, caused the cyclization of the substituted carboxamides. High *cis*/*trans* ratios were observed with all the substrates exploited, (Scheme 68).

In 2006, electrochemically induced synthesis of β-lactams, by cyclization of haloamides, has been achieved in suitable solvent-supporting electrolyte solutions previously electrolyzed under galvanostatic control [166, 167]. The yields and the stereochemistry of the process were influenced by the nature of the R^1–R^4 substituents, by the solvent-supporting electrolyte solutions, and by the electrolysis conditions (Scheme 69).



R = CH_3; CH_2CH_3; $CH(CH_3)_2$; $(CH_2)3CH_3$; *c*-C_5H_9; *c*-C_6H_{11}

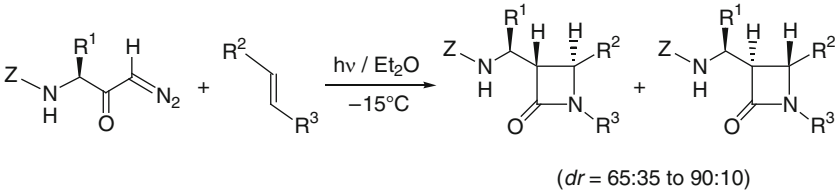
Scheme 68 Synthesis of disubstituted β-lactams by galvanostatic electrolysis



X = Cl; Br
R^1 = $CH(CH_3)_2$; $(CH_2)_3CH_3$; *o*-C_6H_{11}; Ph; CH_3; H
R^2 = CH_2Ph; *p*-CH_3O-Ph; *p*-NO_2-Ph

R^3 = CO_2Et; CN; COPh; Ph; H
R^4 = CO_2Et; H

Scheme 69 Electrochemical synthesis of β-lactams



Scheme 70 Stereoselective synthesis of β-lactams by photochemical rearrangement

More recently, electrochemically induced cyclization of linear bromoamides to β-lactams has been reported to be achieved in room-temperature ionic liquids [168].

Photo-Irradiation

In 2001, diazoketones [169, 170] derived from suitably protected amino acids have been reported to be photochemically rearranged in the presence of imines leading exclusively to *trans*-substituted β-lactams with up to 84% yield [171]. Selectivities were dependent on the steric demand of the amino acid side-chain with *dr* ranging from 65:35 to 90:10, (Scheme 70).

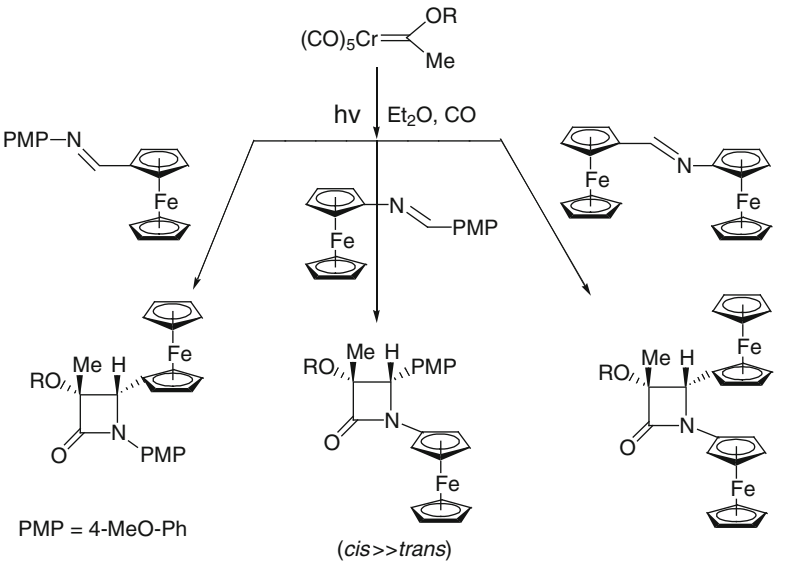
The photochemical reaction of alkoxychromium(0)carbene complexes and ferrocene mono- and disubstituted imines have been reported to form 2-azetidinones having one or two ferrocene moieties in good yields [136]. The chromium(0) carbene complex reacted smoothly with ferrocene imines that allowed to place ferrocene substituents at the N-1, and the C-4, or simultaneously at the N-1 and the C-4 positions of the β-lactam ring, with *cis* stereoselectivity (Scheme 71).

By reacting the imine with the aminochromium(0)carbene complex, having the ferrocene group attached to the amino moiety, the corresponding 2-azetidinone was isolated as a *cis-trans* mixture (10:1), (Scheme 72).

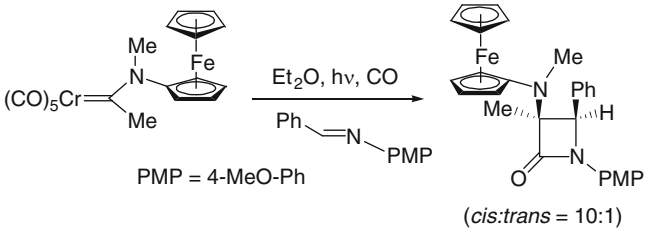
In 2002, α-oxoamides have been reported to be transformed into β-lactams via photochemical rearrangement [172]. Good results were obtained via irradiation of ionic and covalent chiral auxiliary-containing reactants in the crystalline state and in the interior supercages of zeolites (Scheme 73).

The group of Podlech has reported that *trans*-substituted β-lactams (*dr* 70:30) can be prepared treating an Fmoc-protected leucine-derived diazoketone with a benzylidene-protected glycine ester in a photochemically induced Staudinger-type reaction [173]. Separation of the isomers, deprotection, and attachment of Fmoc-proline using the pentafluorphenyl ester activation protocol yielded the protected peptidomimetic in 93% yield, (Scheme 74). Deprotection and amidation resulted in formation of the *trans*-substituted β-lactam.

In 2003, irradiation of isoxazolium anhydrobase in acetonitrile has been reported to give a novel β-lactam system such as a 4,5-dihydrofuroazetidinone (yield 60%) [174]. The mechanistic interpretation of this result involved a photochemical N–O bond cleavage, followed by the formation of a cyclopropanone intermediate (Scheme 75).

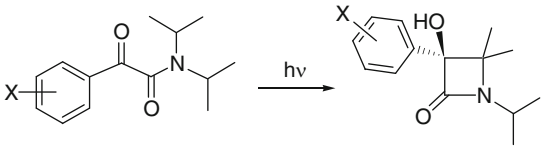


Scheme 71 Synthesis of N-1 and C-4 ferrocene-substituted 2-azetidinones

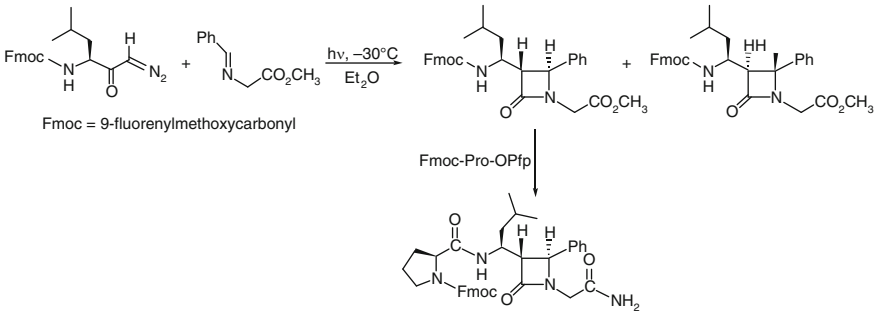


Scheme 72 Synthesis of C-3 ferrocene-substituted 2-azetidinones

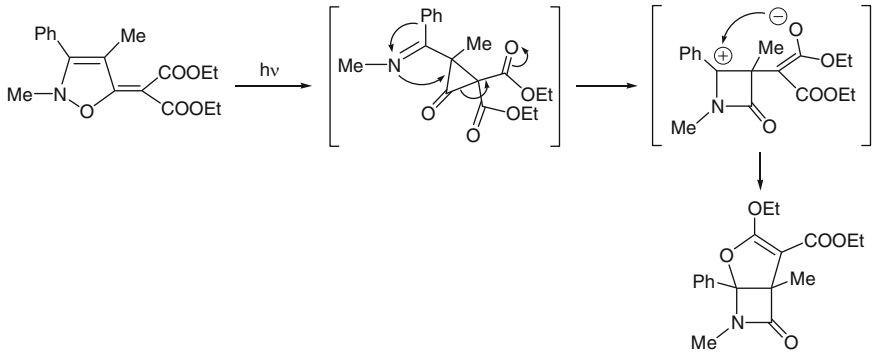
Scheme 73 β-Lactams synthesis via photochemical rearrangement of α-oxoamides



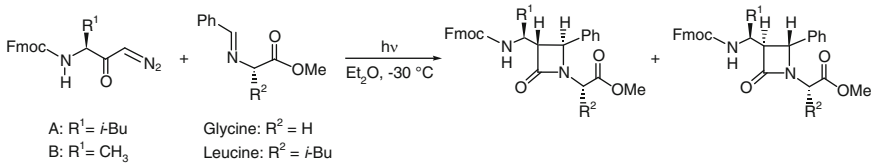
In 2004, Podlech and coworkers have reported some further advances in the photochemical treatment of Fmoc-protected diazoketones A and B, (Scheme 76), derived from leucine and alanine, respectively, with *N*-(benzylidene)glycine and leucine methyl ester to produce a mixture of the corresponding diastereomeric *trans*-substituted β-lactams [175].



Scheme 74 *trans*-Substituted β-lactams synthesis by photochemically induced Staudinger reaction



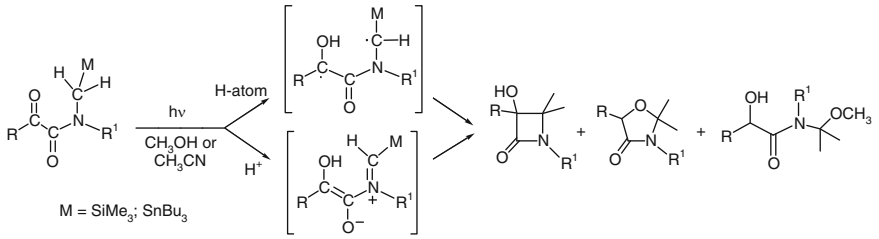
Scheme 75 Synthesis of β-lactam system by photorearrangement of isoxazolium anhydrobase



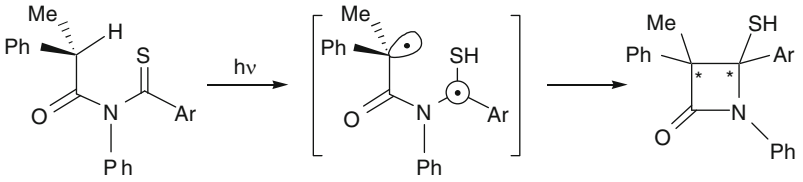
Scheme 76 Synthesis of β-lactam-containing dipeptide analogs

The moderate selectivity was in accordance with the bulkiness of the diazo ketone's side-chains.

α-Silylketoamides and α-stannylketoamides, irradiated in MeOH or MeCN with pyrex glass filtered light ($\lambda > 290$ nm), have been converted into β-lactams alongwith other products, including oxazolidinones and α-hydroxamides (Scheme 77), [176].



Scheme 77 β-Lactam-forming photochemical reaction starting from α-silyl- and α-stannylketoamides



Scheme 78 Photochemical β-lactam synthesis by γ-hydrogen abstraction by a thiocarbonyl group

Two mechanisms were proposed for the β-lactam-forming photoreactions, one radical involving excited-state H-atom abstraction while the other following a sequential single-electron-transfer (SET)-proton-transfer route.

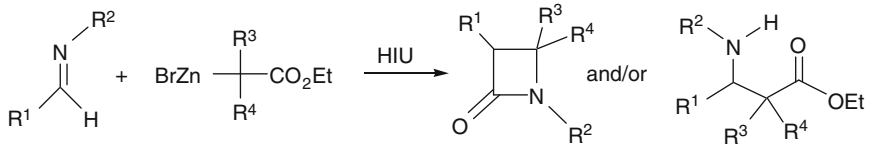
In 2008, Sakamoto and coworkers have reported the synthesis of optically active β-lactams via photochemical intramolecular γ-hydrogen abstraction reaction of thioimides [177]. This reaction provides the first example of a chiral-memory effect for the photochemical γ-hydrogen abstraction reaction of thiocarbonyl or carbonyl compounds, and a useful synthetic methodology for preparing optically active β-lactams (Scheme 78).

Ultra-Sound Irradiation

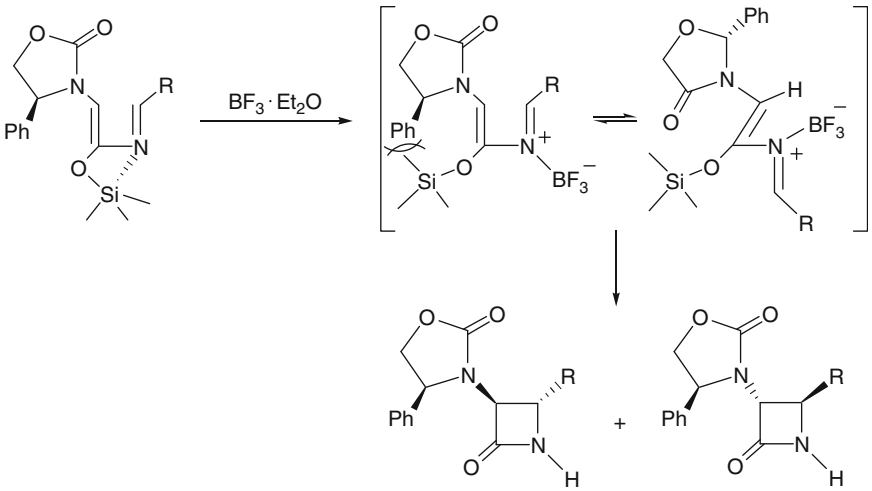
In 2004, the Reformatsky reactions of imine, α-bromoester, zinc dust, and a catalytic amount of iodine in dioxane under high intensity ultrasound (HIU) irradiation have been reported to afford β-lactam and the corresponding β-aminoester [178]. The reactions were performed in short reaction times and high yields of both products or a mixture of the two products were obtained, depending on the starting imine and on the α-bromoester (Scheme 79).

Lewis-Acid Catalysis

A Lewis acid-catalyzed cyclization of 2-aza-3-trimethylsilyloxybuta-1,3-diene has been reported in 2003 and the stereochemical differences with the uncatalyzed



Scheme 79 Reformatsky reaction of imines and α-bromoesters affording β-lactams and β-aminoesters



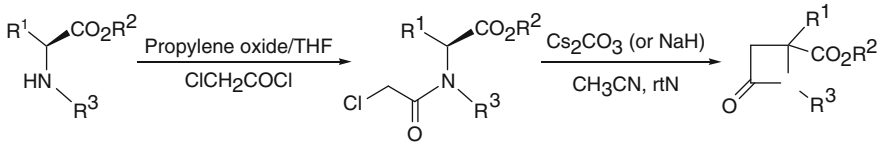
Scheme 80 Lewis acid-catalyzed synthesis of *trans*-β-lactams

cyclization have been discussed [179]. The data reported showed that in analogy to the uncatalyzed reaction, diastereomeric *trans*-azetidinones were obtained (Scheme 80).

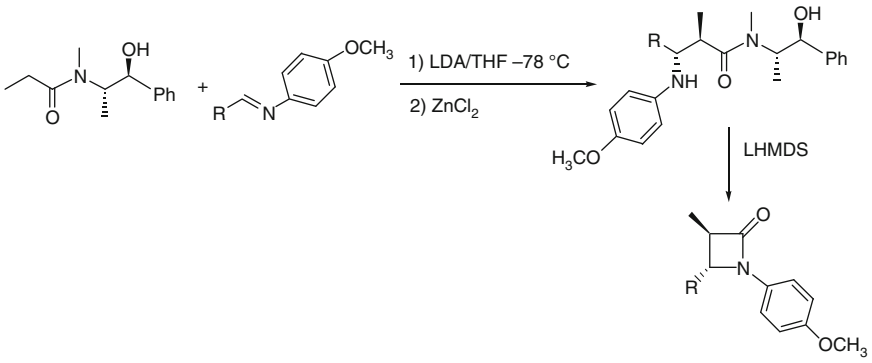
Base Catalysis

In 2001, 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinones have been reported to be prepared by base-assisted intramolecular alkylation of *N*-benzyl-*N*-chloroacetyl amino acid derivatives [180]. *N*-benzyl or *N*-(*p*-methoxybenzyl) amino acid derivatives in THF, treated with propylene oxide and chloroacetyl chloride afforded the *N*-chloroacetyl amino acid derivatives. The treatment of the latter in CH_3CN with Cs_2CO_3 (or NaH) produced the intramolecular cyclization of 4,4-disubstituted β-lactams, (Scheme 81).

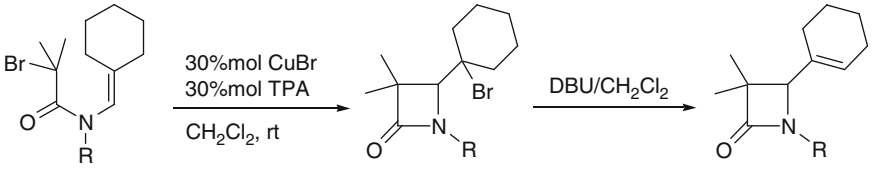
An asymmetric synthesis of α,β-disubstituted β-amino esters and β-lactams has been reported [181]. Chiral β-amino esters were prepared by a stereocontrolled Mannich reaction with enolizable imines using an enolate derived from



Scheme 81 Synthesis of 4,4-disubstituted β-lactams by base-assisted intramolecular alkylation



Scheme 82 Asymmetric synthesis of β-lactams by base-promoted cyclization of β-amino esters

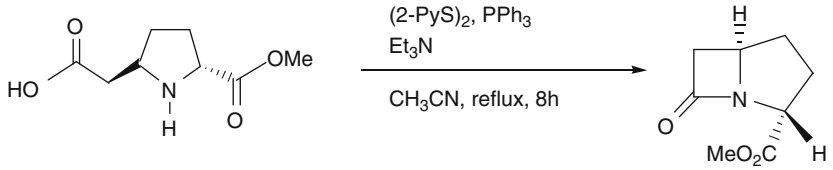


Scheme 83 Synthesis of β-lactams by bromo-enamides radical cyclization

(*S*,*S*)-(+)-pseudoephedrine propionamide as chiral auxiliary. The obtained β-amino esters were subjected to a reported base-promoted cyclization [182, 183] affording the β-lactams in good yields and as unique detectable stereoisomer (Scheme 82).

Bromo-enamides have been reported to give radical cyclization in excellent yields (82–99%) to β-lactams using catalytic amounts (30%) of tripyridylamine (TPA) copper(I) halide complex [184]. The β-lactam developed under mild conditions via 4-*exo* bromine atom transfer and subsequent elimination of the tertiary bromide that could be readily achieved by reaction with DBU (Scheme 83).

In 2002, 3,5-*trans*-(+)-(3*R*,5*R*)-3-carbomethoxycarbapenam has been reported to be prepared via a known cyclization reaction [185] starting from enantiopure carboxy pyrrolidine with di(2-pyridyl)disulfide, triphenylphosphine, and triethylamine in refluxing acetonitrile for 8 h (Scheme 84), [186].



Scheme 84 Synthesis of 3,5-*trans*-(+)-(3*R*,5*R*)-3-carbomethoxycarbapenam starting from an enantiopure amino acid

The starting enantiopure pyrrolidine was prepared from 3-hydroxypyridine following the five-step sequence of the established route [187–189] and the piperidine-pyrrolidine ring-contraction reaction [190, 191].

A general approach towards the asymmetric synthesis of amino acid derived 4-alkyl-4-carboxy-2-azetidinones has been described [192]. The (+)- or (−)-10-(*N*, *N*-dicyclohexylsulfamoyl)isoborneol was used as chiral auxiliary in the intramolecular cyclization of *N*-(*p*-methoxybenzyl)-*N*-chloroacetyl Phe and Ala derivatives for the stereocontrolled base-catalyzed construction of the β-lactam ring (Scheme 85).

In 2003, dicarboxamides *E* and *Z* derived from fumaric and maleic acids, respectively, were reported to yield the same product, a single *syn* diastereomer of the β-lactam, when treated with LDA at 0°C (Scheme 86), [193].

The *N*-alkyl-*N*-chloroacetyl amino acid derivatives [180] have been reported to undergo the base-promoted cyclization to β-lactams [194]. The stereoselectivity, due to memory of chirality, was highly dependent on the substituents of the starting amino acids. The amino acid side-chain (R^3) appeared to be the principal stereodirecting element, offering additional support for the explanation that the memory of chirality was caused by a hindered rotation around the C–N bond (Scheme 87).

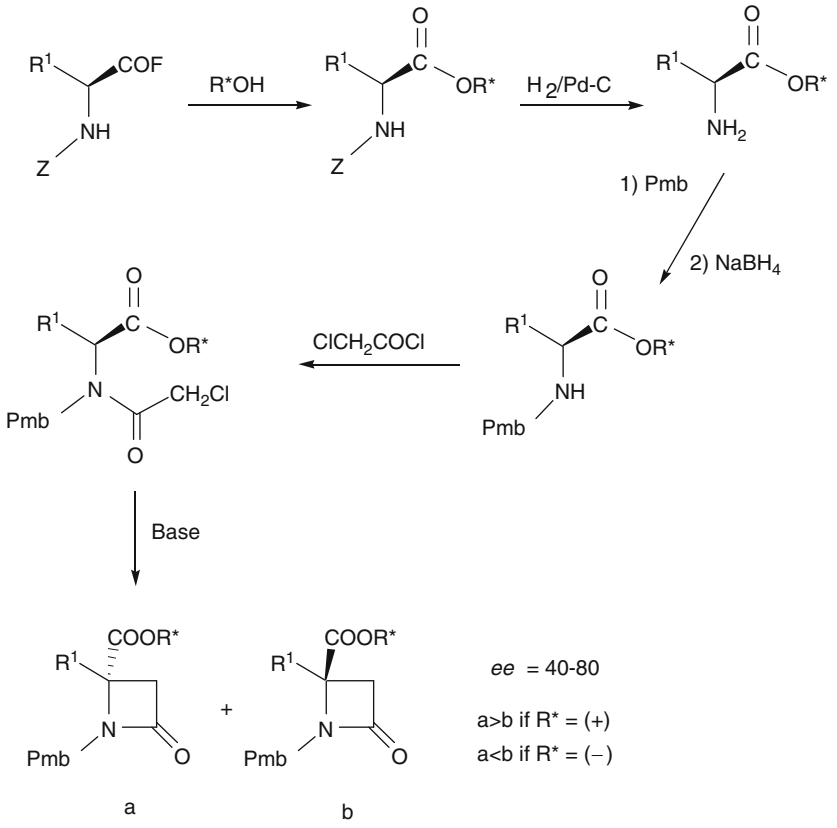
Treatment of isonicotinamide with LDA at −40°C and addition of an acylating or alkylating agent were reported in 2005 to form in good yield, a dearomatized product with spirocyclic β-lactam structure (Scheme 88), [195]

In 2007, the desulfinylation and deprotonation of chiral 1′-aminodioxolanones followed by the based-induced cyclization was reported to afford the corresponding chiral tetrasubstituted 3-hydroxy-2-azetidinones (Scheme 89), [196, 197].

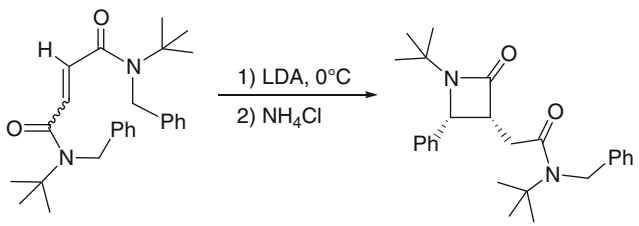
In 2008 Yang and coworkers have reported an efficient synthesis of substituted α-alkilidene-β-lactams via a NaOH- promoted intramolecular aza-Michael addition of α-carbamoyl, α-(1-chlorovinyl) ketene-S,S-acetals and subsequent nucleophilic vinylic substitution reaction in alcoholic media (Scheme 90), [198].

4.1.8 Heterocyclic Rearrangement

In 2002, alicyclic *cis*-β-amino acids have been reported to react with cyclohexyl isocyanide and substituted benzaldehyde via a liquid-phase Ugi four-center

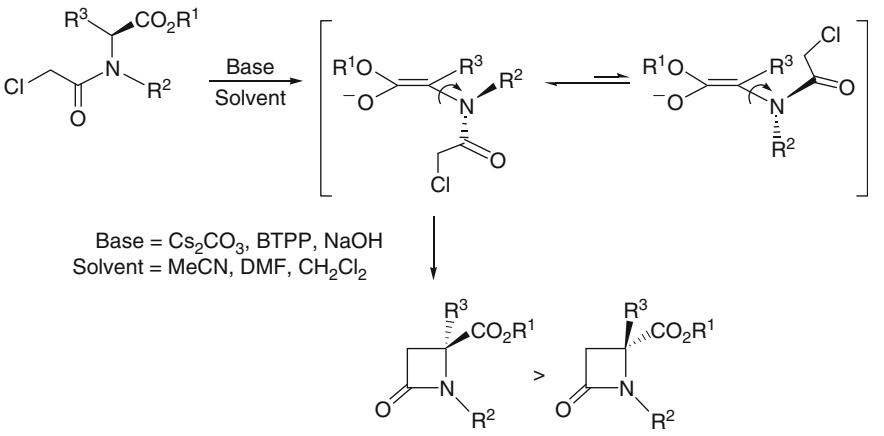


Scheme 85 Stereocontrolled construction of the β-lactam ring

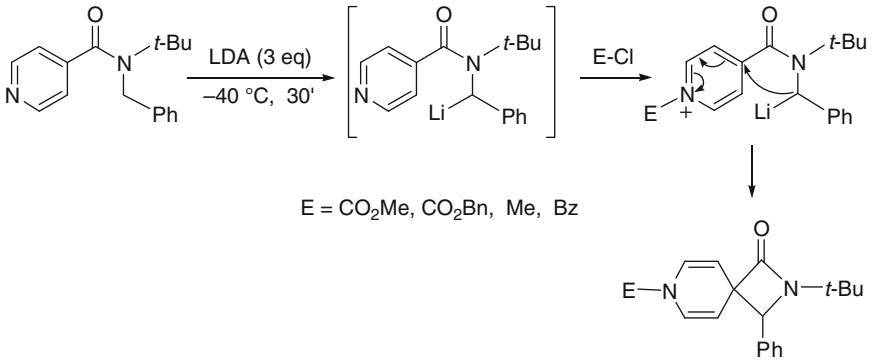


Scheme 86 Selective synthesis of *syn* β-lactams from *E* and *Z* dicarboxamides

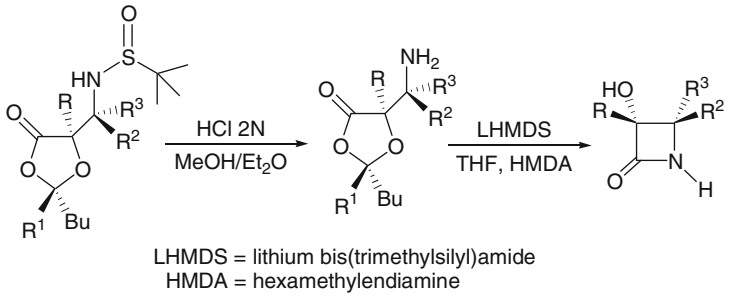
three-component reaction to afford β-lactams derivatives [199]. The products were isolated after 24 h at room temperature from the mixture in methanol, in moderate to good yields. Plausible reaction intermediates have been proposed (Scheme 91).



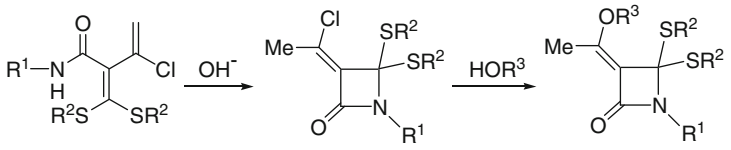
Scheme 87 Stereoselective synthesis of β-lactams from amino acid derivatives



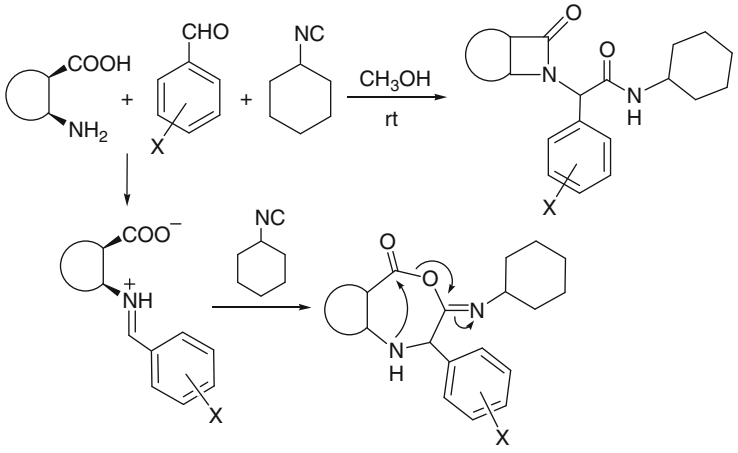
Scheme 88 Synthesis of spirocyclic β-lactams by dearomatizing cyclization reaction



Scheme 89 Deprotection of 1′-aminodioxolanones to give the corresponding β-lactam



Scheme 90 Synthesis of α-alkilidene-β-lactams from α-acyl, α-carbamoyl ketene-S,S-acetals



Scheme 91 Liquid-phase synthesis of alicyclic β-lactams via Ugi three-component reaction

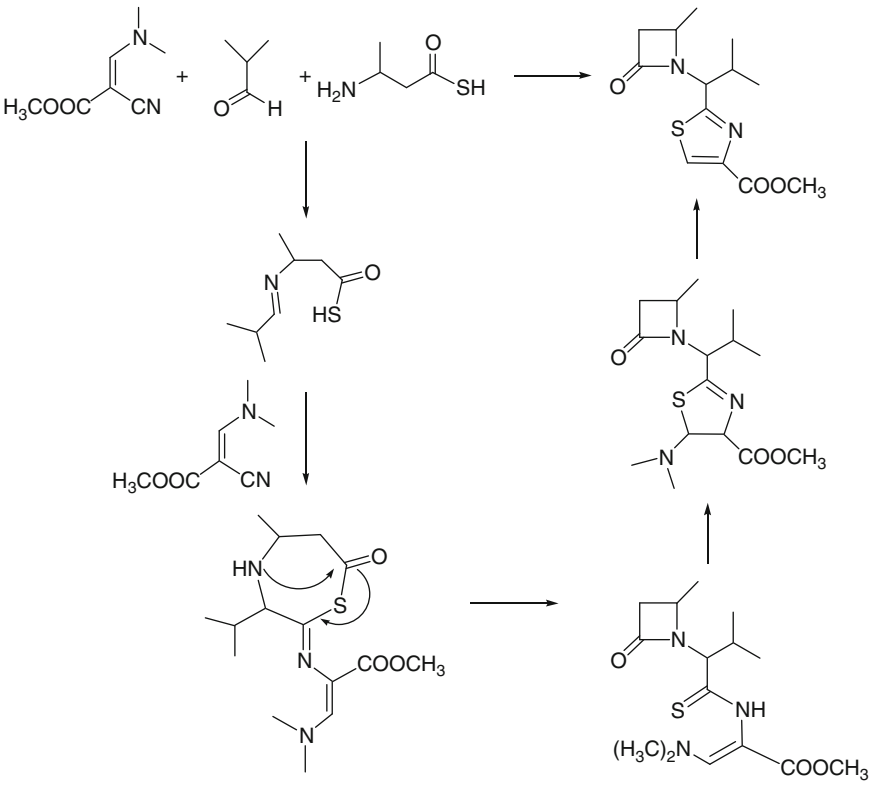
A β-lactam ring substituted by a thiazole moiety has been reported to be formed simultaneously and under mild condition during the course of a multicomponent reaction [200]. When the 3-dimethylamino-2-isocyanoacrylate was reacted with the aldehyde in the presence of a β-aminothiocarboxylic acid, substituted 1-thiazole-2-yl-methyl-azetidin-2-one was smoothly formed (Scheme 92). Plausible reaction intermediates have been proposed.

In 2003, the thermolysis of 3,4-*cis* ring-fused 5-spirocyclopropane isoxazolidines, in the presence of a protic acid (TFA) at 70–110°C, has been reported to yield 3,4-*cis* ring-fused azetidin-2-ones with concomitant extrusion of ethylene, in good yields (Scheme 93), [201].

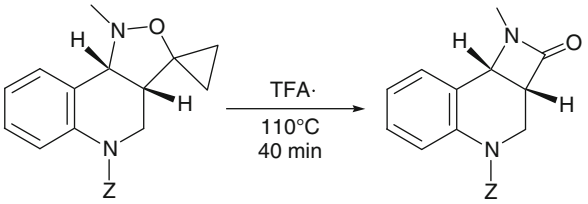
Analogously, in 2004, it has been reported that the treatment of bis-spirocyclopropanated isoxazolidines [202–207] with TFA in acetonitrile furnished the 3-spirocyclopropanated β-lactams in 75–96% yields [208].

The β-lactamic ring was also formed by the acidic thermal rearrangement of spiro[cyclopropane-1,5′-isoxazolidines], [209]. The rearrangement was almost instantaneous at 90°C, as the starting material was completely converted after 2 min.

In 2008, a very mild reductive N–O bond cleavage of fluorinated isoxazolidines was reported to provide a novel and general entry to β-lactams and ester of β-amino acids containing a trifluoromethyl group (Scheme 94), [210].

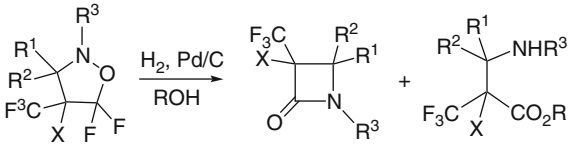


Scheme 92 Simultaneous assembly of β-lactam and thiazole moiety by a multicomponent reaction



Scheme 93 Selective ring contraction of 5-spirocyclopropane isoxazolidines mediated by acids

Scheme 94 Synthesis of α-trifluoromethyl-β-lactams via reductive cleavage of isoxazolidines



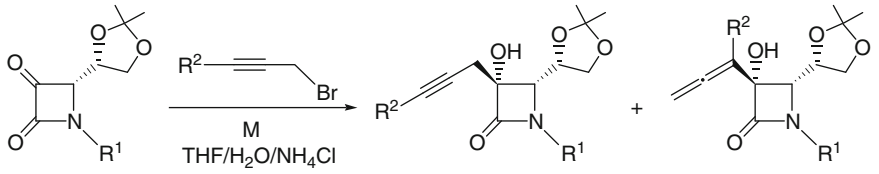
4.2 Other Reactions

In 2000, the metal-mediated carbonyl propargylation or allenylation of enantiomerically pure azetidine-2,3-diones [211] has been reported to afford stereoselectively functionalized 3-substituted 3-hydroxy-β-lactams (Scheme 95), [212].

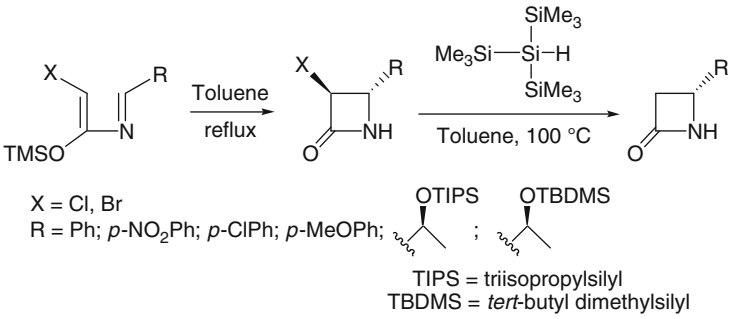
A new protocol for the stereoselective synthesis of β-lactams [213] has been reported to be performed by a conrotatory ring closure of 1-halo-3-aza-4-alkyl-1, 3-dienes, previously prepared by Staudinger methodology, (for the synthesis and chemistry of *N*-silyl imines see [214]; for [2+2] cycloaddition of *N*-silyl imines and ketenes see [215]) in refluxing toluene (Scheme 96).

When R was a stereogenic center, of the four possible stereoisomers only the two *trans*-3-halo-isomers were obtained. A modification of the so-obtained β-lactams [216] has been also reported consisting in a dehalogenation procedure giving rise to 3-unsubstituted β-lactams, (Scheme 96).

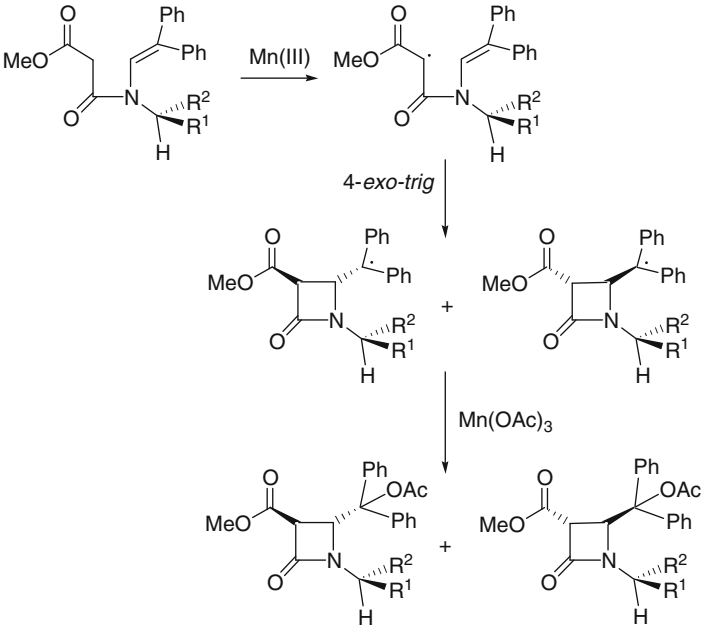
The Mn(III)-mediated 4-*exo-trig* cyclization of enamides to β-lactams has been reported to be carried out with good diastereoselection by placing suitable chiral substituents on the nitrogen atom (Scheme 97), [217].



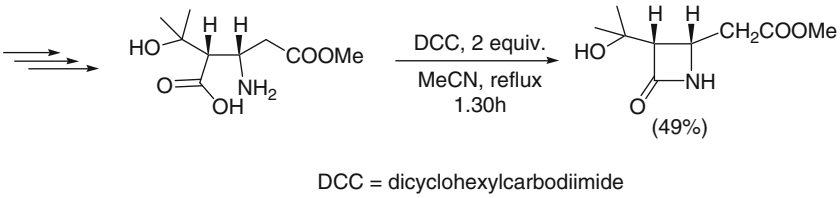
Scheme 95 Metal-mediated carbonyl propargylation or allenylation of pure azetidine-2,3-diones



Scheme 96 Stereoselective synthesis of 3-unsubstituted β-lactams by conrotatory ring closure of 1,3-diene derivatives



Scheme 97 Mn(III)-mediated cyclization of enamides to β-lactams



Scheme 98 Synthesis of β-lactams from substituted β-amino acids

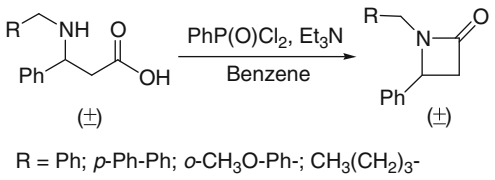
β-Lactam structures have been reported to be constructed by treatment of substituted β-amino acids with dicyclohexylcarbodiimide (DCC) in refluxing acetonitrile (Scheme 98), [218]. The substrates were prepared by a multistep synthetic protocol previously reported [219].

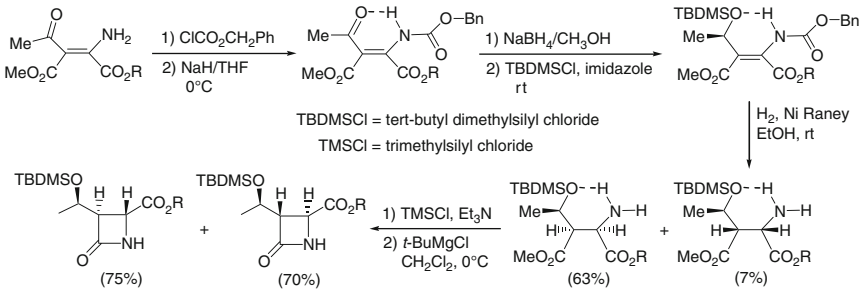
In 2001, 3-(benzylamino)-3-phenylpropanoic acid [220] has been reported to give β-lactam in good yield, by cyclization reaction in the presence of phenylphosphonic dichloride and triethylamine in refluxing benzene (Scheme 99), [221].

β-Enaminoketoesters [222] have been reported to be used for preparing (±)-2-azetidinones by a simple route (Scheme 100), [223].

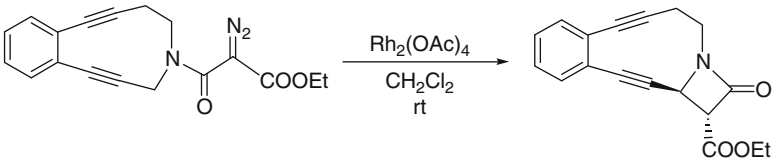
β-Enaminoketoesters were reacted with benzyl chloroformiate in the presence of sodium hydride to furnish the *N*-protected enaminoketoesters. The reduction of the carbonyl group with $NaBH_4$ in methanol was followed by transformation of the derived hydroxyl group into the corresponding *tert*-butyl dimethylsilyl ether by

Scheme 99 Synthesis of β-lactam by β-amino acid cyclization





Scheme 100 Synthesis of (±)-2-azetidinones starting from β-enaminoketoesters

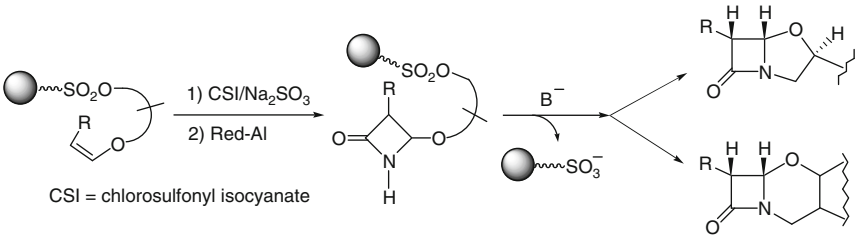


Scheme 101 Catalytic synthesis of β-lactam fused enediynes

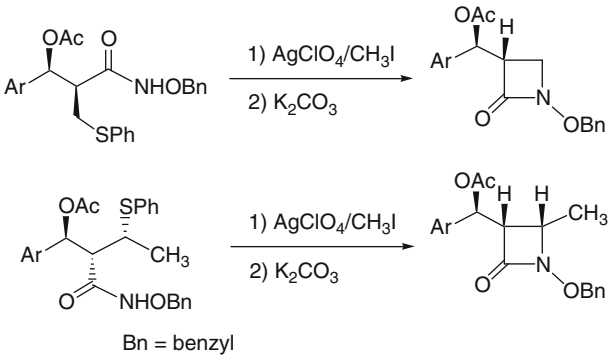
reaction with *tert*-butyl dimethylsilyl chloride (TBDMSCl) in the presence of imidazole. The reduction of the carbon-carbon double bond was easily achieved by catalytic hydrogenation in the presence of Raney Nickel W-2. Finally, treatment with trimethylsilyl chloride (TMSCl) and triethylamine involved the formation in situ of the *N*-trimethylsilyl derivatives which, treated with *tert*-butyl magnesium chloride, gave the expected (±)-2-azetidinones.

A methodology was reported in 2002 for the synthesis of β-lactam fused enediynes [224]. When a solution of a diazo enediyne [225] was treated with a catalytic amount of rhodium acetate for 30 min, the β-lactam fused enediyne was obtained as the only product, (Scheme 101). The yield in the carbene insertion step was about 50%, the rest being decomposition products.

Chiral vinyl ethers attached to a Wang resin through the *p*-oxyphenylsulfonyl linker, have been reported to give the [2+2] cycloaddition reaction with chloro-sulfonyl isocyanates (CSI) [226]. The intramolecular alkylation of the β-lactam nitrogen atom gave mixtures of the corresponding diastereomeric clavams or oxacephams, (Scheme 102).



Scheme 102 Solid-phase synthesis of clavams and oxacephams trough β-lactam intermediate



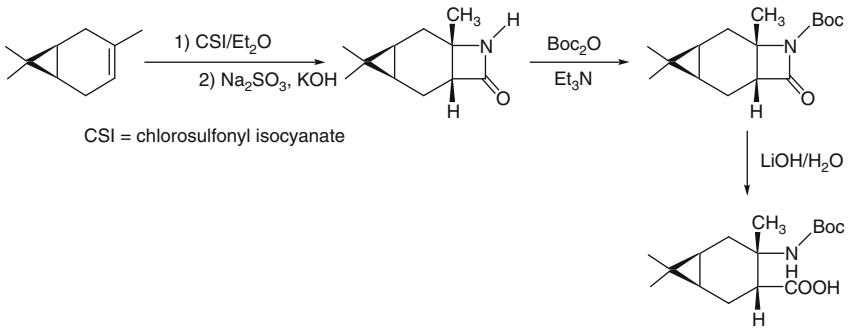
Scheme 103 Synthesis of β-lactams by intramolecular SN_2 reaction

In 2003, β-hydroxyacetyl-α-thioalkylamides have been reported to give a cyclization reaction to β-lactams through an intramolecular SN_2 mechanism (Scheme 103), [227]. The β-lactams were obtained in a diastereomerically pure form.

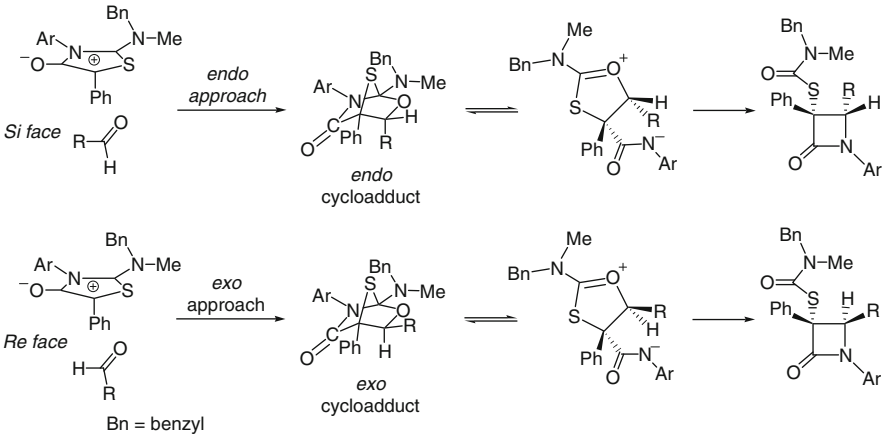
Starting from the commercially available (+)-3-carene, the cycloaddition of chlorosulfonyl isocyanate [228] has been reported to furnish the enantiomeric β-lactam in a regio- and stereoselective manner [229]. Treatment of the β-lactam with di-*tert*-butyl dicarbonate resulted in *N*-Boc β-lactam, that could be readily opened under mild conditions (Scheme 104).

The reactions of 1,3-thiazolium-4-olates with aliphatic aldehydes carried out in refluxing benzene or dichloromethane, have been reported to produce a series of highly functionalized β-lactams and thiiranes at the same time [230]. The critical issue of the stereoselection was discussed in terms of the *endo* and *exo* approaches (respective to the aldehyde substituent) to any enantiotopic face of the heterocyclic dipole. Such orientations involved either the *Re* or the *Si* faces of the prochiral aldehydes (Scheme 105).

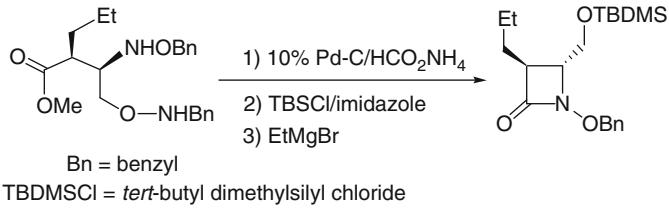
In 2004, β-lactams were obtained by the cyclization of β-amino esters [231]. The treatment of the latter with 10% Pd-C in the presence of ammonium formiate for 3 h, followed by silylation of the resulting hydroxyl esters gave the silyloxy esters that were subjected to cyclization using the Breckpot reaction [232, 233] to give the β-lactams (Scheme 106).



Scheme 104 Regio- and stereoselective synthesis of β-lactams by cycloaddition reaction

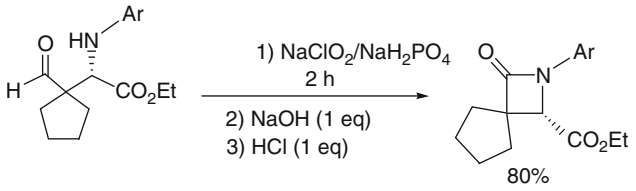


Scheme 105 Mechanism suggested for the formation of highly functionalized β-lactams

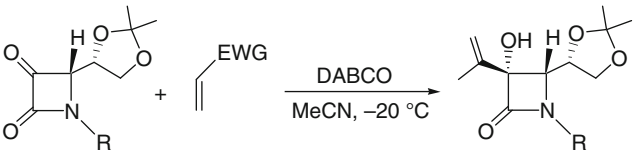


Scheme 106 Synthesis of β-lactams by cyclization of β-amino esters

Quaternary β-formyl α-amino acid derivatives have been converted into spiro β-lactams in excellent yield, using oxidation followed by simple base and acid treatment (Scheme 107), [234].

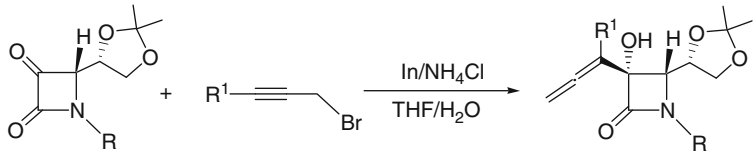


Scheme 107 Synthesis of spiro β-lactams starting from formyl amino acid derivatives



EWG = COMe; CN; CO_2Me; SO_2Ph
R = 4-MePh; 2-propenyl; 3-butenyl; etc.
DABCO = 1,4-diazabicyclo[2.2.2]octane

Scheme 108 Baylis-Hillman reaction of enantiopure azetidine-2,3-diones

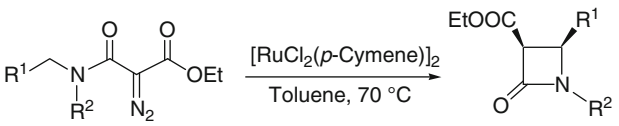


Scheme 109 Synthesis of α-allenols from enantiopure azetidine-2,3-diones

The Baylis-Hillman reaction of optically pure azetidine-2,3-diones [235, 236] with methyl vinyl ketone in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in acetonitrile at –20°C for 1 h have been reported to give functionalized allylic alcohols, having the β-lactam scaffold, in good yields (80%) and complete diastereoselectivity [237]. In terms of achieving good yields with a reasonable rate of reaction, 50 mol% of DABCO seemed to be the catalyst amount of choice for this reaction. No significant solvent effect was observed in the overall yield (Scheme 108).

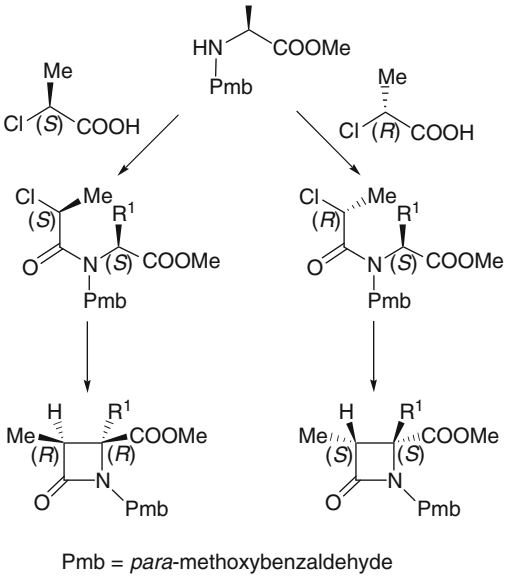
α-Allenols, containing the 2-azetidinone ring, have been reported to be obtained by reacting the same azetidine-2,3-diones with propargyl bromides in the presence of Indium as catalyst (Scheme 109), [238].

In 2005, the group of Choi has reported a catalytic system based on [$RuCl_2$ (p-cymene)$_2$] that produced the stereoselective cyclization of α-diazoacetamides by intramolecular carbenoid C-H insertion and afforded β-lactams in excellent yield (>97%) with *cis*-stereoselectivity (>99%), (Scheme 110), [239].

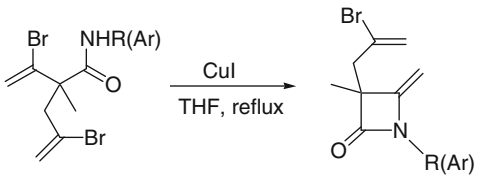


Scheme 110 *cis*-Stereoselective synthesis of β-lactams by catalytic systems

Scheme 111 Synthesis of 1,3,4,4-tetrasubstituted β-lactams from different amino acids



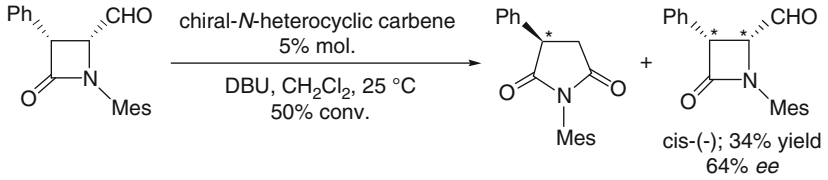
Scheme 112 Synthesis of 4-alkylidene-2-azetidinones



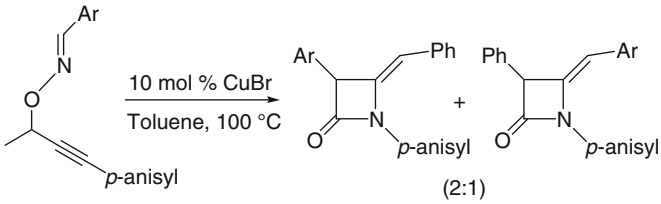
The reaction became enantioselective in the presence of a chiral pyridine-bis-(oxazoline) ligand yielding *trans*-β-lactam with *ee* of 50%.

In 2007, 1,3,4,4-tetrasubstituted β-lactams have been synthesized with exceptional stereoselectivity from amino acids [240]. The stereochemical control of the cyclization to the four-membered ring was fully dictated by the configuration of the *N*-2-chloropropionyl group in the linear precursor (Scheme 111).

In 2008, Zhao and coworkers have reported a general and highly efficient method for the synthesis of 4-alkyliden-2-azetidinones via copper-catalyzed intramolecular C–N coupling of 3-bromobut-3-enamides [241]. Under Cu(I) catalysis



Scheme 113 Chiral *N*-heterocyclic carbene-catalyzed kinetic resolution of *cis*-4-formyl-β-lactams



Scheme 114 Five-bond-cleavage rearrangement of *O*-propargyl oximes to β-lactams

the 4-*exo* ring closure was found to be fundamentally preferred over other modes of cyclization (Scheme 112).

Li and coworkers have previously found that in the presence of an *N*-heterocyclic carbene catalyst *cis*-4-formyl-β-lactams underwent the ring expansion reaction to afford succinimide derivatives [242]. More recently, they reported the kinetic resolution version of this transformation attempted with a chiral *N*-heterocyclic carbene (Scheme 113), leading to *cis*-4-formyl-β-lactams with moderate *ee* of 64% [243].

An unprecedent skeletal rearrangement of *O*-propargyl oximes has been reported to go via copper complex catalysis, involving cleavage of five different covalent bonds (C=N, N–O, C–O, C–C, and C≡C) and leading to reorganization into β-lactams in good to excellent yields (Scheme 114), [244].

4.3 Structural Modifications to the N-1, the C-3, and the C-4 Positions

The modification of the substituents linked to the 2-azetidinone ring can afford a new family of β-lactams having, often, a stronger and more efficient biological and pharmacological activity. A brief list of the more significant modifications performed on the groups linked at the N-1, the C-3, and/or the C-4 positions are reported in this paragraph, with the figures related to the new structures obtained.

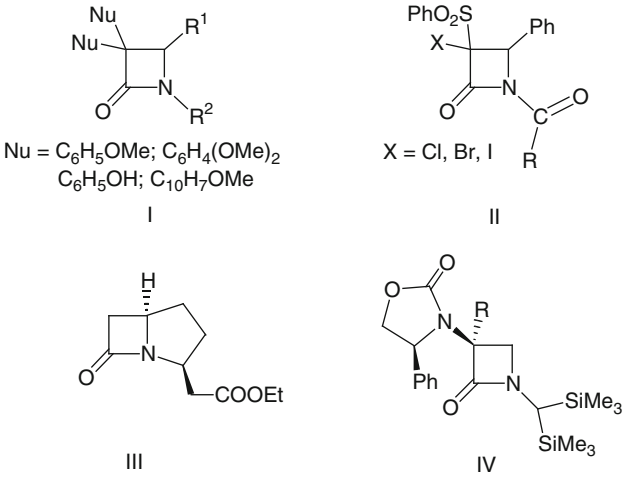


Fig. 3

In 2000, a route to novel C-3 substituted 2-azetidinones (I, Fig. 3) has been reported involving a reaction of a β-lactam carbocation equivalent with active aromatic nucleophiles in the presence of a Lewis acid [245].

3-halo-3-(phenylsulfonyl)-4-phenylazetidinones (II, Fig. 3) have been obtained by *N*-halosuccinimides [246].

The radical cyclization of *N*-acrylate-4-(2-bromoethyl)azetidin-2-ones [247] has been reported to form a bicyclic β-lactam (III, Fig. 3).

The synthesis of α-branched 3-amino-4-unsubstituted β-lactams (IV, Fig. 3) could be performed efficiently via an asymmetric alkylation of a single 3-oxazolidinyl azetidin-2-one [248].

The addition of lithium bis(methylenecyclopropyl)cuprates to acetoxy azetidinones has been reported to give methylenecyclopropyl azetidinones (Fig. 4) which could be further converted into various *N*-functionalized β-lactams [249].

4-Alkenyl-2-azetidinone systems could be converted to bicyclic β-lactam carboxylic esters and hence carboxylic acids (Fig. 5) via tandem Ireland-Claisen rearrangement and subsequent alkene metathesis [250].

The addition of nucleophiles to azetidinones has been reported to afford penems, carbapenems, and aza analogs of cephem (I, II and III, respectively, Fig. 6), [251].

In 2001, tetracyclic 3.6.6.4 ring systems fused to a β-lactam (IV, Fig. 6) have been reported to form via 6-*exo-trig* radical cyclization [252].

Carbapenams (V, Fig. 6) have been produced by warming a solution of β-lactams having a propargyl carbonate moiety linked at the C-4 position [253].

Carbapenems (VI Fig. 6) have been, instead, obtained when a solution of β-lactams having an allyl carbonate substituent at the C-4 was warmed [254].

(*R*)-4′-Alkoxy-azetidin-2-one has been reported to be transformed into 5-oxacepham (VII, Fig. 6) by intramolecular alkylation of the β-lactam nitrogen atom [255].

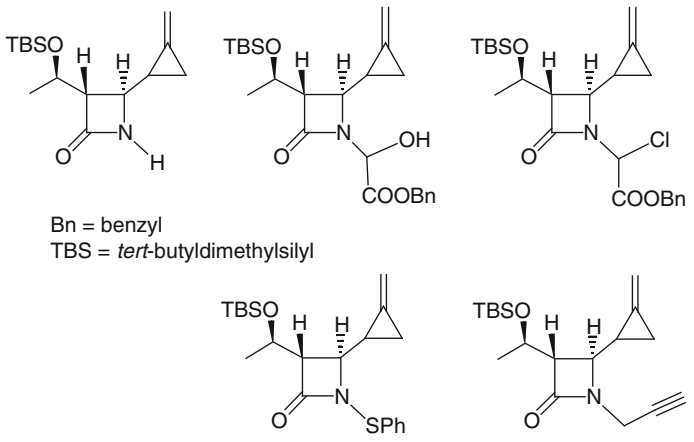


Fig. 4

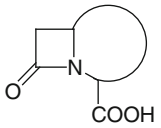


Fig. 5

β-Lactams like structures VIII and IX of Fig. 6 have been obtained from α-benzyloxy α-CF_3-β-lactams by the enolate [1, 2]- and the *ortho*-[2, 3]-Wittig rearrangements, respectively [256].

Optically pure *cis*-2-azetidinone-tethered dienes have been reported to undergo intermolecular Diels-Alder reaction with a variety of symmetric and unsymmetric dienophiles [257] providing a synthetic entry to various types of racemic and homochiral 1,3,4-trisubstituted 2-azetidinones (I, Fig. 7).

Starting from substituted 2-azetidinones, a family of tribactams (II, Fig. 7) has been reported to be prepared by using two main steps: an intramolecular metathesis reaction and a Diels-Alder cyclization [258].

The combination of Baylis-Hillman reaction and tandem radical addition/cyclization sequences [259], has been reported as a useful synthetic tool for the asymmetric synthesis of functionalized monocyclic and bicyclic β-lactams (III and IV, Fig. 7).

1,3,3-Trisubstituted β-lactams have been reported to be obtained through oxidative removal of the *N*-alkyl group from more complex β-lactams by treatment with cerium ammonium nitrate [260]. Anologous methodology was employed for a general synthesis of *cis*- and *trans*-β-lactams bearing a quinone moiety at the N-1, the C-3, or the C-4 position (I, II and III, respectively, Fig. 8), [261].

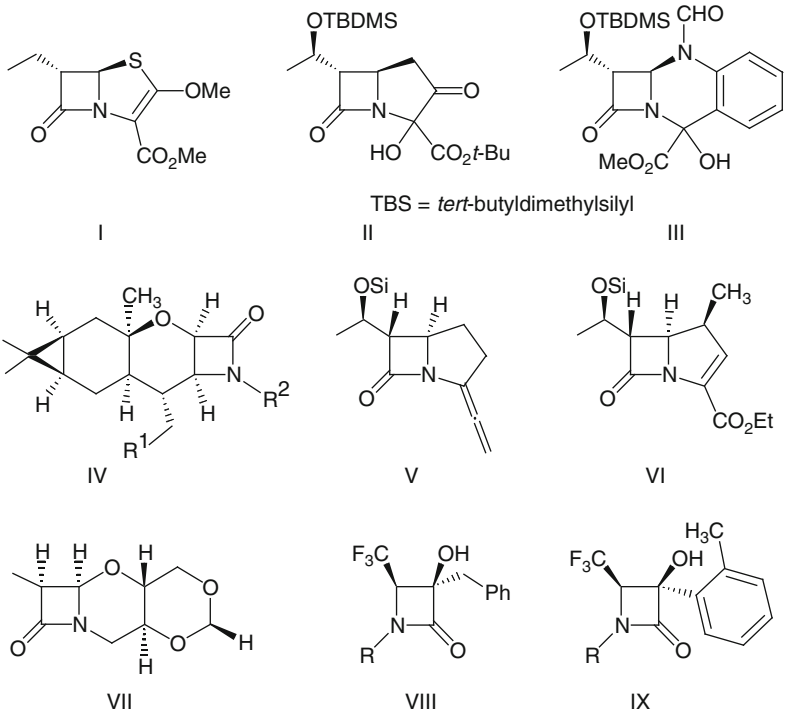

OTBDMS
CHO
TBS = tert-butyldimethylsilyl
I
II
III
IV
V
VI
VII
VIII
IX

Fig. 6

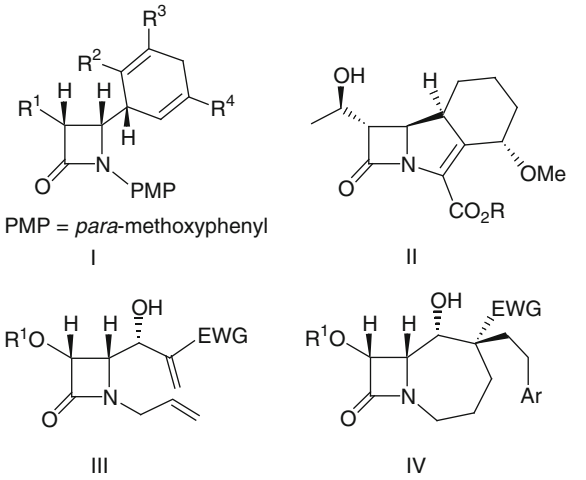

PMP = para-methoxyphenyl
I
II
III
IV

Fig. 7

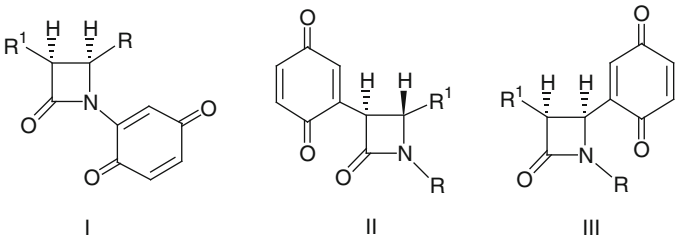


Fig. 8

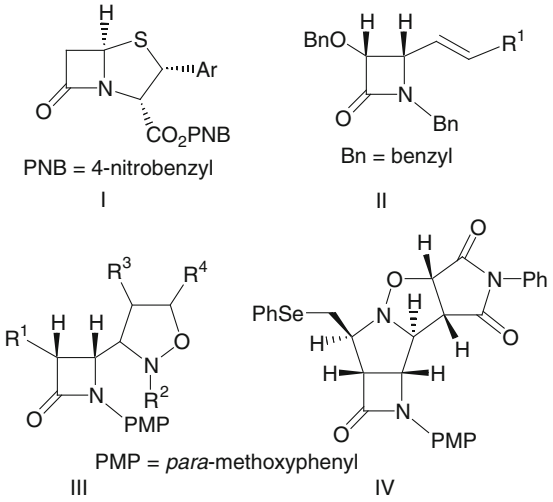


Fig. 9

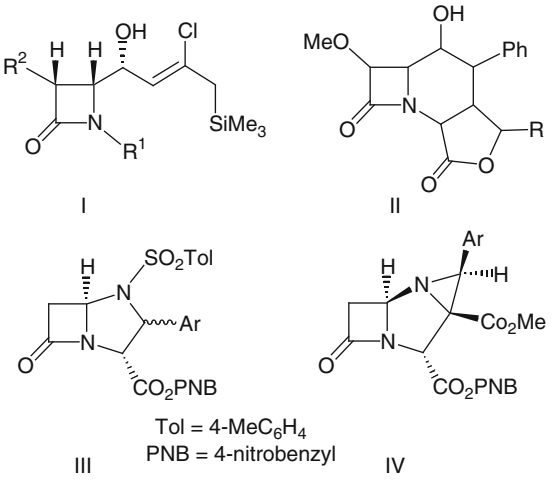
2-Substituted penam (I, Fig. 9) has been reported to be obtained by coupling of thioaldehyde with azomethine ylide which was derived from the β-lactam based oxazolidinone [262].

The preparation of 4-alkenyl β-lactams (II, Fig. 9) has been reported through either Horner-type olefination of a common 4-formyl β-lactam or the Corey-Winter alkene synthesis applied to 4-dihydroxyalkyl β-lactams [263].

Alcaide and coworkers have reported in 2002 the synthesis of various types of racemic and homochiral 1,3,4-trisubstituted- or fused polycyclic β-lactams (III and IV, respectively, Fig. 9) via intermolecular 1,3-dipolar cycloaddition reaction of 2-azetidinone-tethered nitrones with a variety of alkenes or alkynes [264].

The same authors have also reported the direct preparation of β-chlorovinyl alcohols (I, Fig. 10) by the coupling reaction of enantiopure 4-oxoazetidine-2-carbaldehydes with a variety of propynyl-, and allenylmetal reagents [265].

Fig. 10



The synthesis of tricyclic β-lactams (II, Fig. 10) has been reported to be promoted by titanoncene (III) chloride (Cp_2TiCl) on the epoxymonobactams in the presence of intramolecular π systems (i.e., conjugated alkenes and lactones and amide carbonyls) [266, 267].

The reaction of the β-lactam-based oxazolidinone with *N*-sulfonylimines has been reported to provide the *exo* and *endo* azapenams (III, Fig. 10), whereas the reaction with azirines provided cycloadducts (IV, Fig. 10) that are precursors of azacephams [268].

The synthesis of new "selectively activated" enediyne prodrugs (I, Fig. 11) has been reported to start from suitably substituted β-lactams [269].

The group of Palomo has reported in 2003 the preparation of short pseudopeptides containing enantiopure α-substituted α-amino-β-lactam fragments (II, Fig. 11) by α-alkylation of suitable *N*-[bis(trimethylsilyl)methyl]-β-lactams through a totally stereocontrolled way [270].

3-Alcoxycarbonyl-1β-methylcarbapenem and 3-alcoxycarbonyl-1α-methylcarbapenem (III and IV, respectively, Fig. 11) have been reported to be prepared by using a palladium-catalyzed C–N bond-forming coupling of vinyl halide and β-lactam nitrogen [271].

Using a similar methodology but starting from a β-lactam having a propargyl moiety, the synthesis of 1β-methylcarbapenem and 1α-methylcarbapenem (V and VI, respectively, Fig. 11) has also been reported [272].

Alcaide and coworkers have reported the thermolysis of β-lactam-tethered enallenyl alcohols to give tricyclic ring structures (Fig. 12) via a formal [2+2] cycloaddition of the alkene with the distal bond of the allene [273].

The same authors have also reported the preparation of tricyclic β-lactams containing eight, nine, and 10 medium-sized central rings and four-, five-, and six-membered distal rings (I, II and III, respectively, Fig. 13) starting from

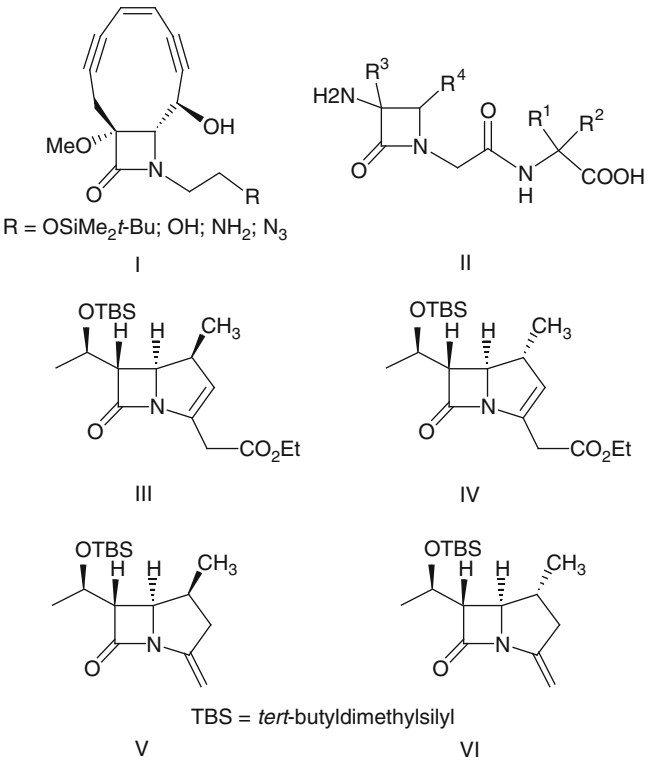


Fig. 11

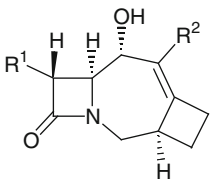


Fig. 12

conveniently substituted bis-β-lactams, pyrrolidinyl-β-lactams, and piperidinyl-β-lactams, which underwent ring-closing methatesis using Grubbs'carbene, $Cl_2(Cy_3P)_2Ru{=}CHPh$ [274].

Furthermore, they have reported the preparation of aza-Diels-Alder cycloadducts (I and II, Fig. 14) arising from a useful dual Diels-Alder behavior. Imines derived from 4-oxoazetidine-2-carbaldehydes have been found to behave as azadienophiles with the Danishefsky's reagent, and as azadiene with alkenes [275].

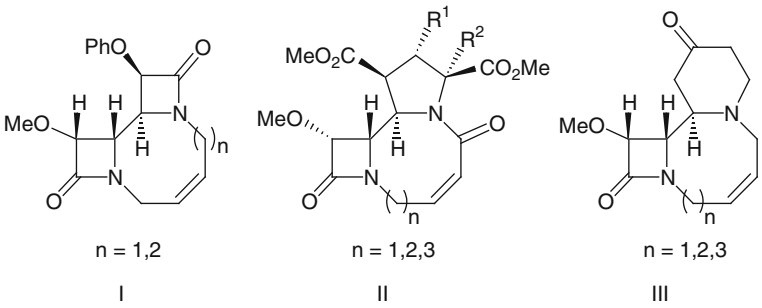


Fig. 13

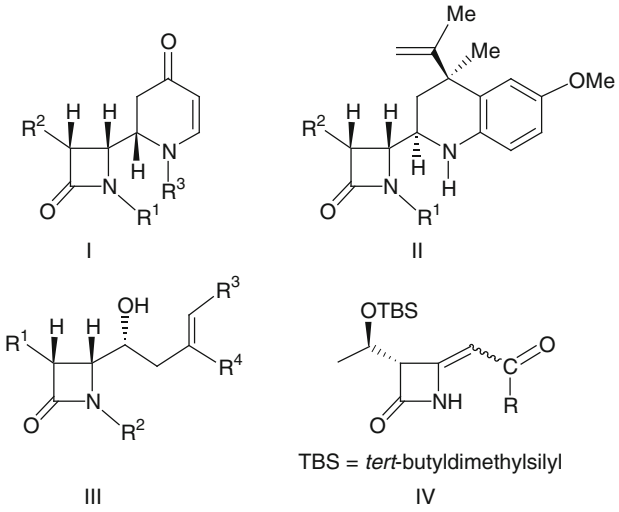


Fig. 14

Using enantiopure 4-oxoazetidine-2-carbaldehydes, the same authors have also reported the coupling reaction with various activated alkenes, in the presence of a Lewis acid, leading to homoallyl β-lactams (III, Fig. 14), [276].

Cainelli and coworkers have reported the synthesis of a class of 4-(2-oxoethylidene)azetidin-2-ones (IV, Fig. 14) that could be carried out by a novel Lewis acid mediated reactions of 4-acetoxyazetidin-2-ones with α-diazocarbonyl compounds [277].

The same authors have also reported that the (*E*)- and (*Z*)-4-alkylidene-β-lactams have shown a different reactivity in the acylation reactions under basic conditions [278]. For instance, the *E* isomer formed readily the *N*-acyl-4-alkylidene-β-lactam, while the *Z* isomer reacted sluggishly rearranging to the corresponding oxazin-6-one (I and II, respectively, Fig. 15).

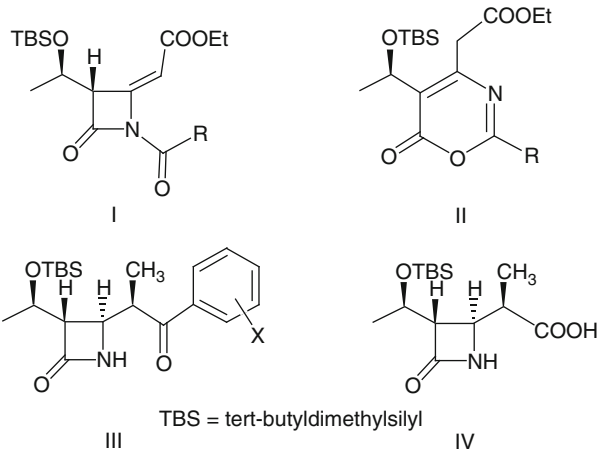


Fig. 15

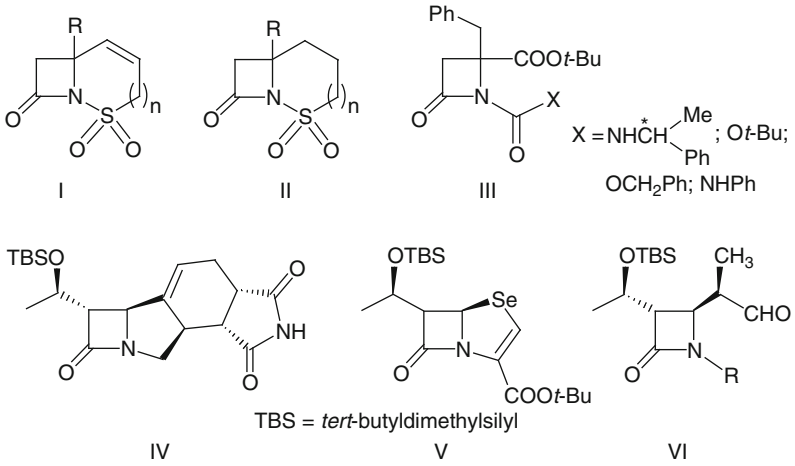


Fig. 16

Lee and coworkers reported in 2004 the preparation of a key 1-β-methylcarbapenem intermediate (III, Fig. 15) by condensation of 4-acetoxy-β-lactam with a titanium enolate of 2′-hydroxypropiophenone [279]. The resulting ketone was converted into the corresponding carboxylic acid (IV, Fig. 15) by a dry ozonation method.

A simple synthetic protocol for the production of β-lactams fused to a sultam moiety (I and II, Fig. 16) using a ring closure metathesis has been developed [280].

Using suitable acylating agents and under the right conditions, different 1-acyl-β-lactams (III, Fig. 16) have been reported to be prepared from phenyl-derived 2-azetidinones [281].

An efficient route to 4/5/6 polycyclic β-lactams (IV, Fig. 16) by enzyme metathesis and Diels-Alder reactions has been described starting from 4-acetoxy-3-substituted-2-azetidinones [282].

Selenopenams (V, Fig. 16) have been reported to be prepared in good to moderate yields in processes that presumably involved intramolecular homolytic substitution at selenium, starting from 2-azetidinone derivatives [283, 284].

The asymmetric hydroformylation of *N*-substituted 4-vinyl β-lactams, catalyzed by rhodium(I) complexes, leading to 1-β-methylcarbapenem precursors (VI, Fig. 16) has been reported [285].

In 2005, the group of Alcaide has reported the regiocontrolled preparation of biaryl-2-azetidinones (I and II, Fig. 17), via aryl-aryl radical cyclization and/or rearrangement of β-lactam-tethered haloarenes [286].

Moreover, using the same starting materials, they have reported the regio- and stereoselective synthesis of enantiopure or racemic benzofused tricyclic β-lactams such as benzocarbapenems and benzocarbacephems (III and IV, Fig. 17) via intramolecular aryl radical cyclization [287].

The same authors have reported the conversion of 4-oxoazetidine-2-carbaldehydes into thiazolyl derivatives, firstly (I, Fig. 18), and subsequently into α-alcoxy β-lactam acetaldehydes (II, Fig 18), through a three-step reaction [288].

They have also reported a direct route to optically pure, fused, or bridged tricyclic β-lactams (III and IV, Fig. 18) as further advances in the intramolecular nitrone-alkene cycloaddition reactions of monocyclic 2-azetidinone-tethered alkenylaldehydes [289].

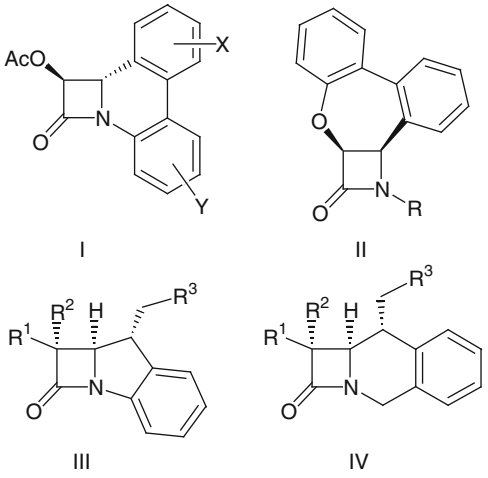


Fig. 17

Fig. 18

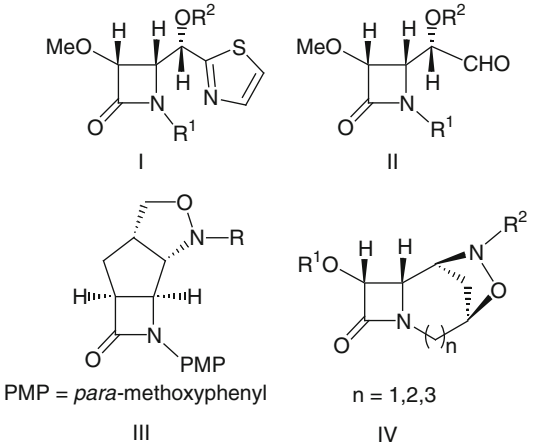
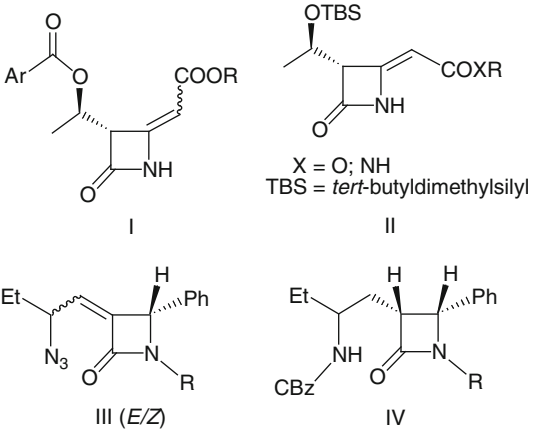


Fig. 19

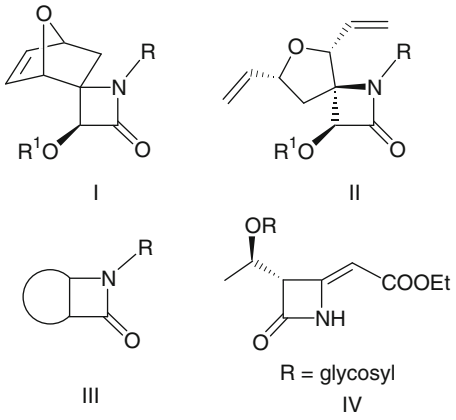


A series of 4-alkyliden-β-lactams (I and II, Fig. 19) has been reported to be prepared combining the β-lactam with a polyphenol scaffold [290].

A mixture of diastereomeric azides (*E*/*Z*) in fast equilibrium (III, Fig. 19) has been obtained by treatment of 3-alkenyl-3-bromoazetidin-2-ones with NaN_3 [291]. The subsequent hydrogenation and the following protection with CBz derivatives afforded 3-(2′-amino)-β-lactams as single diastereomers (IV, Fig. 19).

A procedure based on Ru-catalyzed metathesis sequences with oxanorbornene precursors (I, Fig. 20), obtained by the Staudinger [2+2] cycloaddition of related imines, has been reported to lead to spiro-β-lactams tethered to tetrahydrofuran rings (II, Fig. 20), [292].

Fig. 20



A method has been developed for obtaining the *N*-alkylation of bicyclic β-lactams (III, Fig. 20) using silica supported cesium carbonate under solvent free conditions [293].

Cainelli and coworkers have reported in 2006, some further advances in the preparation of 4-alkyliden-β-lactams starting from 4-acetoxy azetidinones and diazoesters [294].

A new class of glycoconjugated β-lactams (IV, Fig. 20) has been reported to be obtained by direct glycosidation of a suitable 4-alkylidenazetidin-2-one acceptor with several glycosyl donors activated by catalytic $Yb(OTf_3)$ [295].

Two classes of structures containing azido- and aziridino-hydroxyl-β-lactam (I and II, respectively, Fig. 21) have been prepared by means of a stereo- and regioselective epoxide ring opening reaction [296].

The treatment of *cis*-3-(prop-2-ynyloxy)- or *cis*-3-(enyloxy)-β-lactam with one equiv. of iodine in dichloromethane at room temperature has been reported to produce two types of spiro-β-lactam (III and IV, respectively, Fig. 21) [297].

The same authors have also investigated the stereoselective synthesis of unsymmetrically disubstituted azetidin-2-ones (V, Fig. 21) by using Lewis acid mediated functionalization of β-lactams with various active aromatic substrates [298].

The preparation of novel, strained tricyclic β-lactams (Fig. 22) containing a cyclobutane ring has been developed to be performed by intramolecular [2+2] cycloaddition reactions of 2-azetidinone-tethered enallenols [299].

The group of Cainelli has reported in 2007, the direct vinylic substitution of 4-alkylidenazetidin-2-ones to give the corresponding chloro, bromo, iodo, and nitro derivatives (I, Fig. 23), [300].

The reductive radical cyclization of δ- and ε-epoxynitrile has been reported to be achieved using titanocene monochloride affording fused bi- and tricyclic β-lactams (II and III, respectively, Fig. 23), [301].

As an advancement of previous work, the group of Alcaide has reported the preparation of fused bi- and tricyclic β-lactams by a two step reaction: the carbonyl allenylation of substituted 4-oxoazetidine-2-carbaldehydes, followed by

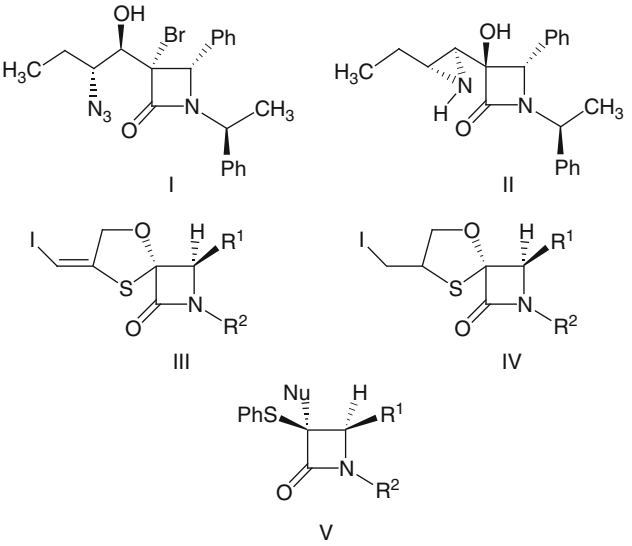


Fig. 21

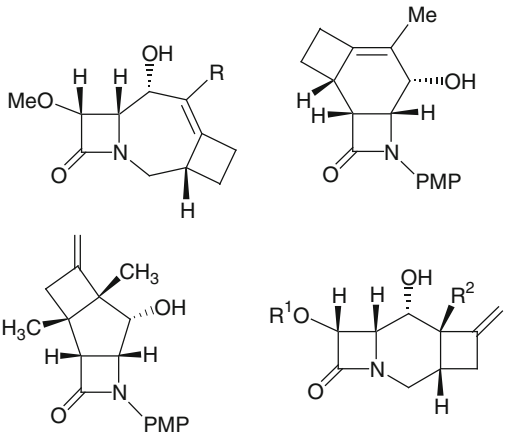


Fig. 22

the tin-promoted radical cyclization of the resulting allene-β-lactams (I and II, Fig. 24), [302].

Benfatti and coworkers have reported further advancements in the intramolecular ring-opening reaction of β-hydroxy epoxides affording spiro-oxetanes and tetrahydrofurans (III and IV, respectively, Fig. 24), [303].

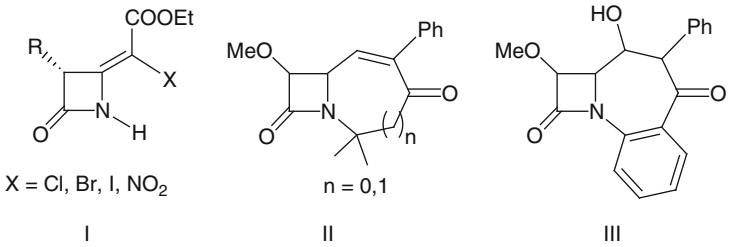


Fig. 23

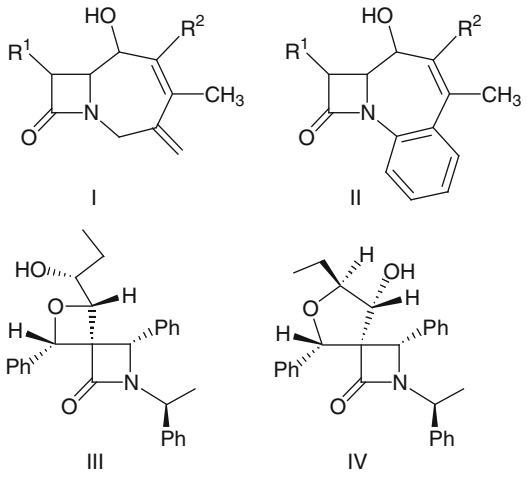


Fig. 24

The reaction of chlorosulfonyl isocyanate with 1,4-cycloesadiene [304] was previously reported to provide β-lactams in quantity. More recently, these CSI-derived building blocks have been reported to be modified in various β-lactams bearing at C-3 and C-4 protected polar substituents (I, II and III, Fig. 25), [305].

Moreover, the C-3 and the C-4 positions of the azetidinone ring have been reported to be stereoselectively functionalized inserting various groups through the generation of a stable azetidinyl carbanion which can be captured by various electrophiles [164].

The Diels-Alder cycloaddition reaction of both *cis*- and *trans*-dienyl-2-azetidinones with unsymmetrical dienophiles in the presence of Lewis acid catalysts has been reported to give in regio-, stereo-, and remarkably high π-facial selectivity novel 1,3,4-trisubstituted-2-azetidinone derivatives in good yields (I and II, Fig. 26), [306].

$Cu(OAc)_2$ in combination with a solid base such as K_2CO_3 has been reported to be an extremely efficient system in promoting the homocoupling of 2-azetidinones-tethered alkynes, whereas the cross-coupling of bromoalkynyl-β-lactams with

Fig. 25

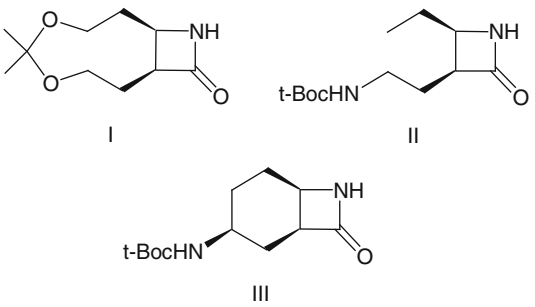


Fig. 26

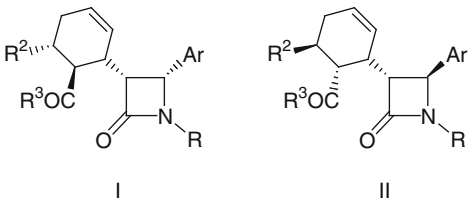
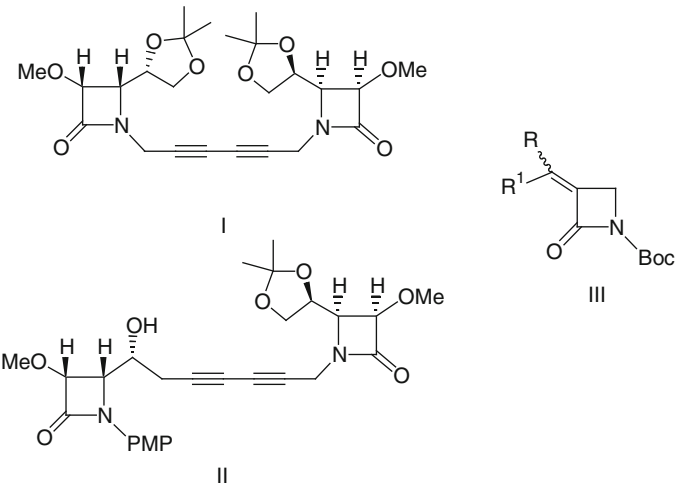


Fig. 27



terminal alkynyl-β-lactams could be easily achieved by a copper-catalyzed Cadiot-Chodkiewicz reaction. These methodologies offered a convenient method for the preparation of both racemic and enantiopure C2-symmetrical and unsymmetrical bis(-β-lactam)-1,3-diyne hybrids (I and II, Fig. 27), [307].

Electron-poor α-methylene-β-lactams were reported to undergo cross-metathesis more rapidly and efficiently than more electron-rich analogs. Significantly, tetrasubstituted alkenes have for the first time been accessed by cross-metathesis reactions (III, Fig. 27), [308].

4.4 Biological Activity

The most significant biological and pharmacological applications of the 2-azetidinones are reported in this paragraph, highlighting the SAR studies applied for the design of new and more efficient molecules.

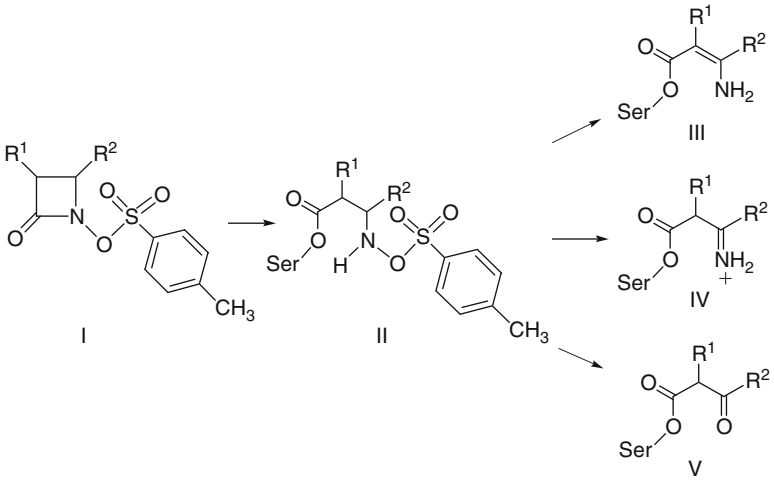
4.4.1 Antibacterial Activity: Inhibitors of β-Lactamases

Three of the four classes of β-lactamases, A, C, and D are serine nucleophile-based enzymes, while the fourth, class B, contains zinc metallo-β-lactamases. Among the serine β-lactamases, classes A and C are currently the most intensely studied. However, extended spectrum class D enzymes have, of late, been growing in clinical importance [309–314].

The action mechanism of a novel class of monobactams, inhibitors for the class A β-lactamases has been reported in 1999 and is showed in Scheme 103 [310–313]. As exemplified by structure I, the inhibitor acylated rapidly the active site serine of β-lactamase and the tosylate was released from species II. The acyl-enzyme underwent fragmentation, resulting in enzyme inhibition by formation of three distinct products, depending on the type of functionality linked to the inhibitor (III, IV, or V, Scheme 115).

The presence of a phenyl group at the C-4 position of the azetidinone ring favored a specific hydrophobic interaction with the active site of class A β-lactamases. Instead, the stereochemistry of the C-4 position appeared to be not important for the inhibition [310]. Studies recently reported for the structure-function analyses of the sulfonate moiety have argued for the requirement of a hydrophobic functionality, but its size did not appear to be restrictive. The absence of any hydrophobic functionality at this position lowered the ability of the molecules to inhibit β-lactamases [314].

Many serine-based β-lactamases are susceptible to inhibition by compounds containing a β-lactam nucleus such as clavulanic acid and sulbactam. Moreover, β-lactams that contain large substituents at the C-6 position, such as imipenem, moxalactam, and cefoxitin, inhibit both class A and class C β-lactamases. Previous studies have shown that conformational changes induced by large C-6 substituents destabilized these enzymes upon binding [315, 316]. The group of Beadle, in 2002, has reported crystallographic data of these inhibitors suggesting a different mechanism of action towards class A and class C enzymes, respectively [317].



Scheme 115 The action mechanism of a novel class of monobactams, inhibitors for the class A β-lactamases

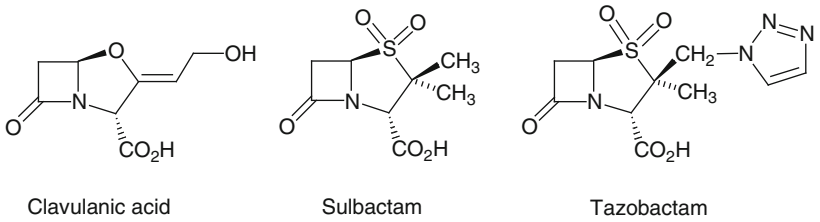


Fig. 28

Known inhibitors of the class A, C, and D serine β-lactamases acylate the active site serine. The commercial inhibitors showed in Fig. 28 are selective for class A enzymes, since they structurally resemble penicillins more closely than they resemble cephalosporins.

As in penicillin, the carboxylates of these commercial inhibitors are bonded to an sp^3-hybridized carbon. Therefore, Buynak and coworkers in 2005 have hypothesized that a C-3-homologated penam-derived β-lactamase inhibitor might have broader specificity for both the A and C classes of β-lactamase than that performed by current commercial inhibitors [318]. The enhanced conformational flexibility of the carboxylate of the homologated penam derivative could enable the molecule to fulfill the geometric requirements of both A and C classes of serine β-lactamase. The longer chain might also enable the carboxylate to penetrate deeper into the positively charged pocket. In the second instance, they have hypothesized that placing a double bond in direct conjugation with the nitrogen, but exocyclic to the five membered ring, might also enhance acylation efficacy. The same group has

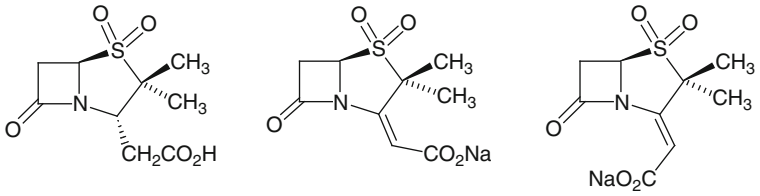


Fig. 29

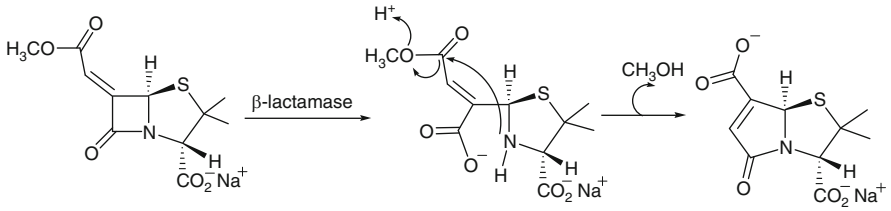
reported the synthesis of these prospective inhibitors (Fig. 29) together with a preliminary investigation of their ability to inactivate serine β-lactamases.

The inhibitory data obtained indicated that the homologated sulbactam analog I (Fig. 29), had a 10-fold improved inhibitory activity against the class C β-lactamase enzyme, as compared with sulbactam itself. The additional carbon could allow greater conformational flexibility, thus allowing the carboxylate of structure I to occupy a space similar to that occupied in a typical cephalosporin substrate. It may be noted, however, that the compounds having the exocyclic unsaturation (II and III, Fig. 29) did not display a significant ability to inactivate either class A or class C serine β-lactamases. This could be due to the conformational rigidity imposed by the exocyclic unsaturation. These compounds were slowly hydrolyzed in buffered aqueous media and this hydrolysis was accelerated in the presence of the class A serine β-lactamase, thus indicating that they were good substrates. As in the penems and carbapenems, the unsaturation present on the five-membered ring (endocyclic or exocyclic) presumably further activated the β-lactam moiety towards hydrolysis. This could explain the reduced hydrolytic stability of structures II and III (Fig. 29).

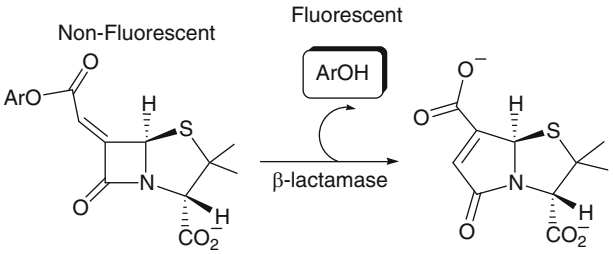
As far as the metallo-β-lactamases (class B) are concerned, their emergence posed a new challenge as they are not susceptible to known inhibitors, and the newer generation of these enzymes acts on a broad variety of β-lactam structures-penicillins, cephalosporins, and carbapenems. Further, the 2-azetidinone nucleus has been employed in 2004 by Ruddle and Smyth to prepare β-lactamase-dependent prodrugs which have hidden or latent reactivity that is triggered by scission of the β-lactam ring [319]. Thus, the penam nucleus could be modified to behave as a β-lactamase-dependent "prodrug" by incorporation of a vinyl ester side chain at the C-6 position. β-Lactamase-catalyzed hydrolysis of the β-lactam ring uncovered the thiazolidine-ring nitrogen as a nucleophile that drove a rapid intramolecular displacement on the side chain (Scheme 116).

Attachment of 7-hydroxy-4-methylcoumarin as the releasable group of this side chain generated a penicillin structure that can function as a fluorescence-based reporter substance/diagnostic for the presence of low levels of β-lactamase enzyme in solution (Scheme 117), [320].

Clavulanic acid, a naturally occurring powerful inhibitor of bacterial β-lactamases is a major β-lactam antibiotic produced by organism Streptomyces



Scheme 116 Suggested mechanism of action ofa β-lactamase-dependent prodrug



Scheme 117 Fluorescence-based penicillin structure having a 7-hydroxy-4-methylcoumarin as releasable group

clavuligerus and is active against a wide spectrum of Gram-pos. and Gram-neg. bacteria. The biosynthetic pathway, the fermentative production, the downstream processing, and applications of clavulanic acid has been reviewed in 2008 [321].

Another interesting review has been reported on Meropenem which is a broad-spectrum antibacterial agent of the carbapenem family. It is indicated as empirical therapy prior to the identification of causative organisms, or for disease caused by single or multiple susceptible bacteria in both adults and children with a broad range of serious infections. Meropenem has a broad spectrum of in vitro activity against Gram-pos. and Gram-neg. pathogens, including extended-spectrum β-lactamase- and AmpC-producing Enterobacteriaceae [322].

4.4.2 Antibacterial Activity: Inhibitors for Pilus Formation

Bacteria need to adhere to host tissue in order to cause disease. Many pathogenic bacteria assemble pili, i.e., extracellular protein organelles, to mediate attachment to host epithelial cells. Pilus assembly is performed by periplasmic chaperones, which bring subunits to the outer cell membrane where they are incorporated in the growing pilus [323]. A drug inhibiting pilus formation, termed a pilicide, would therefore have the potential of being an effective antibiotic. It has been shown, both by nuclear magnetic resonance (NMR) spectroscopy [324] and by X-ray

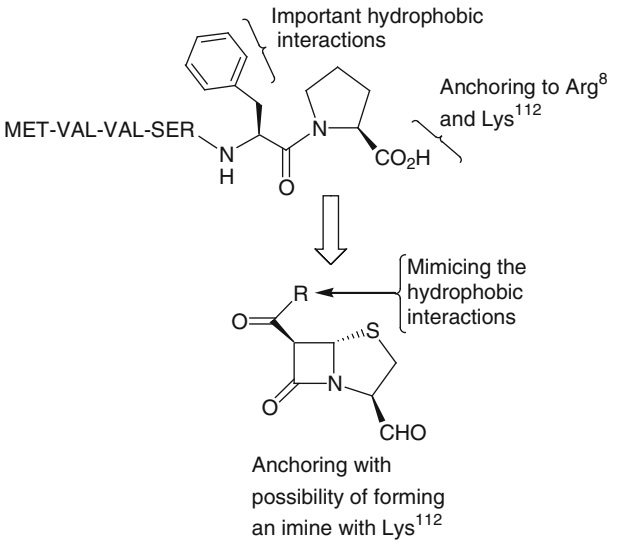


Fig. 30

crystallography [325, 326], that synthetic peptides from the conserved *C*-termini of the pilus proteins are bound by the PapD chaperone (found in uropathogenic Escherichia Coli, which is the main cause of urinary tract infections). Thus, it has been found that PapD binds polypeptides by anchoring the peptide carboxyl terminus to the side chains of Arg^8 and Lys^{112} (Fig. 30), two residues that are invariant in all periplasmic chaperones and are required for pilus assembly. On the basis of the crystal structures of peptide-PapD complexes [325, 326], β-lactams have been selected as potential chaperone inhibitors with the requirement of having different stereochemistry than the original penicillin's, thus having a chance to withstand enzymatic degradation by penicillin-resistant bacteria. The overall strategy consisted in creating small organic molecules with a rigid framework, which would locate the pharmacophores in the right position in the space [57]. In addition, this class of compounds allowed hydrophobic substituents (indicated by R) to interact with the chaperone while maintaining the important anchoring to Arg^8 and Lys^{112}. Moreover, the crystal structures showed that the C-terminal carboxyl group was within such a distance from Lys^{112} that replacing it with an aldehyde would allow an imine to be formed with Lys^{112}.

4.4.3 Antibacterial Activity: Various Inhibitors

In 2000, a new family of *N*-methylthio-substituted β-lactams having promising antibacterial properties has been identified by Turos and coworkers. Curiously, most of this activity is directed towards Staphylococcus bacteria, including methicillin-resistant strains of *Staphylococcus aureus* (MRSA). These β-lactams showed

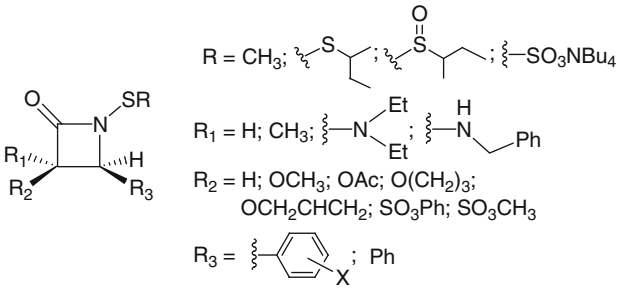


Fig. 31

a different behavior compared to all other β-lactam antibiotics [327]. Rather than interfering directly with cell wall biosynthesis, through irreversible acylation of penicillin binding transpeptidases, these compounds seemed to affect cellular processes through transfer of the *N*-organothio group to a bacterial thiol. It has been also noted that these lactams exert antiproliferative properties against only a narrow range of bacterial genera, most significantly, Staphylococcus (including MRSA), Micrococcus, and Neisseria. This selectivity seems to be related to the levels and types of cellular thiols present in each microbe that is sensitive to the lactams, not to whether the microbes are Gram positive or Gram negative classes. The anti-Bacillus properties of a selected number of differentially substituted β-lactams based on the structure of Fig. 31 were also investigated by the same authors in 2006 [328].

The β-lactams have been individually tested for antibacterial activity against *Bacillus anthracis* and six other species of Bacillus by the well known Kirby-Bauer method on agar plates [329]. In general, lipophilic acyloxy or alkoxy groups at the C-3 carbon of the lactam ring led to the strongest growth inhibition properties against each of the seven Bacillus microbes examined. The most important substituent influencing the anti-Bacillus activity, as in the case of MRSA, was found to be the *N*-organothio moiety, with the *sec*-butylthio group having the best overall bioactivity. The mechanism of action of these lactams in Bacillus most likely paralleled that in Staphylococcus, with transfer of the *N*-organothio substituent from the lactam to a cellular thiol occurring within the cytoplasm of the bacterium [328]. Recent findings in 2007 indicated that N-thiolated-β-lactams react rapidly within the bacterial cell with CoA through in vivo transfer of the N-thio group to produce an alkyl-CoA mixed disulfide species, which then interferes with fatty acid biosynthesis. The studies on CoA disulfide reductase showed that the CoA thiol-redox buffer was not perturbed by these compounds; however, the lactams appeared to act as prodrugs. The evidence that these β-lactams inhibit fatty acid biosynthesis in bacteria, and the elucidation of CoA as a primary cellular target, offers opportunities for the discovery of other small organic compounds that can be developed as therapeutics for MRSA and anthrax infections [330]. The same authors have found in 2008 that these lactams also possess antifungal activity against Candida

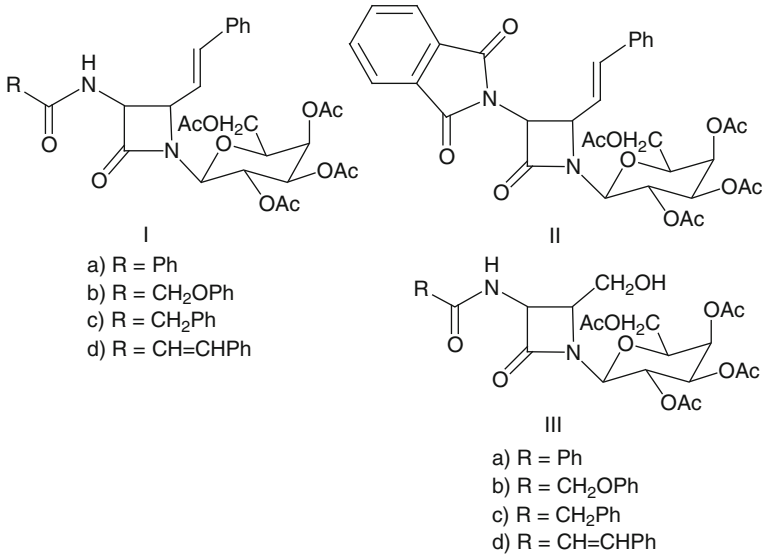


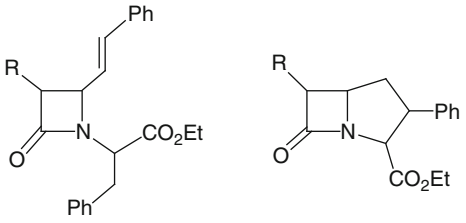
Fig. 32

and other fungi by exerting powerful cytostatic effects that disrupt the structural integrity of cytoplasmic membranes. The mode of action and structure-activity trends of these lactams as antifungals parallel that previously seen in their antibacterial studies [331].

Jarrahpour and coworkers in 2004 have prepared and tested some new sugar-based monocyclic β-lactams possessing several other functionalities, in addition to the carbohydrate moiety [88]. The presence of a carbohydrate moiety side chain in a drug may also overcome the frequently observed water insolubility problem [332]. Moreover, the bacteria may utilize a carbohydrate uptake mechanism, which allows for a better transport of the monocyclic β-lactams across the membrane. The antibacterial activities of compounds depicted in Fig. 32 have been tested against one strain each of a Gram positive bacteria (*Staphylococcus citrus*), a Gram negative bacteria (*Escherichia coli*), a Gram negative containing capsule (Klebsiella), and a Gram positive spore (*Bacillus subtilis*). The antimicrobial activity tests have been performed according to the disk diffusion method [333], using Ampicillin and Gentamycin as reference compounds. The inhibition zones caused by the various compounds on the microorganisms have been measured and the activity rated on the basis of the size of the inhibition zone.

The data obtained have shown that compound II (Fig. 32) was highly active against *Staphylococcus citrus*, *Klebsiella pneumoniae*, *Escherichia coli,* and *Bacillus subtilis* while β-lactams Ib and Ic were moderately active against these four microorganisms. Compound IIIb was highly active against *Bacillus subtilis*, while compound IIId was moderately active against *Bacillus subtilis*. Compounds IIIa–d were slightly active against *Staphylococcus citrus* [88].

Fig. 33



R = PhtN; $PhCH_2COHN$; $PhOCH_2COHN$; CH_2OH; CHO; PhCOHN; PhCH=CHCOHN

The same group of Jarrahpour has also synthesized a few mono and bicyclic β-lactams (Fig. 33) and tested their antimicrobial activity [92].

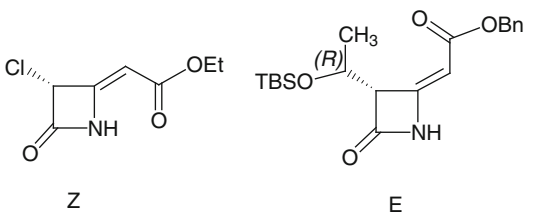
These compounds have been tested against one strain each of Gram positive bacteria (*Staphylococcus citrus*), Gram negative bacteria (*Escherichia coli*), a Gram negative containing capsule (Klebsiella), and a Gram positive spore (*Bacillus subtilis*). Monocyclic β-lactams with R = PhtN, $PhCH_2COHN$, $PhOCH_2COHN$ were highly active against *Bacillus subtilis* and moderately active against *Staphylococcus citrus*. Other compounds were all inactive against these four pathogenic microorganisms [92].

Broccolo and coworkers in 2006 have reported the synthesis and antibacterial activity of a new class of monocyclic β-lactams substituted at the C-4 position with an alkyliden carboxy side chain [294]. Preliminary results of the antibacterial activity of some of these 4-alkyliden-β-lactams have disclosed the opportunity for the application of molecular modeling to relate chemical structures to antibiotic activity and to point out structural modifications that might increase antibiotic potency. Despite significant advances in the elucidation of the structures of penicillin-binding proteins (PBPs), the overall structural basis for multidrug bacterial resistance has not been clarified. PBPs are a heterogeneous family of enzymes with transpeptidase and transcarboxylase activities involved in the synthesis and cross-linking of the peptidoglycan component of bacterial cell walls, which is fundamental for the maintenance of bacterial cell morphology and integrity. On the basis of these considerations, the authors adopted a molecular modeling approach to identify attractive drug candidates and to contribute to the rationalization of functional group effects on the SARs. Thus, a series of β-lactams have been synthesized such as compounds of Fig. 34, that exhibited an inhibitory effect, generally more marked against Gram positive pathogens, although the spectrum of activity varied.

Interestingly, the undifferentiated antibacterial activity against both methicillin-susceptible and -resistant strains of *Staphylococcus aureus* was suggestive of an alternative mechanism of action compared to that of typical β-lactams. The molecular modeling approach allowed the identification of interactions through oxygenated functions such as phenolic OH, which are valuable for the antibacterial activity [294].

Bactericidal effects have been reported for two β-lactams: amoxicillin and its combination with clavulanic acid. They showed in vitro effects on the oxidative

Fig. 34



metabolism of PMN neutrophils. These cells play the major role in the "respiratory burst" as they produce superoxide anion to kill the infectious agent. An activation of this process by the injected antibiotics could enhance the bactericidal action or explain some of the adverse effects. Amoxicillin could either activate PMN neutrophils NADPH-oxidase or cause its activation by a membrane effect, or interfere with the zymosan activation way [334].

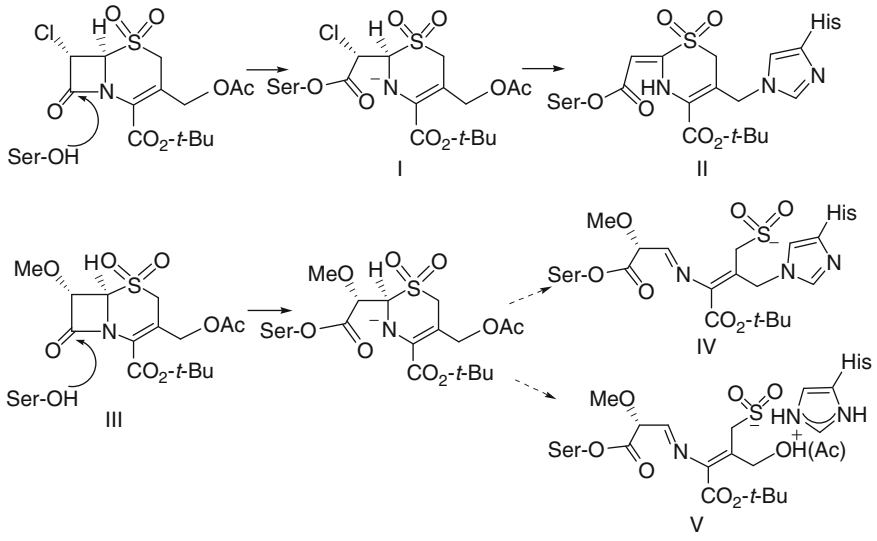
Amoxicillin has been reported among the amino-β-lactams like cefadroxil, and ampicillin as aminating agent of catechols to obtain novel cephalosporins, penicillins, and carbacephems using fungal laccase. All isolated monoaminated products inhibited the growth of several Gram pos. bacterial strains in the agar diffusion assay, among them methicillin-resistant Staphylococcus aureus strains and vancomycin-resistant Enterococci [335].

Antifungal and antibacterial activity have also been reported for bile acid dimers linked through 1,2,3-triazole and bis-β-lactam [336].

Investigations towards novel glycopeptide/β-lactam heterodimers were reported in 2008. Employing a multivalent approach to drug discovery, vancomycin and cephalosporin synthons were chemically linked to yield heterodimer antibiotics. These novel compounds were designed to inhibit Gram-pos. bacterial cell wall biosynthesis by simultaneously targeting the principal cellular targets of both glycopeptides and β-lactams. The positional attachment of both the vancomycin and the cephalosporin central cores has been explored and the SAR was reported. This novel class of bifunctional antibiotics all displayed remarkable potency against a wide range of Gram-pos. organisms, including methicillin-resistant Staphylococcus aureus [337].

4.4.4 Inhibitors of Human Leukocyte Elastase

The first β-lactams LE inhibitors were naturally occurring bicyclic compounds, such as clavams and cephalosporins [338], but more recently, synthetic monocyclic β-lactams have been developed. Time-dependent inhibitors of enzyme HLE, based on the cephem nucleus, have been reported. A series of cephalosporin *tert*-butyl esters have been examined, and the activity of these compounds has been found to be very sensitive to the C-7 substituents, the greatest activity being showed by small, α-oriented, and electron-withdrawing groups. Additionally, the oxidation

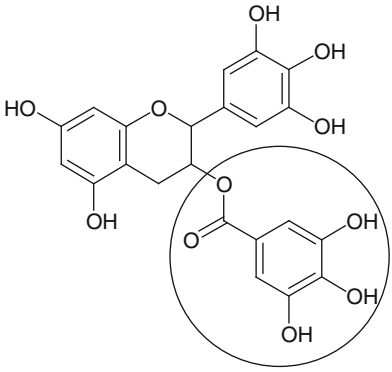


Scheme 118 Action mechanism of inhibitors for the HLE

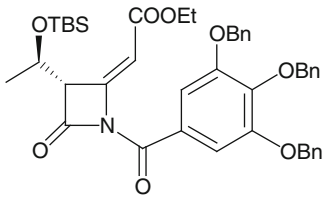
state of the sulphur atom has been found to play a strategic role in strengthening molecular activity. For instance, sulfones showed considerably greater activity than the corresponding sulfides or β-sulfoxides, resulting the latter inactives [339]. The mechanisms thought to be at work when molecules of this type inhibit HLE have been studied (Scheme 118), [339].

Two types of inhibited complexes can be formed, at least, with HLE. The starting step, in all cases, is considered to be the β-lactam ring-opening performed by the OH of the Ser-195 belonging to the enzyme catalytic triad (Ser-195, His-57, Asp-102), to form the complex I. If the C-7 substituent is a chlorine atom, the expulsion of the 3′-acetate, followed by loss of HCl and Michael addition of His-57 imidazole ring to the N-1 nitrogen, led to the inhibited complex II. However, when the C-7 substituent is a poorer leaving group, such as methoxide (III, Scheme 118), crystallographic data suggested that this group is not lost but the thiazoline ring-opening reaction generated an inhibited species. At this point, it is not possible to discern if there is a second covalent linkage between the inhibitor and the enzyme (IV, Scheme 118) or, alternatively, if a critical salt bridge between the released sulfinate and the His-57 imidazole is formed. In this latter case, the hydrolysis of the intermediate V is presumably slowed as the imidazole moiety is not properly aligned to deliver water to the serine carbonyl ester.

In 2003, Cainelli and coworkers have shown that monocyclic β-lactams substituted at the C-3, the C-4, and the N-1 positions are the most active in inhibiting LE and gelatinases MMP-2 and MMP-9 [340]. They have also reported that C-4 unsaturation on the β-lactam ring raised the inhibitory activity towards these proteases, with selectivity over LE by 3-[1-(*tert*-butyldimethylsilyloxy)ethyl] derivatives, and over the gelatinase MMP-2 by C-3-unsubstituted 4-[1-ethoxycarbonyl]



I
(–) epigallocatechin-3-gallate (EGCG)
with encircled galloxyl moiety



II
(*N*-galloxyl-4-alkyliden-β-lactam)
TBS = *tert*-butyldimethylsilyl

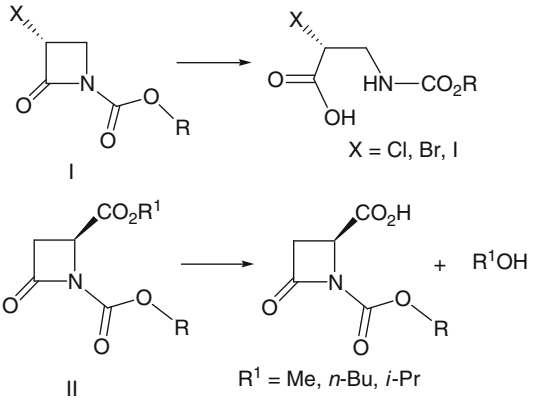
Fig. 35

ethylidene-β-lactams. Some catechins (vegetable secondary metabolites of the flavonoid family), and in particular those with a galloyl group (I, Fig. 35), have been shown previously by the same authors, to exert a very powerful inhibition of LE activity [341–343], but their absorption, bioavailability, and metabolic fate awaited full clarification. Thus, in 2005 a number of monocyclic β-lactam derivatives with a galloyl moiety-like group in different positions were synthesized and tested [290]. Some of these, such as the *N*-galloxy-4-alkyliden-β-lactam (II, Fig. 35) appeared to exert an improved anti-LE activity.

In 2002 Gérard and coworkers have studied two series of compounds, namely, 3-halide- [344, 345] and 4-alkoxycarbonyl-1-alkoxycarbonyl-2-azetidinones [346], (Scheme 119). These β-lactams behaved as reversible inhibitors of porcine pancreatic elastase (PPE) [347–350], which are considered good models of HLE and more readily available than HLE. The action mechanism of these 2-azetidinone derivatives was different, depending on the C-3/C-4 substitution. Indeed, after a transient inhibition of PPE, enzyme hydrolysis of structure I (Scheme 119) led to the β-lactam bond cleavage without expulsion of OR leaving group, while PPE processing of structure II led to the OR^1 ester cleavage, without the β-lactam ring opening.

Thus, the group of Gerard has designed structural modifications of the β-lactams II in two directions: a) decreasing the reactivity of the C-4 carbonyl substituent, b) increasing the β-lactam carbonyl reactivity and the consequent N-1 substituent expulsion, after C2–N1 bond cleavage. A series of 4-alkylaminocarbonyl-1-alkoxycarbonyl-2-azetidinones and 4-(alkoxycarbonyl)-2-azetidinones, bearing various carbonyl and thiocarbonyl functionalities at the N-1 position, have been prepared [351]. The results showed the potential interest towards *N*-thiocarbonyl-2-azetidinones as reactive structures for the design of novel elastase inhibitors. However, an electron-withdrawing substituent (activating group) placed at the C-4 position (or the C-3) was systematically required to reach a good level of enzyme inhibition. For

Scheme 119 Different action mechanism of 2-azetidinone derivatives depending on the C-3/C-4 substitution



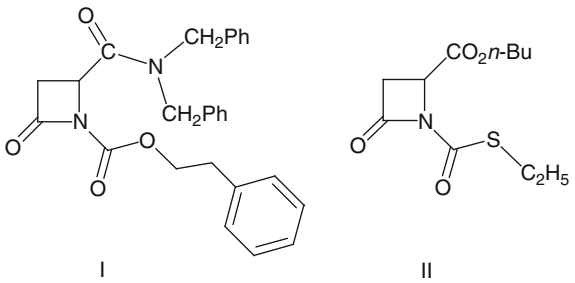


Fig. 36

instance, compound I of Fig. 36 was a good reversible inhibitor of PPE and HLE, acting most probably like 3-halide-1-alkoxycarbonyl-2-azetidinones (I, Scheme 119). Compound II (Fig. 36) was more active against PPE and HLE, but behaved in the same way as 1,4-bis(alkoxycarbonyl)-2-azetidinones (II, Scheme 119) [351].

4.4.5 Inhibitors of Cysteine Protease

The cysteine proteases cathepsin B, L, K, and S are involved in diseases such as osteoporosis, cancer metastasis, rheumatoid arthritis, and infectious diseases [352–357]. Thus, the proteases became an important target for developing inhibitors as therapeutic agents [358–363].

Recently, a series of 4-substituted-3-Cbz-phenyl-β-lactams (Fig. 37) has been identified as a novel class of cysteine protease inhibitors [364].

Several studies have suggested the importance of the (3*S*) stereoconfiguration of the C-3 carbon atom on the enzyme interactions, which is equivalent to the natural L-amino acids configuration. The different substitution at the C-4 position has shown significant effect on the inhibitory power: substituents such as

Fig. 37

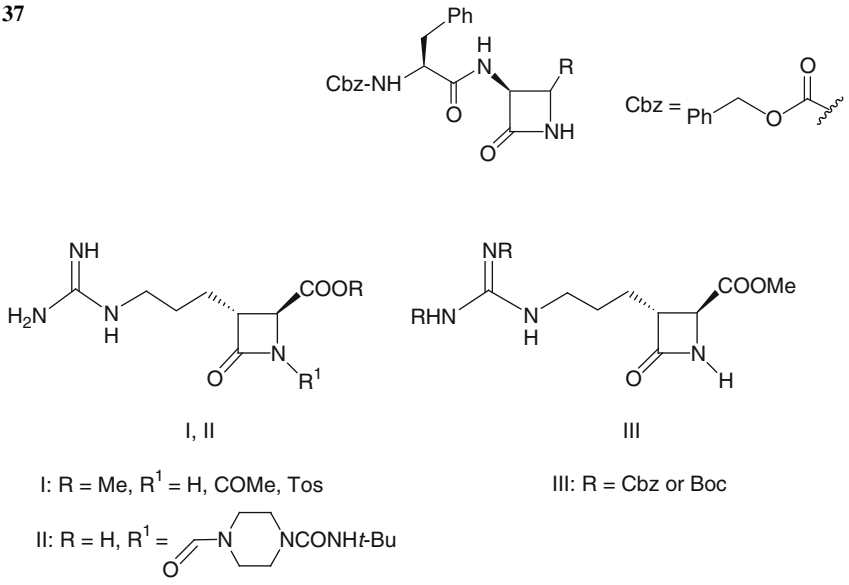


Fig. 38

–OR′, –OCOR′ (R′ = generic aliphatic group), –OPh, –SPh and $–S(O)_2Ph$ appeared to be necessary for a good inhibitory activity. However, the C-4 substituents might not behave only as a leaving group, but they were involved also in the interactions with the enzyme S′ subsite. The C-4 stereo-configuration requirements depended, then, on the nature of the substituents [364].

In 2005 highly potent and selective inhibitors of cathepsin K were reported based on the 3,4-disubstituted azetidin-2-one which seemed to transiently acylate the sulfhydrile of cathepsin K [365].

4.4.6 Inhibitors of Thrombin and Tryptase

Several representatives of the class of the β-lactams can effectively inhibit proteases [366, 367]. For instance, the 2-azetidinone I of Fig. 38 has been identified [368] as a powerful and selective inhibitor of thrombin, a serine protease involved in both venous and arterial thrombotic episodes [369]. More recently, β-lactam II (Fig. 38) has been found to display inhibition of tryptase at the subnanomolar level and suppress induced inflammation in animal lungs [370]. These compounds featured an *ω*-guanidyl-substituted *n*-propyl side chain at the C-3 position and a carboxylic residue at the C-4, both essential for biological activity.

In 2003, Annunziata and coworkers [84] have reported an efficient synthesis of the stereoisomerically pure *trans* compound III (Fig. 38) which represented a convenient, advanced precursor of structures I and II and differently *N*-substituted

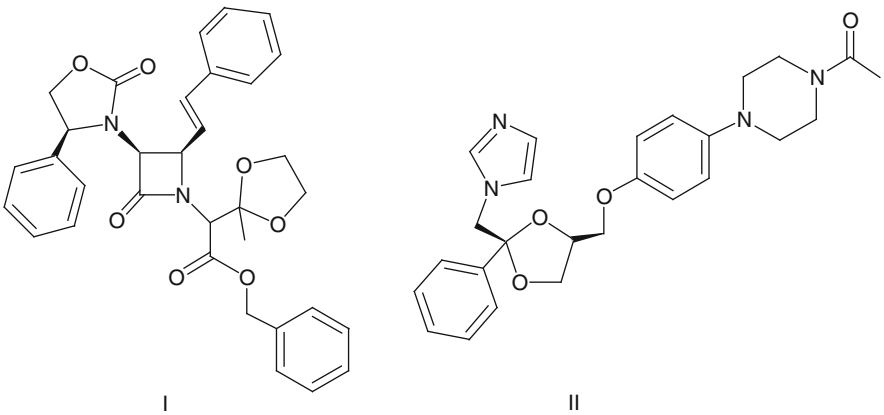
derivatives thereof. The new synthesis of compound III (R = Boc) started from readily available and inexpensive D-glyceraldehyde and opened access to both enantiomers of the target molecules in enantiopure form. Since the thrombin inhibitor I has been described so far only in the racemic form, and no stereochemistry/activity relationship has been reported, the possibility of obtaining both enantiomers of compound III was worth investigating.

β-Lactam compounds variously substituted at C-3, C-4, and N-1 were reported, more recently, as useful inhibitors of tryptase, and thrombin [371, 372].

4.4.7 Azetidinones as Vasopressin V1a Antagonists

Several research groups have prepared antagonists directed to the vasopressin V1a receptor [373–378]. Vasopressin, through the vasopressin 1a receptor (V1a), can stimulate aggressive behavior. Using a novel monocyclic beta lactam platform, a series of orally active vasopressin V1a antagonists was developed, by the group of Guillon, showing high affinity for the human receptor. SRX251 was chosen from this series of V1a antagonists to screen for effects on serenic activity in a resident-intruder model of offensive aggression. The data obtained from this investigation corroborate previous studies showing a role for vasopressin neurotransmission in aggression and suggest that V1a receptor antagonists may be used to treat interpersonal violence co-occurring with such illness as autism, bipolar disorder, and substance abuse [379].

While V1a antagonists have been synthesized, none of these have been reported to penetrate the central nervous system efficiently. In 2007, the same authors have identified the azetidinone LY307174 (I, Fig. 39), for a screening based on 59% molecular similarity to ketoconazole (II, Fig. 39), a marketed antifungal agent

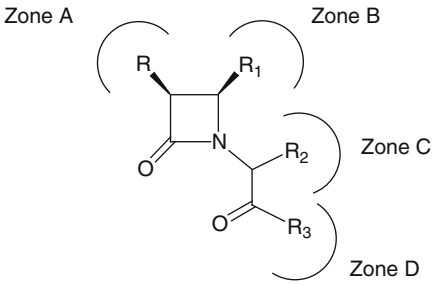


I
LY307174

II
Ketoconazole

Fig. 39

Fig. 40



known to cause reproductive side-effects due to antagonism of the luteinizing hormone releasing hormone receptor [380]. Some features of structure II, such as the dioxolane ring and the terminal phenyl moiety were conserved in structure I, while others group were totally replaced.

Beyond the simple issue of affinity, compound I has been considered an attractive lead for several reasons. First of all, LY307174 is a monocyclic β-lactam (monobactam). Unlike fused-ring β-lactams, such as penicillins and cephalosporins, simple monobactams such as structure I are highly stable to chemical or enzymatic hydrolysis of the azetidinone. The *cis* geometry of the rigid four-membered ring forces the three side-chains together into a fixed geometric configuration, enabling, presumably, the complementarity with subpockets of the receptor. Although the molecular weight of compound I is relatively high, its compactness provided some hope that the series might show significant oral absorption [381]. Thus, SAR studies have been performed, based on the modification of the four zones A–D of the azetidinone molecule, as depicted in Fig. 40.

Further, a novel series of vasopressin V1a antagonists has been synthesized, and subnanomolar affinities at the human V1a receptor have been achieved. On oral dosing, two members of the series, structures I and II of Fig. 41, reached brain levels ~100 times their in vitro receptor affinities. These molecules have been further developed for human clinical evaluation [381].

4.4.8 Hypocholesterolemic Activity

Burnett and coworkers have described the synthesis of a very potent class of cholesterol absorption inhibitors (CAI) typified by the original lead compound in this series: the compound I showed in Fig. 42 (SCH 48461). This 2-azetidinone has resulted as an effective inhibitor of cholesterol absorption in a cholesterol-fed hamster model [9]. Subsequently, the same molecule has been shown to reduce serum cholesterol in human clinical trials [382]. Although this class of compounds has been initially designed as acyl coenzyme A cholesterol transferases (ACAT) inhibitors, early structure-activity studies demonstrated a striking divergence of in vitro ACAT inhibition and in vivo activity in the cholesterol-fed hamster. A detailed examination of this molecule indicated that the hypocholesterolemic

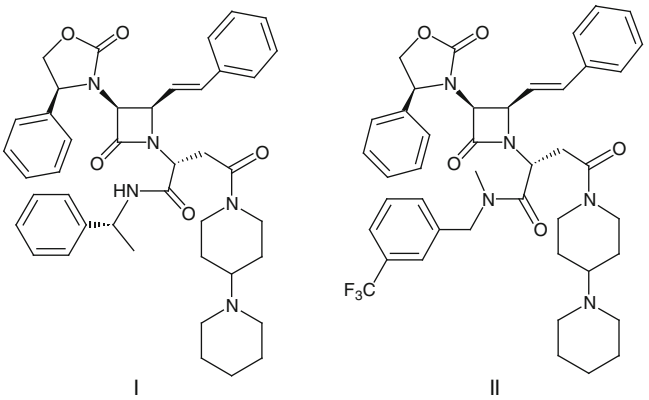


Fig. 41

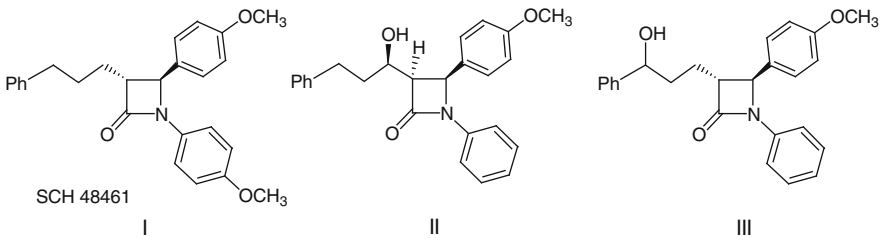
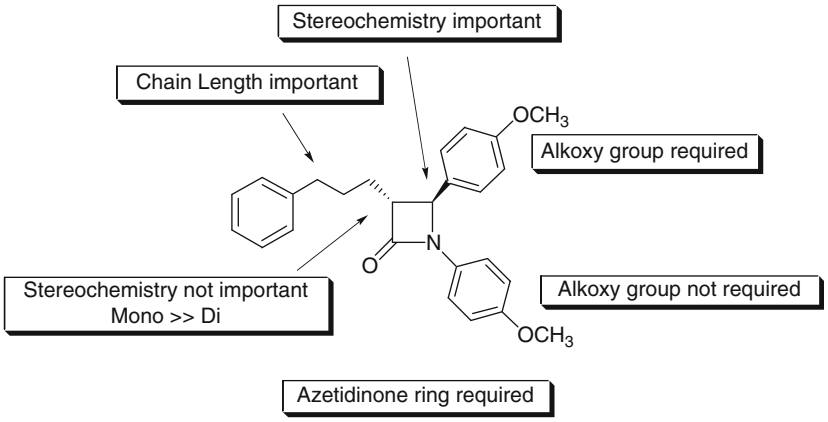


Fig. 42

activity was exerted at the intestinal wall by inhibiting the cholesterol absorption [383].

Reported studies on the structure I of Fig. 42 and analogs of this class have shown that the azetidinone nucleus is a critical element for in vivo activity [384]. On the basis of these findings, an investigation on SAR around the 2-azetidinone nucleus has been performed. The results have revealed a clear SAR for cholesterol absorption inhibition which is different from the modest ACAT inhibitory activity shown by these compounds. Thus, these molecules appeared to be acting via a mechanism which might be fundamentally important in the intestinal absorption of cholesterol [8]. Moreover, structurally related 2-azetidinones (II and III Fig. 42) containing hydroxyl groups on the phenylalkyl substituent at the C-3, have been reported as CAIs more active than their deshydroxy analogs [9, 385]. β-Lactams having a substituent containing a ketonic moiety at the C-3 have also been reported as good inhibitors for cholesterol absorption [386].

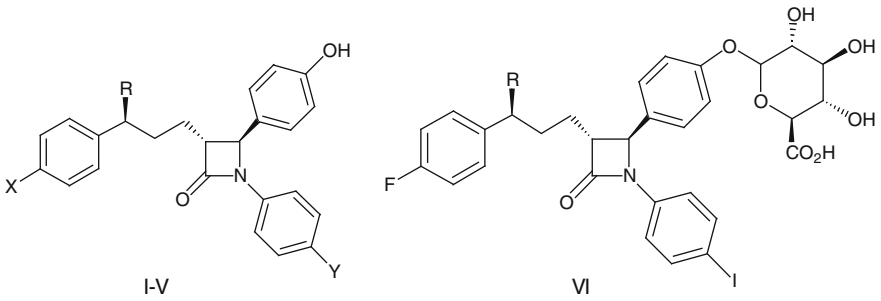


Scheme 120 Summary of the basic SARs in the 2-azetidinone compounds

A summary of the basic SARs in the 2-azetidinone compounds is shown in Scheme 120. The presence of a 4-methoxyphenyl or similar hydrogen bonding moiety and a proper absolute stereochemistry at the C-4 carbon atom, are both critical in producing the activity. The phenylalkyl group at the C-3 and the mono-substitution at the C-3 and the C-4 positions seem to be less critical. A *N*-aryl group seems to be required, but there is considerable tolerance for the substitution at the phenyl ring. The azetidinone ring is required, but there is no evidence that it acts as anything more than a scaffold to correctly position the pharmacophore groups [384].

More development on the SAR studies have revealed the importance of side-chain metabolic hydroxylation to activity and led to the synthesis of compound I of Fig. 43 (SCH 58235), [387, 388]. While this 2-azetidinone together with compound I of Fig. 42 (SCH 48461) are extremely potent inhibitors of cholesterol absorption in vivo, the precise biological mechanism by which this inhibition takes place has yet to be discovered [383]. Data presented previously have suggested that there was a molecular target for these compounds, which has been designated as the CAI binding protein (CAIBP). The initial approach of Burnett and coworkers has been to use radiolabeled binding compounds for the identification of subcellular localization sites in intestinal cells [140, 389]. Having some knowledge of where the compounds were binding, they hoped to identify any specific proteins that had high affinity for this class of CAIs using other techniques. Based on their extensive SAR developments of the azetidinone CAI series, in 2002 the same authors have found that the two best structural sites for elaboration, while maintaining in vivo activity, were the *N*-aryl ring and the pendant aryl ring. For sensitivity reasons, their initial binding studies required radioiodinated analogs and thus, targets II and III (Fig. 43) came to the fore [140].

In the cholesterol fed hamster assay, these compounds were both active in vivo, with the *N*-iodophenyl analog III having slightly better potency. The derivatives bearing a benzylic hydroxyl moiety displayed a significant potency advantage over



SCH58235(–) I : R = OH, R' = H, X = Y = F
II: R = H, X = I, Y = OMe
III: R = H, X = H, Y = I
IV: R = OH, X = I, Y = F
V: R = OH, X = F, Y = I

Fig. 43

compounds II and III while the *N*-iodophenyl analog V was slightly more potent than the pendent iodophenyl derivative IV. Since it has been discovered that compound I (SCH 58235) in vivo exists predominantly as its glucuronide [388], in the absence of a clear understanding of the mechanism of action, neither the free phenol nor the glucuronide could be precluded as the bioactive species. Therefore, the corresponding iodinated glucuronide of derivative V was required. This compound, depicted as VI in Fig. 43, has shown significant reduction of hepatic cholesterol esters. Thus, the same group of researchers has designed and prepared a number of potent CAIs with fluorescent absorption and emission properties making them suitable for use as biological tools in the investigation of the mechanism of action of this important class of new pharmacological agents [139].

4.4.9 Antihyperglycemic Activity

Goel and coworkers in 2004 have examined the effect of some monocyclic β-lactams for antihyperglycemic activity against alloxan-induced diabetes in rats (Fig. 44), as these 2-azetidinones have been shown to control disturbances in cholesterol metabolism induced by diabetes. The antihyperglycemic effect of test compounds was evaluated by monitoring their effect on blood glucose and liver glycogen contents [390]. In the diabetic rats, high glucose levels and depression in hepatic glycogen contents could be attributed to less availability of the active form of enzyme glycogen synthetase, which in turn has been reported to be responsible for incorporation of glucose moieties in pre-existing glycogen chain [391, 392].

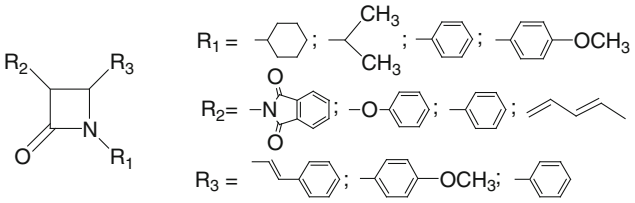


Fig. 44

Test compounds significantly lowered the serum glucose levels indicating their antihyperglycemic activity. This activity may be due to increased utilization of glucose, as indicated by decreased serum glucose levels, and increase in the activity of glycogen synthetase enzyme, as evidenced by augmented liver glycogen contents in test groups. Concerning the antidiabetic activity of test compounds the following structure activity relationships were observed:

- At the C-3 position, the phthalimido substitution showed the best activity followed by phenyl and phenoxy substitution, while 1,3-butadienyl substitution resulted in total loss of activity
- At the N-1 position, cyclohexyl and isopropyl group favored activity more than the phenyl and the 4-methoxyphenyl substitution
- At the C-4 position, styryl and 4-methoxy-phenyl substitution were more favorable than the phenyl group

This study has revealed that 2-azetidinones are effective as antihyperglycemic agents and might act either through increased utilization of glucose or through increased insulin activity or induction of glycogen synthetase enzyme.

4.4.10 Anticancer Activity

In 2002, Turos and coworkers have discovered and characterized the apoptosis-inducing properties of a family of novel β-lactam antibiotics against human solid tumor cell lines such as breast, prostate, and head-and-neck [44]. They have found a lead compound (structure I, Fig. 45), with an *N*-methylthio group, which was able to induce DNA damage, inhibit DNA replication, and activate the apoptotic death program in human leukemic Jurkat T cells within a 2 h treatment. Several important SARs have been observed. First and most significantly, the *N*-methylthio group was required for the apoptosis-inducing activity of β-lactam I, (Fig. 45). In the second instance, an increase in the number of carbons on the *N*-alkylthio group was inversely proportional to the apoptosis-inducing ability of these β-lactams. Moreover, replacement of the *N*-methylthio moiety with an *N*-benzylthio group (IV, Fig. 45) also decreased the apoptosis inducing activity by ~70%. Another SAR was found for the chlorophenyl group in β-lactam I. Among the isomers I, II, and III, having a chlorine group in *ortho*-, *meta*-, and *para*-positions, respectively, on the

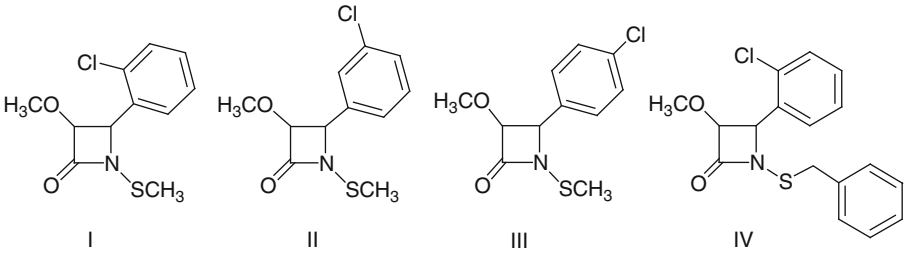


Fig. 45

phenyl ring, β-lactams II and III were less potent than β-lactam I (by ~20%). Because of their simple synthesis and their easy structurally manipulation for selective studies, these β-lactams may have great potential to be developed into anticancer drugs [44].

In 2008 the same authors reported two N-thiolated-β-lactam analogs, both containing a branched-chain moiety at C3 of the lactam ring exhibiting potent apoptosis-inducing activity. Furthermore, the branched β-lactams were able to inhibit growth of mice bearing breast cancer xenografts, associated with induction of DNA damage and apoptosis in tumor tissues [393, 394].

In 2003, the group of Banik has assayed some 2-azetidinones against nine human cancer cell lines as a measure of cytotoxicity [86]. Structure-activity studies have revealed that *N*-chrysenyl- and *N*-phenantrenyl-3-acetoxy-4-aryl-2-azetidinones (Fig. 46), respectively, have potent anticancer activity. The comparable *N*-anthracenyl, *N*-pyrenyl, and *N*-naphthalenyl derivatives became inactive. It is evident that the minimal structural requirement of the aromatic moiety for cytotoxicity is at least three aromatic rings in an angular configuration. The presence of the acetoxy group at the C-3 position of the β-lactams has proved to be obligatory for their antitumor activity [86].

Moreover, potent inhibiting properties exhibited by 7-alkylidene substituted cephalosporanate sulfones against tumor strains, both in vitro and in vivo [42], motivated researchers to subject penicillanate sulfones, together with 4-heteroaryldithio- and 4-methylsulfonylazetidin-2-ones, containing alkylidene side-chain, respectively, at the C-6 and the C-3 positions, to similar biological investigations. Veinberg and coworkers in 2004 have tested in vitro the cytotoxic properties of these compounds [395]. Their analysis has evidenced that the incorporation of *tert*-butoxycarbonylmethylene, benzylidene, and 4-nitrobenzylidene structures at the C-6 position of penicillanate sulfoxides and sulfones and at the C-3 position of 4-heteroaryldithio- and 4-methylsulfonylazetidin-2-ones, in many cases provided antitumor effect.

Salinosporamide A and omuralide (I and II, respectively, Fig. 47), are potent naturally derived substances that inhibit proteasome function with very high selectivity [396–402].

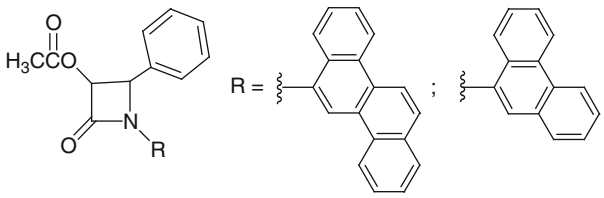


Fig. 46

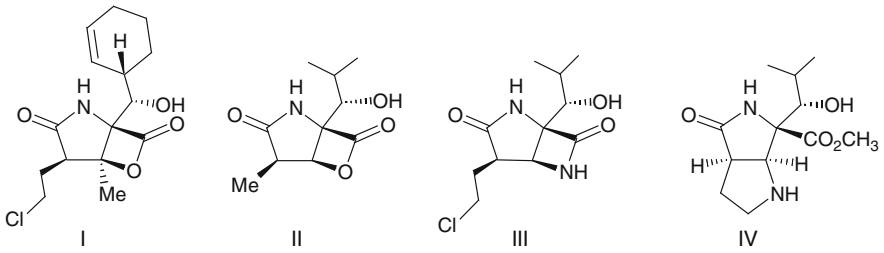


Fig. 47

Proteasome inhibition offers considerable promise in the therapy of a number of types of cancer and is already used for multiple myeloma [403–405]. A potential problem with the use of compounds I or II as therapeutic agents, is their short half-life in solution at pH 7 or in serum (estimated as 5–10 min).

Because of this potential shortcoming, in 2005 Hogan and coworkers have developed a synthesis of the β-lactam III of Fig. 47, which is expected to be much more stable than the corresponding β-lactone (I or II, Fig. 47), [406]. The pathway of proteasome inhibition by the β-lactam III followed that of omuralide and salinosporamide A, that consisted in the acylation of a catalytically active threonine of a proteolytic β-subunit. This acylation was made irreversible by ring closure involving the chloroethyl group as an electrophile, as in the case of salinosporamide A [407], since treatment of III with methanolic base afforded the bicyclic pyrrolidine IV (Fig. 47). These results, together with the observation of proteasome inhibition in vitro, and the indefinite stability in neutral aqueous solution suggested that compound III was a worthy candidate for further biological evaluations.

In 2006 the preparation of simplified analogs of natural occurring enediynes, e.g. antitumor antibiotic dynemicin, was reported by Banfi and coworkers. They succeeded in synthesizing two different classes of such compounds where the embedded 10-membered enediyne system is fused either with a β-lactam ring (lactenediynes) or with an epoxide. Biological tests on these molecules have demonstrated that some representatives are able to cleave the double strand of DNA even at very low concentrations [408].

In 2007 a series of β-lactam derivatives was designed and synthesized to inhibit the chymotrypsin-like activity of the human 20S proteasome. The most potent compounds of this new structural class of β-subunit exhibit good selectivity over the trypsin-like and post-glutamyl-peptide hydrolytic activities of the enzyme [409].

In 2008 a series of novel β-lactam containing compounds were described as antiproliferative agents and potential selective modulators of the estrogen receptor. The compounds were designed to contain three aryl ring substituents arranged on the heterocyclic azetidin-2-one (β-lactam), thus providing conformationally restrained analogs of the triarylethylene arrangement exemplified in the tamoxifen type structure. These molecules showed high antiproliferative effects on human breast cancer cell line at low micromolar to nanomolar concentrations with low cytotoxicity and moderate binding affinity to the estrogen receptor. The effect of a number of aryl and amine functional group substitutions on the antiproliferative activity of the β-lactam products was reported and a brief computational SAR with molecular simulation was investigated [410].

4.4.11 Antiviral Activity

HCMV, a β-herpesvirus, is an opportunistic pathogen in immunocompromised individuals such as AIDS patients and organ transplant recipients [411]. Thus HCMV protease has become a viable target for antiviral chemotherapy [412, 413].

Several monobactams incorporating a benzyl side-chain at the C-4 carbon atom, such as compounds of Fig. 48, have been reported to be selective inhibitors of HCMV protease [367].

Substitution at the C-3 position was tolerated and gave small increases in stability and enzymatic activity. These compounds were much less selective however, than the corresponding inhibitors that were unsubstituted at the C-3 position. Substitution of the urea moiety suggested that benzyl groups were the best choice at this position. Both tri- and tetra-substituted ureas were effective, with tetra substitution giving a slight stability advantage. Modification of the benzyl function indicated that strong electron-withdrawing groups at the *para* position had the best activity. Moreover, mechanistic investigations indicated that these compounds are reversible and competitive inhibitors of HCMV protease and that inhibition involved the formation of an acyl-enzyme species [367].

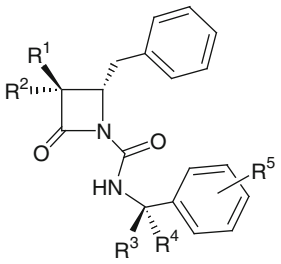
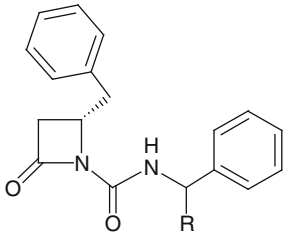
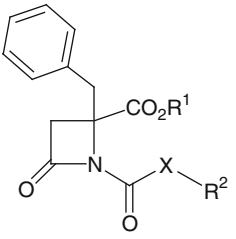


Fig. 48

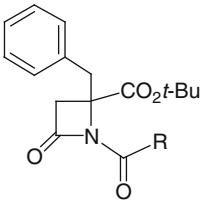


Ia: R = H
Ib: R = (*R*)-Me
Ic: R = (*S*)-Me

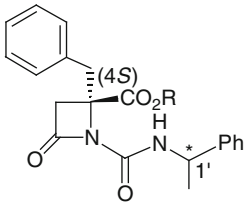


II: X = NH, O; R^1= *t*-Bu, H
R^2 = Ph, $CH(CH_3)Ph$, *t*-Bu, CH_2Ph

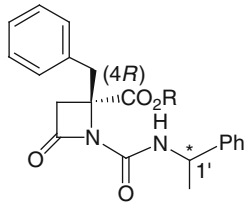
Fig. 49



a: R = H–N–Ph
f: R = –O–Ph
g: R = –O–*t*-Bu



(4*S*, 1'*S*)-b: R = *t*-Bu
(4*S*, 1'*R*)-c: R = *t*-Bu



(4*R*, 1'*S*)-d: R = *t*-Bu
(4*R*, 1'*R*)-e: R =*t*-Bu

Fig. 50

Among these latter inhibitors, a series of monocyclic β-lactams I (compound Ia being the prototype, Fig. 49), has resulted in highly potent derivatives in the isolated enzyme assay, but their efficacy in cell culture was quite limited, as described for all inhibitors of this enzyme [367, 414–416].

Gerona-Navarro and coworkers in 2004 have reported the synthesis and the evaluation of a series of new 2-azetidinones (Fig. 50), derived from phenylalanine [281], which were designed on the basis of the structure of the reported β-lactam inhibitors [367] and the residues implicated in the active site of the HCMV protease [417]. These compounds have been evaluated against HCMV in human embryonic lung cells [418], and the results compared to those obtained for the reference compounds, which were the model β-lactam Ia of Fig. 49, the viral DNA polymerase inhibitors DHPG (ganciclovir), and HPMPC (cidofovir).

The obtained results have shown that the trisubstituted β-lactams a–e of Fig. 50 exhibited some antiviral activity, slightly higher than that reported for the prototype 2-azetidinone Ia of Fig. 49. No appreciable influence of the absolute configuration, either at the C-4 or at the 1-phenylethyl substituent, on the inhibition of viral replication, was observed. The presence of an aromatic group at the 1-acyl

substituent seemed to be important for the antiviral activity, as deduced from the lack of activity of the *tert*-butoxycarbonyl derivative g and the presence of activity of the benzyloxycarbonyl analog f, (Fig. 50). This latter compound showed the highest anti-HCMV activity within the β-lactam series, but with a very narrow therapeutic window, having a cell toxicity value close to the IC50 data for viral inhibition [263]. Interestingly, removal of the carbonyl group from the β-lactam ring, most likely acting as the serine trap, resulted in an azetidine derivative with anti-HCMV activity comparable to that of the reference compound ganciclovir [281, 419].

5 Concluding Remarks

A comprehensive overview of the most significant and interesting developments on the synthesis of novel β-lactam compounds has been presented. The contributions examined are those published from 2000 till date; the literature survey was organized by type of reaction, and, among them, by year. The synthetic strategies reported are based either on novel methodologies or on already known but efficient and versatile protocols. An alternative methodology, reported in a separate paragraph, was the modification of preexisting groups linked at the different positions of the 2-azetidinone ring. Considering that the core structure of four-membered cyclic amide is the common feature of the antibacterial compounds, and that their biological and pharmacological activity are strictly related to the substituents linked to this small heterocycle, the modification of these linked groups not only afford new β-lactam derivatives, more complex and polyfunctionalized, but can produce molecules even more efficient in their activity. For this reason, a single paragraph of this chapter was focused on the studies reported in literature concerning the SARs of the β-lactams examined, with the aim of highlighting the possibility of designing new and even more efficient β-lactam compounds.

We believe that this chapter can become an essential part of the knowledge of organic chemists who can plan the synthesis of novel substituted 2-azetidinones. Moreover, medicinal chemists can have an overview, covering the latest developments in the biological and pharmacological applications of these 2-azetidinone compounds, thereby giving focus to their future investigations.

References

1. Bose AK, Manhas MS, Banik BK, Srirajan V (2000) In: Greenberg A, Breneman CM, Liebman J F (eds) The amide linkage: selected structural aspects in chemistry, biochemistry, and material science. Wiley-Interscience, New York, p 157, chap 7
2. Singh GS (2004) In: β-Lactams in the new millenium. Part. I: monobactams and carbapenems. Mini Rev Med Chem 4:69

3. Manhas MS, Banik BK, Mathur A, Vincent JE, Bose AK (2000) Tetrahedron 56:5587
4. Bose AK, Mathur C, Wagle DR, Manhas MS (2000) Tetrahedron 56:5603
5. Ojima I (1995) Acc Chem Res 28:383
6. Banik BK, Manhas MS, Bose AK (1994) J Org Chem 59:4714
7. Banik BK, Manhas MS, Bose AK (1993) J Org Chem 58:307
8. Clader JW, Burnett DA, Caplen MA, Domalski MS, Dugar S, Vaccaro W, Sher R, Browne ME, Zhao H, Burrier RE, Salisbury B, Davis HR (1996) J Med Chem 39:3684
9. Burnett DA, Caplen MA, Davis HR, Burrier RE, Clader JW (1994) J Med Chem 37:1733
10. Finke PE, Shan SK, Fletcher DS, Ashe BM, Brause KA, Chandler GO, Dellea PS, Hand KM, Maycock AL, Osinga DG, Underwood DJ, Weston H, Davies P, Doherty JB (1995) J Med Chem 38:2449
11. Cohn ML (1992) Science 257:1050
12. Neu HC (1992) Science 257:1064
13. Davies J (1994) Science 264:375
14. Shlaes D, Levy S, Archer G (1991) ASM News 57:455
15. World Health Organization (1996) In: The world health report 1996. Geneva, Switzerland
16. Lederberg J, Shope RE (1992) (eds) Emerging infections: microbial threats to health in the United States. National Academy Press, Washington DC
17. Bush K, Jacoby GA, Medeiros AA (1995) Antimicrob Agents Chemother 39:1211
18. Massova I, Mobashery S (1997) Acc Chem Res 30:162
19. Kuzin AP, Nukaga M, Nukaga Y, Hujer A, Bomono RA, Knox JR (2001) Biochemistry 40:1861
20. Yang Y, Rasmussen BA, Shales DM (1999) Pharmacol Ther 83:141
21. Bush K, Mobashery S (1998) In: Rosen BP, Mobashery S (eds) Resolving the antibiotic paradox: progress in understanding drug resistance and development of new antibiotics. Plenum Press New York, p 71
22. Ambler RP (1980) Philos Trans R Soc London Ser B 289:155
23. Bush K (1988) Clin Microbiol Rev 1:109
24. Bush K (1997) Antibiotic and chemotherapy. Churchill Livingstone, Edinburgh UK, p 306
25. Vedel G, Belaaouaj A, Gilly L, Labia R, Phillippon A, Nevot P, Paul GJ (1992) Antimicrob Chemother 30:449
26. Sirot D, Chanal C, Henquell C, Labia R, Sirot J, Cluzel RJ (1994) Antimicrob Chemother 33:1117
27. Belaaouaj A, Lapoumeroulie C, Canica MM, Vedel G, Nevot P, Krishnamoorthy R, Paul G (1994) FEMS Microbiol Lett 120:75
28. Brun T, Péduzzi J, Canica MM, Paul G, Nevot P, Barthélémy M, Labia R (1994) FEMS Microbiol Lett 120:111
29. Stemmer WPC (1994) Nature 370:389
30. Vakulenko SB, Geryk B, Kotra LP, Mobashery S, Lerner SA (1998) Antimicrob Agents Chemother 43:1542, and references cited therein
31. Sternlicht M D, Werb Z (1999) In: Kreis T, Vale R (eds) Extracellular matrix, anchor and adhesion proteins. Oxford University Press Oxford, UK, p 543
32. Balckwill F, Mantovani A (2001) Lancet 357:539
33. Delclaux C, Delacourt C, D'Ortho MP, Boyer V, Lafuma C, Harf A (1996) Am J Respir Cell Mol Biol 14:288
34. Esparza J, Kruse M, Lee J, Michaud M, Madri JA (2004) FASEB J 18:1682
35. Konaklieva MI (2002) Med Chem Rev 1:133
36. Jard S, Elands J, Schmidt A, Barberis C (1998) In: Imura H, Shizume K, (eds) Progress in endocrinology. Elsevier, Amsterdam, p 1183
37. The Nutrition Committee of the American Heart Association (1988) In: Dietary guidelines for healthy american adults: a statement for physicians and health professionals Circulation 77:721A

38. The Expert Panel in summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evalution, and treatment of high blood cholesterol in adults (adult treatment panel II) (1993) J Am Med Assoc 269:3015
39. Krause BR, Sliskovic DR, Bocan TMA (1995) Exp Opin Invest Drugs 4:353
40. Otani T, Oie S, Matsumoto H, Tempest M, Micetich RG, Singh R, Yamashita T (1994) WO 01,109, 1994 Chem Abstr 121:57497
41. Alpegiani M, Bissolino P, Perrone E, Pesenti E (1995) WO 02,603 1995 Chem Abstr 122:205179
42. Veinberg G, Vorona M, Shestakova I, Kanepe I, Zharkova O, Mezapuke R, Turovskis I, Kalvinsh I, Lukevics E (2000) Bioorg Med Chem 8:1033
43. Finke PE, Dahlgren ME, Weston H, Maycock AL, Doherty JB (1993) Bioorg Med Chem Lett 3:2277
44. Smith DM, Kazi A, Smith L, Long TE, Heldreth B, Turos E, Dou QP (2002) Mol Pharmacol 61:1348
45. Field AK (1999) Antiviral Chem Chemother 10:219
46. Holwerda BC (1997) Antiviral Res 35:1
47. Waxman L, Darke PL (2000) Antiviral Chem Chemother 11:1
48. Déziel R, Malenfant E (1998) Bioorg Med Chem Lett 8:1437
49. For comprehensive general review see Koppel GA (1983) In: Hassner A (ed) Small ring heterocycles, vol 42. Wyley, New York, p 219
50. De Kimpe N (1996) In: Katritzky AR, Rees CW, Scriven EFV, Padwa A (eds) Comprehensive heterocyclic chemistry II, vol 1B. Pergamon, Oxford, p 507
51. Bose AK, Banik BK, Mathur C, Wagle DR, Manhas MS (2000) Tetrahedron 56:5603
52. Banik BK, Ghatak A, Becker FF (2000) J Chem Soc Perkin Trans 1 2179
53. Baldoli C, Del Buttero P, Maiorana S, Jaouen G, Top S (1991) J Organomet Chem 413:125
54. Del Buttero P, Baldoli C, Molteni G, Pilati T (2000) Tetrahedron: Asymmetry 11:1927
55. Yamamoto Y, Watanabe Y, Ohnishi S (1987) Chem Pharm Bull 35:1860
56. Almqvist F, Guillaume D, Hultgren SJ, Marshall GR (1998) Tetrahedron Lett 39:2293
57. Emtenas H, Soto G, Hultgren SJ, Marshall GR, Almqvist F (2000) Org Lett 2:2065
58. Fernández R, Ferrete A, Lassaletta JM, Llera JM, Monge A (2000) Angew Chem Int Ed 39:2893
59. Mihovilovic MD, Feicht A, Kayser MM (2000) J Prakt Chem 342:585
60. Thiagarajan K, Puranik VG, Deshmukh ARAS, Bhawal BM (2000) Tetrahedron 56:7811
61. Saul R, Kopf J, Köll P (2000) Tetrahedron: Asymmetry 11:423
62. Taggi AE, Hafez AM, Wack H, Young B, Drury WJ, Lectka T (2000) J Am Chem Soc 122:7831
63. Costa MF, Da Costa MRG, Curto MJM, Magrinho M, Damas AM, Gales L (2001) J Organomet Chem 632:27
64. Alcaide B, Almendros P, Rodríguez-Acebes R (2002) J Org Chem 67:1925
65. Alcaide B, Almendros P (2001) Org Prep Proced Int 33:315
66. E Alonso, Del Pozo C, González J (2002) J Chem Soc Perkin Trans 1 571
67. Arjona O, Csákÿ AG, Murcia MC, Plumet J (2002) Tetrahedron Lett 43:6405
68. Boger DL, JBJr M (1991) J Org Chem 56:5385
69. Delpiccolo CML, Mata EG (2002) Tetrahedron: Asymmetry 13:905
70. Dasgupta SK, Banik BK (2002) Tetrahedron Lett 43:9445
71. Fernández R, Ferrete A, Lassaletta JM, Llera JM, Martín-Zamora E (2002) Angew Chem Int Ed 41:831
72. Martín-Zamora E, Ferrete A, Llera JM, Munoz JM, Pappalardo RR, Fernández R, Lassaletta JM (2004) Chem Eur J 10:6111
73. France S, Wack H, Hafez AM, Taggi AE, Witsil DR, Lectka T (2002) Org Lett 4:1603
74. France S, Shah MH, Weatherwax A, Wack H, Roth JP, Lectka T (2005) J Am Chem Soc 127:1206
75. Hodous BL, Fu GC (2002) J Am Chem Soc 124:1578

76. Taggi AE, Hafez AM, Wack H, Young B, Ferraris D, Lectka T (2002) J Am Chem Soc 124:6626
77. Le Roy I, Mouysset D, Mignani S, Vuilhorgne M, Stella L (2003) Tetrahedron 59:3719
78. Costero AM, Pitarch M, Cano ML, (1994) J Chem Res (S) 316
79. Look GC, Murphy MM, Campbell DA, Gallop MA (1995) Tetrahedron Lett 36:2937
80. Hevia E, Pérez J, Riera V, Miguel D (2002) Angew Chem Int Ed 41:3858
81. Hevia E, Pérez J, Riera V, Miguel D, Campomanes P, Menéndez MI, Sordo TL, García-Granda S (2003) J Am Chem Soc 125:3706
82. Delpiccolo CML, Fraga MA, Mata EG (2003) J Comb Chem 5:208
83. Testero SA, Mata EG (2006) Org Lett 8:4783
84. Annunziata R, Benaglia M, Cinquini M, Cozzi F, Maggioni F, Puglisi A (2003) J Org Chem 68:2952
85. Arun M, Joshi SN, Puranik VG, Bhawal BM, Deshmukh ARAS (2003) Tetrahedron 59:2309
86. Banik I, Becker FF, Banik BK (2003) J Med Chem 46:12
87. Wack H, France S, Hafez AM, Drury WJ III, Weatherwax A, Lectka T (2004) J Org Chem 69:4531
88. Jarrahpour AA, Shekarriz M, Taslimi A (2004) Molecules 9:29
89. Khasanov AB, Ramirez-Weinhouse MM, Webb TR, Thiruvazhi M (2004) J Org Chem 69:5766
90. Dondoni A, Massi A, Sabbatini S, Bertolasi V (2004) Adv Synth Catal 346:1355
91. Govande VV, Deshmukh ARAS (2004) Tetrahedron Lett 45:6563
92. Jarrahpour AA, Shekarriz M, Taslimi A (2004) Molecules 9:939
93. Diez E, Fernandez R, Marques-Lopez E, Martin-Zamora E, Lassaletta JM (2004) Org Lett 6:2749
94. Delpiccolo CML, Mata EG (2004) Tetrahedron Lett 45:4085
95. Sternbach LH, Reeder E (1961) J Org Chem 26:4936
96. Sternbach LH, Fryer RI, Metlesics W, Reeder E, Sach G, Saucy G, Stempel A (1962) J Org Chem 27:3788
97. Del Pozo C, Macias A, Lopez-Ortiz F, Maestro MA, Alonso E, Gonzalez J (2004) Eur J Org Chem 535
98. Liang Y, Jiao L, Zhang S, Xu J (2005) J Org Chem 70:334
99. Banik BK, Banik I, Becker FF (2005) Bioorg Med Chem 13:3611
100. Cremonesi G, Dalla Croce P, La Rosa C (2005) Helvetica Chimica Acta 88:1580
101. Cremonesi G, Dalla Croce P, Fontana F, Forni A, La Rosa C (2005) Tetrahedron: Asymmetry 16:3371
102. Delpiccolo CML, Méndez L, Fraga MA, Mata EG (2005) J Comb Chem 7:331
103. Lee EC, Hodous BL, Bergin E, Shih C, Fu GC (2005) J Am Chem Soc 127:11586
104. Pelotier B, Rajzmann M, Pons J-M, Campomanes P, López R, Sordo TL (2005) Eur J Org Chem 2599
105. Sato K, Tarui A, Matsuda S, Omote M, Ando A, Kumadaki I (2005) Tetrahedron Lett 46:7679
106. Xu J (2005) Mol Divers 9:45
107. Jarrahpour AA, Jahaniani AR (2005) Molbank M439
108. Jiao L, Zhang Q, Liang Y, Zhang S, Xu J (2005) J Org Chem 71:815
109. Arumugam N, Raghunathan R (2006) Tetrahedron Lett 47:8855
110. Jarrahpour A, Zarei M (2006) Molecules 11:49
111. Nahmany M, Melman A (2006) J Org Chem 71:5804
112. Shaickh AL, Puranik VG, Deshmukh ARAS (2006) Tetrahedron Lett 47:5993
113. Van Brabandt W, Vanwalleghem M, D'Hooghe M, De Kimpe N (2006) J Org Chem 71:7083
114. Viso A, de la Pradilla RF, Flores A (2006) Tetrahedron Lett 47:8911
115. Zanobini A, Brandi A, de Meijere A (2006) Eur J Org Chem 1251
116. Benaglia M, Cozzi F, Puglisi A (2007) Eur J Org Chem 2865
117. Coantic S, Mouysset D, Mignani S, Tabart M, Stella L (2007) Tetrahedron Lett 48:4301

118. Jiao L, Liang Y, Xu J (2006) J Am Chem Soc 128:6060
119. Cariou CCA, Clarkson GJ, Shipman M (2008) J Org Chem 73:9762
120. Tato F, Reboul V, Metzner P (2008) J Org Chem 73:7837
121. Zhang Y-R, He L, Wu X, Shao P-L, Ye S (2008) Org Lett 10:277
122. Yang Y-Y, Shou W-G, Hong D, Wang Y-G (2008) J Org Chem 73:3574
123. D'hooghe M, Dejaegher Y, De Kimpe N (2008) Tetrahedron 64:4575
124. Marques-Lopez E, Martin-Zamora E, Diez E, Fernandez R, Lassaletta JM (2008) Eur J Org Chem 17:2960
125. D'hooghe M, Van Brabandt W, Dekeukeleire S, Dejaegher Y, De Kimpe N (2008) Chem A Eur J 14:6336
126. Hegedus LS, Montgomery J, Narukawa Y, Snustad DC (1991) J Am Chem Soc 113:5784
127. Georg GI, He P, Kant J, W ZJ (1993) J Org Chem 58:5771
128. Cossio FP, Ugalde JM, Lopez X, Lecea B, Palomo C (1993) J Am Chem Soc 115:995
129. Arrieta A, Ugalde JM, Cossio FP (1994) Tetrahedron Lett 35:4465
130. Arrieta A, Lecea B, Cossio FP (1998) J Org Chem 63:5869
131. Georg GI, Ravikumar VT (1993) In: Georg GI (ed) The Organic chemistry of β-lactams. Verlag Chemie, New York, p 295
132. Benaglia M, Cinquini M, Cozzi F (2000) Eur J Org Chem 563
133. Schunk S, Enders D (2000) Org Lett 2:907
134. Shindo M (1998) Chem Soc Rev 27:367
135. Shindo M, Oya S, Murakami R, Sato Y, Shishido K (2000) Tetrahedron Lett 41:5943
136. Sierra MA, Mancheno MJ, Vicente R, Gómez-Gallego M (2001) J Org Chem 66:8920
137. Annunziata R, Benaglia M, Cinquini M, Cozzi F, Puglisi A (2002) Bioorg Med Chem 10:1813
138. Arai Y, Yoneda S, Masuda T, Masaki Y (2002) Chem Pharm Bull 50:615
139. Burnett DA, Caplen MA, Browne ME, Zhau H, Altmann SW, HRJr D, Clader JW (2002) Bioorg Med Chem Lett 12:315
140. Burnett DA, Caplen MA, Dolmaski MS, Browne ME, HRJr D, Clader JW (2002) Bioorg Med Chem Lett 12:311
141. Schunk S, Enders D (2002) J Org Chem 67:8034
142. Townes JA, Evans MA, Queffelec J, Taylor SJ, Morken JP (2002) Org Lett 4:2537
143. Boyer N, Gloanec P, De Nanteuil G, Jubault P, Quirion J-C (2007) Tetrahedron 63:12352
144. Davoli P, Moretti I, Prati F, Alper H (1999) J Org Chem 64:518
145. Davoli P, Forni A, Moretti I, Prati F, Torre G (2001) Tetrahedron 57:1801
146. Aggarwal VK, Alonso E, Ferrara M, Spey SE (2002) J Org Chem 67:2335
147. Mahadevan V, Getzler YDYL, Coates GW (2002) Angew Chem Int Ed 41:2781
148. Getzler YDYL, Mahadevan V, Lobkovsky E, Coates GW (2002) J Am Chem Soc 124:1174 and references therein cited
149. Ardura D, López R (2007) J Org Chem 72:3259
150. Lu S-M, Alper H (2004) J Org Chem 69:3558
151. Ardura D, López R, Sordo TL (2006) J Org Chem 71:7315
152. Meloni MM, Taddei M (2001) Org Lett 3:337
153. Calcagni A, Rossi D, Lucente G (1981) Synthesis 445
154. Broadrup RL, Wang B, Malachowski WP (2005) Tetrahedron 61:10277
155. Angelaud R, Zhong Y-L, Maligres P, Lee J, Askin D (2005) J Org Chem 70:1949
156. Lo MM-C FuGC (2002) J Am Chem Soc 124:4572
157. Bask A, Pal R (2005) Bioorg Med Chem Lett 15:2015
158. Zhang X, Hsung RP, Li H, Zhang Y, Johnson WL, Figueroa R (2008) Org Lett 10:3477
159. Troisi L, De Vitis L, Granito C, Epifani E (2004) Eur J Org Chem 1357
160. Troisi L, De Vitis L, Granito C, Pilati T, Pindinelli E (2004) Tetrahedron 60:6895
161. Torii S, Okumoto H, Sadakane M, Hai AKMA, Tanaka H (1993) Tetrahedron Lett 34:6553
162. Troisi L, Ronzini L, Granito C, De Vitis L, Pindinelli E (2006) Tetrahedron 62:1564

163. Troisi L, Ronzini L, Granito C, De Vitis L, Pindinelli E, Troisi A, Pilati T (2006) Tetrahedron 62:12064
164. Troisi L, Granito C, Pindinelli E (2008) Tetrahedron 64:11632
165. Feroci M, Lessard J, Orsini M, Inesi A (2005) Tetrahedron Lett 46:8517
166. Feroci M, Orsini M, Rossi L, Sotgiu G, Inesi A (2006) Electrochim Acta 51:5540
167. Feroci M, Orsini M, Palombi L, Rossi L, Inesi A (2005) Electrochim Acta 50:2029
168. Sotgiu G, Chiarotto I, Feroci M, Orsini M, Rossi L, Inesi A (2008) Electrochim Acta 53:7852
169. Podlech J, Seebach D (1995) Liebigs Ann 1217
170. Podlech J, Seebach D (1995) Helv Chim Acta 78:1238
171. Linder MR, Frey WU, Podlech J (2001) J Chem Soc Perkin Trans 1 2566
172. Natarajan A, Wang K, Ramamurthy V, Scheffer JR, Patrick B (2002) Org Lett 4:1443
173. Maier TC, Frey WU, Podlech J (2002) Eur J Org Chem 2686
174. Donati D, Fusi S, Ponticelli F (2003) Tetrahedron Lett 44:9247
175. Maier TC, Podlech J (2004) Eur J Org Chem 4379
176. Wang R, Chen C, Duesler E, Mariano PS (2004) J Org Chem 69:1215
177. Sakamoto M, Kawanishi H, Mino T, Fujita T (2008) Chem Commun 18:2132
178. Ross NA, MacGregor RR, Bartsch RA (2004) Tetrahedron 60:2035
179. Bongini A, Panunzio M, Tamanini E, Martelli G, Vicennati P, Monari M (2003) Tetrahedron: Asymmetry 14:993
180. Gerona-Navarro G, Bonache MA, Herranz R, García-López MT, González-Muñiz R (2001) J Org Chem 66:3538
181. Vicario JL, Badía D, Carrillo L (2001) J Org Chem 66:9030
182. Guanti G, Narisano E, Banfi L (1987) Tetrahedron Lett 28:4331
183. Gennari C, Venturini I, Gislon G, Schimperna G (1987) Tetrahedron Lett 28:227
184. Clark AJ, Battle GM, Bridge A (2001) Tetrahedron Lett 42:4409
185. Kobayashi S, Iimori T, Izawa T, Ohno M (1981) J Am Chem Soc 103:2405
186. Tanaka H, Sakagami H, Ogasawara K (2002) Tetrahedron Lett 43:93
187. Sakagami H, Kamikubo T, Ogasawara K (1996) Chem Commun 1433
188. Sakagami H, Ogasawara K (2000) Synthesis 521
189. Lindgren BO, Nolsson T (1973) Acta Chem Scand 27:888
190. Poitout L, Le Merrer Y, Depezay J-C (1996) Tetrahedron Lett 37:1609
191. Sakagami H, Ogasawara K (2001) Synlett 45
192. Gerona-Navarro G, García-López MT, González-Muñiz R (2002) J Org Chem 67:3953
193. Clayden J, Watson DW, Helliwell M, Chambers M (2003) Chem Commun 2582
194. Bonache MA, Gerona-Navarro G, García-Aparicio C, Alìas M, Martìn-Martìnez M, García-López MT, López P, Cativiela C, González-Muñiz R (2003) Tetrahedron: Asymmetry 14:2161
195. Clayden J, Hamilton SD, Mohammed RT (2005) Org Lett 7:3673
196. Guerrini A, Varchi G, Samorì C, Rizzo D, Battaglia A (2007) Tetrahedron Lett 48:5081
197. Guerrini A, Varchi G, Rizzo D, Samorì C, Battaglia A (2007) Tetrahedron 63:7949
198. Yang Y, Xiang D, Zhao X, Liang Y, Huang J, Dong D (2008) Tetrahedron 64:4959
199. Gedey S, Van der Eycken J, Fulop F (2002) Org Lett 4:1967
200. Kolb J, Beck B, Dömling A (2002) Tetrahedron Lett 43:6897
201. Cordero FM, Pisaneschi F, Salvati M, Paschetta V, Ollivier J, Salaun J, Brandi A (2003) J Org Chem 68:3271
202. Brandi A, Cicchi S, Cordero FM, Goti A (2003) Chem Rev 103:1213
203. Goti A, Cordero FM, Brandi A (1996) Top Curr Chem 178:1
204. Tamura O, Okabe T, Yamaguchi T, Gotanda K, Noe K, Sakamoto M (1995) Tetrahedron 51:107
205. Cicchi S, Corsi M, Goti A (1999) J Org Chem 64:7243
206. Tokuyama H, Kuboyama T, Amano A, Yamashita T, Fukuyama T (2000) Synthesis 1299
207. Shimizu T, Ishizaki M, Nitada N (2002) Chem Pharm Bull 50:908

208. Zanobini A, Gensini M, Magull J, Vidovic D, Kozhushkov SI, Brandi A, De Meijere A (2004) Eur J Org Chem 4158
209. Cordero FM, Salvati M, Pisaneschi F, Brandi A (2004) Eur J Org Chem 2205
210. Jakowiecki J, Loska R, Makosza M (2008) J Org Chem 73:5436
211. Alcaide B, Almendros P, Aragoncillo C (1999) Tetrahedron Lett 40:7537
212. Alcaide B, Almendros P, Aragoncillo C (2000) Org Lett 2:1411
213. Bandini E, Favi G, Martelli G, Panunzio M, Piersanti G (2000) Org Lett 2:1077
214. Panunzio M, Zarantonello P (1998) Org Process Res Dev 2:49
215. Bennet DM, Okamoto I, Danheiser RL (1999) Org Lett 1:641
216. Chatgilialoglu C (1992) Acc Chem Res 25:188
217. D'Annibale A, Nanni D, Trogolo C, Umani F (2000) Org Lett 2:401
218. Mauduit M, Kouklovsky C, Langlois Y, Riche C (2000) Org Lett 2:1053
219. Dalcanale E, Montanari F (1986) J Org Chem 51:567
220. Simpkins NS, Cain CM, Cousins RPC, Coumbarides G (1990) Tetrahedron 46:523
221. Escalante J, González-Tototzin MA, Avina J, Munoz-Muniz O, Juaristi E (2001) Tetrahedron 57:1883
222. Veronese AC, Gandolfi V, Longato B, Corain B, Basato M (1989) J Mol Catal 54:73
223. De Risi C, Pollini GP, Veronese AC, Bertolasi V (2001) Tetrahedron 57:10155
224. Basak A, Mandal S (2002) Tetrahedron Lett 43:4241
225. Ghosh S, Datta I (1991) Synth Commun 21:191
226. Lysek R, Furman B, Cierpucha M, Grzeszczyk B, Matyjasek L, Chmielewski M (2002) Eur J Org Chem 2377
227. Kamimura A, Morita R, Matsuura K, Mitsudera H, Shirai M (2003) Tetrahedron 59:9931
228. Kamal A, Sattur PB (1987) Heterocycles 26:1051
229. Gyónfalvi S, Szakonyi Z, Fülöp F (2003) Tetrahedron: Asymmetry 14:3965
230. Avalos M, Babiano R, Cintas P, Clemente FR, Gordillo R, Jimenez JL, Palacios JC (2003) J Org Chem 68:6338
231. Miyata O, Namba M, Ueda M, Naito T (2004) Org Biomol Chem 2:1274
232. Tsubata SK, Okinaga N (1984) J Org Chem 49:1056
233. Breckpot R (1923) Bull Soc Chim Belg 32:412
234. Chowdari NS, Suri JT, Barbas CF III (2004) Org Lett 6:2507
235. Alcaide B, Almendros P, Aragoncillo C, Rodriguez-Acebes R (2001) J Org Chem 66:5208
236. Alcaide B, Almendros P (2001) Org Prepr Proced Int 33:315
237. Alcaide B, Almendros P, Aragoncillo C, Rodriguez-Acebes R (2004) J Org Chem 69:826
238. Alcaide B, Almendros P, Martinez-del Campo T, Rodriguez-Acebes R (2004) Tetrahedron Lett 45:6429
239. Choi MK-W YuW-Y, Che C-M (2005) Org Lett 7:1081
240. Pérez-Faginas P, O'Reilly F, O'Byrne A, García-Aparicio C, Martín-Martínez M, Pérez de Vega MJ, García-López MT, González-Muñiz R (2007) Org Lett 9:1593
241. Zhao Q, Li C (2008) Org Lett 10:4037
242. Li G-Q, Li Y, Dai L-X, You S-L (2007) Org Lett 9:3519
243. Li G-Q, Li Y, Dai L-X, You S-L (2008) Adv Synth Catal 350:1258
244. Nakamura I, Araki T, Terada M (2009) J Am Chem Soc 131:2804
245. Madan S, Arora R, Venugopalan P, Bari SS (2000) Tetrahedron Lett 41:5577
246. Freihammer PM, Detty MR (2000) J Org Chem 65:7203
247. Lee E, Kim SK, Kim JY, Lim J (2000) Tetrahedron Lett 41:5915
248. Palomo C, Aizpurua JM, Galarza R, Benito A, Khamrai UK, Eikeseth U, Linden A (2000) Tetrahedron 56:5563
249. Penfold DJ, Pike K, Genge A, Anson M, Kitteringham J, Kilburn JD (2000) Tetrahedron Lett 41:10347
250. Barrett AGM, Ahmed M, Baker SP, Baugh SPD, Braddock DC, Procopiou PA, White JP, Williams DJ (2000) J Org Chem 65:3716
251. Wasserman HH, Xia M, Carr AJ, Han WT, Siegel MG (2000) Tetrahedron 56:5621

252. Joshi SN, Puranik VG, Deshmukh ARAS, Bhawal BM (2001) Tetrahedron: Asymmetry 12:3073
253. Kozawa Y, Mori M (2001) Tetrahedron Lett 42:4869
254. Kozawa Y, Mori M (2001) Tetrahedron Lett 43:111
255. Borsuk K, Suwińska K, Chmielewski M (2001) Tetrahedron: Asymmetry 12:979
256. Garbi A, Allain L, Chorki F, Ourévitch M, Crousse B, Bonnet-Delpon D, Nakai T, Bégué J-P (2001) Org Lett 3:2529
257. Alcaide B, Almendros P, Salgado NR, Martínez-Alcázar MP, Hernández-Cano F (2001) Eur J Org Chem 2001
258. Duboc R, Hénaut C, Savignac M, Genet J-P, Bhatnagar N (2001) Tetrahedron Lett 42:2461
259. Alcaide B, Almendros P, Aragoncillo C (2001) J Org Chem 66:1612
260. Bull SD, Davies SG, Kelly PM, Gianotti M, Smith AD (2001) J Chem Soc Perkin Trans 1 3106
261. Alcaide B, Almendros P, Salgado NR (2001) Tetrahedron Lett 42:1503
262. Brown GA, Anderson KM, Large JM, Planchenault D, Urban D, Hales NJ, Gallagher T (2001) J Chem Soc Perkin Trans 1 1897
263. Palomo C, Oiarbide M, Landa A, Esnal A, Linden A (2001) J Org Chem 66:4180
264. Alcaide B, Almendros P, Alonso JM, Aly MF, Pardo C, Sáez E, Torres MR (2002) J Org Chem 67:7004
265. Alcaide B, Almendros P, Aragoncillo C (2002) Chem Eur J 8:1719
266. Ruano G, Grande M, Anaya J (2002) J Org Chem 67:8243
267. Anaya J, Fernández-Mateos, Grande M, Martiánez J, Ruano G, Rubio-González MR (2003) Tetrahedron 59:241
268. Brown D, Brown GA, Andrews M, Large JM, Urban D, Butts CP, Hales NJ, Gallagher T (2002) J Chem Soc Perkin Trans 1 2014
269. Banfi L, Guanti G (2002) Eur J Org Chem 3745
270. Palomo C, Aizpurua JM, Benito A, Miranda JI, Fratila RM, Matute C, Domercq M, Gago F, Martin-Santamaria S, Linden A (2003) J Am Chem Soc 125:16243
271. Kozawa Y, Mori M (2003) J Org Chem 68:3064
272. Kozawa Y, Mori M (2003) J Org Chem 68:8068
273. Alcaide B, Almendros P, Aragoncillo C (2003) Org Lett 5:3795
274. Alcaide B, Almendros P, Alonso JM, Redondo MC (2003) J Org Chem 68:1426
275. Alcaide B, Almendros P, Alonso JM, Aly MF (2003) Chem Eur J 9:3415
276. Alcaide B, Almendros P, Pardo C, Rodríguez-Ranera C, Rodríguez-Vicente A (2003) J Org Chem 68:3106
277. Cainelli G, Giacomini D, Galletti P, Quintavalla A (2003) Eur J Org Chem 1765
278. Cainelli G, Giacomini D, Gazzano M, Galletti P, Quintavalla A (2003) Tetrahedron Lett 44:6269
279. Lee Y-S, Choung W-K, Kim KH, Kang TW, Ha D-C (2004) Tetrahedron 60:867
280. Freitag D, Schwab P, Metz P (2004) Tetrahedron Lett 45:3589
281. Gerona-Navarro G, Pérez de Vega MJ, García-López MT, Andrei G, Snoeck R, Balzarini J, De Clercq E, González-Muñiz R (2004) Bioorg Med Chem Lett 14:2253
282. Desroy N, Robert-Peillard F, Toueg J, Duboc R, Hénaut C, Rager M-N, Savignac M, Genêt J-P (2004) Eur J Org Chem 4840
283. Carland MW, Schiesser CH (2004) Molecules 9:466
284. Carland MW, Martin RL, Schiesser CH (2004) Org Biomol Chem 2:2612
285. Cesarotti E, Rimoldi I (2004) Tetrahedron: Asymmetry 15:3841
286. Alcaide B, Almendros P, Pardo C, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:7894
287. Alcaide B, Almendros P, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:2767
288. Alcaide B, Almendros P, Redondo MC, Ruiz MP (2005) J Org Chem 70:8890
289. Alcaide B, Sáez E (2005) Eur J Org Chem 1680

290. Cainelli G, Galletti P, Garbisa S, Giacomini D, Sartor L, Quintavalla A (2005) Bioorg Med Chem 13:6120
291. Cardillo G, Fabbroni S, Gentilucci L, Perciaccante R, Piccinelli F, Tolomelli A (2005) Org Lett 7:533
292. Csákÿ AG, Medel R, Murcia MC, Plumet J (2005) Helv Chim Acta 88:1387
293. Nivsarkar M, Kaushik MP (2005) Catal Commun 6:367
294. Broccolo F, Cainelli G, Caltabiano G, Cocuzza CEA, Fortuna CG, Galletti P, Giacomini D, Musumarra G, Musumeci R, Quintavalla A (2006) J Med Chem 49:2804
295. Adinolfi M, Galletti P, Giacomini D, Iadonisi A, Quintavalla A, Ravida A (2006) Eur J Org Chem 69
296. Benfatti F, Cardillo G, Gentilucci L, Perciaccante R, Tolomelli A, Catapano A (2006) J Org Chem 71:9229
297. Bhalla A, Venugopalan P, Bari SS (2006) Eur J Org Chem 4943
298. Bhalla A, Rathee S, Madan S, Venugopalan P, Bari SS (2006) Tetrahedron Lett 47:5255
299. Alcaide B, Almendros P, Aragoncillo C, Redondo MC, Torres MR (2006) Chem Eur J 12:1539
300. Cainelli G, Galletti P, Giacomini D, Licciulli S, Quintavalla A (2007) Eur J Org Chem 2526
301. Monléon LM, Grande M, Anaya J (2007) Tetrahedron 63:3017
302. Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2007) J Org Chem 72:1604
303. Benfatti F, Cardillo G, Gentilucci L, Tolomelli A (2007) Eur J Org Chem 3199
304. Graf R, Lohaus G, Borner K, Schmidt E, Bestian H (1962) Angew Chem Int Ed 1:482
305. Lee M-R, Stahl SS, Gellman SH (2008) Org Lett 10:5317
306. Bhargava G, Anand A, Mahajan MP, Saito T, Sakai K, Medhi C (2008) Tetrahedron 64:6801
307. Alcaide B, Almendros P, Carrascosa R, Rodriguez-Acebes R (2008) Eur J Org Chem 9:1575
308. Liang Y, Raju R, Le T, Taylor CD, Howell AR (2009) Tetrahedron Lett 50:1020
309. Naas T, Nordmann P (1999) Curr Pharm Des 5:865
310. Bulychev A, O'Brien ME, Massova I, Teng M, Gibson TA, Miller MJ, Mobashery S (1995) J Am Chem Soc 117:5938
311. Swarén P, Massova I, Bellettini JR, Bulychev A, Maveyraud L, Kotra LP, Miller MJ, Mobashery S, Samama J-P (1999) J Am Chem Soc 121:5353
312. Mourey L, Kotra LP, Bellettini J, Bulychev A, O'Brien ME, Miller MJ, Mobashery S, Samama J-P (1999) J Biol Chem 274:25260
313. Teng M, Nicas TL, Grissom-Arnold J, Cooper RDG, Miller M (1993) J Bioorg Med Chem 1:151
314. Bulychev A, Bellettini JR, O'Brien ME, Samama CP, J-P MMJ, Mobashery S (2000) Tetrahedron 56:5719
315. Matagne A, Lamotte-Brasseur J, Dive G, Knox JR, Frere JM (1993) Biochem J 293:607
316. Maveyraud L, Mourey L, Kotra LP, Pedelacq J, Guillet V, Mobashery S, Samama J (1998) J Am Chem Soc 120:9748
317. Beadle BM, Shoichet BK (2002) Antimicrob Agents Chemother 46:3978
318. Buynak JD, Ghadachanda VR, Vogeti L, Zhang H, Chen K (2005) J Org Chem 70:4510
319. Ruddle CC, Smyth TP (2004) Chem Commun 2332
320. Ruddle CC, Smyth TP (2007) Org Biomol Chem 5:160
321. Saudagar PS, Survase SA, Singhal RS (2008) Biotechnol Adv 26:335
322. Baldwin CM, Lyseng-Williamson KA, Keam SJ (2008) Drugs 68:803
323. Hultgren SJ, Abraham S, Caparon M, Falk P, St. Geme JW III, Normark S, (1993) Cell 73:887
324. Flemmer Karlsson K, Walse B, Drakenberg T, Roy S, Bergquist K-E, Pinkner JS, Hultgren SJ, Kihlberg J (1998) Bioorg Med Chem 6:2085
325. Kuehn MJ, Ogg DJ, Kihlberg J, Slonim LN, Flemmer K, Bergfors T, Hultgren SJ (1993) Science 262:1234
326. Soto GE, Dodson KW, Ogg D, Liu C, Heuser J, Knight S, Kihlberg J, Jones CH, Hultgren SJ (1998) EMBO J 17:6155

327. Turos E, Konaklieva MI, Ren RXF, Shi H, Gonzalez J, Dickey S, Lim D (2000) Tetrahedron 56:5571
328. Turos E, Long TE, Heldreth A, Leslie JM, Reddy GSK, Wang Y, Coates C, Konaklieva M, Dickey S, Lim D, Alonso E, Gonzalez J (2006) Bioorg Med Chem Lett 16:2084
329. Di Matthew JL, Stanley SR (1976) In: Saunders WB Co (eds) Lynch's Medical Laboratory Technology. p 742
330. Revell KD, Heldreth B, Long TE, Jang S, Turos E (2007) Bioorg Med Chem 15:2453
331. O'Driscoll M, Greenhalgh K, Young A, Turos E, Dickey S, Lim D (2008) Bioorg Med Chem 16:7832
332. Kamel MM, Naser ME (1979) Die Pharmazie 34:440
333. Finegold SM, Martin WJ (1982) In: Louis S Diagnostic microbiology, 6th ed. London, p 450
334. Behra-Miellet J, Darchy A, Gressier B, Dine T, Luyckx M, Brunet C, Dubreuil L (2007) Pathol Biol 55:390
335. Mikolasch A, Wurster M, Lalk M, Witt S, Seefeldt S, Hammer E, Schauer F, Juelich W-D, Lindequist U (2008) Chem Pharm Bull 56:902
336. Vatmurge N, Hazra B, Pore V, Shirazi F, Deshpande MV, Kadreppa S, Chattopadhyay S, Gonnade RG (2008) Org Biomol Chem 6:3823
337. Long DD, Aggen JB, Chinn J, Choi S-K, Christensen BG, Fatheree PR, Green D, Hegde SS, Judice JK, Kaniga K, Krause KM, Leadbetter M, Linsell MS, Marquess DG, Moran EJ, Nodwell MB, Pace JL, Trapp SG, Turner SD (2008) J Antibiot 61:603
338. Knight WB, Maycock AL, Green BG, Ashe BM, Gale P, Weston H, Finke PE, Hagmann WK, Shah SK, Doherty JB (1992) Biochemistry 31:4980
339. Doherty JB, Ashe BM, Barker PL, Blacklock TJ, Butcher JW, Chandler GO, Dahlgren ME, Davies P, Dorn CP, Finke PE, Firestone RA, Hagmann WK, Halgren T, Knight WB, Maycock AL, Navia MA, O'Grady L, Pisano JM, Shah SK, Thompson KR, Weston H, Zimmerman M (1990) J Med Chem 33:2513
340. Cainelli G, Galletti P, Garbisa S, Giacobini D, Sartor L, Quintavalla A (2003) Bioorg Med Chem 11:5391
341. Garbisa S, Sartor L, Biggin S, Salvato B, Benelli R, Albini A (2000) Cancer 91:822
342. Sartor L, Pezzato E, Dell'Aica I, Caniato R, Biggin S, Garbisa S (2002) Biochem Pharmacol 64:229
343. Sartor L, Pezzato E, Garbisa S (2002) J Leukoc Biol 71:73
344. Gérard S, Nollet G, Vande Put J, Marchand-Brynaert (2002) J Bioorg Med Chem 10:3955
345. Beauve C, Tjoens G, Touillaux R, Lamotte-Brasseur J, Marchand-Brynaert J, Fastrez J (1999) Eur J Org Chem 1441
346. Gérard S, Dive G, Clamot B, Touillaux R, Marchand-Brynaert J (2002) Tetrahedron 58:2423
347. Radhakrishnan R, Presta LG, EFJr M, Wildonger R (1987) J Mol Biol 198:417
348. EFJr M, Cole G, Radhakrishnan R, Epp O (1988) Acta Crystallogr B44:26
349. Bode W, EFJr M, Powers JC (1989) Biochemistry 28:1951
350. Wurtele M, Hahn M, Hilpert K, Hohne W (2000) Acta Crystallogr D56:520
351. Gérard S, Galleni M, Dive G, Marchand-Brynaert J (2004) Bioorg Med Chem 12:129
352. Delaisse JM, Ledent P, Vales G (1991) Biochem J 279:167
353. Maciewicz RA, Van der Stapper JWJ, Paraskewa C, Williams AC, Hague A (1991) Biochem Soc Trans 19:362
354. Esser RE, Angelo RA, Murphey MB, Watts LM, Thornburg LP, Palmer JT, Talhouk JW, Smith RE (1994) Arthritis Rheum 37:236
355. Thomson SK, Halbert SM, Bossard MJ (1997) Proc Natl Acad Sci USA 94:14249
356. Semenov A, Olson JE, Rosental PJ (1998) Antimicrobiol Agents Chemother 42:2254
357. Engel C, Doyle P, Hsieh I, McKerrow JH (1998) J Exp Med 188:725
358. Chapman HA, Riese RJ, Shi GP (1997) Annu Rev Physiol 59:63
359. Smith WW, Abdel-Meguid SS (1999) Exp Opin Ther Pat 9:683
360. Henkin J (1993) Annu Rep Med Chem 28:151
361. Michaud S, Gour BJ (1998) Exp Opin Ther Pat 8:645

362. Elliott E, Sloane BF (1996) Exp Opin Ther Pat 6:12
363. Veber DF, Thomson SK (2000) Curr Opin Drug Disc Dev 3:362
364. Zhou NE, Guo D, Thomas G, Reddy AVN, Kaleta J, Purisima E, Menard R, Micetich RG, Sing R (2003) Bioorg Med Chem Lett 13:139
365. Setti E, Davis D, Janc JW, Jeffery DA, Cheung H, Yu W (2005) Bioorg Med Chem Lett 15:1529
366. Wilmouth RC, Kassamally S, Westwood NJ, Sheppard RJ, Claridge TDW, Aplin R T, Wright PA, Pritchard GJ, Schofield CJ (1999) Biochemistry 38:7989
367. Yoakim C, Ogilvie WW, Cameron DR, Chabot C, Guse I, Haché B, Naud J, O'Meara JA, Plante R, Déziel R (1998) J Med Chem 41:2882
368. Han WT, Trehan AK, Wright JJK, Federici ME, Seiler SM, Meanwell NA (1995) Bioorg Med Chem 3:1123
369. Talbot MD, Butler KD (1992) Drug News Perspect 3:357
370. Qian X, Zheng B, Burke B, Saindane MT, Kronental DR (2002) J Org Chem 67:3595
371. Bisacchi GS, Sutton JC, Slusarchyk WA, Treuner U, Zhao G (2004) US Pat Appl Publ 109
372. Bannister T, Celatka C, Chandrakumar NS, Deng H, Guo Z, Jin L, Lazarova T, Lin J, Moe ST, Nagafuji P, Navia M, Ripka A, Rynkiewicz MJ, Spear KL, Strickler JE, Xie R (2006) PCT Int Appl 348
373. Tahara A, Tsukada J, Tomura Y, Kusayama T, Wada K, Ishii N, Taniguchi N, Suzuki T, Yatsu T, Uchida W, Shibasaki M (2005) Pharmacol Res 51:275
374. Xiang MA, Chen RH, Demarest KT, Gunnet J, Look R, Hageman W, Murray WV, Combs DW, Patel M (2004) Bioorg Med Chem Lett 14:2987
375. Derdowska I, Prahl A, Kowalczyk W, Janecki M, Melhem S, Trzeciak HI, Lammek B (2005) Eur J Med Chem 40:63
376. Serradeil-Le Gal C, Derick S, Brossard G, Manning M, Simiand J, Gaillard R, Griebel R, Guillon G (2003) Stress 6:199
377. Shimada Y, Taniguchi N, Matsuhisa A, Akane H, Kawano N, Suzuki T, Tobe T, Kakefuda A, Yatsu T, Tahara A, Tomura Y, Kusayama T, Wada K, Tsukada J, Orita M, Tsunoda T, Tanaka A (2006) Bioorg Med Chem Lett 14:1827
378. Galanski ME, Erker T, Studenik CR, Kamyar M, Rawnduzi P, Pabstova M, Lemmens-Gruber R (2005) Eur J Pharm Sci 24:421
379. Ferris CF, Lu S-F, Messenger T, Guillon CD, Heindel N, Miller M, Koppel G, Bruns FR, Simon NG (2006) Pharmacology. Biochem Behav 83:169
380. De B, Plattner JJ, Bush EN, Jae HS, Diaz G, Johnson ES, Perun TJ (1989) J Med Chem 32:2036
381. Guillon CD, Koppel GA, Brownstein MJ, Chaney MO, Ferris CF, Lu S, Fabio KM, Miller MJ, Heindel ND, Hunden DC, Cooper RDG, Kaldor SW, Skelton JJ, Dressman BA, Clay MP, Steinberg MI, Bruns RF, Simon NG (2007) Bioorg Med Chem 15:2054
382. Bergam M, Morales H, Mellars L, Kosoglou T, Burrier R, Davis HR, Sybertz EJ, Pollare T, (1995) 12th International Symposium on Drugs Affecting Metabolism, Houston TX, Nov 7–10
383. Salisbury B, Davis HR, Burrier RE, Burnett DA, Boykow G, Caplen MA, Clemmons AL, Compton DS, Hoos LM, McGregor DG, Schnitzer-Polokoff R, Smith AA, Weig BC, Zilli DL, Clader JW, Sybertz EJ (1995) Atherosclerosis 115:45
384. Dugar S, Kirkup MP, Clader JW, Lin SI, Rizvi R, Snow ME, Davis HR, McColombie SW (1995) Bioorg Med Chem Lett 5:2947
385. McKittrick BA, Ma K, Huie K, Yumibe N, HRJr D, Clader JW, Czarniecki M, McPhail AT (1998) J Med Chem 41:752
386. Altmann SW, Davis HRJr, Zhu L, Yao X, Hoos LM, Tetzloff G, Iyer SPN, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP (2004) Science 303/5661:1201
387. Rosenblum SR, Huynh T, Afonso A, HRJr D, Yumibe N, Clader JW, Burnett DA (1998) J Med Chem 41:973
388. Van Heek M, France CF, Compton DS, McLeod RL, Yumibe N, Alton KB, Sybertz EJ, HRJr D (1997) J Pharmacol Ext Ther 283:157

389. Van Heek M, Farley C, Compton DS, Hoos L, Alton KB, Sybertz EJ, HRJr D (2000) J Pharmacol 129:1748
390. Goel RK, Mahajan MP, Kulkarn SK (2004) J Pharm Sci 7:80
391. Goldstein S, Simpson A, Saenger P (1990) Acta Endocrinologica 12:3550
392. Mathieu B, Willey S (1984) Biochem J 21:7427
393. Frezza M, Garay J, Chen D, Cui C, Turos E, Dou QP (2008) Int J Mol Med 21:689
394. Chen D, Falsetti SC, Frezza M, Milacic V, Kazi A, Cui QC, Long TE, Turos E, Dou QP (2008) Cancer Lett 268:63
395. Veinberg G, Shestakova I, Vorona M, Kanepe I, Lukevics E (2004) Bioorg Med Chem Lett 14:147
396. Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W (2003) Angew Chem Int Ed 42:355
397. Corey EJ, Li W-DZ (1999) Chem Pharm Bull 47:1
398. Corey EJ, Reichard GA, Kania R (1993) Tetrahedron Lett 34:6977
399. Corey EJ, Reichard GA (1992) J Am Chem Soc 114:10677
400. Fenteany G, Standaert RF, Reichard GA, Corey EJ, Schreiber SL (1994) Proc Natl Acad Sci USA 91:3358
401. Omura S, Fujimoto T, Otoguro K, Matsuzaki K, Moriguchi R, Tanaka H, Sasaki Y (1991) J Antibiot 44:113
402. Omura S, Matsuzaki K, Fujimoto T, Kosuge K, Furuya T, Fujita S, Nakagawa A (1991) J Antibiot 44:117
403. Richardson PG, Hideshima T, Anderson KC (2003) Bortezomib (Velcade), a peptidyl boronic acid which is a reversible (0.6 nM *K*i) proteasome inhibitor is currently in use and approved for the treatment of multiple myeloma. In addition, there are numerous ongoing clinical trials on the use of this agent for treatment of other malignant diseases Cancer Control 10:361
404. Steinberg D (2003) The Scientist 17:S18
405. Adams J (2004) Proteasome inhibitors in cancer therapy. Human Press, New York
406. Hogan PC, Corey EJ (2005) J Am Chem Soc 127:15386
407. Reddy LR, Fournier J-F, Reddy BVS, Corey EJ (2005) J Am Chem Soc 127:8974
408. Banfi L, Basso A, Guanti G, Riva R (2006) ARKIVOC 7:261
409. Imbach P, Lang M, Garcia-Echeverria C, Guagnano V, Noorani M, Roesel J, Bitsch F, Rihs G, Furet P (2007) Bioorg Med Chem Lett 17:358
410. Meegan MJ, Carr M, Knox AJS, Zisterer DM, Lloyd DG (2008) J Enzyme Inhib Med Chem 23:668
411. Alford CA, Britt WJ (1993) In: Roizman B, Whitley RJ, Lopez C (eds) The human herpesviruses. Raven Press, New York, p 227
412. Welch AR, McNally LM, Gibson W (1991) J Virol 6:4091
413. Welch AR, Woods AS, McNally LM, Cotter RJ, Gibson W (1991) Proc Natl Acad Sci USA 88:10792
414. Yoakim C, Ogilvie WW, Cameron DR, Chabot C, Grand-Maitre C, Guse I, Haché B, Kawai S, Naud J, O'Meara JA, Plante R, Déziel R (1998) Antiviral Chem Chemother 9:379
415. Ogilvie W, Yoakim C, Do F, Haché B, Lagacé L, Naud J, O'Meara JA, Déziel R (1999) Bioorg Med Chem Lett 7:1521
416. Bonneau P, Hasani F, Plouffe C, Malenfant E, Laplante SR, Guse I, Ogilvie WW, Plante R, Davidson WC, Hopkins JL, Morelock MM, Cordingley MG, Déziel R (1999) J Am Chem Soc 121:2965
417. Shieh H-S, Kurumbail RG, Stevens AM, Stegeman RA, Sturman EJ, Pak JY, Wittwer AJ, Palmier MO, Wiegand RC, Holwerda BC, Stallings WC (1996) Nature 383:279
418. Snoeck R, Andrei G, Bodaghi B, Lagneaux L, Daelemans D, De Clercq E, Neyts J, Schols D, Naesens L, Michelson S, Bron D, Otto MJ, Bousseau A, Nemecek C, Roy C (2002) Antiviral Res 55:413
419. Gerona-Navarro G, Perez de Vega MJ, Garcia-Lopez MT, Andrei G, Snoeck R, De Clercq E, Balzarini J, Gonzalez-Muniz R (2005) J Med Chem 48, 2612

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β-Lactam Ring Opening: A Useful Entry to Amino Acids and Relevant Nitrogen-Containing Compounds

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Abstract The main strategies for the ring opening of β-lactams by chemical means are described. The discovery of each approach is put into context, sometimes in connection to processes occurring in biological systems, and the synthetic opportunities each approach offers are shown. Thus, this β-lactam route affords a number of synthetically relevant building-blocks, including α-amino acids, β-amino acids, their derived peptides, and other nitrogen containing heterocycles and open chain molecules. The content, which encompases references to initial work, further major development, and the most relevant recent literature contributions, is categorized according to the ring bond cleavaged (N_1–C_2, C_2–C_3, C_3–C_4, N_1–C_4), to finish with ring opening strategies leading to large heterocyclic compounds. Within each category, distinction has been made according to the type of nucleophilic agent employed, principally *O-, N-,* and *C*-nucleophiles. Also, a variety of applications of the strategy to the synthesis of interesting target compounds are shown.

Keywords α-Amino acids · β-Amino acids · β-Lactams · Peptides · Ring opening

Contents

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Abbreviations

Ac	Acetyl
AcOH	Acetic acid
AD	Asymmetric dihydroxylation
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cbz	Benzyloxycarbonyl
*c*Hex	Cyclohexyl
CSA	Camphorsulfonic acid
DCC	*N*,*N*-dicyclohexylcarbodiimide
DIBAL	Lithium diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMD	Dimethyldioxirane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Fmoc	9-fluorenylmethoxycarbonyl
Gly	Glycine (glycinyl)
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoric triamide
HOBt	*N*-hydroxyl benzotriazole
LDA	Lithium diisopropylamide
Leu	Leucine (leucinyl)
LHMDS	Lithium hexamethyldisilazide
mCPBA	3-chloroperoxybenzoic acid
Me	Methyl
MS	Molecular sieves
NCA	*N*-carboxy anhydride

NDC	Nicotinium dichromate
NMM	*N*-methyl morpholine
Nu	Nucleophile
PDC	Pyridinium dichromate
Ph	Phenyl
Phe	Phenylalanine (phenylalaninyl)
PMP	4-(methoxy)phenyl
Pr	Propyl
p-Tos	4-(methylphenyl)sulfonyl
p-Tolyl	4-methylphenyl
SEM	2-(trimethylsilyl)ethoxymethyl
Succ	Succinyl
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinyl-1-oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thz	2-thiazolyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet
Val	Valine (valinyl)

1 Introduction

After the first successful attempts in 1928 to identify the active biochemicals found in antibacterial molds, followed the rediscovery of penicillin by Fleming, identification of its chemical structure by Hodgkin, and subsequent synthesis by Chain, Heatley, and Florey, which led to the commercial production of penicillin in the mid 1940s [1]. Since then, other families of β-lactam antibiotics have been developed [2, 3], and their massive use worldwide continues to be a forefront line of action against infectious pathogens [4–6]. In recent years, β-lactams have found other biomedical applications, such as inhibitors of serine protease ([7, 8]; for a review, see [9]) and inhibitors of acyl-CoA cholesterol acyltransferasa (ACAT) [10]. Encouraged by their bioactivity, the synthesis and chemistry of β-lactam antibiotics have been the focus of active research, and chemical modification of some basic structures available from biosynthesis (semisynthetic approaches) as well as the discovery of fully chemical routes to de novo synthesis of β-lactam

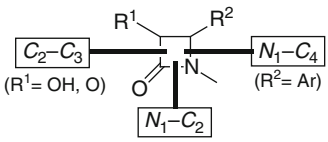


Fig. 1 Principal strategies for the selective ring opening of β-lactams

compounds, have been pursued ([11–13]; for synthetic strategies and medicinal properties of β–lactams, see [14]). Subsequent to this effort, a number of methods have become available for the delivery of the 2-azetidinone core ring present in all β-lactam compounds [15–20]: namely, the ketene-imine cycloaddition or Staudinger reaction ([21]; for reviews, see [22]; [23–25]), the ester enolate-imine condensation (for reviews, see [26]; [27–32]), the hydroxamate approach [33], the alkene-isocyanate cycloaddition [34], and the alkyne-nitrone cycloaddition (Kinugasa reaction) ([35–39]; for a highlight, see [40]).

Complementing the interest in the formation of the 2-azetidinone ring, the cleavage of 2-azetidinones also bears important biological as well as chemical implications. On the one hand, the irreversible ring opening of the 2-azetidinone core accounts for one of the key biomolecular events during both the β-lactams antibiotic action [5, 12–14] and their inhibition by β-lactamases [12–14, 41–45]. On the other hand, the chemically controlled ring opening of the 2-azetidinone system has been demonstrated as a powerful tool for the synthesis of important building blocks, especially heterocycles, α- and β-amino acids, and derivatives (for chemical methods, see [46]; for a review on enzymatic methods, see [47]; [48–51]; for a recent example [52]; [53]). In this chapter, the most general approaches for the selective ring opening of the β-lactam unit are described and a selection of relevant developments are shown, including the most recent examples in the area.

Three major bond breaking strategies of the β-lactam unit have been developed so far, Fig. 1. The most intuitive scission corresponds to that of the amide bond (N_1–C_2) cleavage, and involves the attack of some nucleophile species, most often *N*- and *O*-centered nucleophiles. A second strategy is feasible for β-lactams bearing a hydroxyl group attached at the C_3 position (also for α-keto β-lactams), and consists of the oxidative Baeyer-Villiger type rearrangement of the derived α-keto β-lactams. The third strategy can be applied for β-lactams bearing an aryl group attached at the C_4 position. The selective N_1–C_4 bond cleavage in these substrates can be achieved under hydrogenolytic conditions.

2 Ring Opening at N_1–C_2 Bond of β-Lactams

β-Lactams can act as acylating agents to those nucleophiles that effect the cleavage of the β-lactam N_1–C_2 bond. Indeed, irreversible acylation of an enzyme amino acid unit belonging to a bacterial cell is the most common type of molecular mechanism for the β-lactam antibiotics mode of action. Similarly, the process is on grounds of

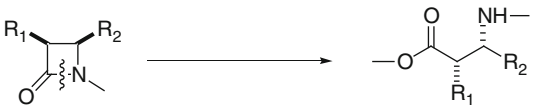
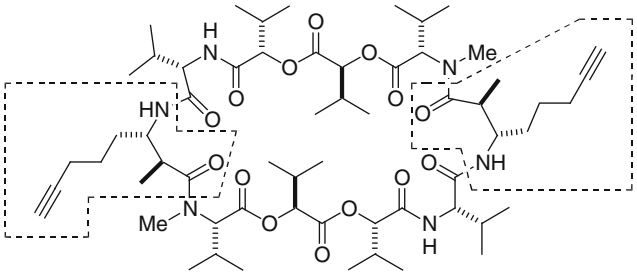
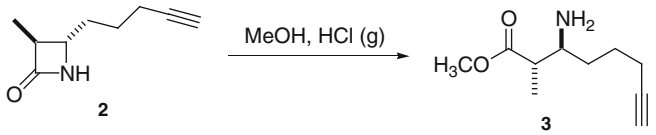


Fig. 2 N_1–C_2 bond cleavage leading to β-amino acid derivatives



Onchidin **1**



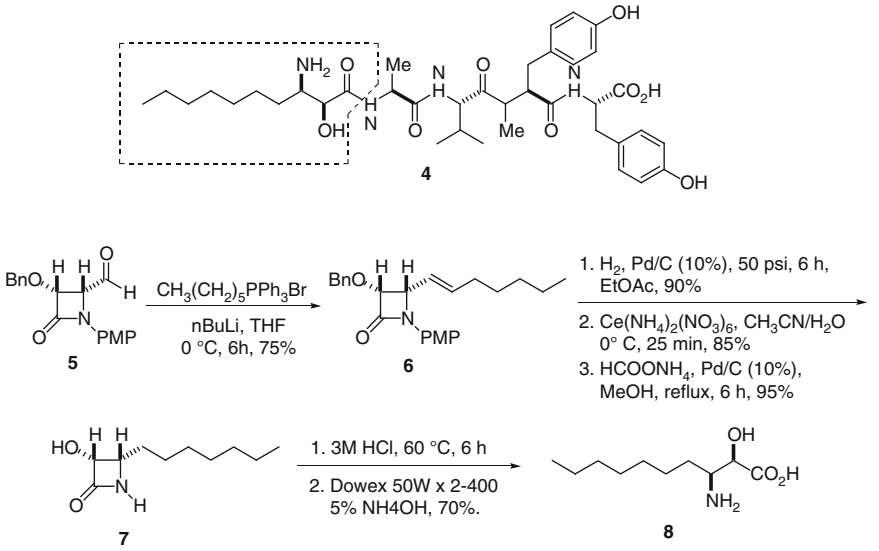
Scheme 1 Acid methanolysis of β-lactam **2** in the synthesis of key β-amino acid unit of onchidin, **1**

their inhibition by β-lactamases. This reactivity of the β-lactam ring has been exploited in the laboratory in the context of the synthesis of β-amino acid derivatives, Fig. 2.

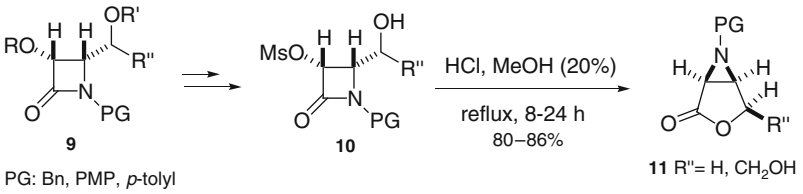
The majority of the early procedures for the cleavage of the β-lactams N_1–C_2 bond deal with hydrolysis and alcoholysis processes under rather harsh acid or basic reaction conditions. One example is the ring opening of β-lactam **2** under acidic conditions to afford almost quantitative β-amino ester **3**, a component of the dimeric cyclic depsipeptide onchidin, **1**, isolated from the marine mollusc *Onchidium sp*., Scheme 1 [54].

Similarly, the acid hydrolysis of β-lactam **7** has been described [55] to give the α-hydroxy β-amino acid **8**, a suggested *N*-terminal component of angiotensin-converting enzyme inhibitor microginin **4**, Scheme 2. The key precursor **7** was obtained through a Wittig olefination of the 4-formyl β-lactam **5**, followed by simple elaboration of the resulting **6** (for a review on the use of 4–formyl β–lactams in synthesis, see [56]).

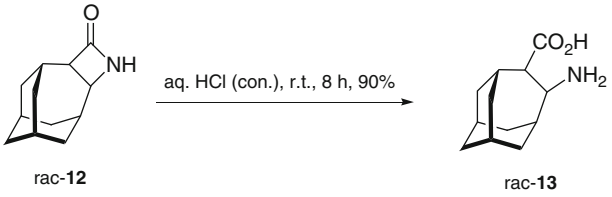
In an intramolecular variation [57], the acid-promoted alcoholysis of the β-lactam ring in **10**, Scheme 3, produced 2,3-aziridino-γ-lactones **11**, which are intermediates of glutamic acid derivatives with potential activity as excitatory neurotransmitter of the central nervous system.



Scheme 2 Acid hydrolysis of *NH*-β-lactam **6** in the synthesis of microginin, **4**

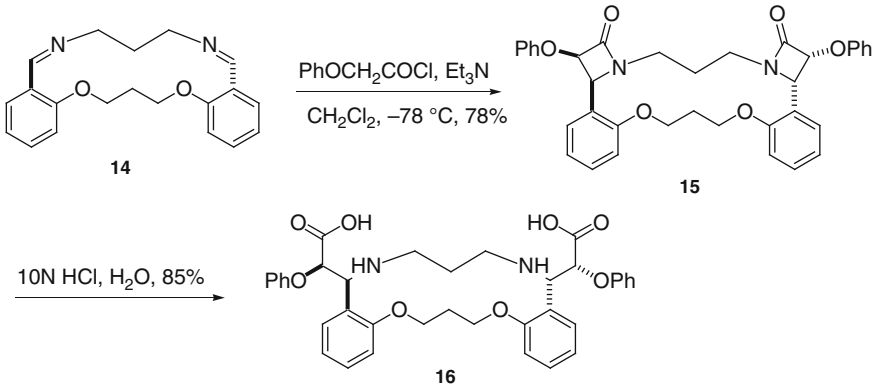


Scheme 3 Intramolecular acid alcoholysis of β-lactams leading to γ-lactones

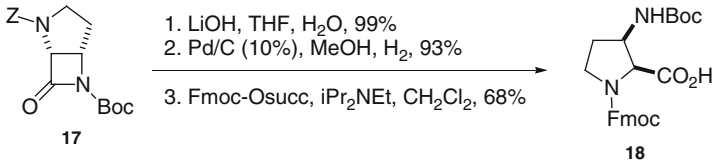


Scheme 4 Acid hydrolysis of *NH* β-lactam to homoadamantyl β-amino acids

A further example of the use of acid hydrolysis of the β-lactam nucleus is the transformation of **12** into homoadamantyl β-amino acid derivatives like **13**, which are precursors of potential candidates for treatment of cancer and degenerative brain diseases [58] (Scheme 4).



Scheme 5 Synthesis and subsequent cleavage of azetidin-2-one ring of bis-β-lactams



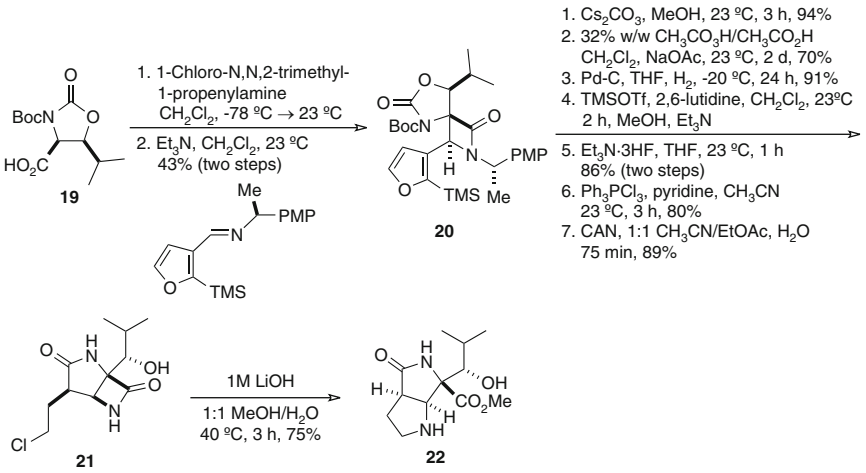
Scheme 6 Basic saponification of the β-lactam amide in compound **17**

In a similar way, formation and subsequent hydrolysis of bis-β-lactams provide a route to peripheral functionalization of macrocyclic imines. For example, racemic bis-β-lactam **15**, Scheme 5, which is formed upon Staudinger reaction of imine **14** and the ketene originated from phenoxyacetyl chloride and triethylamine, led to C_2 symmetric amino acid **16** in high yield [59].

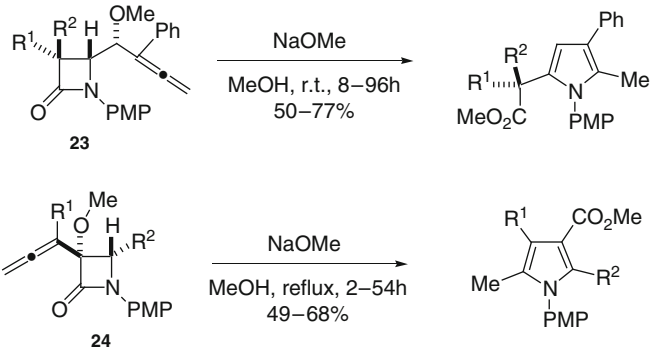
Most traditional methods use hydrochloric acid solutions as the acid reagent for the hydrolysis or alcoholysis of β-lactams. Methanolic solutions of trimethylchlorosilane are able to generate HCl in situ, and the trick has been employed successfully for the methanolysis of β-lactams in a route to aspartic acid derivatives [60, 61] and 2-oxazolidinones[62], respectively. Recently the use of silica-supported acid reagent has been reported as a convenient alternative. The reagent (SiO_2–Cl) prepared from admixing silica gel and $SOCl_2$ in dichloromethane and subjected to dryness, is able to run the methanolysis of β-lactams at room temperature in 20 min [63].

Alternative to the acid hydrolysis of the β-lactam amide system is the base promoted saponification reaction. Robinson and Pluschke [64] have employed the LiOH-promoted hydrolysis of the bicyclic β-lactam **17** as a means to the synthesis of key diamino acid residue **18**, employed in the preparation of a malaria-vaccine candidate, Scheme 6.

Saponification of the bicyclic β-lactam **21** to yield **22** has been employed by Corey [65] as an experimental evidence of the mechanism-based design of



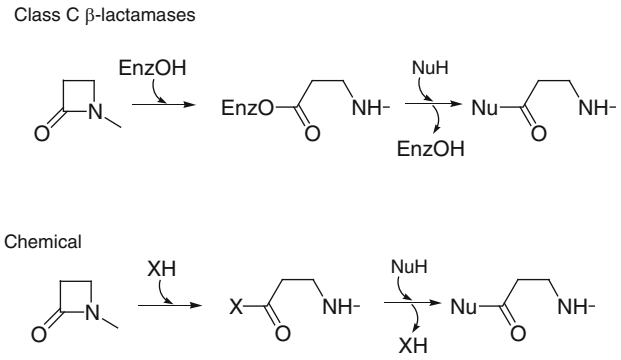
Scheme 7 Saponification of bicyclic β-lactam **21** as a test for the proteasome inhibition activity of parent compound **20**



Scheme 8 Opening of *N*-aryl β-lactams with methoxide leading to pyrroles

proteasome inhibition compound **20**, Scheme 7. Synthesis of β-lactam **21** was carried out by the [2+2] cycloaddition reaction of ketene generated from acid **19** and the corresponding imine, and subsequent elaboration of the resulting β-lactam **20**.

When *N*-substituted β-lactams are involved, the ring opening effected by metal alcoxides is feasible if the substituent group on the nitrogen is a phenyl. In contrast, *N*-alkyl substituted β-lactams ring remained unaltered under such conditions [66]. By using the appropriate β-lactam substrate, such as allenyl derivatives **23** and **24** the ring opening effected by sodium methoxide in methanol yields tetrasubstituted pyrroles, Scheme 8. In these transformations, the evolving amine function adds to the allenyl moiety with concomitant aromatization of the newly formed five-membered ring through β-elimination of an alkanol unit.



Scheme 9 Enzymatic and chemical ring opening of β-lactams via N_1–C_2 bond cleavage

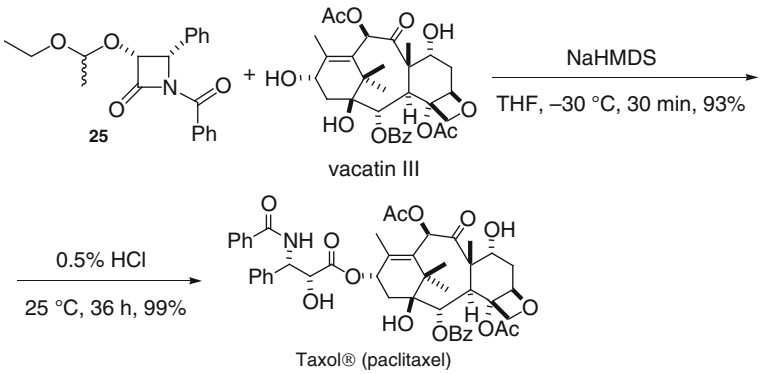
The examples discussed above constitute a selection of recent applications of the acid and basic hydrolysis of β-lactams in synthesis. Hydrolysis and alcoholysis of β-lactams can also be effected under roughly neutral reaction conditions when enzymes are the promoters [47]. The β-lactamases catalyzed hydrolysis of β-lactams is an efficient process for a broad spectrum of substrates, including those β-lactams with base or acid sensitive groups [12–14]. This process proceeds through an acyl enzyme intermediate to give ring opened β-amino acids. The class C β-lactamases in particular, in Scheme 9, have the ability to catalyze the alcoholysis reaction and hence β-amino esters are the products formed.

Besides enzymes, other chemical promoters have been developed for the N_1–C_2 bond cleavage of activated β-lactams under not so drastic acid or basic conditions. To this end, the use of *N*-acyl β-lactams, i.e. *N*-Boc β-lactams, as activated substrates has assumed major importance. The *N*-acyl group on the substrate β-lactam serves not only to activate the β-lactam carbonyl towards the nucleophile attack, but also to protect the amino function in the resulting β-amino acid derivative product (for the application of this concept to γ- and δ- lactams, see [67]).

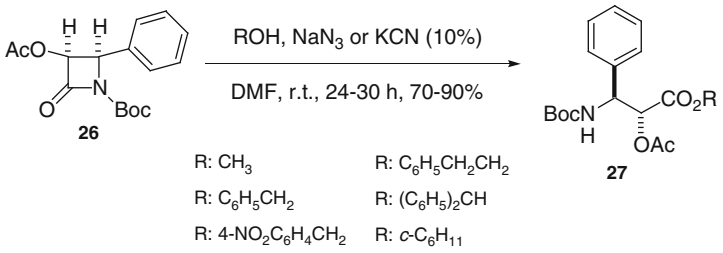
A recent study has revealed *N*-sulfonyl β-lactams as another class of activated β-lactams towards the ring opening by both *N*- and *O*-nucleophiles [68].

2.1 Ring Opening by Oxygen Nucleophiles: β-Amino Esters and Related Products

The most representative example of the utility of β-lactams as acylating agents is the coupling reaction of the β-lactam **25** Scheme 10, with the sodium salt of vacatin III to give paclitaxel ([69–73]; for a recent example involving kinetic resolution of racemic β–lactams, see [74]), after mild deprotection of the TES group.



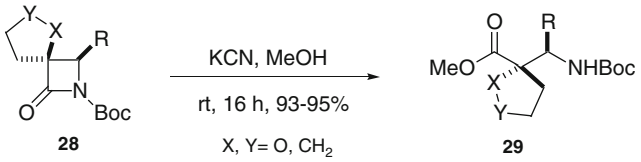
Scheme 10 *N*-acyl β-lactam **25** as acylating reagent of vacatin III in the last synthetic step towards paclitaxel



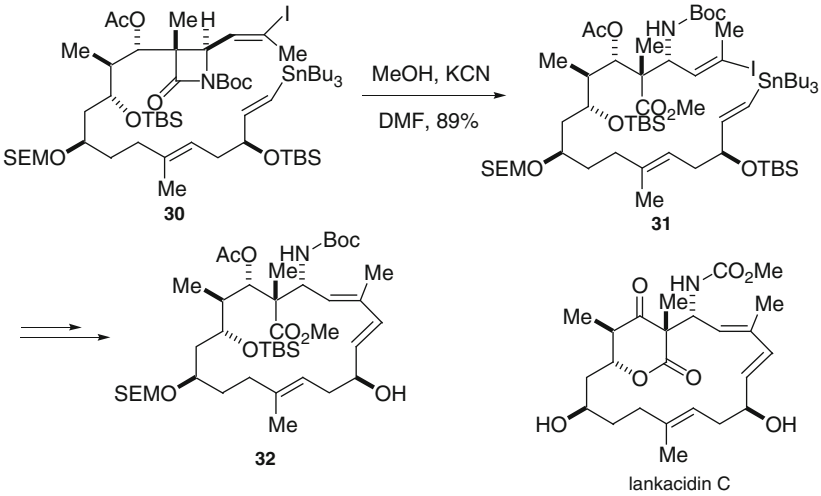
Scheme 11 Alcoholysis of β-lactams in the presence of NaN_3 or KCN as the reaction promoters

In general, the ring opening of *N*-acyl β-lactams by the action of an alkoxylate salt produces the expected esters when the peripheral substituents on the β-lactam ring are not base sensitive. If free alcohols are used instead, with the aim of avoiding the strongly basic media, the coupling reaction is in general so slow that it is not useful. In this context, NaN_3 and KCN were identified in the middle 90s as two very efficient promoters of the ring opening of *N*-Boc β-lactams with free alcohols. This trick permits couplings to take place under almost neutral conditions and makes the method more effective than the use of alkoxylate salts in some instances. For example, the alcoholysis of **26** to give **27**, Scheme 11, in the absence of these additives is exceedingly slow, while in the presence of a 10 mol% of NaN_3 or KCN, the coupling proceeds smoothly to give β-amino esters **27** in good to excellent yields. Interestingly, under these conditions the acetoxy group remains intact, whilst under the basic conditions of MeONa or EtONa, it is also cleaved [75].

Using spiro-β-lactams as substrates, Alonso [76] has applied this trick for the synthesis of α,α-cyclic disubstituted β-amino esters **29**, Scheme 12, which might be useful units for the design of β-peptides with new folding patterns.



Scheme 12 KCN-promoted cleavage of β-lactams leading to α,α-cyclic disubstituted β-mino esters **29**



Scheme 13 KCN-promoted methanolysis of β-lactam **30** en route to lankacidin C synthesis

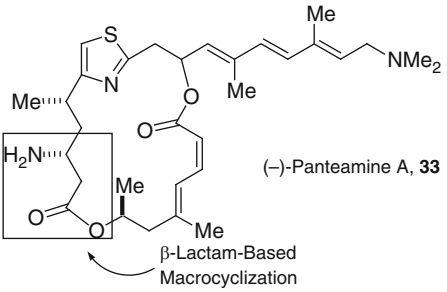
The implementation of this methodology for a synthesis of advanced macrocyclic precursors of antitumor antibiotics lankacidins, which posses a carbocyclic structure, has been reported by Thomas [77]. In such a route, Scheme 13, one of the key steps is the ring opening of the β-lactam nucleus in **30** by methanol, assisted by KCN, to give the corresponding β-amino ester intermediate **31**. The latter, upon cyclization and protecting group manipulation, renders **32**, which on subsequent elaboration affords lankacidin C.

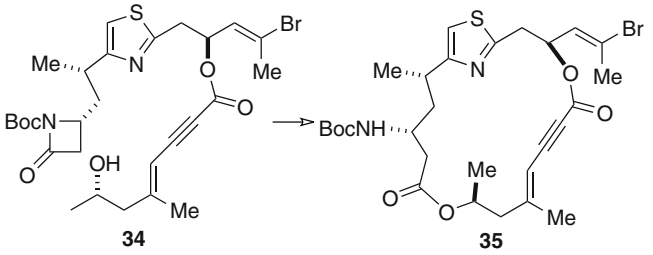
Taking advantage of the same concept in an intramolecular variant, Romo has documented [78] the synthesis of (−)-panteamine A, Fig. 3, in which a β-lactam-based macrocyclization is the crucial step to construct the β-amino macrolactone **33**.

Of the different reaction conditions used for the intramolecular coupling of the secondary alcohol and the β-lactam unit in **34**, Scheme 14, the use of KCN or Et_4NCN as additives give the best results. Further elaboration of **35** leads to the immunosuppressive agent (−)-panteamine A.

A related example (Scheme 15) of the utility of β-lactams as acylating agents for macrolactonization has been reported by Georg in an approach to the antimicotic agent cryptophycin **37** from precursor **36** [79, 80].

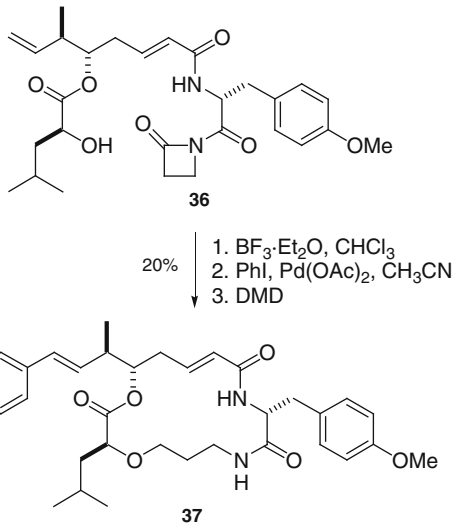
Fig. 3 β-Amino acid unit constituent of panteamine A





Conditions	Temp. ºC	Yield %
1.1 eq. NaHMDS, THF, 45min	–40	37
1.1 eq. LiHMDS, THF, 2.5h	–40	11
1.1 eq. NaH, THF, 1h	–10	42
0.5-0.6M KCN, DMF, 1-2h	25	52-72
9.0 eq. Et_4NCN, CH_2Cl_2, 4-9h	25	59-68

Scheme 14 β-lactams as intramolecular O-acylating reagents (I). A route to (-)-Panteamine macrolactone



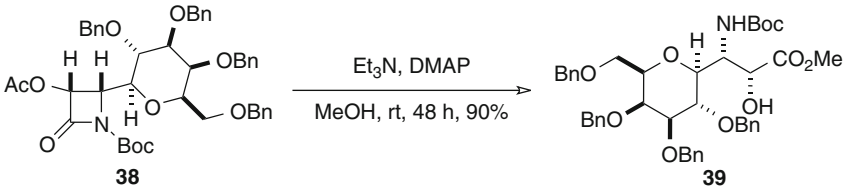
Scheme 15 β-Lactams as intramolecular O-acylating reagents (II). A route to Cryptophycin

More recently, Dondoni [81] has shown the methanolysis of *N*-Boc β-lactams in the presence of excess Et_3N (5 equivalents) and DMAP (3 equivalents), Scheme 16. In this work, β-lactams containing a sugar residue as in **38** were transformed in the corresponding isoserine derivatives **39**, in high yields and without compromising configurational integrity.

2.2 *Ring Opening by Nitrogen Nucleophiles: β-Amino Amides and β-Amino Acid-Derived Peptides*

From the ring opening of β-lactams by amines and α-amino acids, β-amino amides and β-amino acid derived peptides are generated. These structures are of interest because of their presence in several naturally occurring macrocyclic compounds [82, 83]. One example of the latter is the β-hydroxy aspartic acid derived tripeptide **45** found in the macrocyclic peptide lactone antibiotic lysobactin **40** [84], Fig. 4.

The key step of the approach to **45** is the ring opening of *N*-Boc β-lactam **43** with ammonia, Scheme 17. The synthesis starts from the 4-carboxy azetidin-2-one **41**, which is a β-hydroxy aspartic acid form possessing the β-carboxyl group and the α-amino moiety simultaneously protected. The dipeptide unit **42** is obtained in 95% overall yield after activation of the α-carboxy group with cyanuric fluoride and



Scheme 16 Methanolysis of *N*-Boc β-lactams under basic conditions

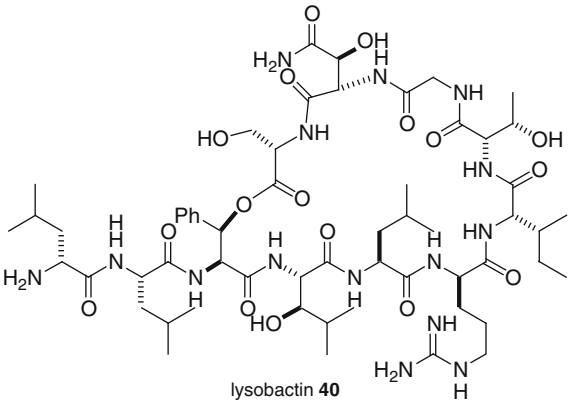
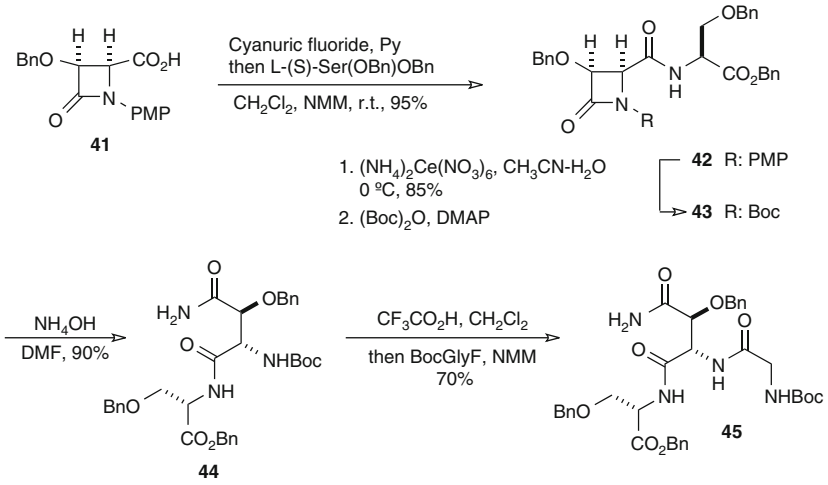


Fig. 4 Structure of antibiotic lysobactin

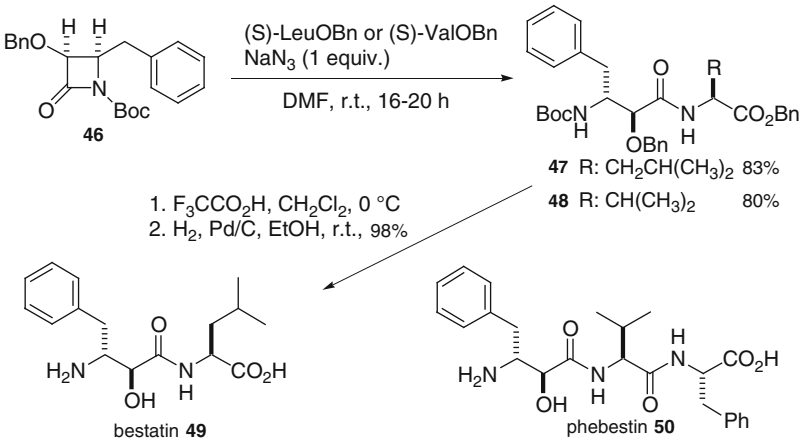


Scheme 17 Ammonolysis of *N*-Boc β-lactams as a route to β-amino acid-containing peptides

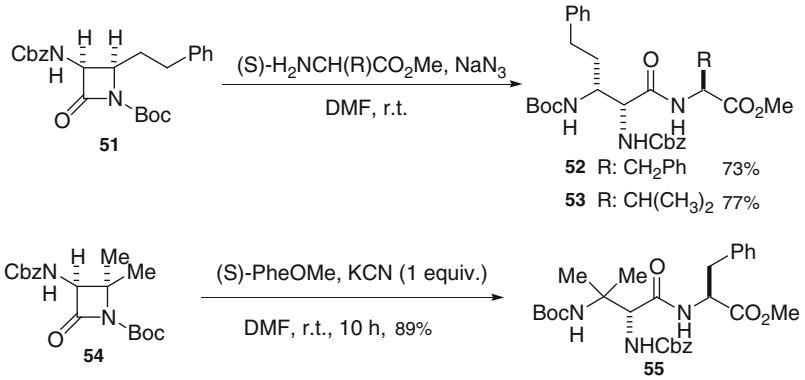
subsequent coupling with *O*-benzyl L-(*S*)-serine benzyl ester. *N*-Dearylation followed by incorporation of the Boc group and ring opening with ammonia in DMF as solvent renders the carboxamide **44** in 90% yield. Subsequent *N*-Boc deprotection and coupling with Boc-GlyF provides tripeptide **45** in 70% yield [85].

Although aminolysis of *N*-acyl β-lactams can be effected in aqueous media by amines without the assistance of any additional promoter [86], the use of some additives can considerably speed up the process in ordinary organic solvents. For instance, although the ammonolysis of the β-lactam **43** proceeded efficiently even in the absence of any additive, the presence of NaN_3 has been shown to be crucial for the coupling of β-lactams with α-amino esters to be efficient ([87]; for a related work, see [88]). It has been found that, for example, coupling of the *N*-Boc β-lactam **46** with (*S*)-LeuOBn, Scheme 18, to give the dipeptide product **47** in an appreciable yield necessitates a fourfold excess of the α-amino ester component, while the same reaction performed in DMF, and in the presence of NaN_3, proceeds in high yield by using just an equimolar amount of both coupling components. Similarly, the reaction of **46** with the more sterically crowded (*S*)-ValOBn in DMF produces **48** in 22% yield when a 1:2 ratio of components is employed, respectively, and only traces of **48** are detected for a 1:1.3 ratio. In contrast, when NaN_3 is used as an additive, the desired product is obtained in 80% yield under the same conditions. Both **47** and **48** can be transformed into bestatin **49** and phebestin **50**, respectively, two low molecular weight peptides that show marked inhibition of aminopeptidases.

The utility of these promoters to achieve an efficient coupling of α-amino β-lactams with α-amino acid esters has also been documented [89]. For example, β-lactam **51**, Scheme 19, upon treatment with (*S*)-PheOMe and (*S*)-ValOMe in DMF, in the presence of NaN_3, furnishes dipeptides **52** and **53** respectively, in good



Scheme 18 NaN_3-promoted opening of β-lactams with α-amino esters

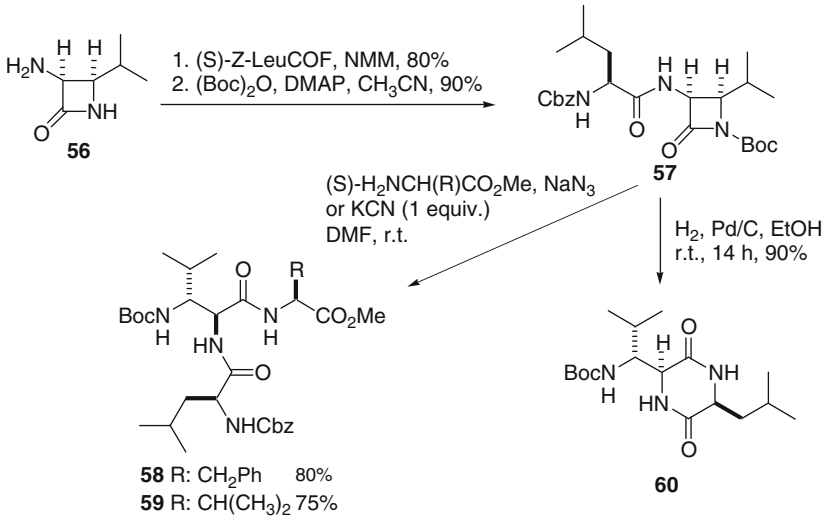


Scheme 19 NaN_3- and KCN-promoted opening of *N*-boc β-lactams

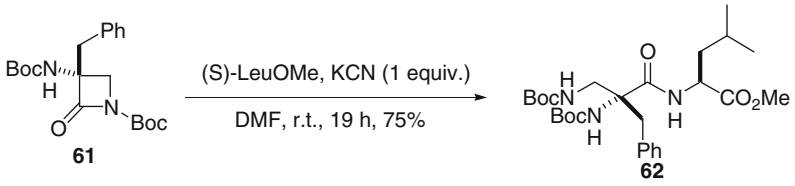
yield. Nevertheless, the β-lactam **54**, possessing a quaternary carbon center at C_4, does not react with these α-amino acid esters even when a twofold excess of NaN_3 is employed to promote the coupling reaction. In this and other instances that involve difficult coupling reactions, KCN may be the additive of choice. For example, dipeptide **55** is produced within about 10 h in 89% isolated yield when KCN is employed instead of NaN_3.

Further examples of the coupling of β-lactams with α-amino acid esters are shown in Scheme 20. For instance, **57**, prepared from **56**, reacts with α-amino acid esters in the presence of NaN_3 to give tripeptides **58** and **59**. In addition, simple exposure of **57** to hydrogen over Pd/C at room temperature produces the piperazinedione **60** in 90% yield.

The effectiveness of KCN in promoting difficult couplings can be further shown in the reaction of α-amino α-branched β-lactams with α-amino esters [90].



Scheme 20 Coupling of *N*-Boc β-lactams with α-amino acid esters

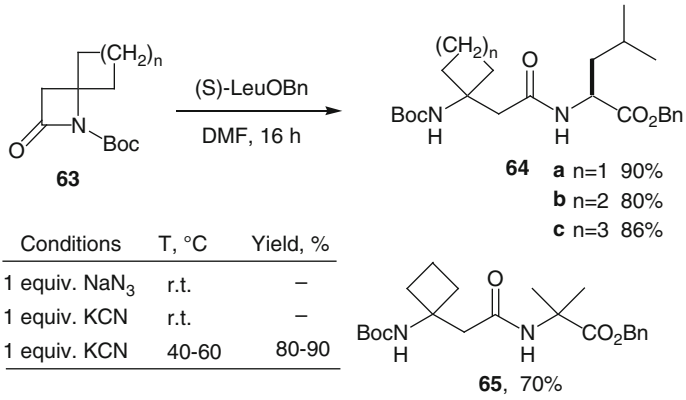


Scheme 21 KCN-promoted opening of β-lactams leading to α,β-diamino acid containing peptides with a quaternary carbon

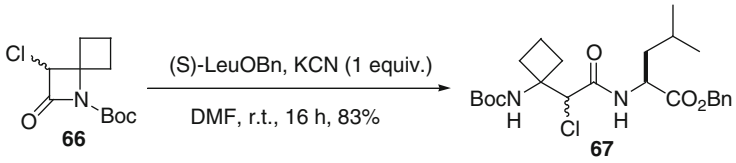
Whilst compound **61**, Scheme 21, upon treatment with (*S*)-LeuOMe and NaN_3 does not produce the corresponding dipeptide product, the reaction in the presence of KCN leads to dipeptide **62** in 75% isolated yield.

The coupling reaction of α-unsubstituted β-lactams, bearing a quaternary carbon atom at C_4, constitutes another good example of the ability of KCN to promote β-lactam ring opening, Scheme 22. In these instances, no coupling reaction from **63** is observed in appreciable extent under the reaction conditions noted above. However, the coupling takes place efficiently in DMF at 40°C in the presence of stoichiometric amounts of KCN to produce **64** in good yields. Under these conditions, even the bulky AibOBn efficiently couples with **63a** to afford the dipeptide **65** in 70% yield.

Interestingly, the 3-chloro β-lactam **66**, Scheme 23, upon treatment with (*S*)-LeuOBn in DMF as solvent, afforded detectable dipeptide formation (15%) in the absence of any promoter. When the same coupling is carried out under identical conditions but with the assistance of 1 equivalent of NaN_3, the yield rises to 85%. Finally, by using KCN instead of NaN_3, a complete reaction at room temperature is



Scheme 22 Opening of spiro β-lactams with α-amino esters



Scheme 23 Opening of α-chloro spiro β-lactams facilitated by KCN

observed and the dipeptide **67** is obtained in 83% isolated yield. These results suggest that the presence of electron-withdrawing substituents at the *C*α position of the β-lactam nucleus is an additional element that facilitates the coupling reaction [91].

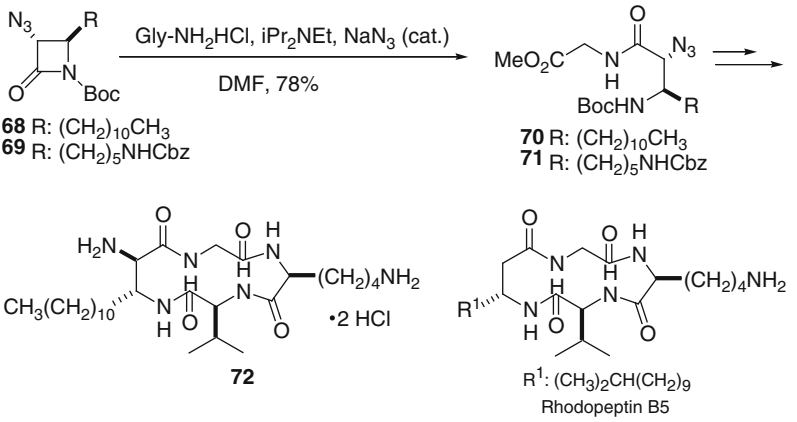
Following a similar strategy, Miller [92] has documented the ring opening of α-azido β-lactams with α-amino acid esters, Scheme 24. Treatment of α-azido β-lactams **68**/**69** with glycine methyl ester thus afforded dipeptides **70**/**71** with differentially protected amino groups. From dipeptide **70**, a synthesis of the rhodopeptin B5 analogue **72** was further demonstrated.

McCarthy and coworkers have used this strategy en route to ADDA conjugates [93, 94], residues that are found in the cyclic peptides microcystin LA **73**, microcystin LR **74**, and nodularin R **75**, Fig. 5.

In particular, the ADDA-containing analogue **77** can be prepared from the coupling of **76** with glycine methyl ester, Scheme 25.

In another application of the approach, Nuss and coworkers have reported the preparation of α-keto amides **79** from **78**, Scheme 26. Again, the best results, particularly with hindered nucleophiles, are attained by performing the ring opening in the presence of KCN [95].

The same authors have shown that activation of the β-lactam ring towards nucleophilic opening can be achieved by sulfonylation of the nitrogen atom.



Scheme 24 Ring opening of α-azido β-lactams with α-amino acid esters

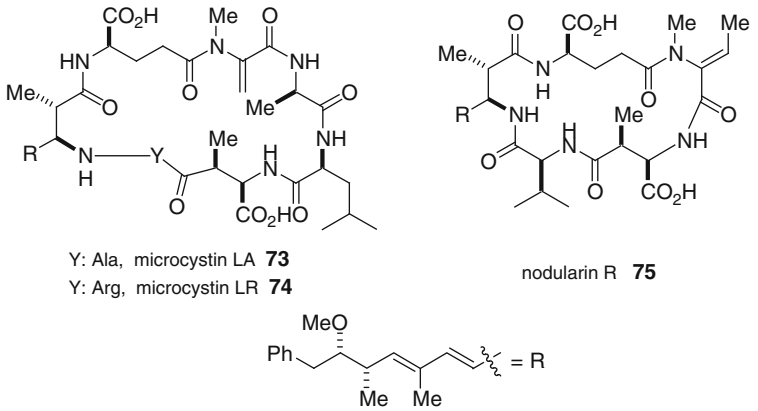
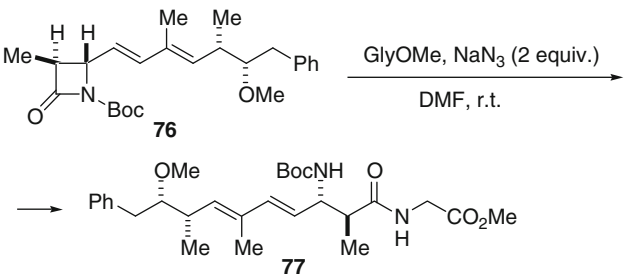
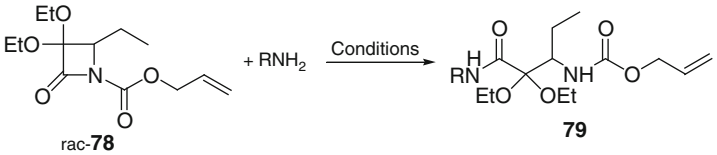
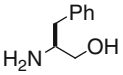
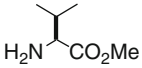
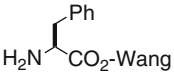


Fig. 5 Cyclic peptides containing ADDA-conjugates



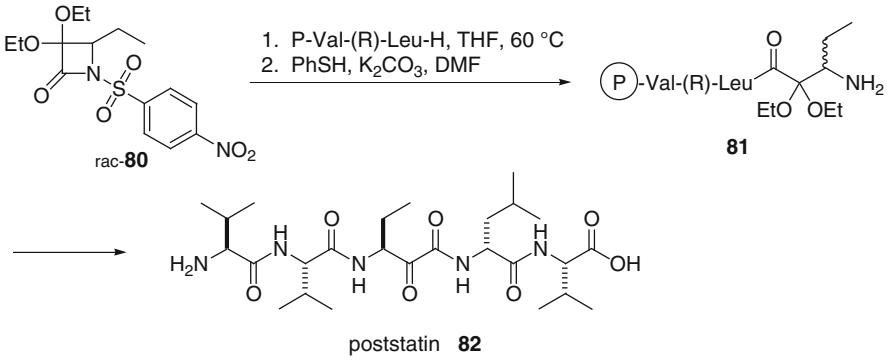
Scheme 25 NaN_3-promoted opening of *N*-Boc β-lactams leading to ADDA-containing analogues



RNH_2	Conditions*	Yield, %
	KCN, DMF, r.t., 4h	87
	KCN, DMF, 70°C	68
	KCN, NMP, 90°C	61

* No coupling observed in the absence of KCN

Scheme 26 Opening of β-lactams with amines leading to α-keto aminoamides

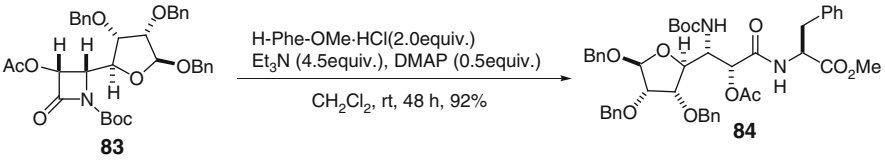


Scheme 27 Ring opening of *N*-sulfonyl β-lactams

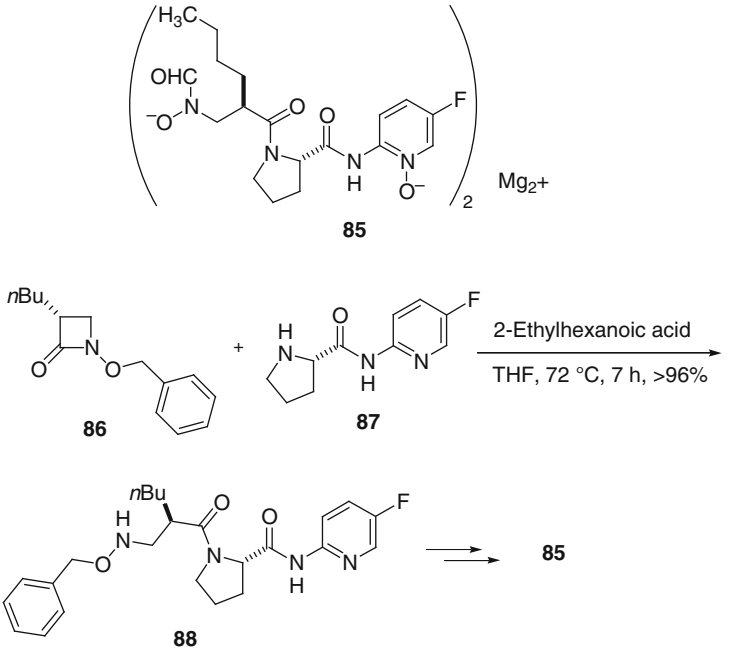
In this respect, Scheme 27, the ring opening of *N*-sulfonyl β-lactam **80** with a dipeptide affords α-keto amide precursor **81**. Subsequent elaboration of **81** and final hydrolysis of the ketal moiety affords poststatin **82**, a naturally occurring pentapeptide which shows inhibitory activity against prolyl endopeptidase.

Although no conclusive evidence has been found yet for this assumption, it is postulated that the β-lactam opening reactions promoted by CN^- or N_3^--containing additives proceed via an acyl azide or an acyl cyanide intermediate. The mode of action of some β-lactamases and the fact that no β-lactam ring opening usually takes place in the absence of such additives support this hypothesis.

Complementing the capacity of CN^- or N_3^--containing additives, Dondoni [81] has shown that the combination of Et_3N (excess equivalents) and DMAP



Scheme 28 Opening of β-lactam ring with amines promoted by the Et_3N/DMAP system



Scheme 29 Acid-promoted opening of *N*-benzyloxy β-lactams

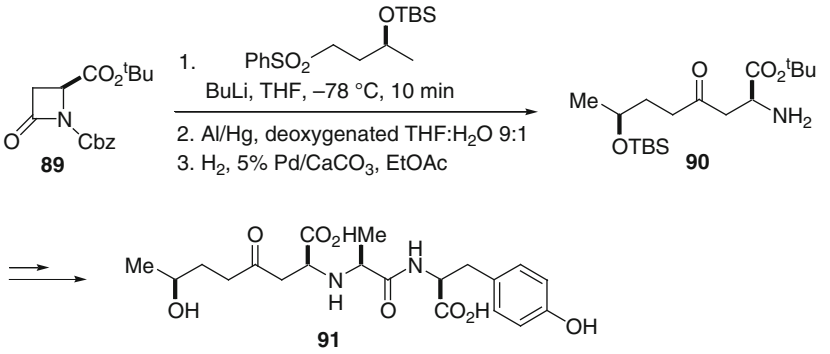
(0.5 equivalents) also promotes the ring opening of *N*-acyl β-lactams by amine nucleophiles. In a recent work, Scheme 28, treatment of β-lactam **83** with phenyl alanine methyl ester under the above conditions was described to provide compound **84** in 92% yield.

In an effort to access peptide-deformylase inhibitor **85**, Prasad [96] has described the aminolysis of *N*-benzyloxy β-lactam **86** with proline derivative **87** to give the β-(*O*-benzyl hydroxylamine) amide **88**. It is worth noting that no acyl activation of the β-lactam nitrogen is operating in this case. After examination of an array of solvents and additives for the ring opening, the best result (>96% yield) was finally obtained with 2-ethylhexanoic acid as the catalyst, and THF was the preferred solvent at 72°C (Scheme 29).

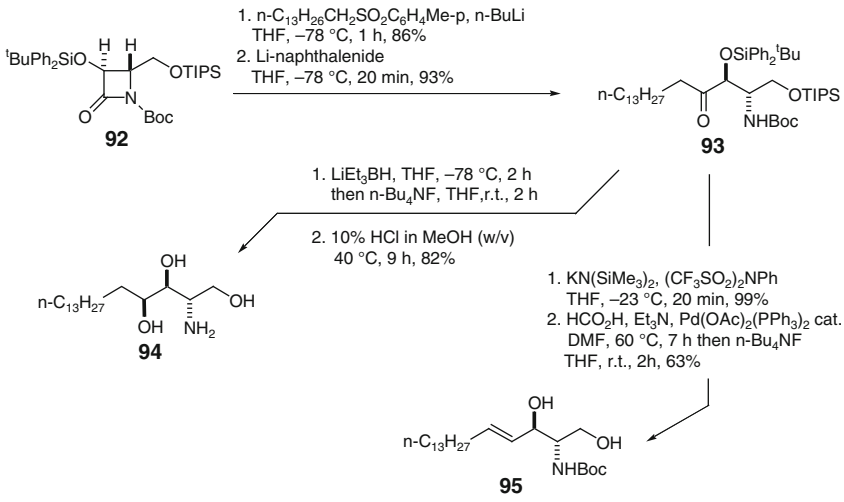
2.3 *Ring Opening by Carbon Nucleophiles: β-Amino Ketones and Related Products*

By analogy with the above reactions that use *O*- and *N*-nucleophiles, it has been shown that ring opening of *N*-Boc β-lactams can be achieved by reaction with metallated carbon nucleophiles. For instance, Baldwin developed the reaction of α-lithiated sulfones, Scheme 30, with β-lactams, such as **89**, to provide access to γ-keto α-amino esters **90**, after desulfonation of the resulting intermediates. In particular, the angiotensin converting enzyme inhibitor WF-10129 **91** has been synthesized by this route [97].

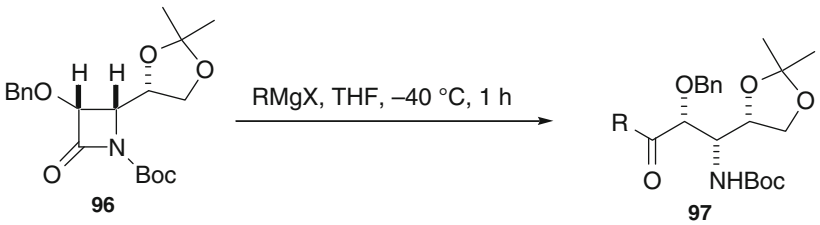
In a more recent example of this methodology, the ring opening of β-lactam **92**, Scheme 31, with a lithiated sulfone proceeds to give after desulfonation compound



Scheme 30 Opening of *N*-Cbz β-lactams by a α-lithium sulfonyl anion



Scheme 31 Access to phytosphingosines through β-lactam ring opening by lithiated sulfones



RMgX	Ratio of **96**:**97**:**98**	Yield, % of **97**
ArMgBr	--:>99:--	≥90
MeMgBr	13:45:42	40
EtMgBr	12:67:21	60
^{n}BuMgBr	--:90:10	80
^{n}HexMgBr	--:89:11	85

Scheme 32 β-lactam ring opening by Grignard reagents

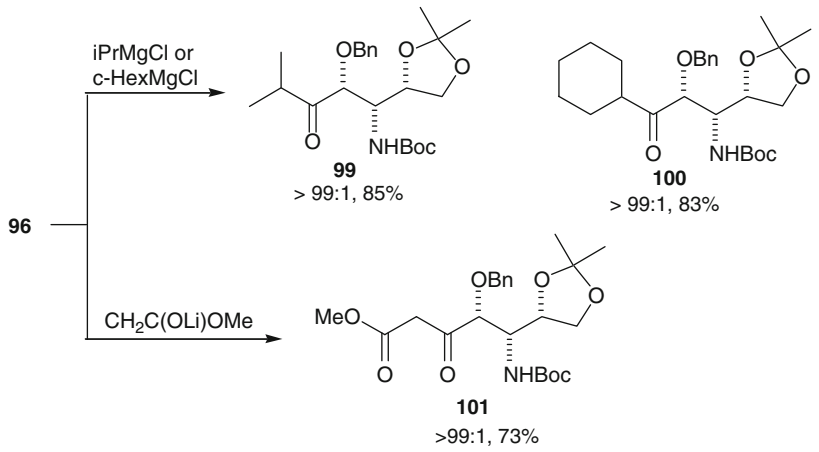
93, which is then converted into L-lyxo-phytosphingosine **94**. The same route has been employed to prepare D-erythro-sphingosine **95**, a potent inhibitory agent against protein kinase C [98, 99].

Other carbon nucleophiles may also be employed in such a coupling reaction that provides β-amino ketones and polyol intermediates. As shown in Scheme 32, aryl-Grignard reagents react at low temperature with the *N*-Boc β-lactam **96** to afford β-aminoketones **97** in 90–96% yields as the exclusive products. In no case over-addition is observed, even when an excess of the Grignard reagent is present in the reaction medium. On the other hand, when the reaction is performed at room temperature, only tertiary carbinols **98** are produced.

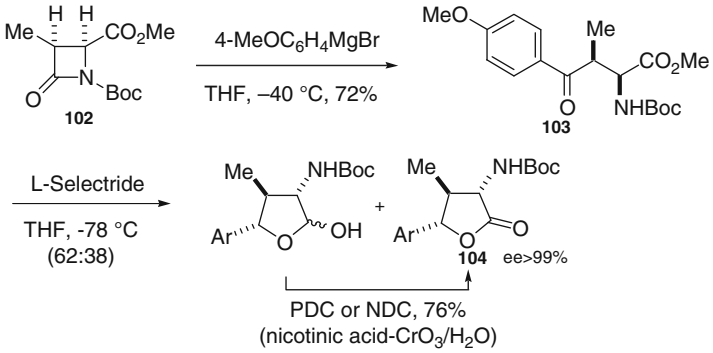
In contrast to these observations, reaction of **96** with primary alkylmagnesium halides leads to a mixture of the corresponding β-amino ketone and β-amino carbinols in variable amounts, depending upon the size of the alkyl moiety as well as the nature of the counterion. As shown in Scheme 33, almost exclusive formation of the corresponding ketones **99**, **100**, and **101** (ketone:carbinol ratio >99:1) takes place when lithium enolates and alkyl magnesium chlorides are the reagents employed [100].

A further interesting example in the context of natural products is shown, in the transformation of the β-lactam **102** into the β-amino ketone **103**, Scheme 34, which upon carbonyl reduction provides the amino lactone **104**, the cyclized form of the *N*-terminal amino acid residue found in the antibiotic family of nikkomycins, Fig. 6 [101].

Thereafter, the groups of Spero and Ojima have independently demonstrated the utility of this approach to the efficient preparation of aminopolyols and hydroxy (keto)ethylene dipeptide isosteres, respectively. Thus, as shown in Scheme 35, the



Scheme 33 Acylation of Mg- and Li-carbanions with *N*-Boc β-lactam



Scheme 34 Opening of β-lactams with a Grignard reagent as an entry to precursors of nikkomycins

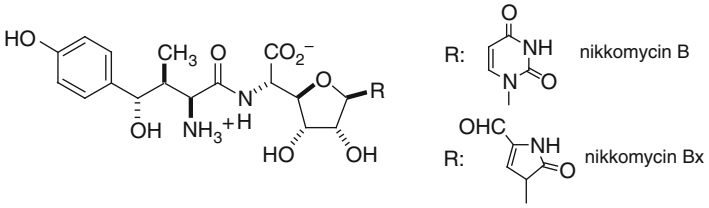
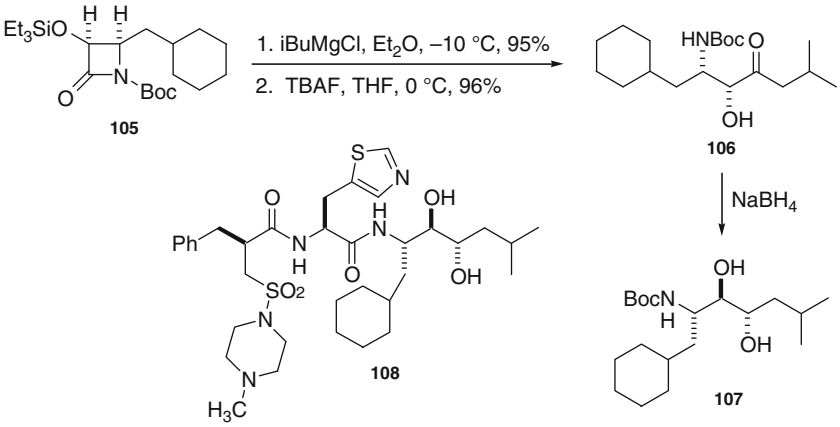
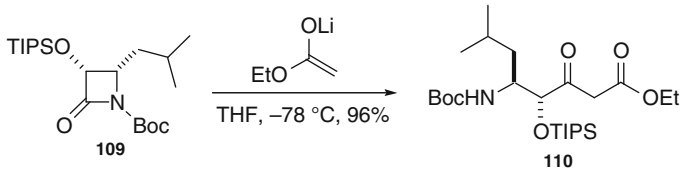


Fig. 6 Structure of nikkomicyn B and Bx antibiotics

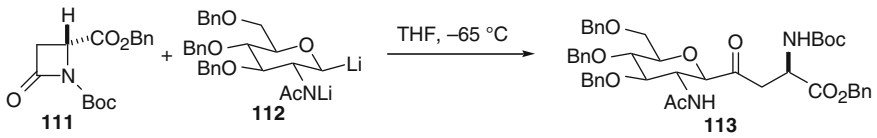
β-lactam **105** upon treatment with isobutylmagnesium chloride and subsequent desilylation furnishes the β-amino ketone **106** in 95% yield. This product on reduction provides 1,2,3-aminodiol **107**, a constituent of the potent inhibitor of human renin A-725-17 **108**, with essentially complete diastereoselectivity [102].



Scheme 35 A route to a fragment of A-725-17 (**108**), a potent inhibitor of human renin



Scheme 36 β-lactam ring opening with Li-enolates of esters. An access to the hydroxy (keto) ethylene dipeptide isostere

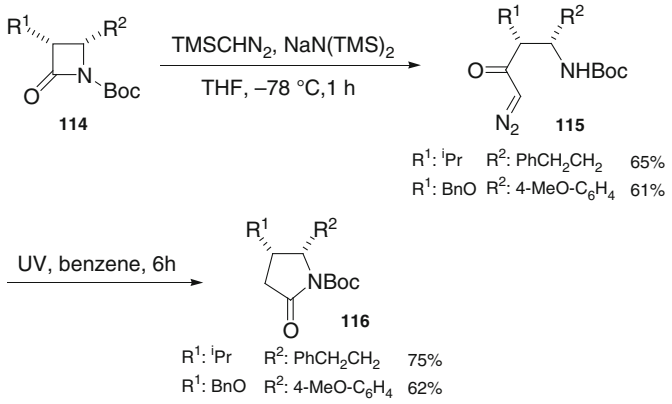


Scheme 37 An approach to C-linked glycosyl amino acids

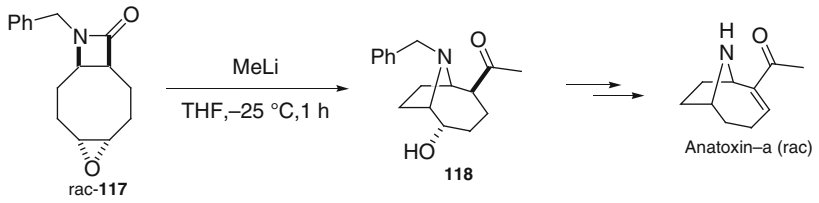
In its turn, the hydroxy(keto)ethylene dipeptide isostere **110** has also been prepared in a straightforward manner from β-lactam **109**, Scheme 36 [103].

Three further interesting examples, which delineate the utility of β-lactams in synthesis, have been described recently. In an approach to *C*-linked glycosyl amino acids, Scheme 37, addition of the lithium dianion **112** to the corresponding *N*-Boc β-lactam **111** provides the β-amino ketone **113** [104].

The sodium anion of trimethylsilyl diazomethane has also been used to open *N*-acyl β-lactams **114**, Scheme 38. The resulting intermediate α-diazoketones **115** affords, after photolytic Wolff rearrangement, the corresponding γ-lactams **116** [105].



Scheme 38 β-lactams opening with the sodium anion of $TMSCHN_2$



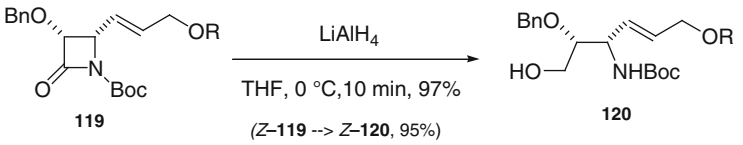
Scheme 39 Synthesis of anatoxin-a precursor **118** via MeLi mediated β-lactam ring opening

In a development involving racemic products, nonactivated *N*-benzyl β-lactam **117**, is shown to be opened selectively with methyllithium to yield, after intramolecular oxirane opening, the methyl ketone **118**, Scheme 39. This compound is transformed through several steps into the nicotinic acetylcholine receptor agonist anatoxin-a [106].

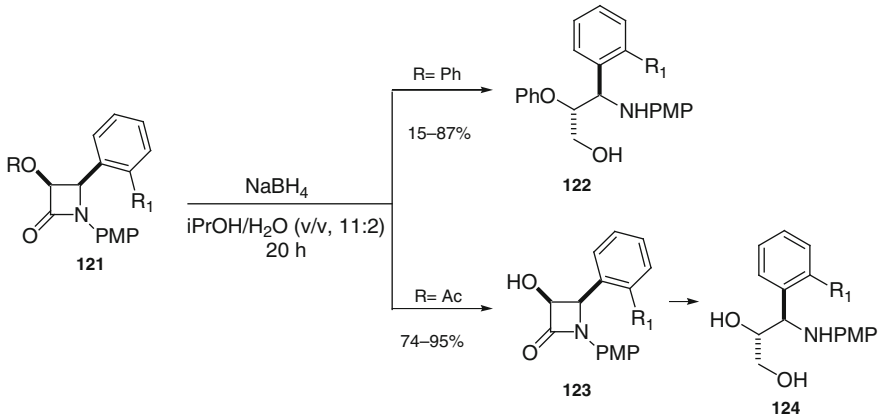
2.4 Ring Opening by Hydrides

Although more rare, the ring opening of *N*-acyl β-lactams has also been realized by using hydrides, giving rise to the corresponding reduction products. In this context, Scheme 40, Lee and Pak [107] have described the treatment of *N*-Boc β-lactam **119** with lithium aluminium hydride to give *N*-protected amino alcohol **120**. Compound **120** could serve as potential intermediate for the synthesis of various hydroxylated indolizidine alkaloids.

Apart from alanes [108–110], and monochloroalanes ([111]; for use of monochloroalanes in the reduction of 2–azetidinones to azetidines, see [112]), boranes have also been employed for the β-lactams N_1–C_2 bond cleavage. Baldwin had reported the sodium borohydride promoted ring opening of *N*-Cbz β-lactams



Scheme 40 Reductive ring opening of β-lactams leading to aminoalcohols



Scheme 41 Cleavage of β-lactams ring with $NaBH_4$

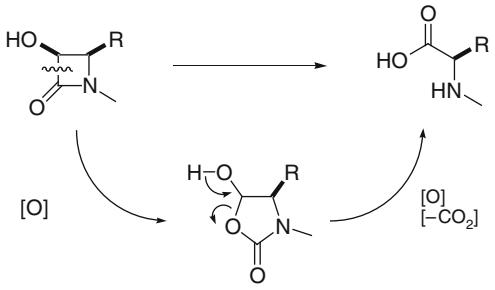
leading to open chain γ-amino alcohols [113]. Reductive opening of the 2-azetidinone ring by sodium borohydride has also been reported with β-lactams lacking the *N*-acyl activating group. Thus, Scheme 41 [114], Buttero has described the reaction of *N*-*p*-methoxyphenyl β-lactams **121** to yield amino alcohols **122** and **124**, respectively. The same strategy has been used by Alcaide and Almendros en route to optically active trisubstituted piperidines, employing lithium borohydride as the reducing agent of the respective *N*-*p*-methoxyphenyl β-lactam [115].

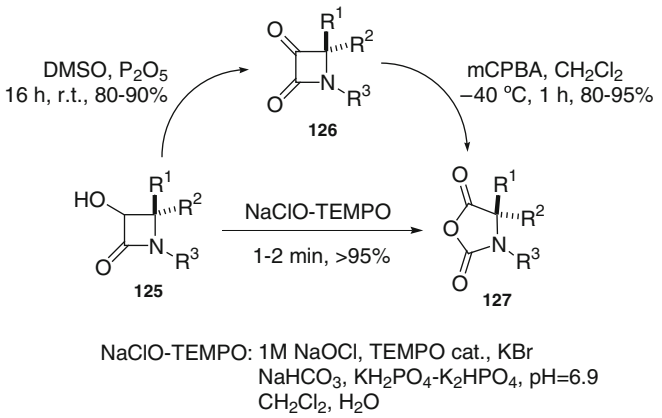
3 Ring Opening at C_2–C_3 Bond of β-Lactams

Work from this laboratory has demonstrated the synthetic potential of the ring opening at C_2–C_3 bond of α-hydroxy β-lactams to produce α-amino acid derivatives, Fig. 7.

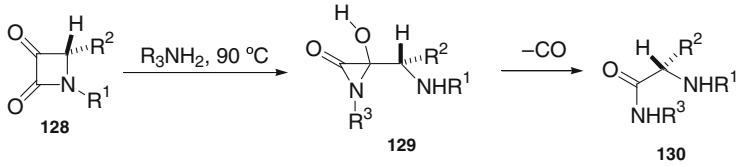
Ring opening of β-lactams at C_2–C_3 with application in peptide synthesis was first reported on α-keto β-lactams **126** ([116]; for applications of α-keto β-lactams, see [117]), Scheme 42. These β-lactams, readily available via oxidation of 3-hydroxy β-lactams **125**, undergoes a Baeyer-Villiger reaction upon exposure to *m*-CPBA and affords *N*-carboxy α-amino acid anhydrides (NCAs) **127** [118]. Shortly after, it was discovered that a more direct, one pot route to these NCAs is feasible by treatment of 3-hydroxy β-lactams with a solution of commercial bleach

Fig. 7 C_2–C_3 bond cleavage leading to α-amino acids





Scheme 42 The β-lactam route to NCA's



Scheme 43 Amine promoted transformation of α-keto β-lactams to α-amino acid derivatives

in combination with a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO).

More recently, the direct reaction of amines and amino esters with azetidin-2,3-diones **128** at 90°C, Scheme 43, leading to peptides **130**, has also been reported. The reaction is believed to occur through formation of an aziridine intermediate **129** which then rearranges to the amino amide with coextrusion [119, 120].

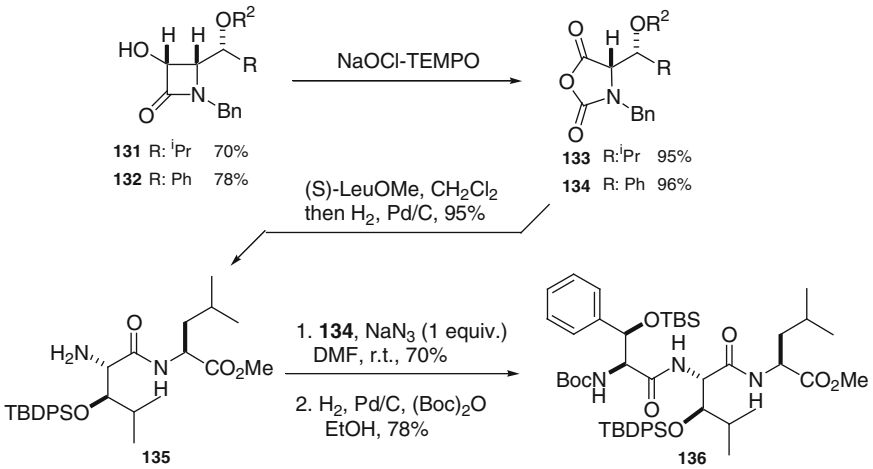
NCAs are well known forms of α-amino acids which present the amino group protected and the carboxylic group activated for a peptide coupling step. The most common access to NCAs is based on dehydration procedures of α-amino acids involving carbonic acid equivalents, which has limited the method to proteinogenic

α-amino acid-derived NCAs [121]. The availability of a concise and general access to enantiopure NCAs from nonα-amino acid precursors has been beneficial in the context of the synthesis of peptides, as will be illustrated below.

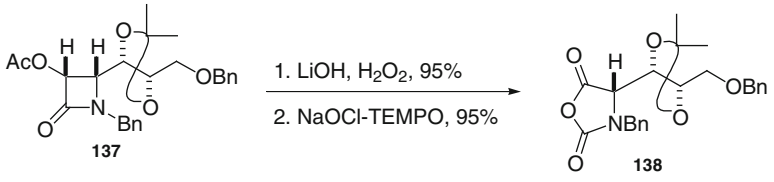
3.1 NCAs Bearing Side Chains from Nonproteinogenic α-Amino Acids

An attractive application of this strategy can be visualized in the synthesis of the tripeptide segment **136**, Scheme 44, present in the macrocyclic antibiotic lysobactin **40**, Fig. 4. It was reported that β-lactams **131** and **132**, upon ring expansion under the NaOCl-TEMPO conditions indicated above, afford NCAs **133** and **134**, respectively. Coupling of the NCA **133** with (*S*)-LeuOMe results in the formation of **135** which upon exposure to **134** provides tripeptide **136** in high overall yield [122].

A related example, Scheme 45, is the synthesis of the NCA **138** from the β-lactam **137**, which proceeds with excellent yields and without epimerization at the α-amino stereocenter.

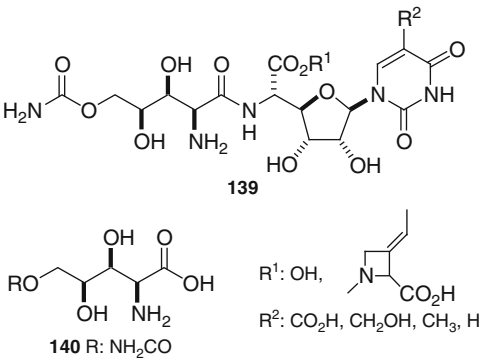


Scheme 44 Ring expansion of 3-hydroxy β-lactams leading to NCA's formally derived from serine analogues



Scheme 45 The β-lactam route to NCA's with polyoxygenated side chains

Fig. 8 Structure of some polyoxins



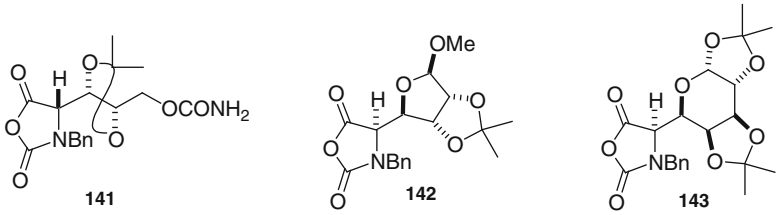


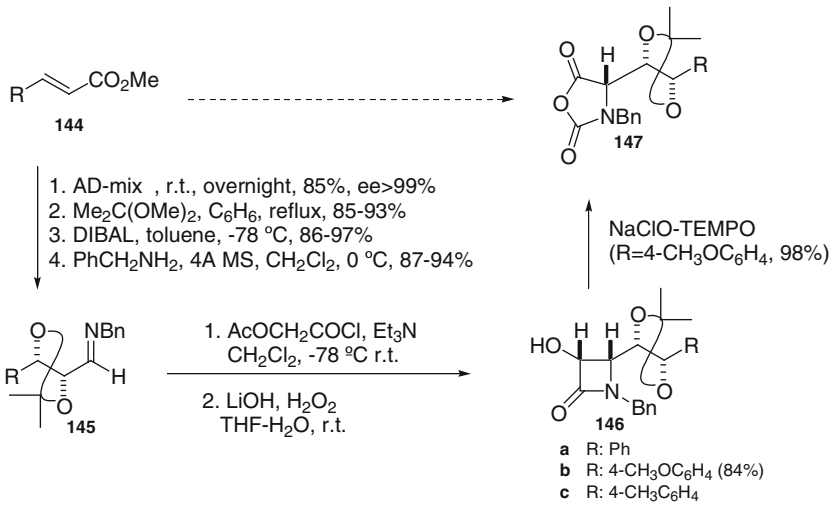
Fig. 9 Polyoxygenated NCAs affordable from β-lactams

The NCA **138** represents the amino-protected and carboxy-activated form of polyoxamic acid **140**, the hydroxylic amino acid portion of the antifungal family of polyoxins **139**, Fig. 8. Other polyolic NCAs such as **141**, **142**, and **143**, Fig. 9, have also been prepared from the corresponding α-hydroxy β-lactams with equal success [123, 124].

The feasibility of the illustrated strategy for the access to oxyalkyl substituted NCAs relies primarily on the high yields and diasteroselectivities generally attained with [2+2] alkoxyketene-imine cycloaddition reactions when α-oxyaldehyde-derived imines are involved. In this respect, nonracemic α-oxyaldehydes are readily available from the chiral pool [125–127] or they can be easily prepared in an enantiodivergent way by the Sharpless AD technique [128]. The exploitation of the latter possibility is shown in the approach to NCAs of β,γ-dihydroxy α-amino acids, Scheme 46, starting from the imines **145**, readily accessible from the respective α,β-unsaturated ester **144**. The cycloaddition of these imines with acetoxyketene occurs with essentially perfect stereocontrol to give, after deprotection, the α-hydroxy β-lactams **146** that undergo ring expansion to provide NCAs **147** in almost quantitative yields.

One example of the utilization of this approach for the synthesis of natural products is the facile access, Fig. 10, to the southwest tripeptide segment of echinocandin B, **148**, a cyclic hexapeptide that is characterized by its antifungal and antiyeast activity.

As Scheme 47 illustrates, the threonine derivative **149** is coupled with **147b** to furnish the dipeptide **150**, which, after protecting group manipulation and further



Scheme 46 NCA's of β,γ-dihydroxy α-amino acids

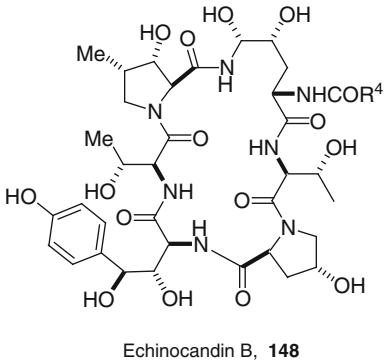
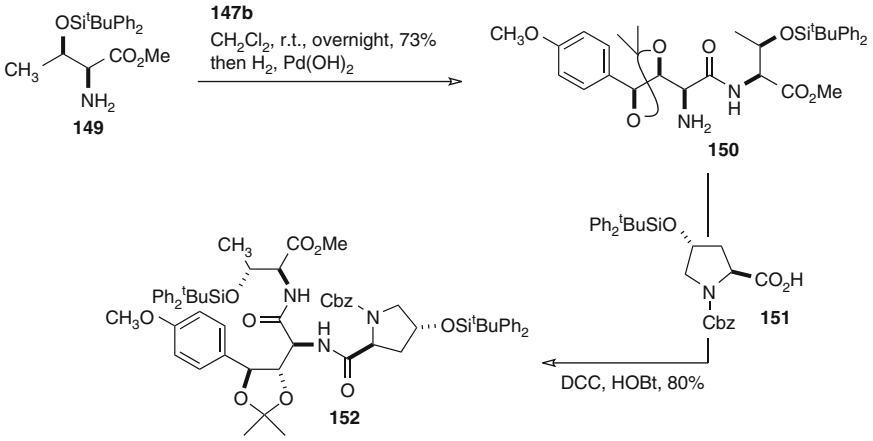


Fig. 10 Structure of echinocandin B which shows antifungal and antiyeast activity

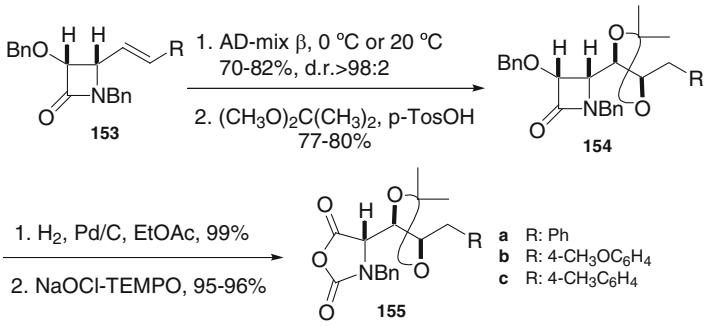
peptide coupling with the 4-hydroxyproline derivative **151**, gives rise to the protected tripeptide **152** in good yield [129].

A combination of the Sharpless AD technique and the ring expansion of 3-hydroxy β-lactams to NCAs has also been applied on compounds **153**, Scheme 48, to provide a route to NCAs **155**. The requisite β-lactams **154**, which exhibit a relative unlike configuration between stereocenters C_4 and $C\alpha$·, are not directly accessible via [2+2] cycloaddition reaction [130].

One important issue in these developments concerns the degree of isomerization during the coupling of NCAs with α-amino acid esters (for observations by other authors regarding partial isomerization, or absence of isomerization, during the NCA–amine couplings, see, respectively [131, 132]). In this respect, both the substitution pattern on the NCA and the nature of the solvent used have been identified as key elements. For instance, while in methylene chloride the isomerization degree during



Scheme 47 NCA route to echinocandin tripeptide segment

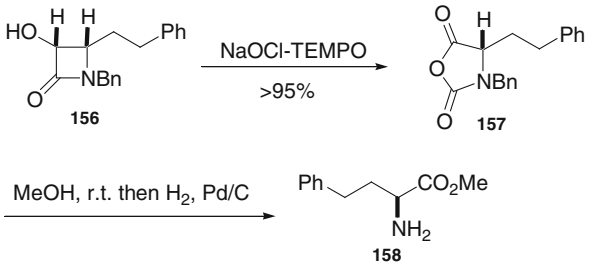


Scheme 48 Reversal of reactions sequence to produce compounds with unlike configuration

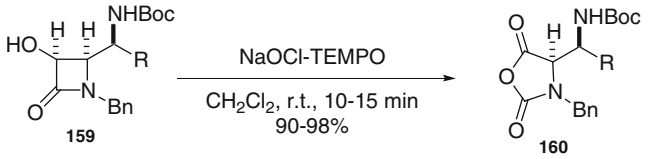
coupling of **138** (Scheme 45) with LeuOBn is below the limit of detection (less than 0.5%), it is significant in more polar solvents such as MeCN (~15%), $MeNO_2$ (~8%), DMF (~50%), and HMPA (~70%) [122, 129]. On the other hand, when NCAs bearing linear chain substituents, Scheme 49, such as **157**, are involved, the coupling reaction with amines or α-amino acid esters is accompanied by racemization to some extent, regardless of the solvent used. Interestingly, even in the latter case, no racemization is observed at all when the methanolysis of **157** to give **158** is performed [133].

3.2 NCAs of α, β-Diamino Acids

α, β-Diamino carboxylic acids are uncommon naturally occurring amino acids which attracted considerable interest. An approach to their NCAs **160**, Scheme 50, takes advantage of the highly diastereoselective cycloaddition of ketenes to imines derived from *N*-Boc α-amino aldehydes, to provide **159** [134].



Scheme 49 NCA's of alkyl chain α-amino acids



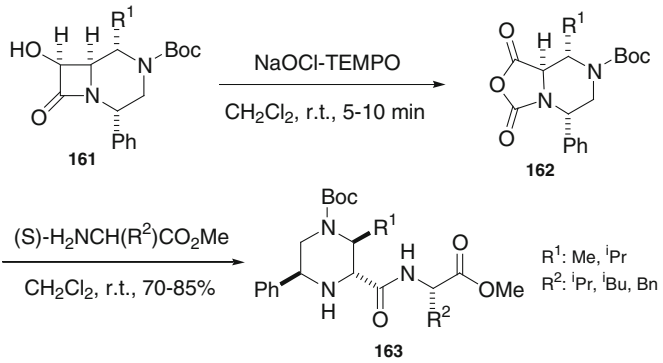
Scheme 50 NCA's of α,β-diamino acids

In this development, both amino moieties are differentially protected and thus, incorporation of these amino acids into peptide chains either at the α- or β-position is possible. This procedure has also been applied to the synthesis of piperazine-2-carboxylic acids and derived peptides [135], Scheme 51. For example, the bicyclic α-hydroxy β-lactam **161**, upon ring expansion and subsequent coupling of the resulting NCA **162** with α-amino esters, affords **163** in good yield.

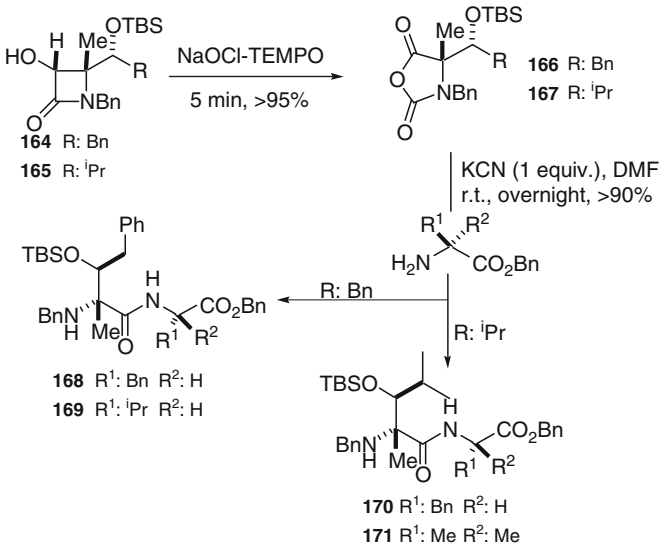
3.3 NCAs of α-Branched α-Amino Acids

Another application of this approach for access to nontrivial NCAs and peptides derived thereof is shown in Scheme 52. The α-hydroxy β-lactams **164** and **165**, bearing a quaternary stereogenic center at C_4 position, upon treatment with NaOCl-TEMPO, lead to NCAs **166** and **167** in yields higher than 95%. In a first observation, the coupling of these NCAs with α-amino acid esters under usual conditions generally gave rise to yields below 10%. Much improvement was observed when the corresponding coupling reactions were carried out using potassium cyanide as additive to furnish the expected dipeptide products **168**, **169**, and **170** in 95, 93, and 95% yield, respectively. Remarkably, the bulky Aib-benzyl ester is also coupled with **167** to afford **171** in 79% yield [136].

The transformation of α-hydroxy β-lactams **173a–c**, Scheme 53, readily available from the 4-formyl 2-azetidinone **172**, into their corresponding NCAs illustrates the scope of the present approach. NCAs **174a** and **174b**, upon treatment with (*S*)-PheOMe and (*S*)-ValOMe in the presence of KCN as promoter, render



Scheme 51 Synthesis of piperazine-2-carboxylic acid peptides

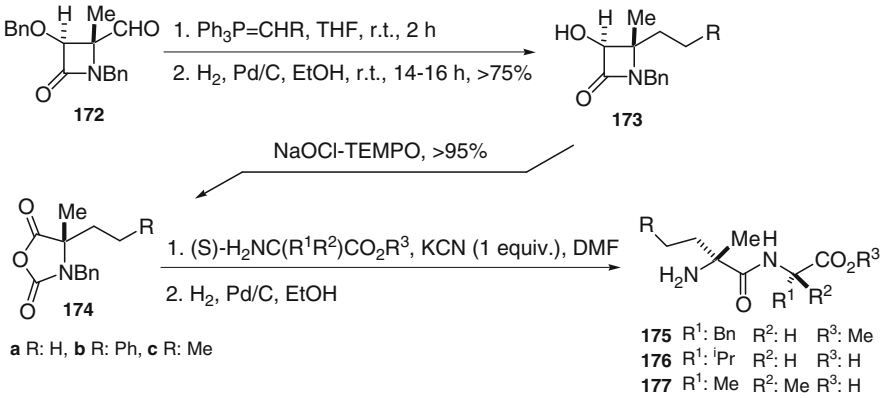


Scheme 52 The β-lactam/NCA route to α-branched β-substituted serine-derived peptides

dipeptides **175a** and **176b** in 78 and 71% yields, respectively. Again, even the Aib-benzyl ester did couple with **174c** to give the corresponding dipeptide product which, upon *N*,*O*-didebenzylation, afforded **177c** in 70% yield [137].

4 Ring Opening at C_3–C_4 Bond of β-Lactams

The ring opening of the β-lactam ring by selective cleavage of the C_3–C_4 bond has been explored to a much lesser extent. A thermally induced [3, 3] sigmatropic



Scheme 53 NCA's formally derived from quaternary α-amino acids

rearrangement on *cis*-2-azetidinone-tethered dienes **178** has led to the tetrahydroazocinones **179**, Scheme 54 [138]. Of practical interest, this Cope-type reaction proceeds stereospecifically to afford the eight-membered lactams.

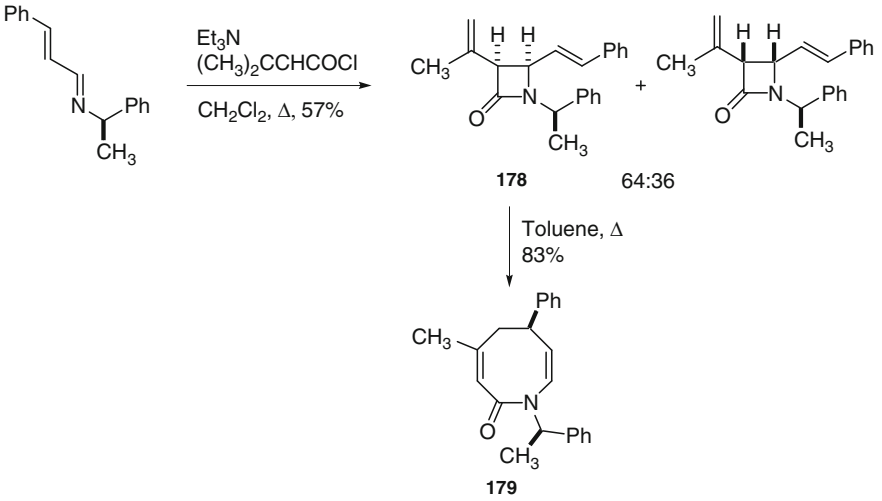
Hydrogenation of 4-formyl spiro-β-lactams like **180**, Scheme 55, accessible from cyclic amino acids and chiral imines, resulted in the formation of bicyclic system like **181**, which was reduced to piperazine **182** [139]. The reductive rearrangement leading to **181** proceeds in high yield and the scission of the C_3–C_4 bond is rationalized in terms of a retro-Mannich process. Unfortunately, however, isomerization occurs during rearrangement, leading to racemic products.

Cis 4-formyl-β-lactams like **183**, Scheme 56, overcome a ring expansion to the corresponding γ-lactams **184** when treated with tert-butyl dimethylsilyl cyanide and 10 mol% iodine at room temperature [140, 141]. The parent *trans* β-lactams remain unchanged under the same conditions. A mechanism has been postulated that implies cationic intermediates in which iodine acts as a Lewis acid.

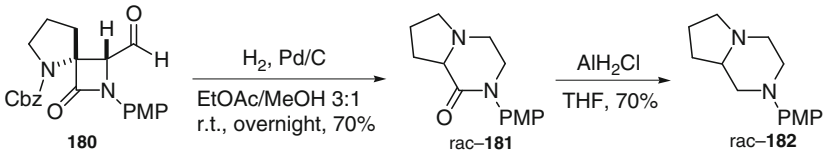
Rearrangement of β-lactams, bearing a bromo-iso-alkyl group at C_4, to γ-lactams via *N*-acyliminium intermediates has been described by De Kimpe [142–144]. Besides the major *trans* γ-lactam product **187** and **188**, respectively, traces of the corresponding *cis* diastereomer and minor quantities of the dehydrohalogenated β-lactam, are also obtained (Scheme 57). Application to the synthesis of bicyclic γ-lactams from monocyclic β-lactams has been described [144].

5 Ring Opening at N_1–C_4 Bond of β-Lactams

The palladium catalyzed hydrogenolysis of 3-amino 4-aryl azetidin-2-ones, Fig. 11, constitutes an excellent and reliable strategy to access α-amino acid derived peptides. The discovery, development, and synthetic opportunities of this approach have been reviewed by Ojima [145–148], and will not be covered here. Only the



Scheme 54 Eight-membered lactams from β-lactams

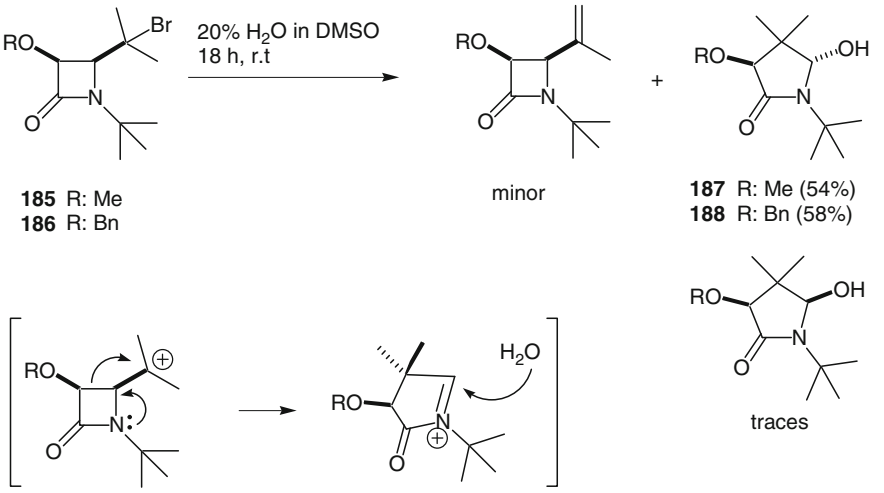


Scheme 55 Piperazines from β-lactams

Scheme 56 Dihydroxylated γ-lactams from β-lactams

general concept and a representative example to illustrate the potential of the approach will be outlined.

The potential of the method is best demonstrated when the ring opening is preceded by chemo- and stereoselective alkylation reactions. As Fig. 12 shows, two main types of alkylation events can be carried out on the designed β-lactam precursor. Type 1 alkylation takes place at the C_3 position of the β-lactam ring, with entrance of the electrophile R group from the side opposite to the Ar group at C_4. The second one (type 2) takes place at the exocyclic carbon directly bonded to the



Scheme 57 Cationic rearrangemente of β-lactams to γ-lactams

Fig. 11 N_1–C_4 bond cleavage leading to α-amino acids

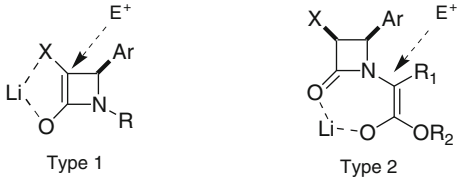
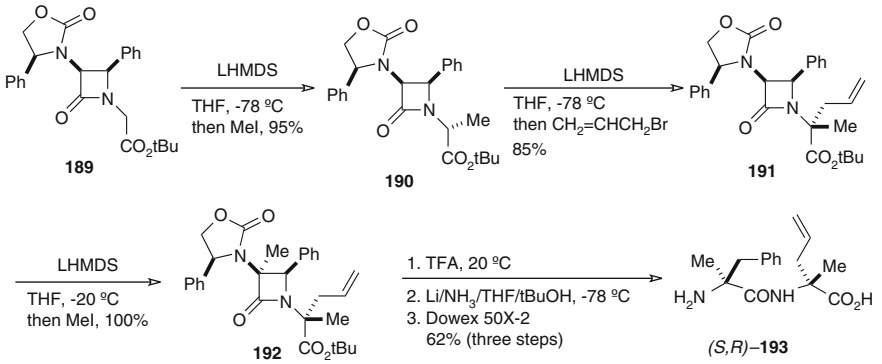
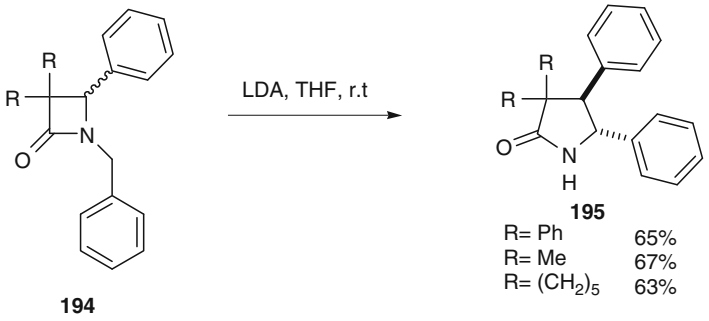


Fig. 12 Asymmetric alkylation of C_3 carbon (type 1) and of a side-chain carbon bonding to the β-lactam nitrogen (type 2)

N_1 nitrogen. In the example in Scheme 58 [149], the realization of the full strategy that combines type 1 and type 2 alkylations with the final ring opening of the β-lactam, is shown. After completion of the asymmetric double alkylation of the glycinate moiety with methyl iodide and allyl bromide, the side chain of the resulting β-lactam ester **191** does not have any acidic proton. Thus a type 1 enolate is generated and the third alkyl substituent (methyl) is introduced to the C_3 position of **191**; hence, the whole process constitutes a unique and highly selective sequential asymmetric triple alkylation to give **192**. Deprotection of the *tert*-butyl ester of **192** by TFA in dichloromethane at 20°C, followed by cleavage of the β-lactam ring as well as removal of the *N*-protection with Li/NH_3/t-BuOH at −78°C, gave (*S*)-α-methylphenyl-alanyl-(*R*)-α-allylalanine, (*S,R*)-**193**, in 62% yield after purification on an ion-exchange column.



Scheme 58 Dipeptides with quaternary α-amino acids from β-lactams

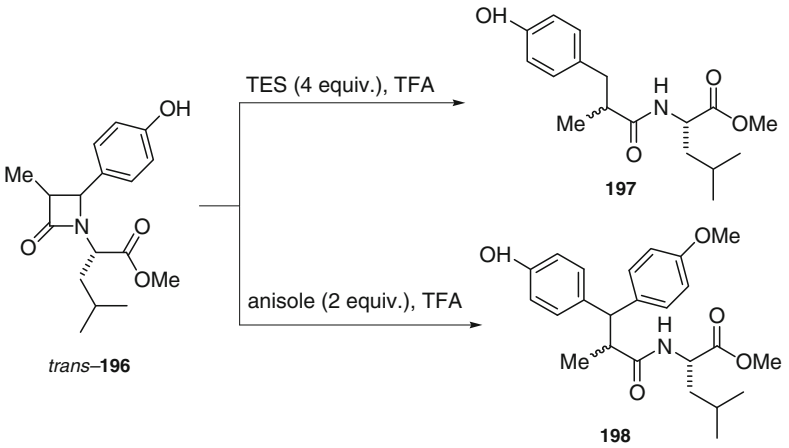


Scheme 59 LDA-promoted ring enlargement of β-lactams to γ-lactams

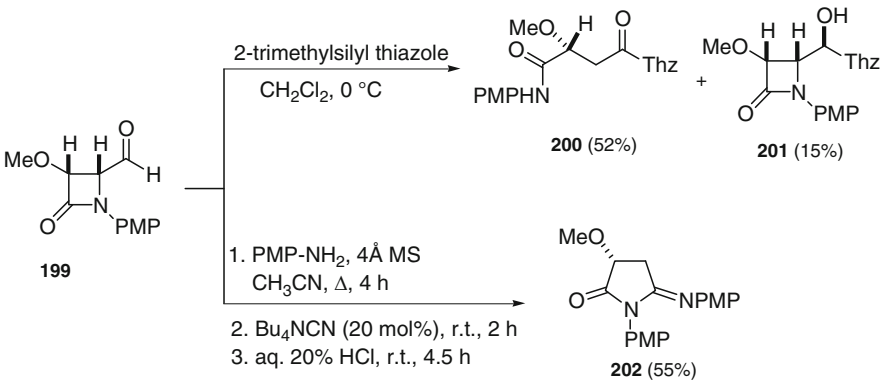
Other strategies for the ring opening of β-lactams via N_1–C_4 bond cleavage have seldom appeared in literature. Ahn [150] has reported the LDA-promoted ring enlargement of *N*-benzyl β-lactams **194** to the corresponding *N*-H γ-lactams, Scheme 59. The reaction proceeds diastereoselectively to provide exclusively the *trans*-4,5-disubstituted γ-lactams **195**.

McMurray [151] has described the acid-assisted cleavage of the N_1–C_4 bond in *trans* 4-hydroxyphenyl β-lactams. The ring opening reaction may proceed with concomitant reduction or formation of carbon–carbon coupling products, as a function of the reagent employed. For instance, Scheme 60, treatment of **196** with 4 equivalents of triethylsilane in neat trifluoroacetic acid led to compound **197**. On the contrary, treatment with anisole in trifluoroacetic acid led to compound **198**. Unfortunately, no data are provided by authors regarding process yield or final diastereomeric ratio.

On the other hand, several nucleophilic reagents and catalysts have been found capable of promoting the ring expansion of 4-formyl β-lactams, and/or their imine derivatives, to afford open chain acyl thiazole or succinimide derivatives. For example, treatment of 4-formyl β-lactam **199** with 2-(trimethylsilyl)thiazole,



Scheme 60 N_1–C_4 bond cleavage of β-lactams under acidic conditions



Scheme 61 Nucleophilic bond cleavage of β-lactam's N_1–C_4 bond

Scheme 61, yielded thiazole **200** as the major product, along with minor amounts of carbinol **201** [152]. On the other hand, treatment of the imine formed from **199** and *p*-methoxyphenylamine with catalytic tetrabutylammonium cyanide, produced succinimide derivative **202**. In both cases, the process is initiated by nucleophilic attack to the carbaldehyde C=O (or azomethine's C=N) group, which is followed up by an anionic rearrangement. A variation of the above process using as catalysts *N*-heterocyclic carbenes (NHC) derived from base treatment of azolium, imidazolium, or triazolium salts, has also been developed to access gem-disubstituted succinimides [153, 154]. Unfortunately, an attempt of kinetic resolution of racemic 4-formyl β-lactams by using chiral NHC resulted in moderate selectivities only [154].

6 Large Ring Heterocycles from β-Lactams

Cycloexpansion of the four-membered β-lactam ring to either medium or large ring heterocycles can be achieved through N_1–C_2 bond cleavage by intramolecular nucleophilic attack from a suitable peripheral substituent, Fig. 13. Some medium rings have been already discussed, and others, like pyrrolidines, pyrrolizidines, piperidines, morpholines, etc. have been reviewed elsewhere [11, 155–158]. Some more recent cases from the literature, including examples leading to cyclopeptidomimetics, spermine backbone containing alkaloids, cyclams, and cycloaromatization processes, have been chosen here for illustration.

In this context, Greene and coworkers [159, 160] have reported the first low-molecular-mass immunoglobulin mimetic **207**, Scheme 62, developed on the basis of an X-ray structure analysis of the antigen–antibody complex. Compound **207** is resistant toward proteases and imitates the binding and functional properties of the native antibody.

The synthesis of **207** is based on an intramolecular aminolysis of the β-lactam ring in **206**. This latter compound was prepared by stereoselective alkylation of **203** with 1-bromo-3-butene and subsequent oxidative cleavage of the double bond to give the carboxylic acid **204**, which next was coupled with **205**. The resulting peptide product **206** rapidly cyclized to a ten-membered ring compound, on reductive deprotection of the hydrazine group, and then coupled with *N*-carbobenzoxytyrosine to give **207**.

Another example is compound **214**, which imitates the trombin-bound structure of the fibrin peptide A, and is an inhibitor of this protease. The first step of this synthesis, Scheme 63, involves opening of **208** to the seven-membered ring compound **209**. Subsequent acylation with **210** to form **211** is followed by an intramolecular oxidative cycloaddition to provide tricyclic lactam **212**. Nucleophilic ring opening proceeds readily with glycine methyl ester to afford lactam **213** in 88% yield, which was transformed into **214** using solid-phase protocols [161].

The same group has also reported the synthesis of the nonpeptide enkephalin β-turn mimetic **216** [162]. The key step of the approach, Scheme 64, involves the simultaneous intramolecular cyclization/β-lactam ring cleavage in derivative **215** leading to compound **216**.

β-Amino acid fragments containing large heterocycles also occur in some alkaloids, and approaches to these compounds using β-lactams as key intermediates have long been known since the pioneering contributions of Wasserman [163] and, later on, of Hesse [164, 165]. In Fig. 14, some of the heterocyclic compounds

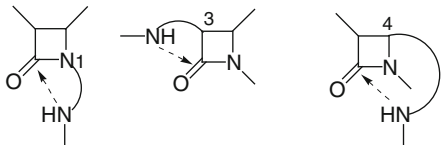
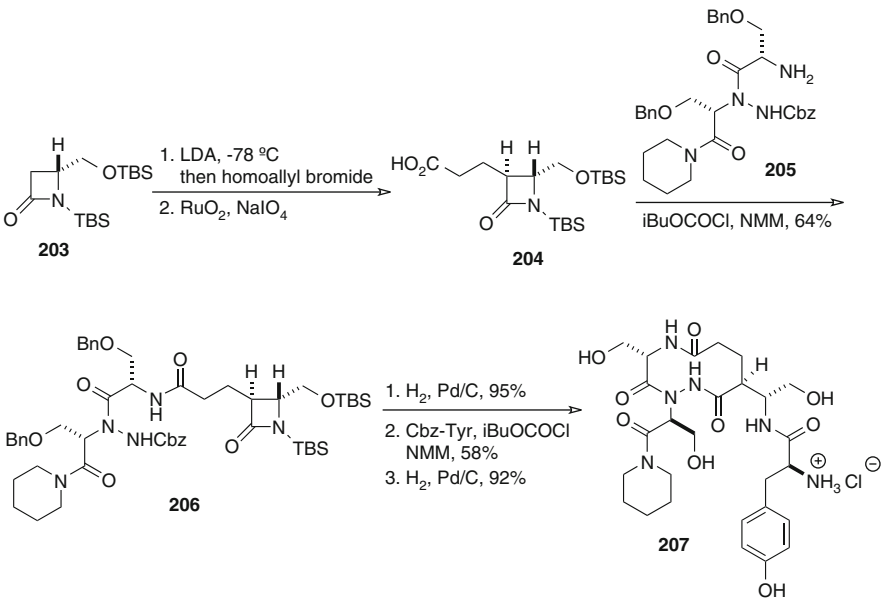


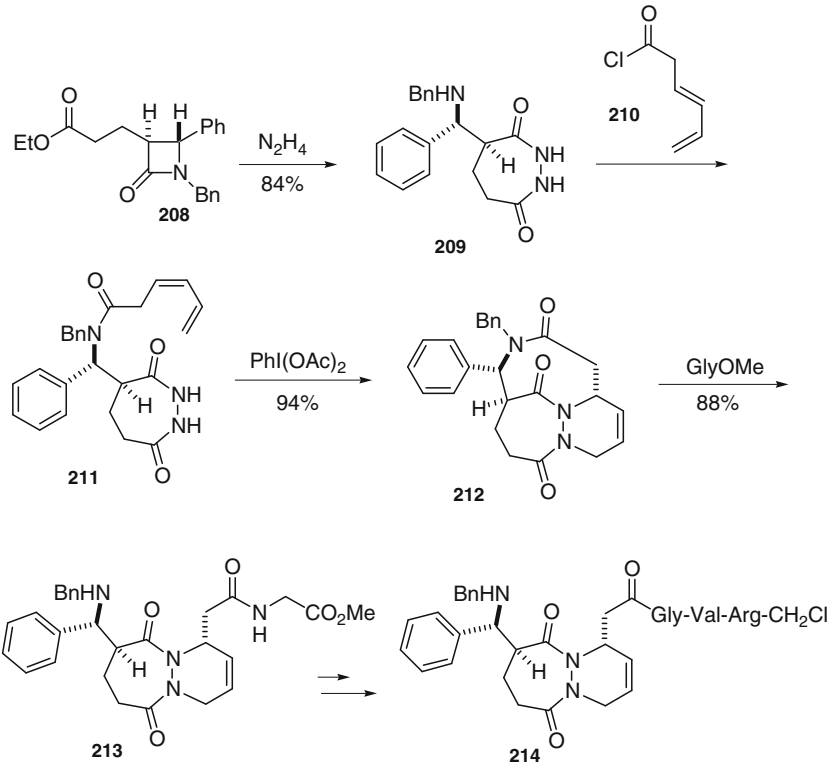
Fig. 13 Types of intramolecular nucleophilic attack on β-lactams leading to expanded rings



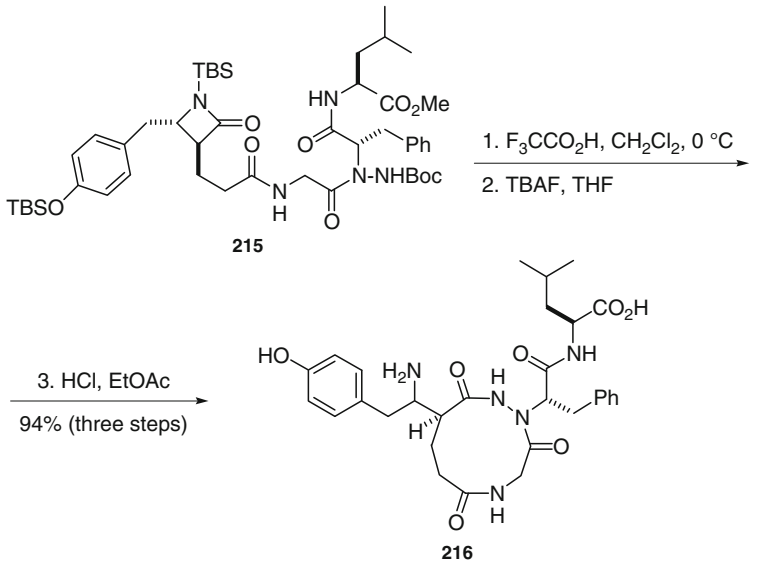
Scheme 62 β-lactam approach to iminoglobulin mimetics

(**217**–**224**) synthesized through β-lactam intermediacy are represented [166]. Using this strategy, Crombie and Jones [167–169] have described the internal rearrangements on N-(ω-haloalkyl) β-lactams as a valuable method for the total synthesis of several homalium alkaloids containing a spermine structural backbone. These include (*S*,*S*)-(−)-homaline **225**, *rac*-hopromine **226**, *rac*-hoprominol **227**, and *rac*-hopromalinol **228**, Scheme 65. As an example, the enantiopure β-lactam **230**, prepared from **229**, experiences a transamidative ring expansion on prolonged standing in liquid ammonia to afford the macrocyclic β-amino amide **231**, which is converted into (*S*,*S*)-(−)-homaline **225**.

Other large cycles containing β-amino acid fragments include dioxocyclams **232** and *bis*-dioxocyclams **233**. Analogues of the latter, bearing nitrogen atoms attached through a three carbon bridge, display high and selective anti-HIV activity [170]. Hegedus has described [171, 172] a very short and original access to these dioxocyclams and *bis*-dioxocyclams using either optically active or racemic 1-*N*-Boc-azapenams **236** as key intermediates. The approach, Scheme 66, involves the photolysis of chromium alkoxycarbene complexes **234** with *N*-Boc-imidazolines **235** to give the expected azapenams **236** in a fully stereoselective way. Remarkably, the hydrogenolysis reaction is very sensitive to the acidity of the medium. Thus the reaction in the presence of camphorsulfonic acid leads to the seven-membered hexahydrodiazepinones **237**, while in the presence of triethylamine, it results in the fourteen-membered dioxocyclams **232**. An extension of this methodology has been reported by the same author to prepare the five-atom



Scheme 63 A β-lactam approach to fibrin peptide A protease inhibitors



Scheme 64 A β-lactam approach to enkephalin mimetics

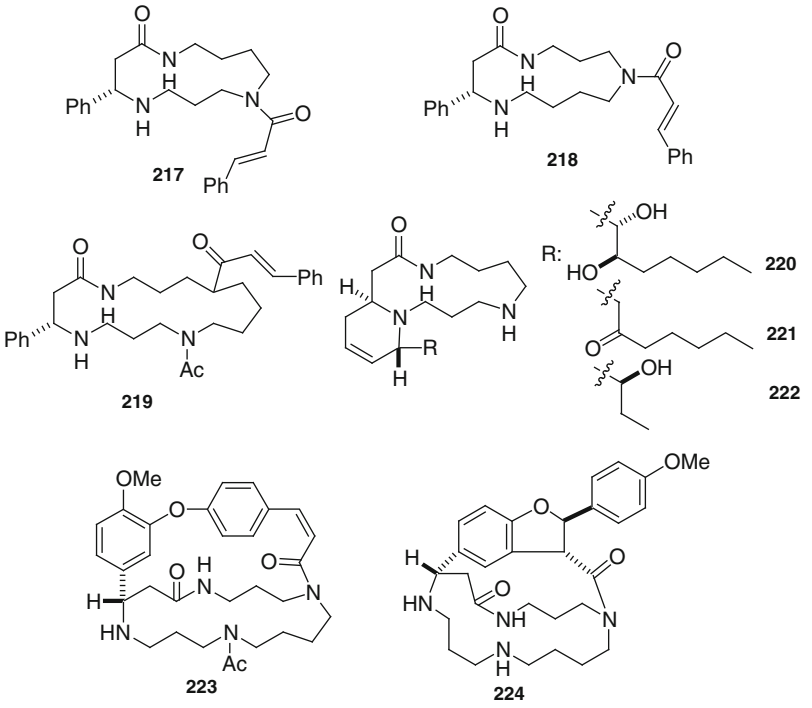


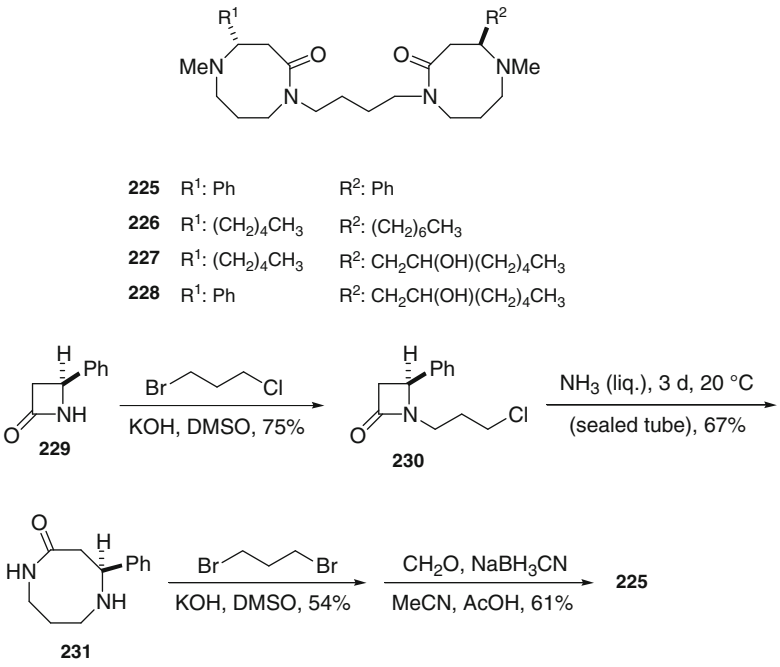
Fig. 14 Some representative large heterocycles accessible from β-lactam compounds

system bridged [–O(CH$_2$)$_3$O–] **233** from *bis*-chromium alkoxycarbene complexes **238** [172].

Intramolecular transamidation in β-lactam enediynes can induce concomitant Bergman type cycloaromatization. For instance, Scheme 67, amine **239**, which can be stored as its hydrochloride salt in the freezer, reacts in THF at reflux in the presence of cyclohexadiene as a hydrogen donor to produce only trace amounts of the expanded lactam **240** along with aromatic compound **241** as the major compound [173].

7 Concluding Remarks and Prospects

The interest in β-lactams had been driven traditionally by the pre-eminence of β-lactam antibiotics, which has over the years fuelled a huge effort devoted to the search for synthetic routes to β-lactams and the subsequent manipulation of the attached groups. The development of improved routes to β-lactams is still appealing, particularly because of the appearance of β-lactam resistance and new



Scheme 65 Internal rearrangement on β-lactams leading to homalium alkaloids containing spermine backbones

biomedical applications of β-lactam compounds. However, β-lactams also constitute versatile precursors of a variety of nonβ-lactam compounds, particularly α- and β-amino acids, their derived peptides, and an array of small and large heterocyclic compounds. All these transformations imply the cleavage of the 2-azetidinone ring, through any of its four bonds. Like enzymes do during the phenomenon of antibiotic action or antibiotic inhibition, selective ring opening of β-lactams is currently a chemically affordable task. Several strategies have been developed for the β-lactam ring scission that proceed under sufficiently smooth conditions to tolerate both functional groups and stereocenters sensibly. This fact, in combination with the arsenal of methods for the stereocontrolled synthesis of β-lactams, enables the β-lactam approach to account for as one realistic option for accessing some functionally and stereochemically complex molecules. The examples included here illustrate this potential and show the maturity of the approach. However, the possibilities β-lactams offer as versatile intermediates in synthesis are not fully addressed yet, and new contributions in the area are foreseen for the near future.

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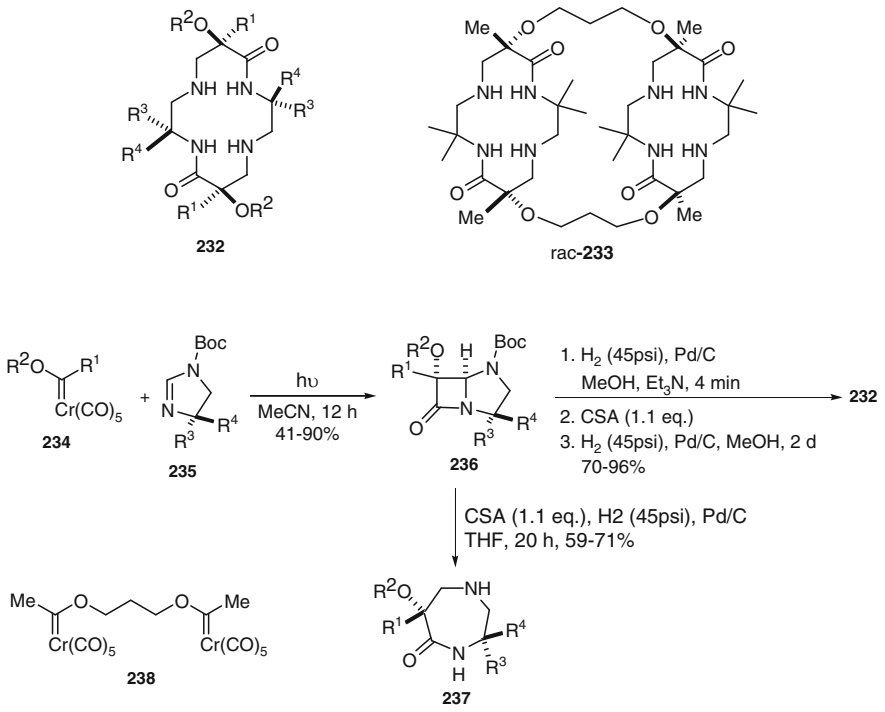
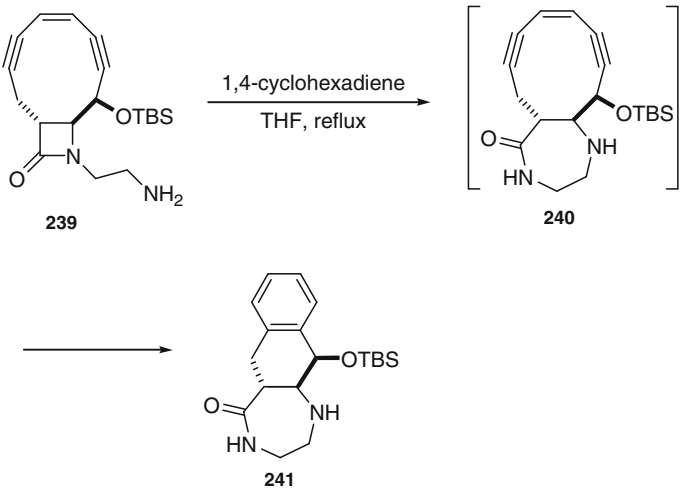


Scheme 66 Synthesis of large cycles containing β-amino acid fragments: dioxocyclams and *bis*-dioxocyclams



Scheme 67 Intramolecular transamidation on β-lactams as a trigger of Bergman type cycloaromatization

References

1. Clark HT, Jonson JR, Robindon R (1949) The chemistry of penicillins. Princeton University Press, New Jersey
2. Morin RB, Goldman M (1982) (eds) Chemistry and biology of β-lactam antibiotics, vol. 1–3. Academic Press, New York
3. Demain AL, Solomon NA (1983) (eds) Antibiotics containing the β-lactam structure, parts 1&2. Springer, Berlin
4. Bentley PH, Ponsford R (1993) (eds) Recent advances in the chemistry of anti-infective agents. The Royal Society of Chemistry, Cambridge
5. Niccolai P, Tarsi L, Thomas RJ (1997) Chem Commun 2333
6. Bronson JJ, Barrett JF (2001) Curr Med Chem 8:1775
7. Edwards PD, Bernstein PR (1994) Med Res Rev 14:127
8. Mascaretti OA, Boschetti CE, Danelo GO, Mata EG, Roveri OA (1995) Curr Med Chem 1:441
9. Wilmouth RC, Kasamally S, Westwood NJ, Sheppard RJ, Claridge TD, Alpin PA, Wright PA, Pritchard GJ, Schofield CJ (1998) Biochemistry 38:7989
10. Burnett DA (2004) Curr Med Chem 11:1873
11. Bruggink A (2001) Synthesis of β–lactam antibiotics. Kluver, Dordecht (The Netherlands)
12. Page MI (1992) (ed) The chemistry of β-lactams. Chapman and Hall, London
13. Georg GI (1993) (ed) The organic chemistry of β-lactams. VCH, New York
14. Kidwai M, Sapra P, Bhushan KR (1999) Curr Med Chem 6:195
15. Koppel GA (1983) In: Hasnner A (ed) Small ring heterocycles, vol. 42. Wiley, New York, p 219
16. Backes J (1991) In: Muller E, Bayer O (eds) Houben-Weyl, Methoden der Organischen Chemie, band E16B. Thieme, Stuttgart, p 31
17. De Kimpe N (1996) In: Katrizky AR, Rees CW, Scriven EFV, Padwa A (eds) Comprehensive heterocyclic chemistry II, vol. 1B. Pergamon, Oxford, p 507
18. Singh GS (2003) Tetrahedron 59:7631
19. Gómez-Gallego M, Manchego MJ, Sierra MA (2000) Tetrahedron 56:5743
20. Alcaide B, Almendros P (2002) Curr Org Chem 6:1
21. Staudinger H (1907) Liebigs Ann Chem 356:51
22. Van der Steen FH, Van Koten G (1991) Tetrahedron 47:7503
23. Georg GI, Ravikumar VT (1993) The organic chemistry of β–lactams. VCH, New York, p 295
24. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (1999) Eur J Org Chem 3223
25. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2004) Curr Med Chem 11:1837
26. Hart DJ, Ha DC (1989) Chem Rev 89:1447
27. Brown MJ (1989) Heterocycles 29:2225
28. Georg GI (1989) In: Atta-ur-Rahman (ed) Natural product chemistry, vol 4. Elsevier, Amsterdam, p 431
29. Cainelli G, Panunzio M, Andreoli P, Martelli G, Spunta G, Giacomini D, Bandini E (1990) Pure Appl Chem 62:605
30. Cainelli G, Panunzio M, Giacomini D, Martelli G, Spunta G, Bandini E (1996) In: Chatgilialoglu C, Snieckus V (eds) Chemical synthesis, gnosis to prognosis. Kluwer, Amsterdam, p 25
31. Fujisawa T, Shimizu M (1996) Rev Heteroatom Chem 15:203
32. Benaglia M, Cinquini M, Cozzi F (2000) Eur J Org Chem 563
33. Miller MJ (1986) Acc Chem Res 19:49
34. Chmielewski M, Kaluza Z, Forman B (1996) Chem Commun 2689
35. Kinugasa M, Hashimoto SJ (1972) Chem Soc Chem Commun 466
36. Miura M, Enna M, Okuro K, Nomura M (1995) J Org Chem 60:4999

37. Lo MM-C, Fu GC (2002) J Am Chem Soc 124:4572
38. Shintani R, Fu GC (2003) Angew Chem Int Ed 42:4082
39. Basak A, Ghosh SC, Bhowmick T, Das AK, Bertolasi V (2002) Tetrahedron Lett 43:5499
40. Marco-Contelles J (2004) Angew Chem Int Ed 43:2198
41. Mascaretti OA, Boschetti CE, Danelon GO, Mata EG, Roveri OA (1995) Curr Med Chem 1:441
42. Page MI, Laws AP (1998) Chem Commun 1609
43. Fisher JF, Meroueh SO, Mobashery S (2005) Chem Rev 105:395
44. Tsang WY, Ahmed N, Hinchliffe PS, Wood JR, Harding LP, Laws AP, Page MI (2005) J Am Chem Soc 127:17556
45. Crowder MW, Spencer J, Vila AJ (2006) Acc Chem Res 39:721
46. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2000) Pure Appl Chem 72:1763
47. Forró E, Fülöp F (2004) Mini-Rev Org Chem 1:93
48. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2001) Synlett 1813
49. Palomo C, Aizpurua JM, Ganboa I (1997) In: Juaristi E (ed) Enantioselective synthesis of β-amino acids. Wiley-VCH, New York, p 279
50. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2005) In: Juaristi E, Soloshonok V (eds) Enantioselective synthesis of β-amino acids, 2nd edn. Wiley-VCH, Hoboken, NJ, p 477
51. Alcaide B, Almendros P (2002) Synlett 381
52. Forró E, Fülöp F (2006) Tetrahedron Asymmetry 17:3193
53. For a recent mechanistic study, see Dal Peraro M, Vila AJ, Carloni P, Klein ML (2007) J Am Chem Soc 129:2808
54. Fernández-Suárez M, Muñoz L, Fernández R, Riguera R (1997) Tetrahedron Asymmetry 8:1847
55. Shirode NM, Rakkeb A, Deshmukh AS (2006) Tetrahedron 62:4615
56. Alcaide B, Almendros P (2001) Chem Soc Rev 30:226
57. Kale AS, Rakeeb A, Deshmukh AS (2005) Synlett 2370
58. Gyarmanti ZC, Liljeblad A, Argay G, Kálmán A, Bernáth G, Kanerva LT (2004) Adv Synth Catal 346:566
59. Sierra MA, Pellico D, Gómez-Gallego M, Manchego MJ, Torres R (2006) J Org Chem 71:8787
60. Palomo C, Arrieta A, Cossío FP, Aizpurua JM, Mielgo A, Aurrekoetxea N (1990) Tetrahedron Lett 31:6429
61. Palomo C, Aizpurua JM, Urchegui R, Iturburu M (1992) J Org Chem 57:1571
62. Mishra RK, Coates CM, Revell KD, Turos E (2007) Org Lett 9:575
63. Sathe M, Ghorpade R, Kaushik MP (2006) Chem Lett 35:1004
64. Pfeiffer B, Peduzzi E, Moehle K, Zurbriggen R, Glück R, Pluschke G, Robinson JA (2003) Angew Chem Int Ed 42:2368
65. Hogan PC, Corey EJ (2005) J Am Chem Soc 127:15386
66. De Vitis L, Troisi L, Granito C, Pindinelli E, Ronzini L (2007) Eur J Org Chem 356
67. Flynn DL, Zelle RE, Grieco PA (1983) J Org Chem 48:2424
68. Coantic S, Mouysset D, Mignani S, Tabart M, Stella M (2007) Tetrahedron 63:3205
69. Holton RA (1990) Eur Pat Appl EP400, 971; Chem Abstr 114:164568q
70. Holton RA, Liu JH (1993) Bioorg Chem Lett 3:2475
71. Ojima I, Habus I, Zhao M, Zucco M, Park YH, Sun CM, Brigaud T (1992) Tetrahedron 48:6985
72. Nicolaou KC, Dai W-M, Guy RK (1994) Angew Chem Int Ed Engl 33:15
73. Kingston DGI (2001) Chem Commun 867
74. Ge H, Spletstoser JT, Yang Y, Kayser M, Georg GI (2007) J Org Chem 72:756
75. Palomo C, Aizpurua JM, Cuevas C, Mielgo A, Galarza R (1995) Tetrahedron Lett 36:9027
76. Alonso E, Pozo CD, Gozález J (2002) Synlett 69
77. Chen A, Nelson A, Tanikkul N, Thomas EJ (2001) Tetrahedron Lett 42:1251

78. Romo D, Rzasa RM, Shea HA, Park K, Langenhan JM, Sun L, Akhiezer A, Liu JO (1998) J Am Chem Soc 120:12237
79. Eggen MJ, Nair SK, Georg GI (2001) Org Lett 3:1813
80. Vidya R, Eggen MJ, Nair SK, Georg GI, Himes RH (2003) J Org Chem 68:9687
81. Dondoni A, Massi A, Sabbatini S, Bertolasi V (2004) Adv Synth Catal 346:1355
82. Cardillo G, Tomasini C (1996) Chem Soc Rev 23:117
83. Juaristi E, López-Ruiz H (1999) Curr Med Chem 6:983
84. von Nussbaun F, Anlauf S, Benet-Buchholz J, Häbich D, Köbberling J, Musza L, Telser J, Rübsamen-Waigmann H, Brunner NA (2007) Structure corroboration and total synthesis. Angew Chem Int Ed 46:2039
85. Palomo C, Aizpurua JM, Ganboa I, Odriozola B, Maneiro E, Miranda JI, Urchegui R (1996) Chem Commun 161
86. Tsang WY, Ahme N, Page MI (2007) Org Biomol Chem 5:485
87. Palomo C, Aizpurua JM, Cuevas C (1994) J Chem Soc Chem Commun 1957
88. Ojima I, Sun CM, Park YH (1994) J Org Chem 59:1249
89. Palomo C, Aizpurua JM, Galarza R, Mielgo A (1996) Chem Commun 633.
90. Palomo C, Aizpurua JM, Galarza R, Benito A, Khamrai UK, Eikeseth U, Linden A (2000) Tetrahedron 56:5563
91. Palomo C, Oiarbide M, Bindi S (1998) J Org Chem 63:2469
92. Durham TB, Miller MJ (2003) J Org Chem 68:35
93. Cundy DJ, Donohue AC, McCarthy TD (1998) Tetrahedron Lett 39:5125
94. Cundy DJ, Donohue AC, McCarthy TD (1999) J Chem Soc Perkin Trans 559
95. Khim S-K, Nuss JM (1999) Tetrahedron Lett 40:1827
96. Jiang X, Prasad K, Prasad M, Slade J, Repič O, Blacklock TJ (2006) Synlett 3179
97. Baldwin JE, Adlington RM, Rusell AT, Smith ML (1995) Tetrahedron 51:4733
98. Nakamura T, Shiozaki M (1999) Tetrahedron Lett 40:9063
99. Nakamura T, Shiozaki M (2001) Tetrahedron 57:9087
100. Palomo C, Aizpurua JM, García JM, Iturburu M, Odriozola JM (1994) J Org Chem 59:5184
101. Palomo C, Aizpurua JM, Gracenea JJ (1999) J Org Chem 64:1693
102. Spero DM, Kapadia S, Farina V (1995) Tetrahedron Lett 36:4543
103. Ojima I, Ng EW, Sun CM (1995) Tetrahedron Lett 36:4547
104. Westermann B, Walter A, Diedrichs N (1999) Angew Chem Int Ed 38:3384
105. Ha D-C, Kang S, Chung C-M, Lim H-K (1998) Tetrahedron Lett 39:7541
106. Parsons PJ, Camp NP, Underwood JM, Harvey DM (1996) Tetrahedron Lett 52:11637
107. Lee HK, Chun JS, Pak CS (2003) J Org Chem 68:2471
108. Lee HK, Chun JS, Pak CS (2001) Tetrahedron Lett 42:3483
109. Lee HK, Chun JS, Pak CS (2003) Tetrahedron 59:6445
110. Birch NJ, Parsons PJ, Scopes DIC (2004) Synlett 2776
111. Krämer B, Franz T, Picasso S, Pruschek P, Jäger V (1997) Synlett 2776
112. Ojima I, Zhao M, Yamato T, Nakahashi K, Yamashita M, Abe R (1991) J Org Chem 56:5263
113. Baldwin JE, Adlington RM, Elend AS, Smith ML (1995) Tetrahedron 51:11581
114. Buttero PD, Molteni G, Roncoroni M (2006) Tetrahedron Lett 47:2209
115. Alcaide B, Almendros P, Cabrero G, Ruiz MP (2007) J Org Chem 72:7980
116. Palomo C, Aizpurua JM, Miranda JI, Mielgo A, Odriozola JM (1993) Tetrahedron Lett 34:6325
117. Alcaide B, Almendros P (2001) Org Prep Proc Int 33:315
118. Palomo C, Aizpurua JM, Ganboa I, Carreaux F, Cuevas C, Maneiro E, Ontoria JM (1994) J Org Chem 59:3123
119. Alcaide B, Almendros P, Aragonzillo C (2000) Chem Commun 757
120. Alcaide B, Almendros P, Aragoncillo C (2002) Chem Eur J 8:3646
121. Kricheldorf HR (1987) α-Amino acid *N*-carboxy-anhydrides and related heterocycles. Springer-Verlag, Berlin
122. Palomo C, Aizpurua JM, Cuevas C, Urchegui R, Linden A (1996) J Org Chem 61:4400

123. Palomo C, Oiarbide M, Esnal A (1997) Chem Commun 691
124. Palomo C, Oiarbide M, Esnal A, Landa A, Miranda JI, Linden A (1998) J Org Chem 63:5838
125. Coppola GM, Schuster HF (1997) α-Hydroxy acids in enantioselective synthesis. VCH, Wienheim
126. Gawronski J, Gawronska K (1999) Tartaric and malic acids in synthesis. Wiley, New York
127. Ghosh AK, Koltun ES, Bilcer G (2001) Synthesis 1281
128. Kolb HC, Van Nieuwenhze MS, Sharpless KB (1994) Chem Rev 94:2483
129. Palomo C, Oiarbide M, Landa A (2000) J Org Chem 65:41
130. Palomo C, Oiarbide M, Landa A, Esnal A, Linden A (2001) J Org Chem 66:4180
131. Sim TB, Rapoport H (1999) J Org Chem 64:2532
132. Durham TB, Miller MJ (2003) J Org Chem 68:27
133. Palomo C, Aizpurua JM, Ganboa I, Maneiro E, Odriozola B (1994) J Chem Soc Chem Commun 1505
134. Palomo C, Cossío FP, Cuevas C, Lecea B, Mielgo A, Román P, Luque A, Martínez-Ripoll M (1992) J Am Chem Soc 114:9360
135. Palomo C, Ganboa I, Cuevas C, Boschetti C, Linden A (1997) Tetrahedron Lett 38:4643
136. Palomo C, Aizpurua JM, Urchegui R, García JM (1995) J Chem Soc Chem Commun 2327
137. Palomo C, Aizpurua JM, Ganboa I, Odriozola B, Urchegui R, Görls H (1996) Chem Commun 1269
138. Alcaide B, Rodríguez-Ranera C, Rodríguez-Vicente A (2001) Tetrahedron Lett 42:3081
139. Macías A, Alonso E, del Pozo C, González J (2004) Tetrahedron Lett 45:4657
140. Alcaide B, Almendros P, Cabrero G, Ruiz P (2008) Chem Commun 615
141. Alcaide B, Almendros P, Cabrero G, Ruiz P (2008) Synthesis 2835
142. Van Brabandt W, De Kimpe N (2005) J Org Chem 70:3369
143. Van Brabandt W, De Kimpe N (2005) J Org Chem 70:8717
144. Dekeukeleire S, D'hooghe M, De Kimpe N (2009) J Org Chem 74:1644
145. Ojima I, Delaloge F (1997) Chem Soc Rev 26:377
146. Ojima I (1995) Adv Asymm Synth 1:95
147. Ojima I (1995) Acc Chem Res 28:283
148. Ojima I (1993) The organic chemistry of β–lactams. Georg GI (ed), VCH, New York, p 197
149. Ojima I, Komata T, Qiu X (1990) J Am Chem Soc 112:770
150. Park J-H, Ha JR, Oh S-J, Kim J-A, Shin D-S, Won TJ, Lam Y-F, Ahn C (2005) Tetrahedron Lett 46:1755
151. Mandal PK, Cabell LA, McMurray JS (2005) Tetrahedron Lett 46:3715
152. Alcaide B, Almendros P, Redondo MC (2004) Org Lett 6:1765
153. Alcaide B, Almendros P, Cabrero G, Ruiz P (2007) Chem Commun 4788
154. Li G-Q, Li Y, Dai L-X, You S-L (2007) Org Lett 9:3519
155. Manhas MS, Amin SG, Bose AK (1976) Heterocycles 5:669
156. Manhas MS, Wagle DR, Chiang J, Bose AK (1988) Heterocycles 27:1755
157. Deshmukh ARAS, Bhawal BH, Krishnaswamy D, Govande VV, Sinkre BA, Jayanthi A (2004) Curr Med Chem 11:1889
158. Alcaide B, Almendros P (2004) Curr Med Chem 11:1921
159. Saragovi HU, Fitxpatrick D, Raktabur H, Nakanishi M, Kahn M, Greene MI (1991) Science 253:792
160. Williams WV, Kieber-Emmons T, VonFeldt J, Greene MI, Weiner DB (1991) J Biol Chem 266:5182
161. Kahn M (1993) Synlett 821
162. Gardner B, Nakanishi H, Kahn M (1993) Tetrahedron 49:3433
163. Wasserman HH (1987) Aldrichim Acta 20:63
164. Hesse M (1991) Ring enlargement in organic chemistry. Weinheim, VCH
165. Ensch C, Hesse M (2002) Helv Chim Acta 85:1659
166. Wasserman HH, Matsuyama H, Robinson RP (2002) Tetrahedron 58:7177

167. Begley MJ, Crombie L, Haigh D, Jones RCF, Osborne S, Webster RAB (1993) J Chem Soc Chem Commun 2027
168. Crombie L, Haigh D, Jones RCF, Mat-Zin R (1993) J Chem Soc Chem Commun 2047
169. Crombie L, Haigh D, Jones RCF, Mat-Zin R (1993) J Chem Soc Chem Commun 2055
170. De Clerq E, Yamamoto N, Pauwels R, Baba M. Schols D, Nakashima H, Balzarini J, Debyser Z, Murrer BA, Schwartz D, Thornton D, Bridger G, Fricker S, Henson G, Abrams M, Pickers D (1995) Proc Natl Acad Sci 117:3368
171. Betschart C, Hegedus LS (1992) J Am Chem Soc 114:5010
172. Dumas S, Lastra E, Hegedus LS (1995) J Am Chem Soc 117:3368
173. Banfi L, Guanti G, Rasparini M (2003) Eur J Org Chem 1319

Top Heterocycl Chem (2010) 22: 261–311
DOI 10.1007/7081_2009_9

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Recent Approaches Toward Solid Phase Synthesis of β-Lactams

Bablee Mandal, Pranab Ghosh, and Basudeb Basu

Abstract Since the discovery of penicillin in 1929, β-lactam antibiotics have been recognized as potentially chemotherapeutic drugs of incomparable effectiveness, conjugating a broad spectrum of activity with very low toxicity. The primary motif azetidin-2-one ring (β-lactam) has been considered as specific pharmacophores and scaffolds. With the advent of combinatorial chemistry and automated parallel synthesis coupled with ample interests from the pharmaceutical industries, recent trends have been driven mostly by adopting solid phase techniques and polymer-supported synthesis of β-lactams. The present survey will present an overview of the developments on the polymer-supported and solid phase techniques for the preparation of β-lactam ring or β-lactam containing antibiotics published over the last decade. Both unsubstituted and substitutions with different functional groups at various positions of β-lactams have been synthesized using solid phase technology. However, Wang resin and application of Staudinger [2+2] cycloaddition reaction have remained hitherto the major choice. It may be expected that other solid phase approaches involving different resins would be developed in the coming years.

Keywords Azitidinone · Penicillin · Solid phase synthesis · β-Lactam · β-Sultam

Contents

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Abbreviations

AM-resin	Aminomethylated polystyrene
BAL	Backbone amide linker
BEMP resin	Resin 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine immobilized on polystyrene resin
BOBA	Benzyloxybenzyl amine
BQ	Benzoylquinine
CAN	Cerric ammonium nitrate
DCC	*N*,*N*′-Dicyclo-hexylcarbodiimide
DEAD	Diethylazodicarboxylate
DIPEA	Diisopropylethyl amine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMTMM	(4,6-Dimethoxy-[1,3,5]-triazin-2-yl)-4-methyl-morpholinium chloride
EDC	*N*-Ethyl-*N*′-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
FDPP	Pentafluoro phenyldiphenyl phosphate
Fmoc	9-Fluorenylmethoxycarbonyl
HOBt	Hydroxybenzotriazol
LiHMDS	Lithium hexamethyldisilazane
MAMP	Merrifield, alpha methoxy phenyl resin
MCPBA	*m*-Chloroperbenzoic acid
MeOPEG	Methoxy polyethylene glycol
NCA	*N*-Carboxy α-aminoacid anhydride
NMP	*N*-Methylpyrrolidone
PAL	Peptide amide linker
PASP	Polymer assisted solution phase
PBP	Penicillin-binding proteins
PEG	Polyethylene glycol
SASRIN	Super acid sensitive resin
TEA	Triethylamine
TFA	Trifluoroacetic acid
TMAD	Tetramethylamine azodicarboxylate.

1 Introduction

The discovery of penicillin by Sir Alexander Fleming in 1929 has been recognized as one of the most fortunate discoveries in modern times [1]. The β-lactam ring is the key component of commonly used antibiotics such as penicillins, cephalosporins, carbapenems, and monobactams [2]. The development of β-lactam antibiotics

help to combat several lethal diseases such as plague, wound sepsis, and tuberculosis [3, 4].

The penicillin antibiotics inhibit transpeptidase enzymes (penicillin-binding proteins (PBPs)) by acylation of the serinyl residue at their active site, which leads to cell wall lysis, since blocking PBPs circumvents proper murein membrane formation [3]. Several peptides and peptidomimetics containing the β-lactam ring have been recently described as effective protease inhibitors and, consequently, as potential drugs for a wide range of diseases implicating proteases [5–8].

Since their introduction, β-lactam antibiotics proved to be chemotherapeutics of incomparable effectiveness, conjugating a broad spectrum of activity with low toxicity [9]. β-Lactams are a large class of antibiotics characterized by the presence of the azetidin-2-one ring, which is the core of the biological activity, and differentiated by side chains, unsaturations, heteroatoms, and in many cases, by the presence of another five- or six- membered ring. The great vivacity of research in this field led to the development of classical β-lactam substrates such as penicillins and cephalosporins together with nonclassical ones such as carbapenems and monobactams obtained via semi or total syntheses. To complete and increase the importance of β-lactams, nonclassical bicyclic and monocyclic β-lactam substrates with different biological activities have appeared in recent literature: serine-dependent enzyme inhibitors [10–13], matrix-metalloprotease inhibitors [14], and even apoptosis inductors [15]. The problem of microbial resistance, related to the use of these agents over the last 50 years, is nowadays widely recognized, and treatment options in clinical practice are limited by multidrug-resistant bacteria [16]. Despite the need for new antibiotics, large pharmaceutical companies are devoting fewer resources to their development because these agents do not provide as great a return on investment relative to that of compounds for some other therapies [17]. However, the phenomenon of bacterial resistance forces the continuous modification of side chains and structures of known active compounds and the development of new ones.

2 Solid-Phase Techniques for β-Lactam Synthesis

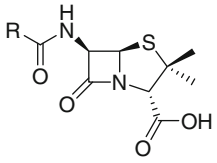
The wide spectrum of activities of β-lactam containing organic molecules has led to the consideration of the motif azetidin-2-one ring (β-lactam) as a general lead structure for the design of new antibiotics [18, 19] and novel inhibitors of enzymes containing a nucleophilic serine in their active site [20–22]. Several intelligent strategies and attractive approaches for the preparation of β-lactam moiety have been developed and reported in the literature. However, with the advent of combinatorial chemistry and automated parallel synthesis, recent trends have been driven mostly by adopting solid phase techniques and polymer-supported synthesis of β-lactam. A considerable number of novel methodologies involving solid supports for the synthesis of azetidinones and its derivatives have been reported in the literature, besides regular reports of solution phase methods applying known and classical methods [23–39]. This chapter will present an overview of the developments on the

polymer-supported and solid phase techniques for the preparation of β-lactam ring or β-lactam containing antibiotics published over the last decade.

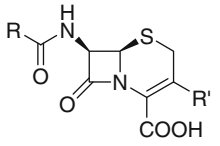
The advent of combinatorial techniques and solid phase organic synthesis may lead to preparation of large numbers of structurally related molecules in short periods of time. This is important especially for the optimization of lead structures in the pharmaceutical industry [40]. It is now well established and documented that the combinatorial technology and solid phase techniques could offer sufficient latitude for preparation of corresponding chemical libraries with broad structural diversity. The diverse potentiality of β-lactam moiety as specific pharmacophores and scaffolds has attracted ample interests from pharmaceutical industries for the synthetic methods based on polymer-supported techniques.

The development of efficient routes to synthesize β-lactams is an area of significant research interest [41–45]. This has been driven, in large part, by the importance of these molecules as constituents of antibiotics, ranging from penicillin-based substrates to a number of more recently developed compounds (e.g., penems, cephems, monobactams, carbapenems, and trinems) [46–51]. β-Lactams have also been demonstrated to be important synthons in organic synthesis (Fig. 1) [52, 53] and to be monomers in the generation of polyamides [e.g., poly(β-peptides)] [54, 55].

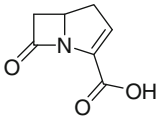
In principle, an attractive approach to prepare molecules such as β-lactams would be to consider their structure. Because of the β-lactams' highly strained four-member ring, the cleavage of any of the four bonds is possible (Scheme 1). The N_1–C_2 bond can be easily cleaved by nucleophiles (e.g., oxygen, nitrogen, and carbon) to obtain β-amino acid derivatives as products [56]. When R^2 is an amino group and R^3 is an aryl group, palladium-catalyzed hydrogenolysis is a good way to



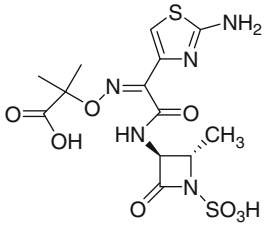
Penicillin



Cephalosporin

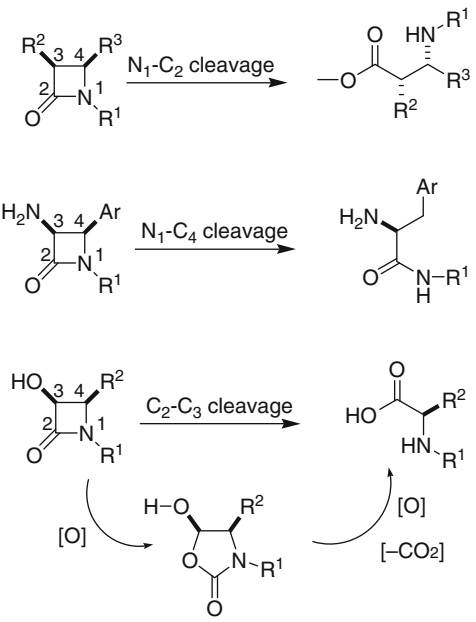


Carbapenem



Aztreonam (Monobactam)

Fig. 1 Examples of few familiar antibiotics

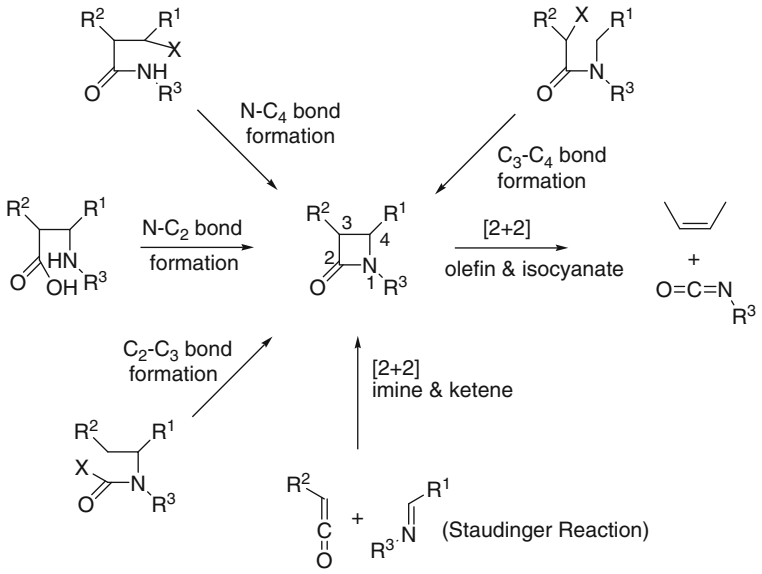


Scheme 1 Possible cleavage of any of the four bonds in β-lactam

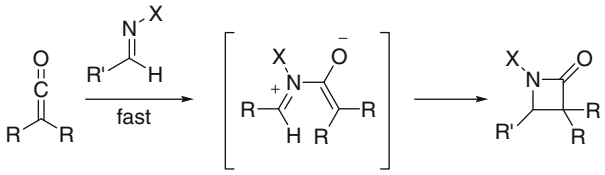
break N_1–C_4 bond and get α-amino acid-derived peptides [57]. The ring-opening at C_2–C_3 bond of α-hydroxy β-lactams can also produce α-amino acid derivatives via *N*-carboxy α-amino acid anhydride (NCA) intermediates [58]. Selective cleavage of the C_3–C_4 bond is, however, rare.

Intensive research has generated numerous methods of synthesizing the β-lactam skeleton [59]. The strained four-member ring, which constitutes the core structure of all β-lactam antibiotics, is the main challenging point in the synthetic efforts for preparation of these compounds. The four-member ring of β-lactam can be constructed by any of the four single-bond formations or by [2 + 2] cycloaddition (Scheme 2). The formation of the amide (N_1–C_2) bond is the most obvious approach and was utilized in the synthesis of penicillin [60]. Among the four single-bond constructions, C_2–C_3 bond formation was rare. One methodology involving a tributylstannane-mediated ring closure has been reported [61]. In a simple sense, the C–C bond construction (C_3–C_4) involves the formation of a nucleophilic center at C_3 and an electrophilic center at C_4, or vice versa [62]. The biosynthetic route to β-lactam has been focused primarily on the C_4–N_1 bond formation [63]. Several approaches have been developed to construct this bond. The idea is to displace a leaving group attached to C_4 intramolecularly with activated nitrogen [64].

Compared with the single-bond construction approach of β-lactam synthesis, the ketene-imine cycloaddition, which includes carbenoid insertion and the Staudinger reaction, have been widely used [56, 65]. Due to the ready availability of both imines and ketenes, the Staudinger reaction has provided a useful and economical approach for the synthesis of β-lactams. In addition, the ketene-imine cycloaddition is efficient, which constructs the β-lactam four-member ring in just one-step



Scheme 2 Possible methods for β-lactam ring construction



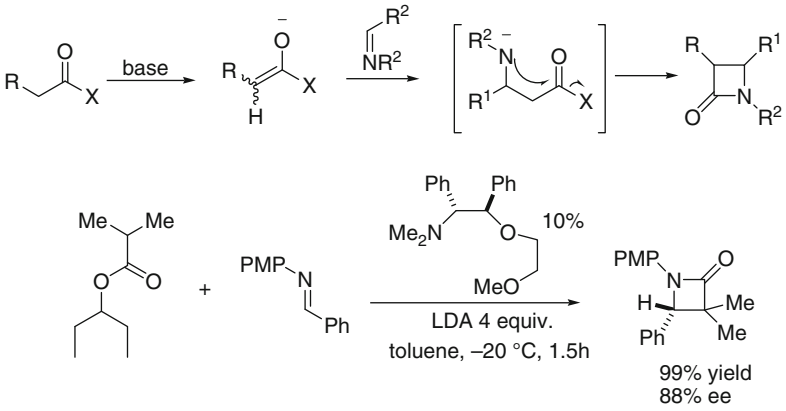
Scheme 3 Mechanism for the Staudinger reaction

reaction. The mechanism for the Staudinger reaction is that the electrophilic ketene is attacked by lone pair electrons of imine nitrogen and the zwitterionic enolate is formed followed by conrotatory ring closure forming the β-lactam (Scheme 3) [66].

The ester enolate-imine condensation, also called Gilman-Speeter reaction, is another well-accepted method for β-lactam synthesis (Scheme 4) [67–69]. In 1997, Tomioka reported the first example of a direct catalytic enantioselective synthesis of β-lactam by using this method [70]. The active reagent is a ternary complex (comprising LDA, the ester enolate, and tridentate amino diether), which finally affords the β-lactam compounds in high yields and good *ee* values.

3 Solid-Phase Synthesis of β-Lactam by Staudinger Reaction

Between the above two methods for the synthesis of β-lactam derivatives, the venerable Staudinger [2+2] imine-ketene cycloaddition [36] is by far the most versatile and simplest entry to the lactam fragment. Application of Staudinger

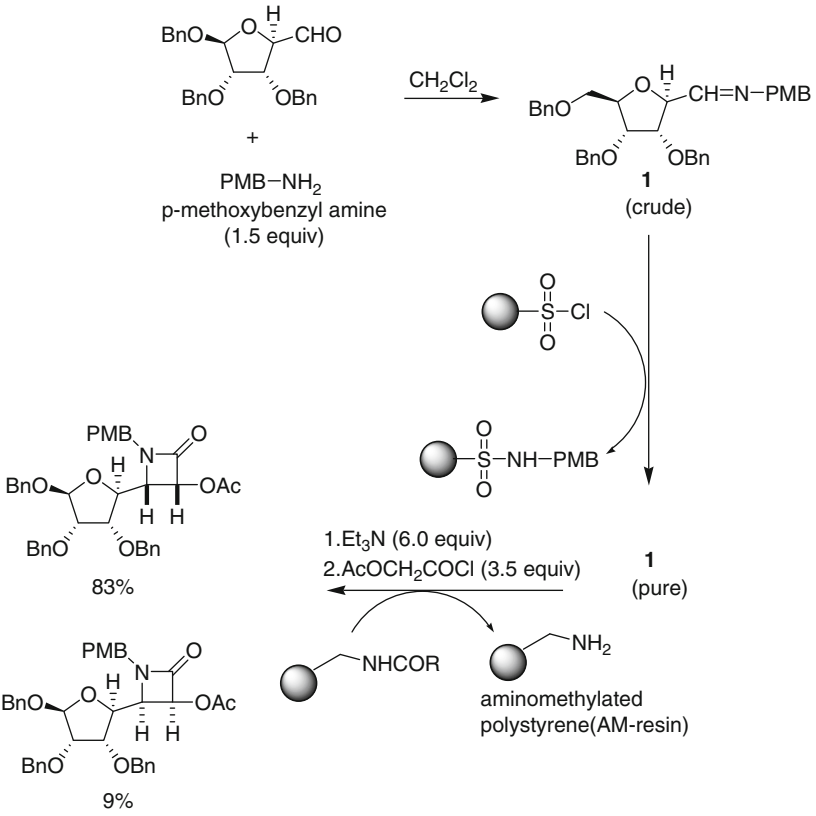


Scheme 4 Gilman-Speeter reaction in β-lactam synthesis

reaction in polymer assisted solution phase (PASP) technique [71] was reported by Dondoni et al. [72]. They reported for the first time the synthesis of *C*-glycosyl β-lactams by generation of the cycloaddition partners in the same reaction vessel from mixtures of sugar aldehyde, amine, and acyl chloride. The unreacted *p*-methoxybenzyl amine (PMBA) was sequestered by treatment with resin-supported sulfonyl chloride. To the resulting heterogeneous mixture was then added (acetoxy)acetyl chloride and triethyl amine to produce the corresponding acetoxy-substituted ketene. After a suitable period of time, the reaction mixture was treated with nucleophilic aminomethylated polystyrene (AM-resin) to remove the excess of ketene and its precursor acetyl chloride, as well as the acid arising from the hydrolysis of the latter (Scheme 5). Simple workup (filtration and washing with water) of the resulting suspension and solvent evaporation afforded a mixture of 4-(C-ribosyl)-β-lactam stereoisomers (*3R,4S*) (major, 83%) and (*3S,4R*) (minor, 9%).

Similar protocols were also adopted by Gordeev et al. [73] for the synthesis of β-sultams (1,2-thiazetidine 1,1-dioxides), which have attracted attention due to their apparent structural analogy to the β-lactams [74]. Their synthetic strategy was based on the [2 + 2] cycloaddition of activated sulfenes with imines as the key step (Scheme 6). Methyl (chlorosulfonyl) acetate was used as a reactive sulfene precursor, which was reacted with the imine generated from Sasrin resin, [75] and immobilized alanine derivatives, in the presence of pyridine as a base. The reaction sequence, intermediates, and products were robust enough to tolerate other types of linkers [e.g., poly(ethylene glycol) (PEG)] and cleavage conditions. The resulting β-sultams were released from the polymeric supports by acidic cleavage (TFA) or photocleavage.

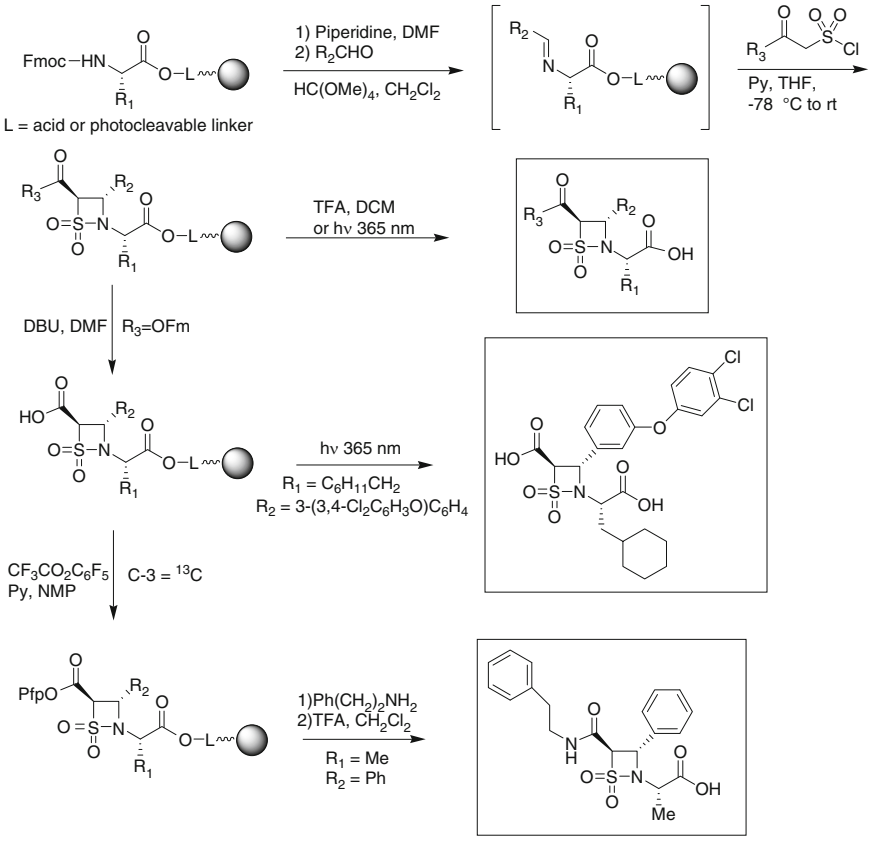
The first synthesis of β-lactams bound to a soluble/insoluble polyethylene glycol monomethylether polymeric matrix has been realized by standard reactions carried out on immobilized imines**.** From the polymer, β-lactams were removed under acidic and basic conditions [76, 77]. The reactivity of the immobilized reagent was tested by synthesizing β-1actam from imines and an enolate **8a** and the



Scheme 5 Application of polymer-assisted solution phase (PASP) technique in Staudinger reaction

cycloaddition with a ketene **8b**, (Scheme 7). While ^{1}H NMR analysis allowed a satisfactory determination of the stereoisomeric composition of the products bound to the polymer, the yield of the β-lactam was better determined by releasing the azetidinone from the MeOPEG matrix, a reaction that served to establish a possible synthetic application of the polymer-supported synthesis of β-lactam.

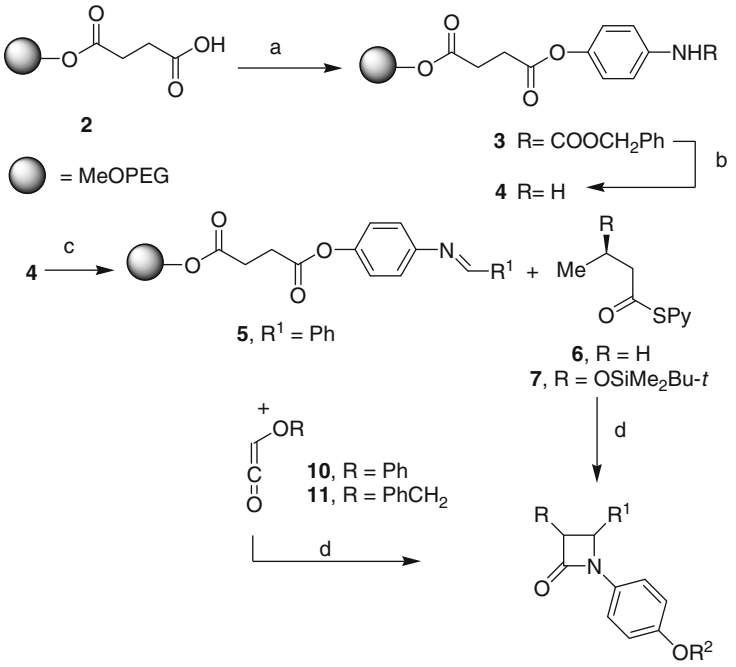
Singh and Nuss [78] described the synthesis of β-1actams via [2 + 2] Staudinger reaction [79] on solid supports with the aim of developing methodology for the rapid synthesis of combinatorial libraries (Scheme 8) [79]. The polymer-supported imine (**20**) was reacted with α-acetoxy acetyl chloride in the presence of triethyl amine to produce the β-lactam (**21**), which was eventually released from the polymeric surface by treatment with 3% TFA in CH_2Cl_2 (Scheme 8). Typically in solution phase this cycloaddition occurs favorably at 0°C and requires chromatographic purification. This problem is however eliminated in solid phase synthesis. The reaction in general was able to tolerate a large excess of amine with no undesirable cleavage of the azetidinone amide bond being observed.



Scheme 6 Synthesis of β-sultams on solid support

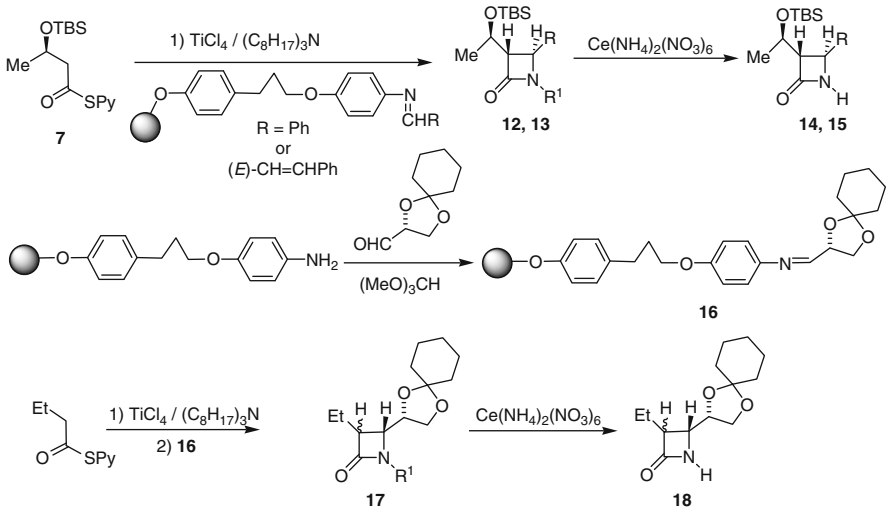
Although yields of the azetidinones from the imines that were generated from a range of amines such as alkyl, aryl, and anilines were obtained in satisfactory ranges, electron deficient heterocyclic amines were found to be problematic. However, as compared to the homogeneous counterpart, undesirable product formation can be avoided and side products resulting from the reaction solution can be washed away from the solid supports. Thus, a successful application of the Staudinger cycloaddition on solid supports has been demonstrated. This group is currently investigating the application of this methodology to the generation of diverse combinatorial libraries.

Gallop et al. [80] reported the preparation of β-lactams via a [2+2] cycloaddition reaction of ketenes with resin-bound imines derived from amino acids (Scheme 9). This is another solid-phase adaptation of the Staudinger reaction, which could lead to the synthesis of structurally diverse 3,4-bis-substituted 2-azetidinones [81]. In addition, a novel approach to the synthesis of *N*-unsubstituted-β-lactams, important building blocks for the preparation of β-lactam antibiotics, and useful precursors of chiral β-amino acids was described [82].



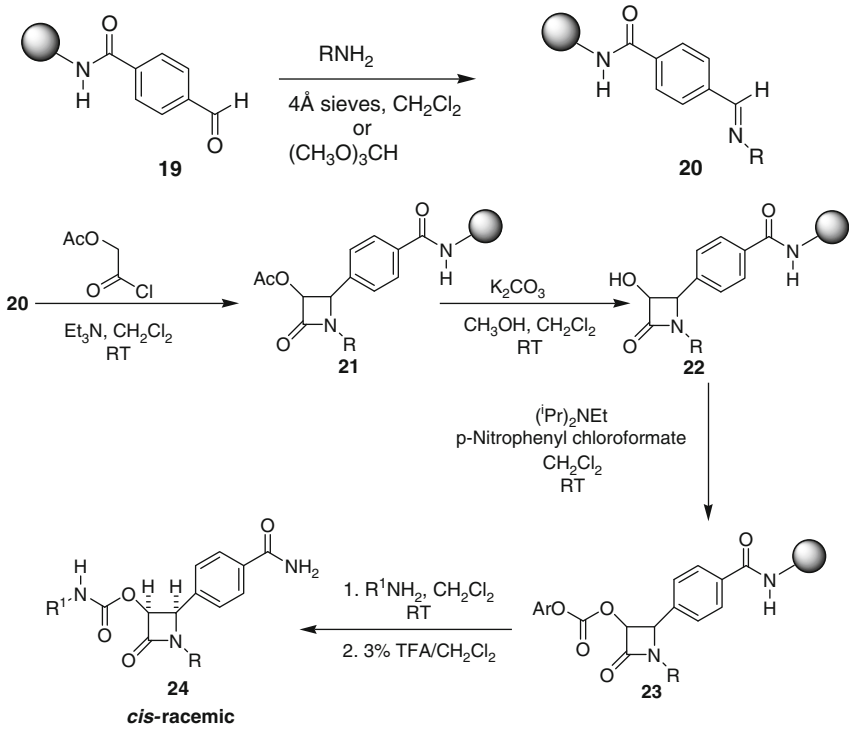
8, R = $PHCH_2O$, R^1= Ph, R^2 = $CO(CH_2)_2COOPEGOMe$;
9, R = Et, R^1 = Ph, R^2 = H; **10**, R = (*R*)-MeCH(OH), R^1 = Ph, R^2 = H;
11, R = PhO, R^1 = Ph, R^2 = H

Reagents. a: 4-$PhCH_2OCONH$-C_6H_4-OH, DCC, DMAP;
b: H_2, 10% Pd/C; c: R^1CHO; d: CH_2Cl_2, 15h, 23 °C

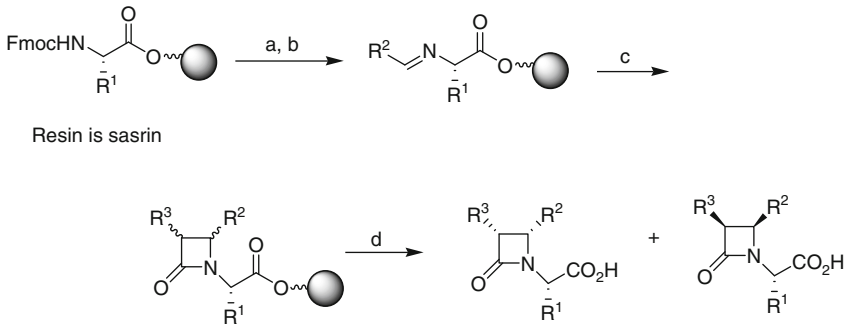


12,14 R = Ph; **13,15** R = (*E*)-PhCh=CH R^1 = $-C_6H_4O(CH_2)_3C_6H_4O$-●

Scheme 7 (**a**) Synthesis of β-lactam bound to a soluble/insoluble polyethylene glycol monomethylether polymeric mallix. (**b**) Stereoselective and solid phase synthesis of β-1actam



Scheme 8 Synthesis of β-1actams using polymer supported imine (**20**)



(a) 30% piperidine in NMP, 45 min; (b) 0.8 M R^2CHO in 1:1 $(MeO)_3CH:CH_2Cl_2$, 3 hrs;
(c) 0.8 M R^3CH_2COCl, 1.1 M NEt_3 in CH_2Cl_2, 0°C to 25°C, 16hrs; (d) 3% TFA in CH_2Cl_2, 45 min

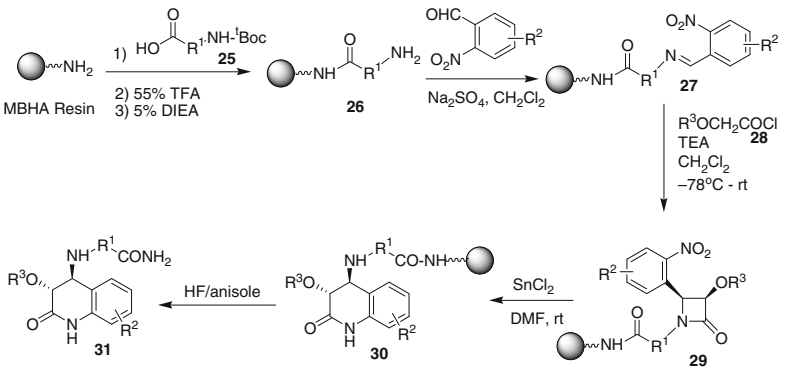
Scheme 9 Use of Sasrin resin bound amino acid for the preparation of β-lactam via [2+2] cycloaddition

The participation of imines derived from amino acid esters in the Staudinger reaction is well known in homogeneous solution. For solid-phase β-lactam synthesis, the carboxylic acid residue of an amino acid is conveniently tethered as an ester or amide to the support. Among several commercially available polystyrene peptide synthesis resins preloaded with Fmoc protected amino acids that were investigated by the authors as supports for solid-phase β-lactam synthesis, the highly acid-labile resin, Sasrin, proved particularly suitable. After removal of the Fmoc protecting group by treatment with piperidine in NMP, the resulting amines were condensed with a 10–15-fold molar excess of an alkyl, aromatic, or α,β-unsaturated aldehyde in a 1/1 mixture of $(MeO)_3CH/CH_2Cl_2$, to yield the resin-bound imines quantitatively [83].

β-Lactam intermediates were constructed through [2 + 2] cycloadditions between ketenes and imines on the solid-phase by Pei et al. [84]. A library of 4,140 dihydroquinolinones has been produced using this synthetic process and is used to prepare 3,4-dihydro-2(1H)-quinolinones through the rearrangement of β−lactam intermediates on the solid-phase.

The reported reaction conditions involved in the synthesis of β−lactams in solution-phase are mild enough to tolerate a large variety of functional groups. Therefore, it is possible to incorporate various substituents into the final products through β-lactam intermediates. In this report, they described the synthesis of 4-amino-3,4-dihydro-2(1H)-quinolinones from amino acids, aldehydes, and acid chlorides, through the rearrangement of β-lactam intermediates on the solid-phase. The synthesis of 4-amino-3,4-dihydro-2(1H)-quinolinones were carried out on the solid-phase using the tea-bag technology [85]. The reaction sequence has been illustrated in Scheme 10.

Resin bound amines **26** were condensed with *ortho*-nitrobenzaldehyde in dichloromethane in the presence of anhydrous sodium sulfate as drying agent to furnish the imines **27**. Cycloaddition [2 + 2] of **27** with ketene was carried out in dichloromethane at −78°C. The ketene was generated in situ from corresponding phenoxyacetyl chloride in the presence of triethylamine. In all cases, *cis*-β-lactams



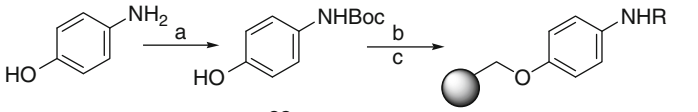
Scheme 10 Synthesis of dihydroquinolinones on MBHA Resin

were obtained as single products in almost quantitative yield. From L-Boc-AIa-OH, a mixture of two diastereomers of the *cis*-β-lactam **29b** was obtained in about 1:1 ratio. The nitro groups of the β-lactam intermediate **29** were reduced to amines using tin(II) chloride (2.0 M) in DMF at room temperature [86]. Under the reaction conditions, the β-lactam ring underwent rearrangement to produce *trans-3,4-dihydro-2(1H)-quinolinones* **30**, through an intramolecular nucleophilic attack of the β−lactam amide moiety by newly generated amino groups. Dihydroquinolinones **31** were obtained in excellent yields after cleavage using HF/anisole (95/5).

In a program to synthesize biologically interesting mono- and multicyclic β-lactam compounds by applying solid-phase methodologies Mata et al. [87] have carried out the polymer-supported Staudinger reaction smoothly under mild conditions to give the corresponding β-lactams in good to high overall yields with excellent *cis*-selectivity using the cost-effective Wang resin as the solid-support. Application of this method constituted an efficient asymmetric synthesis of β-lactams, when chiral acid chlorides or chiral aldehydes were used. These optically active β-lactams are useful precursors for the generation of combinatorial libraries of potential antibiotics and enzyme.

There are a number of amide releasing linkers [88], which possess an amino group for incorporation as –NHCO– into their products. Such linkers include Rink [89], Sieber amide [90], PAL [91], SASRIN [92], BAL [93], and MAMP [94]. These linkers rely on acid-induced S_N1 cleavage mechanisms and incorporate extended aromatic systems to stabilize the resulting cations. A drawback of such systems is that their amino groups are sterically hindered by methoxy groups included in their aromatic systems. For example, the acylation of Rink amide secondary amines with amino acids possessing bulky side chains was reported to occur in only modest yields (60%) [95]. The authors have reported a new amine linker of this category that is cleaved using ceric [96] ammonium nitrate [$Ce(NO_3)_6(NH_4)_2$, CAN]. The linker has been designed for the release of secondary amides and, in particular, β-lactams but will have broader application. Monocyclic β-lactams such as the nocardicins [97] and monobactams [98] are of interest as they have been found to exhibit antibiotic properties. In solution-phase syntheses CAN has been utilized to remove the *p*-methoxyphenyl group from the amide nitrogen of β-lactams to generate their *N*-unsubstituted analogues [99, 100]. Exploitation of CAN in a solid-phase cleavage strategy offers mild, rapid, and selective cleavage conditions. The linker is based on resin bound aniline and is free from steric hindrance and easy to prepare. The benzyloxyaniline linker is also acid stable, which contrasts with the CAN or TFA cleavable benzyloxybenzylamine (BOBA) linker [101] (Schemes 11 and 12) (Table 1).

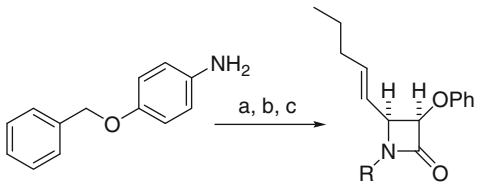
In continuation of the research on solid-phase synthesis of biologically interesting β-lactam compounds towards the development of combinatorial libraries, Mata et al. [102] investigated use of 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) as a key reagent for the construction of the β-lactam ring in a stereoselective manner. The popular explanation involves the reaction of ketene **B** with the imine to form a zwitterionic intermediate **D** (Scheme 13). Alternatively, it is the activated acid **A** that acylates the imine to form the zwitterion **D** by abstraction of proton with



32 **33** R = Boc, **34** R = H

(a)Et_3N (1 equiv), Boc_2O (1 equiv), DMF, 12 h, 0 °C to room temperature, 99%; (b) NaH (3 equiv), 1(3 equiv), DMF, 0 °C, 1 h then add to Br TentaGel resin (1 equiv), DMF, rt, 12 h, 97%; (c) 10% TFA/DCM, rt, 12 h then filter and wash with Et_3N/DCM.

Scheme 11 Protection of amine followed by attachment to resin via esterification

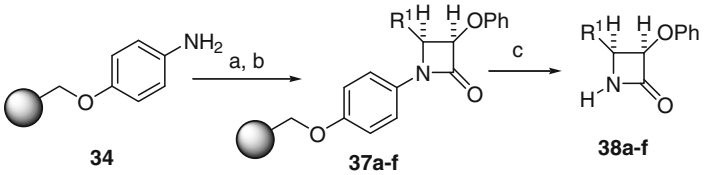


35 R = OBn, **36** R = H

(a) t-Hexenal (1 equiv), 4 Å molecular sieves, DCM, rt, 1 h; (b) Et_3N (5 equiv), phenoxyacetyl chloride (2 equiv), DCM, 0 °C to room temperature, 18 h, 67% for two steps; (c) CAN (3 equiv), MeCN/H_2O (2:1), 0 °C to room temperature, 1 h, 59%.

Scheme 12 Resin-supported free amine and subsequent Staudinger reaction

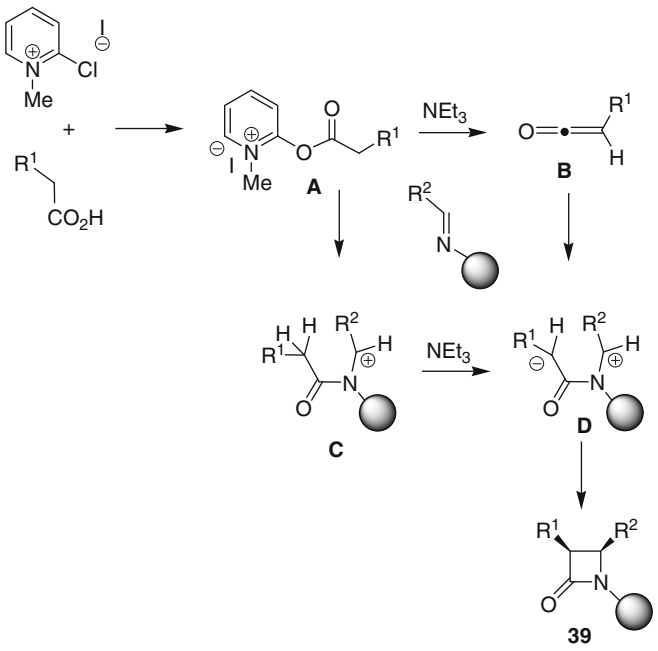
Table 1 Use of CAN in the solid-phase cleavage of linker



34 **37a-f** **38a-f**

38	R^1	%purity[a]	%yield[b]
a	$CH_3(CH_2)_2CH{=}CH–$	98	83
b	4-nitrophenyl	93	88
c	3-chlorophenyl	98	62
d	2-bromophenyl	99	56
e	$(CH_3)_3C–$	96	45
f	4-methoxyphenyl	97	85

[a] Determined by HPLC with UV detection at 220 nm.
[b] Calculated from the loading of resin **34**



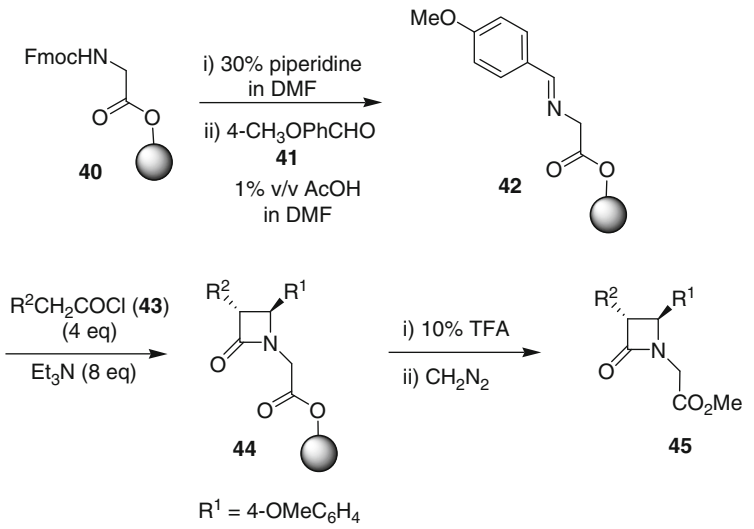
Scheme 13 Mechanistic explanation of Staudinger reaction using Mukaiyama's reagent

a base. The intermediate eventually undergoes a conrotatory ring closure to generate the thermodynamically less stable *cis*-β-lactam **39**. Lower temperatures led to products with better *cis* selectivity without decreasing the overall yield.

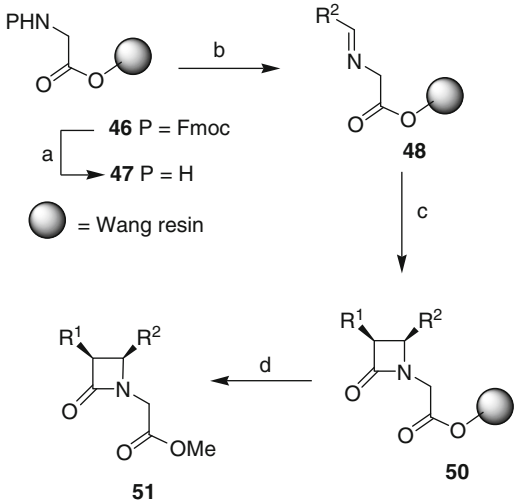
Solid-phase preparation of *trans* 3-alkyl β-lactams was reported by Mata et al. recently (Scheme 14) [103]. The synthetic sequence involved the start from Fmoc-glycine tethered to Wang resin, followed by addition of a controlled excess of **43** (4 equiv) and triethylamine (8 equiv) to the resin bound imine **42** in refluxing toluene. Cleavage form resin surface and esterification afforded the 3-alkyl β-lactams, **45**, as a single product with excellent *trans*-selectivity.

Solid-phase synthesis of 3,4-disubstituted β-lactams was accomplished [104] via reaction of in situ generated ketenes with immobilized aldimines under mild conditions. Initially Fmoc-protected Wang resin strategy was followed (Scheme 15) and the [2+2] cycloaddition was performed by adding phenoxylacetyl chloride (**49**, R^1 = phenoxy) and triethylamine in excess to a suspension of **48** in dichloromethane. The yields ranged from good to very good for the five-step synthetic sequence and exclusive formation of the *cis* isomer was detected in all cases.

A similar reaction sequence was attempted using a Merrifield resin-Boc strategy starting with commercially available Boc-glycine linked to Merrifield resin (**52**) (Scheme 16).



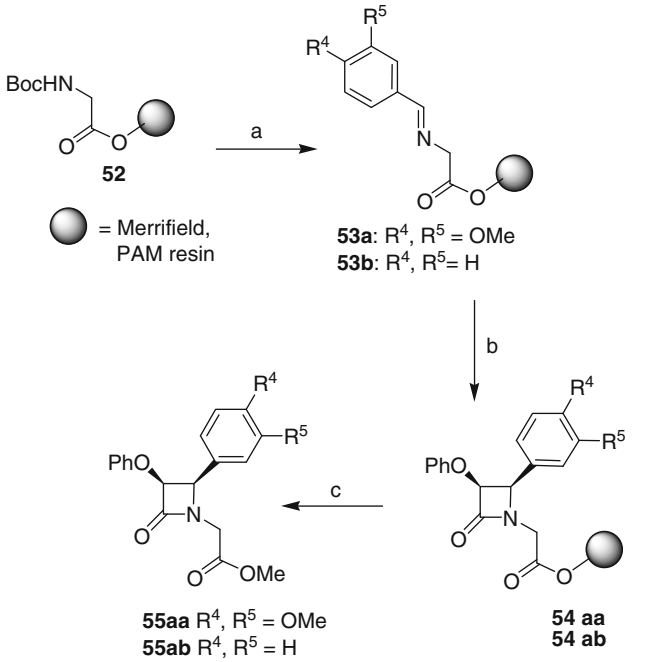
Scheme 14 Solid-phase preparation of *trans* 3-alkyl β-lactams



(a) 30 % piperidine in DMF. (b) R^2CHO (3) (5 equiv), 1% v/v AcOH in DMF. (c) Et_3N (20 equiv), R^1CH_2COCl (**49**) (15 equiv), 0 °C then r.t. overnight. (d) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

Scheme 15 Synthesis of β-lactam using Fmoc-Wang resin

This research group further carried out an asymmetric version of the solid-phase Staudinger reaction using a chiral auxiliary at C-3 for the generation of active carbacephems and other multicyclic β-lactam. Thus, the homochiral (*S*)-4

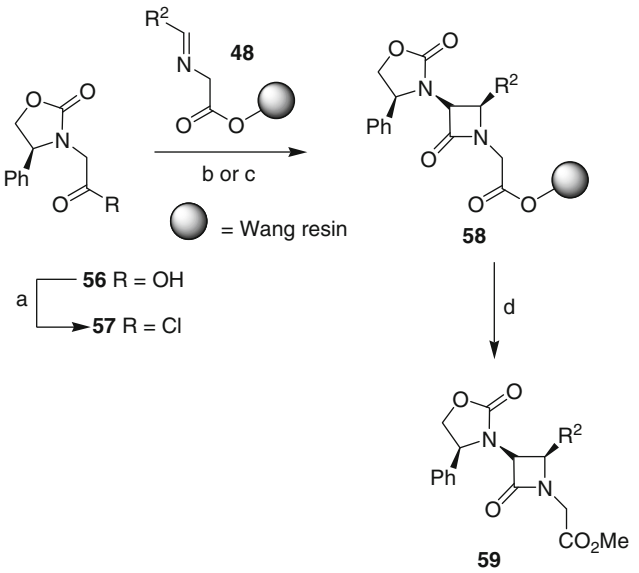


(a) (i) 25% TFA in CH_2Cl_2, 50 min. (ii) aldehyde (5 equiv), 1% v/v AcOH in DMF. (b) Et_3N (20 equiv), $PhOCH_2COCl$ (15 equiv), 0 °C then r.t. overnight. (c) (i) TMTOH, (ii) CH_2N_2

Scheme 16 Synthesis of β-lactam using N-Boc protected Merrifield resin

phenyloxazolidinylacetic acid (**56**) was prepared according to the Evans procedure (Scheme 17). [105] The asymmetric Staudinger reaction on solid support was then performed by adding (*S*)-(4-phenyloxazolidinyl) ketene, generated in situ by treating the crude acid chloride **57** with triethylamine at low temperature, to suspensions of different resin-bound aldimines **48** yielding the optically active β-lactams (**59**) (Scheme 17, path b). Good to very good overall isolated yields were achieved with very high diastereoselectivity.

In another approach, Mata et al. [106] described synthesis of β-lactam analogues of cholesterol absorption inhibitors with excellent geometrical selectivity involving an efficient cross-metathesis on solid support and thus illustrated excellent methodology for introduction of diversity at C-3 and C-4 positions of the β-lactam ring with excellent 3,4-*trans* selectivity and complete *E* selectivity at the C-3 side chain. The efficiency of the cross-metathesis on solid phase and its application to the generation of biologically interesting 3-(aryl)-alkenyl-β-lactam was established by this method. The key intermediate in this protocol was the resin-bound 3-vinyl-β-lactam **65**. The attachment of Fmoc protected *p*-aminophenol to Wang resin was however achieved by using tetramethylamine azodicarboxylate (TMAD) and Bu_3P [107]



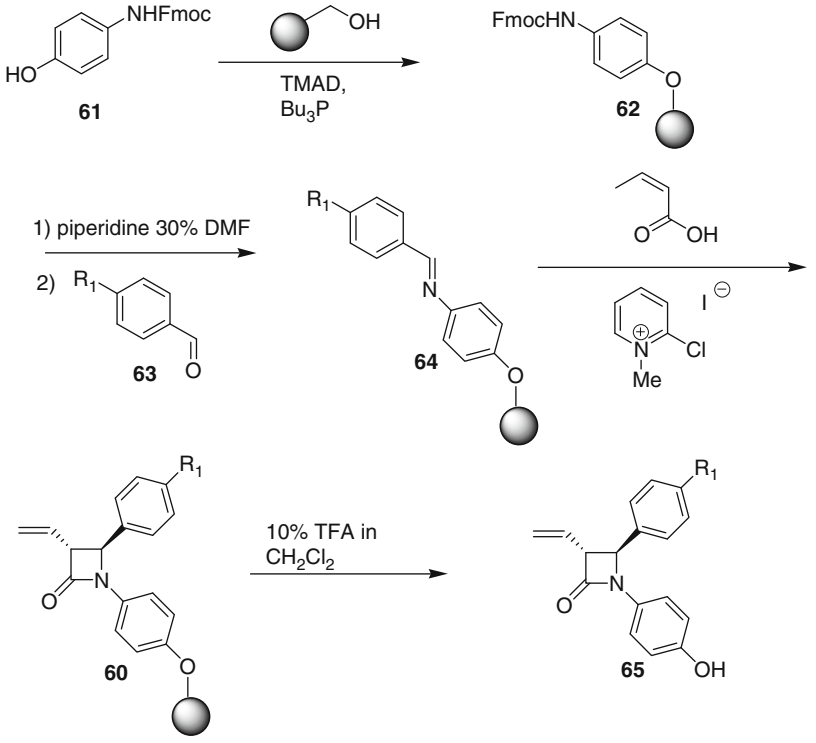
(a) $(COCl)_2$, toluene, 3 h, 60 °C. (b) **48**: CH_2Cl_2, Et_3N (20 equiv), **57** (15 equiv), 0 °C then r.t. overnight. (c) **48**: $CHCl_3$,**56** (2.5 equiv), Et_3N (6 equiv), then **74**, r.t. 24 h. (d) (i) 10% TFA in CH_2Cl_2. (ii) CH_2N_2.

Scheme 17 Asymmetric solid-phase synthesis of carbacephems

instead of classical Mitsunobu conditions [108] (DEAD, Ph_3P). The resin-bound aniline **62** was deprotected following standard procedure and converted to the aldimine **64** by condensation with aldehyde **63**. The synthesis of the β-lactam ring was accomplished through solid-supported Staudinger reaction using the Mukaiyama's reagent as acid activating agent [102]. Thus, the reaction of crotonic acid with the corresponding imine **64,** effectively yielded the supported 3-vinyl-β-lactam **60** (Scheme 18). Treatment of the resin with 10% trifluoroacetic acid in CH_2Cl_2 at room temperature was found to be an efficient procedure for the cleavage of resin, affording the 3-vinyl-β-lactam **65** in 32% overall isolated yield (based on the manufacturer's loading of the Wang resin).

Subsequently, attention was focused on the cross-metathesis reaction on solid-support. The advantages of using olefin cross-metathesis include mild reaction conditions, tolerance to a wide range of functional groups, and availability of a wide variety of commercial olefin partners. The olefin cross-metathesis on solid support using second-generation Grubbs precatalyst, has been conducted to generate a library of analogues of cholesterol absorption inhibitors. (Fig. 2) (Scheme 19)

Recently, Mata et al. [109] described the first solid-phase Staudinger reaction based on immobilization of the activated carboxylic acid, which led to the development of a strategy for the preparation of C3-anchored β-lactam derivatives. In this approach, two linkers, viz. the diethylsilyloxy linker (PS-DES resin) and the Wang resin were tested, of which the latter was found to offer better results.



Scheme 18 Solid-Phase synthesis of 3-Vinyl-β-lactams

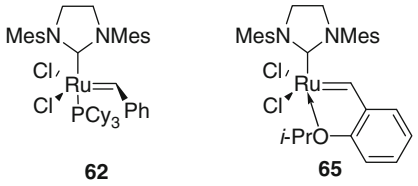
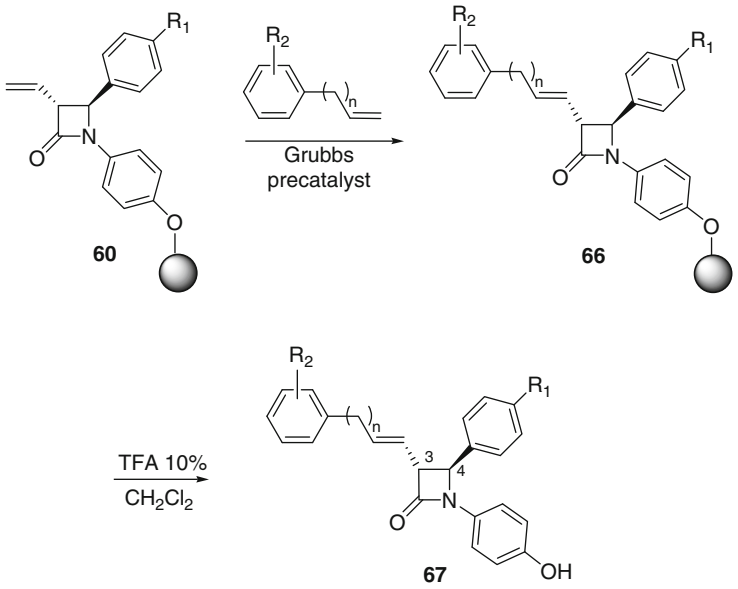


Fig. 2 Precatalysts defined as Grubbs (**62**) and Hoveyda-Grubbs (**65**)

Coupling of **69** with methyl 4-hydroxyphenoxyacetate **70** was carried out in the presence of imidazole and confirmed by gel-phase ^{13}C NMR of PSDES resin **71**. The hydrolysis of resin-bound ester was efficiently achieved using trimethyltin hydroxide (TMTOH) [110–114] to give the corresponding immobilized carboxylic acid **72**. For the key Staudinger reaction, activation of the carboxylic acid **72** by Mukaiyama's reagent **74** was employed (Scheme 20) [115–117]. The *cis*-β-lactam **76** was obtained in a 12–14% isolated yield.

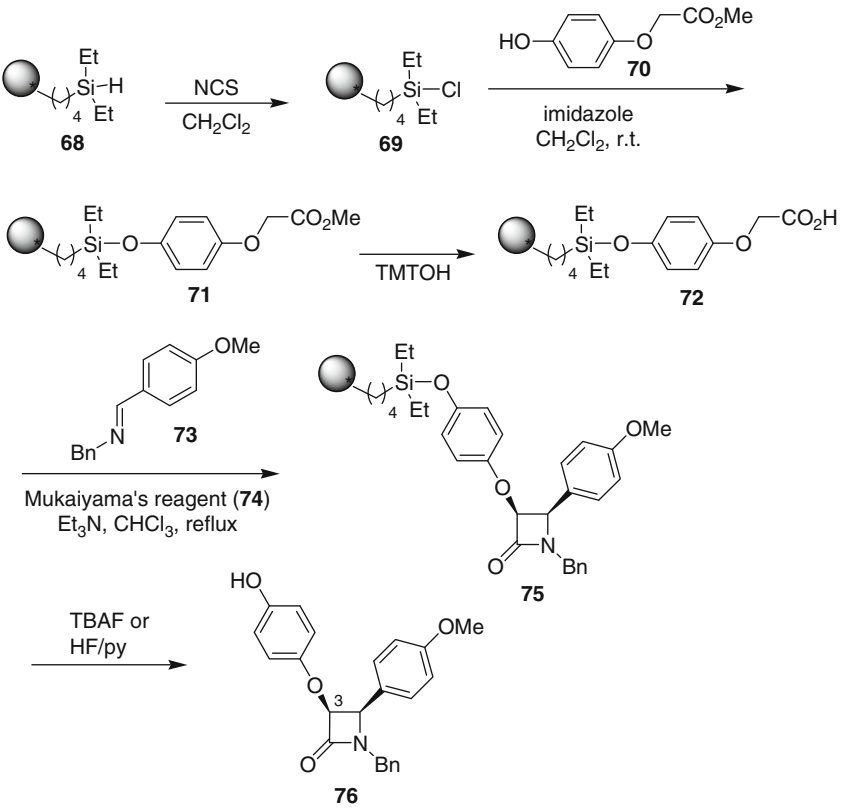
Because of the low yield, the reaction was carried out by using the Wang resin as the polymeric support. The methyl 4-hydroxyphenoxyacetate (**77**) was immobilized to Wang resin under modified Mitsunobu conditions (TMAD, Bu_3P) to yield the



Scheme 19 Synthesis of 3-(Aryl)-alkenyl-β-lactams by olefin cross-Metathesis on solid support

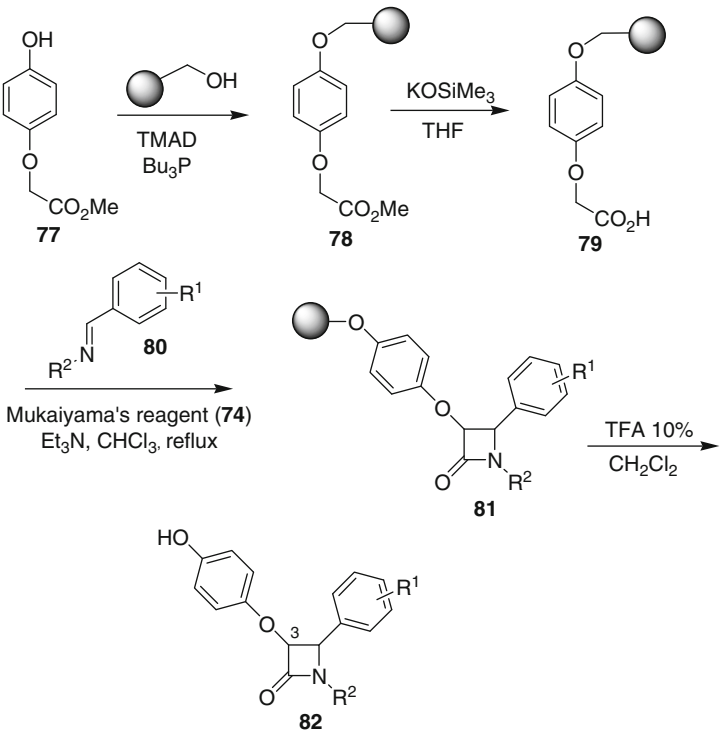
resin-bound ester **78** (Scheme 21). The expected products were obtained in good overall isolated yields for the five reaction steps on solid phase (25–57%). This methodology is based on the Staudinger reaction between an immobilized ketene and different imines. Of the two linkers tested, the Wang resin proved to be better than the diethylsilyloxy linker, allowing an efficient reaction sequence giving good overall isolated yields of the desired β-lactams.

Solid phase synthesis of β-lactams with high degree of chiral selectivity and on a larger scale has been developed by Lectka et al. [118]. The general features of their process are based on a design involving the use of solid-phase reagents and catalysts that constitute the packing of a series of "reaction columns". The assembly designed for this purpose consists of two jacketed columns linked together by a ground glass joint; the top column is packed with a polymer-supported dehydrohalogenating agent that produces analytically pure, extremely reactive ketenes from inexpensive and widely available acid chlorides. The middle column is packed with a nucleophile-based solid-phase asymmetric catalyst. Between the two columns, an imine is added to the system. An optional third column is packed with a scavenger resin to remove any unreacted ketene or imine from the eluent [119]. Several advantages of this column-based technique include: (1) obviating the need to isolate and/or manipulate highly reactive ketenes, (2) separating the different solid-phase components easily, (3) recycling the polymer-supported reagents and catalysts for additional catalytic reactions, and, finally, (4) avoiding vigorous agitation that can degrade resin beads. The well precedented in situ generation of ketenes [36, 120]



Scheme 20 Synthesis of C-3 anchored β-lactam using diethylsilyloxy linker (PS-DES resin)

using triethylamine (or other tertiary amines such as Hünig's base) is problematic because the amine itself catalyzes the cycloaddition of ketene **85** and imino ester **86** [121–123]. Additionally, the by-product hydrochloride salts also interfere with the catalytic, asymmetric reaction [124]. To overcome these difficulties, Lectka et al. employed resin-bound dehydrohalogenation reagents to allow for the simple isolation of the ketene solution under inert atmosphere at reduced temperature. Standard solid-phase bases such as Amberlite IRA-67, a tertiary amine-based polymer, failed to promote ketene formation to any appreciable extent when phenylacetyl chloride in THF was passed through it in a jacketed column at −78°C. However, the extremely basic resin BEMP (Fig. 3) [125], containing a triaminophosphoamide imine bound to a polymeric support, [126] was found to produce ketenes rapidly and quantitatively. At low temperature (−78°C), a solution of phenylketene reacts with the imino ester **86** in the presence of 10 mol% of benzoylquinine (BQ) to afford the desired β-lactam **87** in 65% yield, 98% de, and 96% ee after purification by column chromatography (Schemes 22 and 23) [121–123]. It is significant to note that the length of the catalyst-solid-phase linker is crucial to the success



Scheme 21 Synthesis of C-3 anchored β-lactam using Wang resin

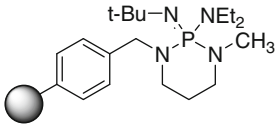
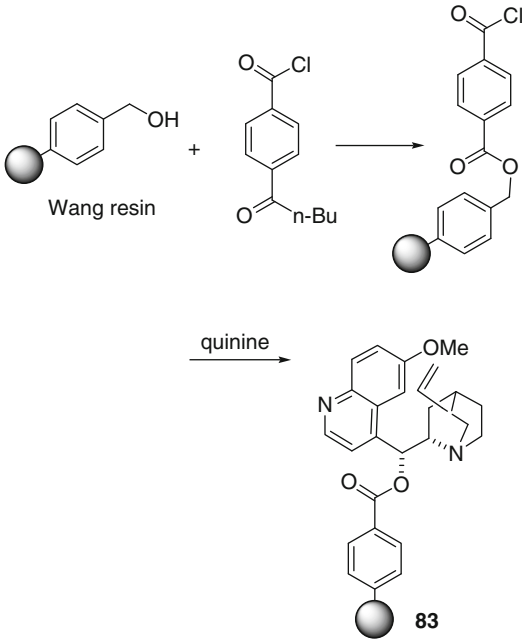


Fig. 3 BEMP Resin

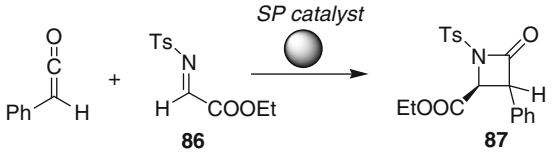
of the reaction; short linkers give inferior results, presumably due to the steric encumbrance of the polymeric support [127, 128]. In the extreme, the reaction has been successfully run through the catalyst column 20 times with no significant loss in stereoselectivity or yield (90% ee and 62% yield for run 20). One can envision practical applications for the synthesis of enantio-pure compounds using this methodology. Reactants can be passed through discrete columns containing recyclable reagents, which upon degradation can be swapped out of the production stream and regenerated. The use of reagents on solid support greatly simplifies the purification of the crude reaction mixture, allowing for shorter production times and thus lower costs under certain circumstances (Fig. 3).

A polymer-supported synthesis of an array of a chirally pure β-lactams in high purity has been demonstrated [129] from a resin-bound chiral oxazolidine aldehyde. Application of resin-bound chiral oxazolidine aldehyde equivalent was explored

Scheme 22 Synthesis of solid-phase chiral catalyst **83**

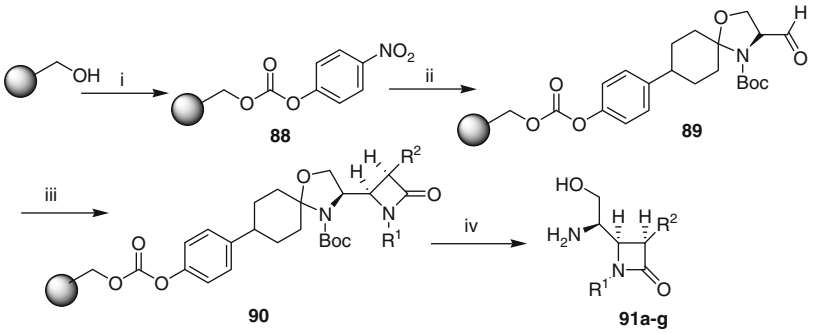


Scheme 23 Synthesis of optically enriched β-lactams through dual solid-phase reagents

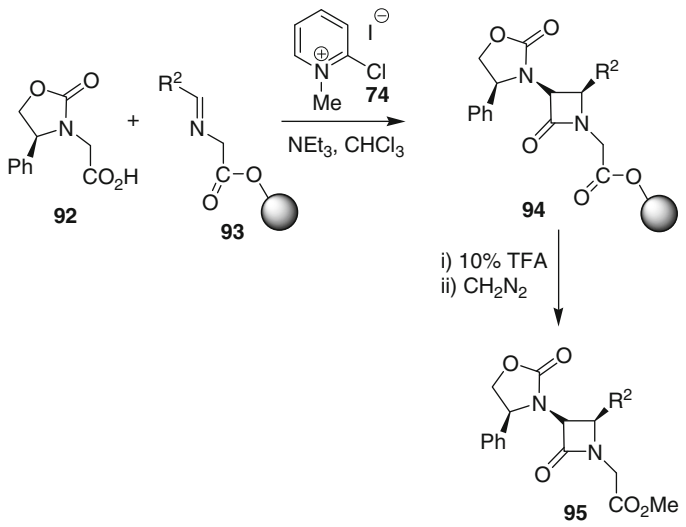


for the synthesis of a small array of β-lactams. The reaction, which is believed to occur via a two-step mechanism, can be controlled exclusively to the generation of β-lactams with *cis* stereochemistry [130]. The aldehyde **89** was thus condensed with four different amines representing varying electronic and steric properties, and the resulting resin-bound imines subsequently underwent cycloaddition with ketenes, which were formed in situ from their corresponding acid chlorides. Finally, the resin-bound β-lactams **90a**-**g** were treated with 10% TFA in DCM to remove the *N*-Boc-protecting group and to cleave the now unstable oxazolidine moiety to unmask the amino alcohol functionality. (Scheme 24)

Asymmetric synthesis on solid support is crucial for the generation of combinatorial libraries of novel optically active carbacephems and other polycyclic β-lactam derivatives [44]. Solid-phase Staudinger reaction of the homochiral

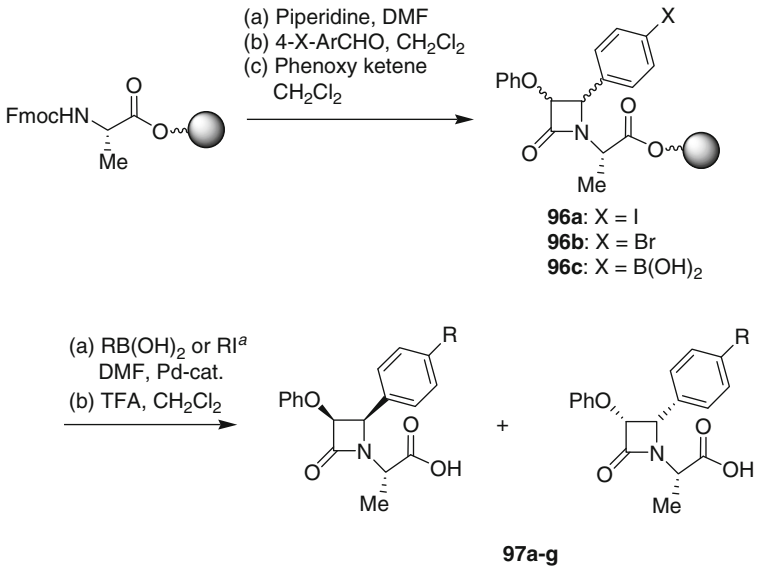


Scheme 24 Application of chiral oxazolidine aldehyde in the synthesis of β-lactam library

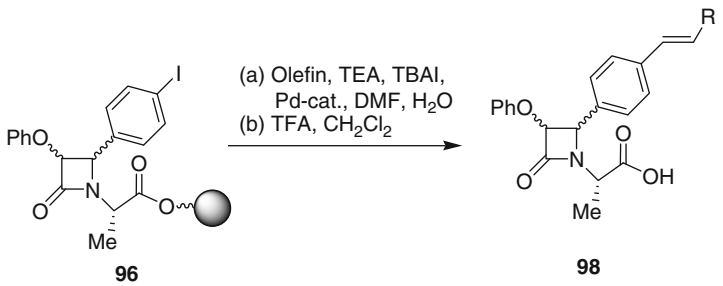


Scheme 25 Synthesis of novel optically active carbacephems

4-phenyloxazolidinylacetic acid **92** [105] with several aldimines, using Mukaiyama's reagent (**74**) as activating agent (Scheme 25) were explored and high diastereoselectivity was observed in all cases.



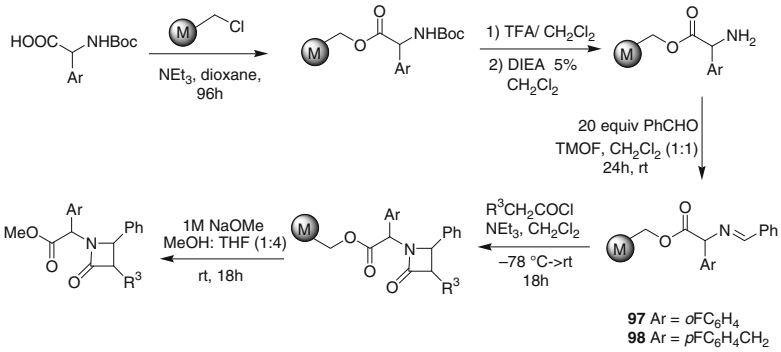
Scheme 26 Synthesis β-lactam and arylation by using Suzuki coupling with aryl boronic acid



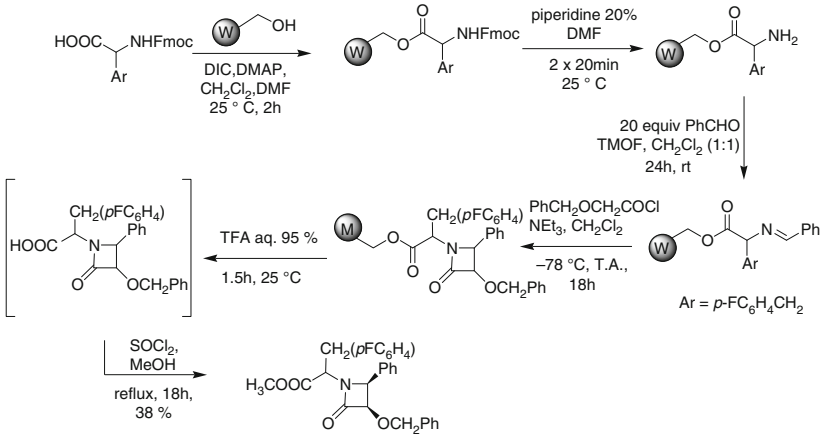
Scheme 27 Synthesis of β-lactam and olefination by Heck coupling reaction

Applications of Suzuki and Heck cross-coupling reactions were adopted by Gallop and coworkers [131] to prepare diverse biaryl- and styryl-substituted β-lactams on solid support. The catalyst system, $[PdCl_2(dppf)]$-TEA, was found to be efficient to promote C–C bond formation around a β-lactam template (Schemes 26 and 27).

Stella et al. [132] considered the use of imines coming from commercially available fluorinated α-amino-acids and applied the following synthetic pathway. The acid function is used to anchor the substrate on a Merrifield or Wang resin and the fluorine atom is used as an analytical probe for the recording of NMR spectra. Thus, each of the chemical products linked to the resin is characterized by a



Scheme 28 Synthesis of β-lactam using Merrifield resin



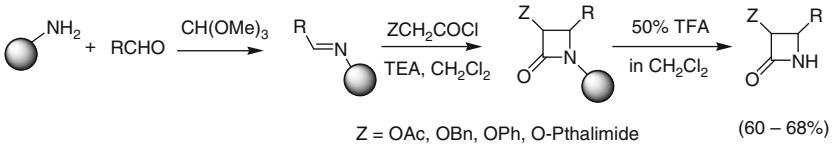
Scheme 29 Synthesis of β-lactam using Wang resin

single ^{19}F NMR-signal while the respective chemical shift value is related to each chemical step according to the close group modifications. Thus, ^{19}F NMR has been used as a simple means to monitor the solid phase synthesis, as shown in schemes 48 and 49 (Schemes 28 and 29).

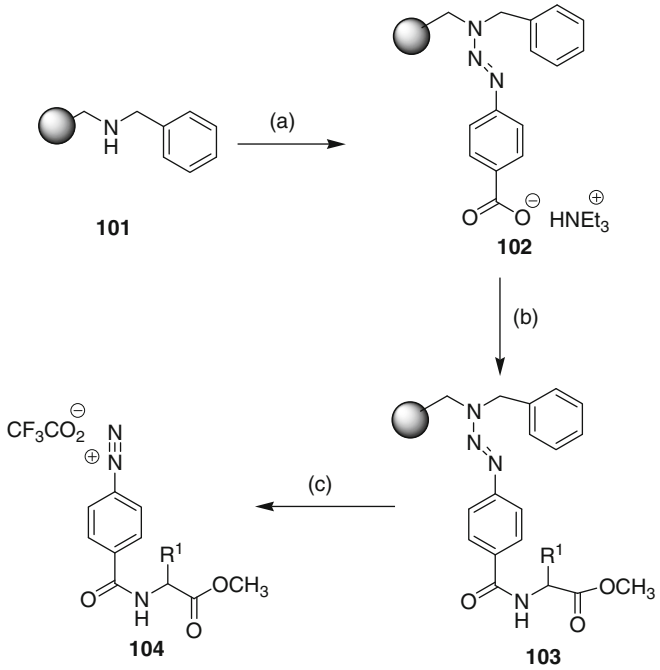
The *N*-unsubstituted β-lactams are important building blocks for the synthesis of several biologically active antibiotics. However, solution phase techniques normally include acidic conditions, which are not tolerable with acid-sensitive functionalities. In an elegant approach, Banik et al. [133] developed a solid phase synthetic route to access *N*-unsubstituted β-lactams directly using Rink resin as the solid support. The method for construction of β-lactam ring was based on Staudinger reaction and subsequent cleavage from the solid support was done with TFA in dichloromethane (Scheme 30).

4 Solid-Phase Synthesis of β-Lactam by Gilman-Speeter Reaction

Schunk and Enders [134] disclosed the first solid-phase synthesis of β-lactams via ester enolate-imine condensation employing an immobilized ester enolate in a simple three-step procedure (Scheme 31). The protocol showed high purity, excellent diastereoselectivity, and good yields of the product. The substrates were attached to the polymer with a T1-triazene linker, which was cleaved traceless. The



Scheme 30 Synthesis of *N*-unsubstituted β-lactam using Rink resin



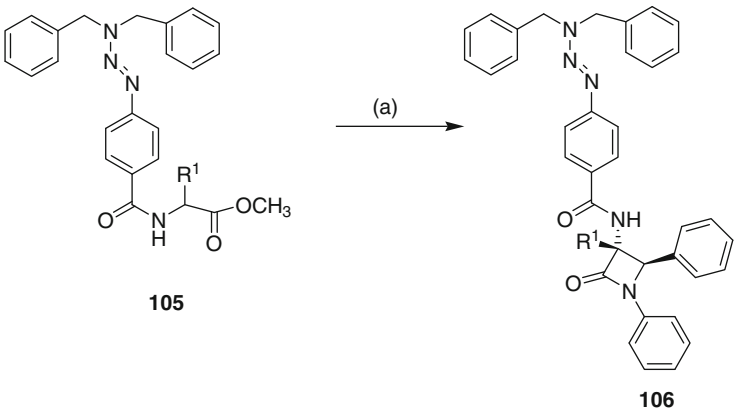
Reagents: (a) *p*-Aminobenzoic acid, $BF_3.Et_2O$, ^tBuONO,THF, -10 °C, 1h; 2. **101**, pyridine/DMF (1:1), rt, 1h; (b) **102**, 3 eq. of amino acid methyl ester.HCl, 2-Chloro-1-methylpyridinium iodide, NEt_3, CH_2Cl_2, rt, 12h; (c) 5% TFA/CH_2Cl_2.

Scheme 31 Preparation of diazonium salt immobilized on T1 triazine linker resin

group is currently employing the established synthesis for the preparation of highly diverse β-lactam libraries.

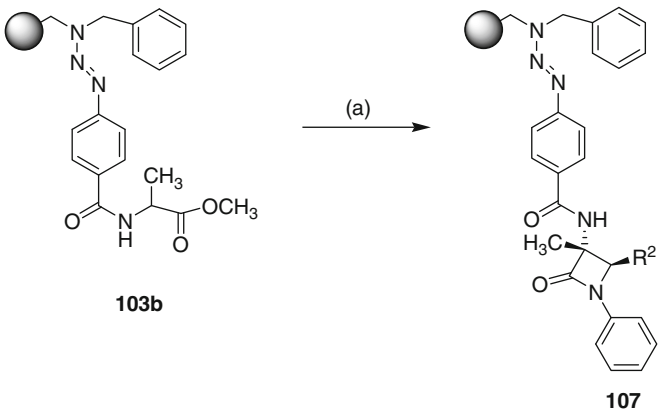
Starting from benzylamine resin **101** via **102** gave ester resins **103** with high loading and excellent purity of the corresponding cleavage products **104**. Treatment of **101** with 4-carboxybenzenediazonium tetrafluoroborate yielded T1-benzoic acid resin **102**. This reaction was carried out under basic conditions, but only pyridine and lutidine were found to be reasonable bases. Other bases, e.g., triethylamine, Huňig's base, DMAP, and *t*-BuOK, resulted in decomposition of the diazonium salt. Several peptide-coupling reagents (e.g., 2-chloro-1-methylpyridinium iodide, *N*-ethyl-*N*′-[3-(dimethylamino)propyl]-carbodiimid hydrochloride/hydroxyl-benzotriazol (EDC/ HOBt), and pentafluorophenyl diphenylphosphinate (FDPP) were tested in the synthesis of resins **103** (step b). Resin **103b** affords diazonium salt **104b** after treatment with 5% TFA/CH_2Cl_2. To obtain pure cleavage products **104**, the triazene formation reaction (step a) had to be carried out at room temperature. Lower temperatures resulted in lower purity of **104** and lower loading of **103**. The ester enolate-imine condensation was initially tested in the liquid phase (Scheme 32) on model compound **105**. This reaction gave β-lactam **106** in 71% yield having *trans*-configuration. The base, LiHMDS, was found to give best results for the generation of dianion.

The liquid-phase reaction conditions were followed on the solid phase (Scheme 33) without any problems. It is most probable that the reaction proceeds, as in liquid phase, via a dianion [135]. The condensation reaction of **103b** was carried out with a range of imines, all of which gave very good results concerning loading of the lactam resin **107** and purity of the cleaved diazonium salt **108** (Scheme 34). Conditions published to date [136] for traceless cleavage from a



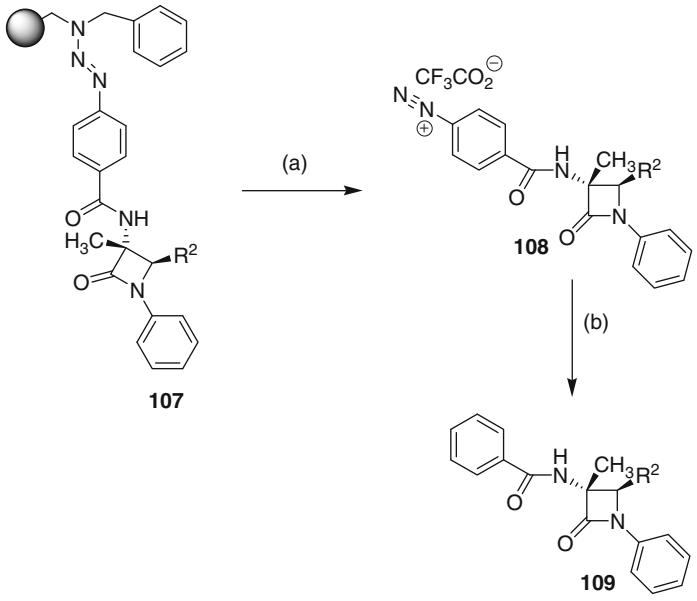
(a) 1. 2.2 eq. of LiHMDS, THF, -78 °C, 20 min;
2.3 eq, of PhCH=NPh, -78 °C to rt, 23h; 3. H_2O

Scheme 32 T1 triazine linker resin for β-lactam synthesis



(a) 1. 2.2 eq. of LiHMDS, THF, -78 °C,1.5h min;
2. 3 eq, of $R^2CH=NPh$, -78 °C to rt, 23h; 3. H_2O

Scheme 33 T1 triazine linker resin for substituted β-lactam synthesis



(a) 5% TFA/CH_2Cl_2; (b) THF/DMF (5/2), 60 °C, 15 min.

Scheme 34 Removal of T1 triazine linker resin after the synthesis of substituted β-lactam

T1-triazene linker resulted in decomposition of the sensitive β-lactams. The relative configuration of β-lactams, was determined by NOE experiments to be the *trans*-configuration as observed in solution-phase synthesis [137].

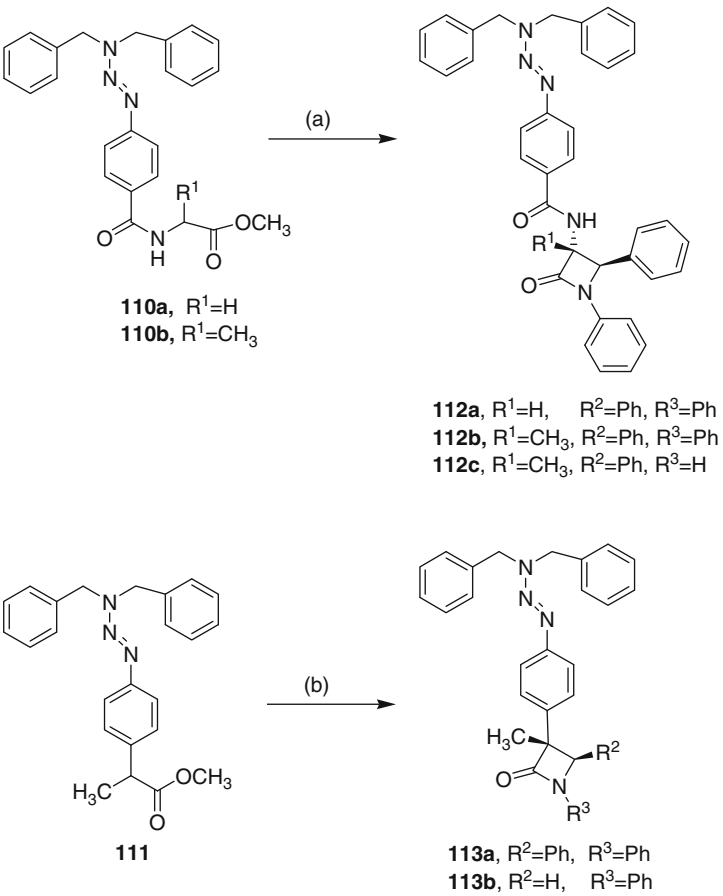
Employing an immobilized ester-enolate moiety Schunk and Enders [138] reported the solid-phase synthesis of diverse monocyclic β-lactams via the ester-enolate imine condensation route. The ester-enolate imine condensation route is a readily developed synthetic methodology for the preparation of β-lactams [69, 139, 140]. However, the main advantage of this approach, from a solid-phase chemists' point of view, is the wide variety of easily available imines and its precursors, which might allow variation of every position of the azetidin-2-one ring [135, 141–144]. The ester-enolate was immobilized by a triazene linker system and found stable under the required basic conditions [136, 145]. The linker paves the way for introduction of a variety of functionalities by applying different cleavage procedures [146]. Monocyclic β-lactams were obtained in good purities after simple workup. Although the method does not provide all desired substitution patterns, it is a versatile tool for the preparation of diverse β-lactam libraries.

The possibility of the triazene linking system for the ester-enolate imine condensation was initially investigated on model compounds **110** and **111** (Scheme 35). Dibenzyltriazene **110** was used as a model compound for monobactam derivatives and prepared by diazotization of hippuric acid methyl ester. Dibenzyltriazene **111** was used as a model compound for 3-phenyl-substituted azetidin-2-ones and prepared by diazotization of 2-(4-aminophenyl)-propionic acid methyl ester and conversion with dibenzylamine in 64% overall yield. The low yields of *N*-unsubstituted lactams, during the model studies, hint at a problematic *trans*fer to solid support.

The triazene linker can be used for the immobilization of aromatic diazonium salts, and therefore for aromatic amines, but not for aliphatic amines due to the instability of their diazonium salts. Cleavage of the linker can be achieved under mild acidic conditions to yield the benzylamine resin and the corresponding diazonium salt [136, 145, 146]. The main difference between the preparation of triazenes in solution and triazenes on solid support is the respective amine, namely bisbenzylamine and polymer-supported benzylamine **114**. In solution, it was used in excess to quench unstable diazonium salts and force the reaction to completion. In the solid-phase approach it was immobilized and cannot be used in excess with respect to low loadings. A simple three-step procedure (Scheme 36) starting from benzylamine resin **114** via carboxylate **115** led to the successful preparation of ester resins **116** in essentially higher loadings. Treatment of resin **114** with 4-carboxybenzene diazonium tetrafluoroborate yielded benzoic acid resin **115**.

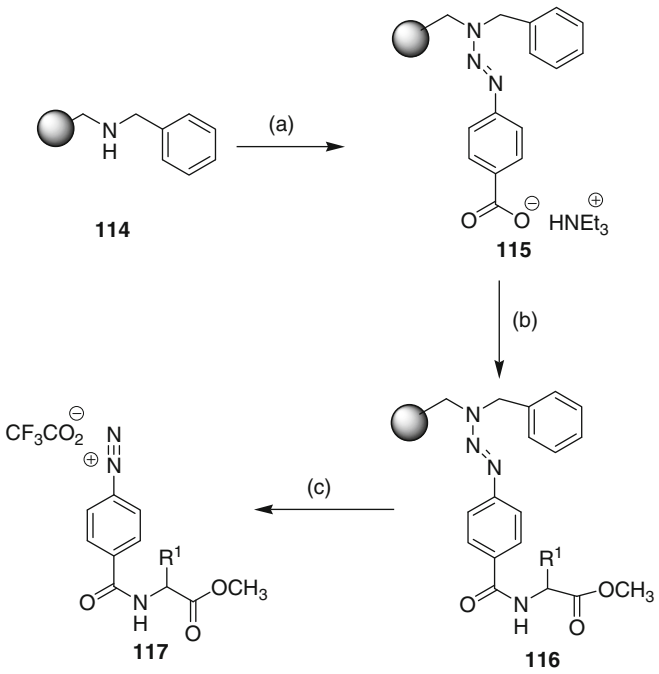
Larger amounts of pyridine drastically enhanced the coupling reaction and loading of **118**, but also led to an increased formation of Japp-Klingemann type by-products **120**. Several procedures to transform the diazonium salts into traceless products were explored before the formation of pure β-lactams. The best conditions for traceless cleavage turned out to be simplified Keumi conditions [147]. (Scheme 37–38)

1,4-Bisaryl β-Lactams. The liquid-phase reaction conditions were employed for the preparation of monobactam like 1,4-bisaryl β-lactams in solid-phase system (Scheme 39) without any difficulties. It was believed that the reaction pathway proceeds via dianion, as in the liquid phase.



Scheme 35 Use of T1 triazine linker for solid phase synthesis of β-lactam

1,4-Bisaryl β-Lactams (125). The preparation of 4-phenyl-substituted β-lactams **127** on the solid phase was performed in an analogous manner, beginning with the bisarylimines (Scheme 40). Excellent results have been obtained concerning loading of the lactam resins **125** and purity of the cleaved diazonium salts **126.** 1,4-Bisaryl β-lactams **127** obtained by traceless cleavage were easily separated from the by-products by dissolving in Et_2O/*n*-pentane and eluting through silica gel. Nine different β-lactams **127** were prepared in reasonable to high purities (68–98%), medium to high diastereomeric excesses (48–96%), and reasonable to good yields (35–92%).



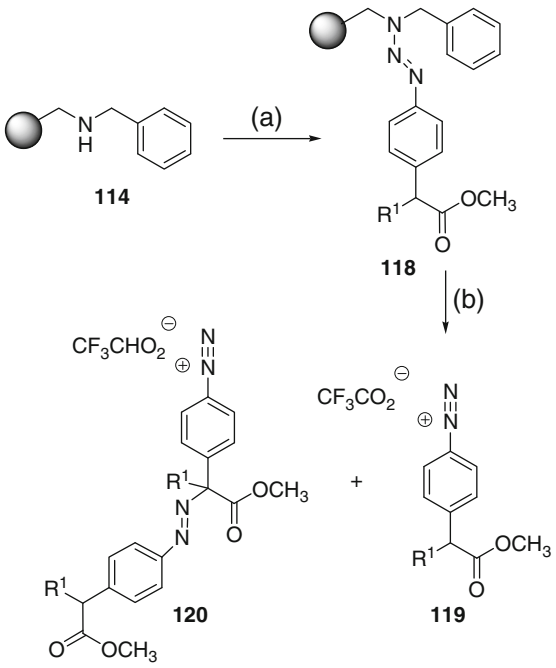
Reagents: (a) (1) 5 eq. of p-aminobenzoic acid, 10 eq. of $BF_3.Et_2O$, 10 eq. of ^tBuONO, THF, -10 °C, 1h **114,** pyridine/DMF (1:1), rt, 1h; (b) **111**, 3 eq. of amino acid methyl ester.HCl, 2 eq. of 2-Chloro-1-methylpyridinium iodide, 20 eq. of NEt_3, CH_2Cl_2, rt, 12h; (c) 5% TFA/CH_2Cl_2.

Scheme 36 Use of T1 triazine linker for solid phase synthesis

Keeping in view the biological and synthetic importance of the β-lactams and the potential of solvent-free microwave chemistry, Kidwai et al. [148] prepared β-lactams via an ester-imine based synthesis under solvent-free microwave irradiation. The *trans*-4-aminocyclohexanol **(128)** was condensed with different aromatic aldehyde to give the respective Schiff base. The Schiff-base was then reacted with ethyl α-mercapto/α-cyano acetate, in the presence of basic alumina, to afford the required 3-mercapto/cyano β-lactams respectively, outlined in Scheme 41.

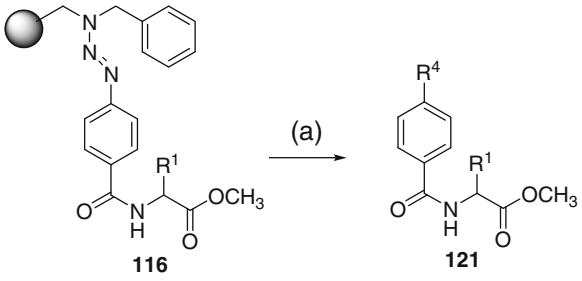
5 Solid-Phase Synthesis of β-Lactams by Miller's Hydroxamate Approach

On the basis of the Miller approach, Meloni and Taddei synthesized β-lactams on solid phase starting from serine, threonine, or other β-hydroxyacids derived from naturally occurring amino acids and a resin-bound hydroxylamine [149]. The ring-



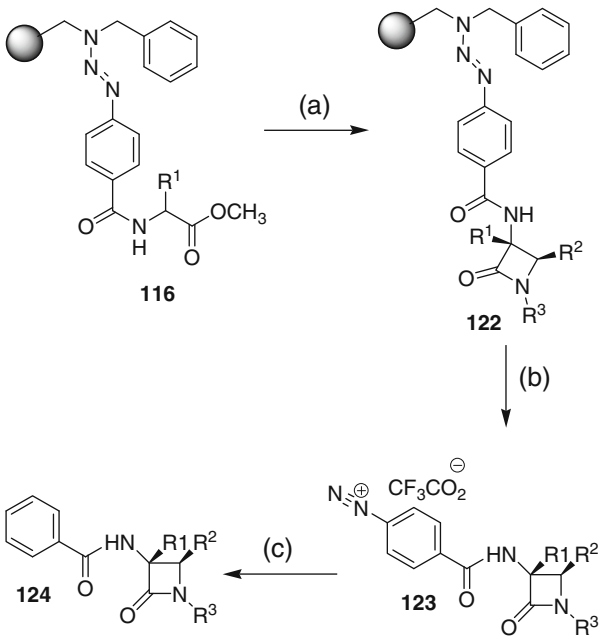
Reagents and conditions: (a) (1) 2-(4-Aminophenyl)propionic acid methyl ester (6 equiv), $BF_3.Et_2O$ (12 equiv), isoamylnitrite (12 equiv), THF, -10 °C, 1 h. (2) 6 (1equiv), pyridine (6 equiv), THF, -10 °C, add diazonium salt (3 equiv), -5 °C, 25 min. (3) filtration of resin under argon, wash with dry THF (x1), suspend in dry THF, repeat step 2.
(b) 5% TFA in CH_2Cl_2.

Scheme 37 Use of T1 triazine linker for solid phase synthesis



Reagents and conditions: (a) 5%TFA in CH_2Cl_2.

Scheme 38 Use of T1 triazine linker for solid phase synthesis

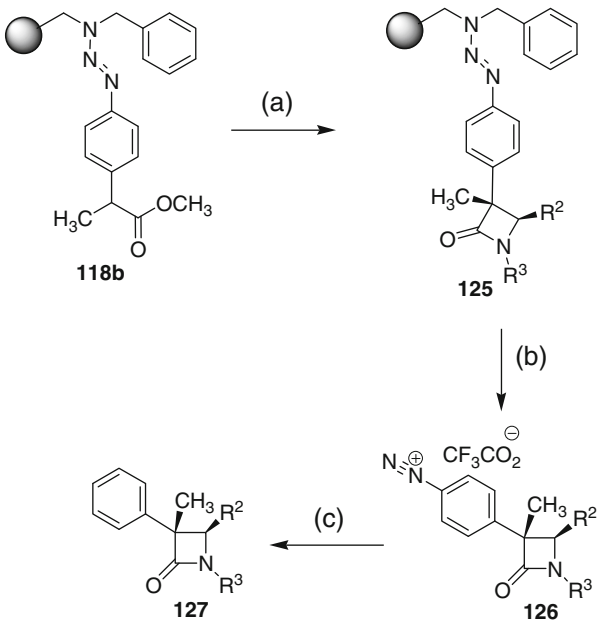


Reagents and conditions: (a) (1) LiHMDS (2.2 equiv), THF, -78 °C, 1.5h. (2) $R^2CH{=}NR^3$ (3 equiv.), THF, -78 °C to room temperature, 23h. (3) H_2O. (b) (1) 5%TFA in CH_2Cl_2. (c) THF/DMF (5:2), 60 °C, 15 min.

Scheme 39 Use of T1 triazine linker for solid phase synthesis

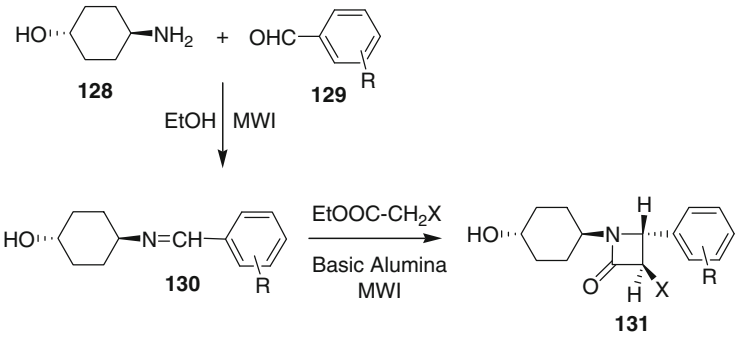
closure was carried out under Mitsunobu conditions. The amino group present on the β-lactam was used to assemble a short peptide. After a reductive cleavage with SmI_2, β-lactam-containing peptides were obtained. They have claimed the first example of Miller hydroxamate synthesis of β-lactams [150] carried out on solid phase.

The strategy was chosen to: (1) link the amino acid derivative to a polystyrene-supported hydroxylamine, (2) carry out the cyclization under Mitsunobu conditions, and (3) assemble a short peptide on the free amino group present in the ring. This approach has been shown to be suitable particularly for solid-phase synthesis, as the supported β-lactam could be easily separated from the by-products of the Mitsunobu reaction. The linker employed was a polystyrene resin carrying *O*-trityl-hydroxylamine linker, prepared according to the literature procedure [151]. After the deprotection of Fmoc group carried out with 20% piperidine in DMF, the L-cbz-serine (or L-cbz-threonine) was coupled using (4,6-Dimethoxy-[1, 3, 5]-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) [152] in *N*-methylpyrrolidone (NMP) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) (Schemes 42–45).



Reagents and conditions: (a) (1) LiHMDS (1.5 equiv), THF, -78 °C, 1.5h. (2) $R^2CH{=}NR^3$ (3 equiv.), THF, -78 °C to room temperature, 23h. (3) H_2O. (b) (1) 5% TFA in CH_2Cl_2. (c) THF/DMF (5:2), 60 °C, 15 min.

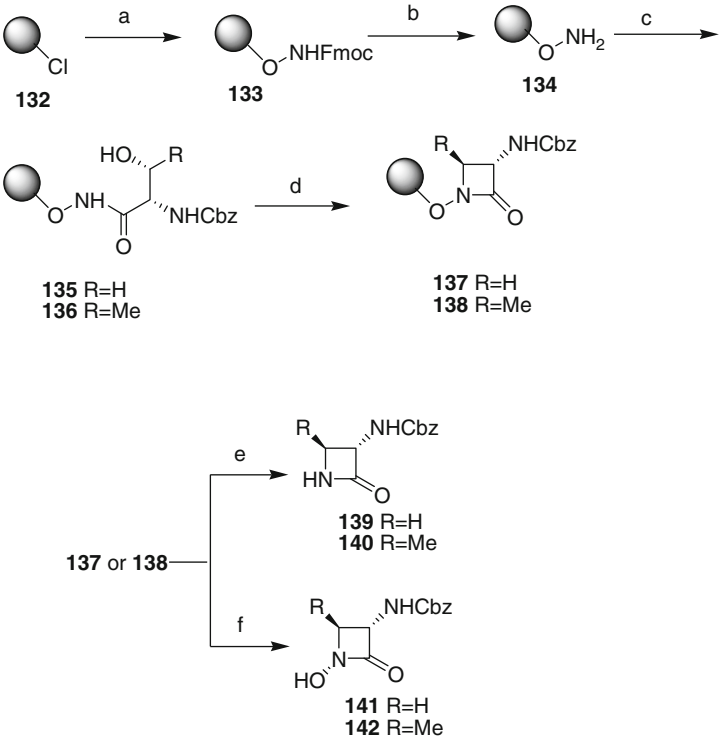
Scheme 40 Use of T1 triazine linker for solid phase synthesis



Scheme 41 Synthesis of β-lactam on basic alumina surface under microwave irradiation

6 Other Solid-Phase Synthetic Approaches to β-Lactams

The chemistry of carbonylation has long been known and widely applied in organic synthesis as a convenient, versatile, and powerful method [153–205]. Recently, Lu and Alper [206] investigated the catalytic efficiency of dendrimer-supported

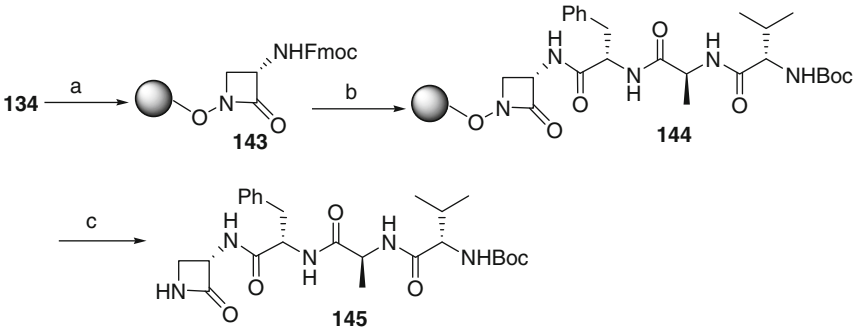


a) FmocNHOH, 2eq. DIPEA, rt, 48h.b) piperidine,DMF, rt, 20min.
c) (L)-Cbz-Ser-OH or (L)-Cbz-Thr-OH, 4eq. DMTMM, 4eq. DIPEA, NMP,rt, 12h.d) 5eq. DEAD, 10eq. PPh3, THF, rt, 24h.e) SmI_2 0.1M in THF, rt,4h.f) 5%TFA in CH_2Cl_2, rt

Scheme 42 β-Lactams on solid phase using the *Miller's hydroxamate approach*

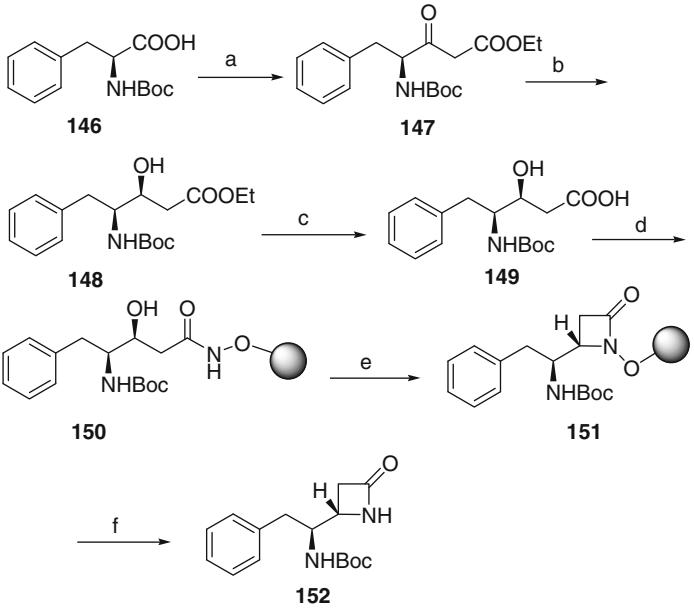
Rh-complexes in carbonylative ring expansion reactions of a variety of aziridines with carbon monoxide, which resulted in the formation of β-lactams in good yields. It was reported that the catalytic system could be easily recovered by simple filtration and recycled without significant loss of activity.

The first account on the carbonylation of heterocyclic compounds with metallo-dendrimers was recently reported by Lu and Alper using Rh-complexed dendrimers on a resin [207]. The building-block techniques of solid-phase chemistry were used to synthesize dendrimers, followed by phosphonation of the dendrimers with diphenylphosphinomethanol. The resulting phosphonated dendrimers were then reacted with chloro(dicarbonyl)rhodium(I) dimer to give dendritic catalysts **A** and **B** (^{31}P NMR, $\delta = 25$ ppm; loading of rhodium: **A**, 0.74 mmol g^{-1}; **B**, 0.83 mmol g^{-1}). As a model study, the reaction of 1-*tert*-butyl-2-phenylaziridine with carbon monoxide in catalytic presence of **A** afforded the desired β-lactam



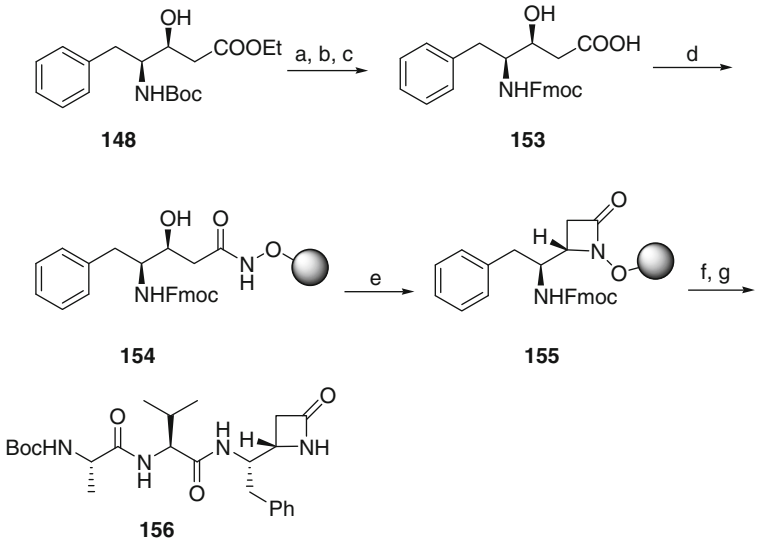
(a) N-Fmoc-Ser-OH, DMTMM, NMM, NMP, rt, 4 h followed by DEAD, PPh_3, THF, rt, 24 h. (b) Fmoc deprotections with 25% piperidine in DMF followed by couplings using DMTMM in NMP with N-Fmoc-Phe-OH; N-Fmoc-Ala-OH, and N-Boc-Val-OH. (c) SmI_2 0.1 M in THF, rt, 4 h.

Scheme 43 Solid phase synthesis of β-lactam tetrapeptide



(a) CDI, THF, rt, 24 h followed by EtAc/LDA in THF, -78 °C, 1 h. (b) TiCl4 in CH_2Cl_2, 30 min, followed by BH_3.Py, -78°C, 1 h. (c) LiOH, THF/H_2O, 24 h, followed by aqueous citric acid. (d) **134**, NMP, DMTMM, NMM, 2 h. (e) DEAD, uiv PPh_3, THF, rt, 24 h. (f) SmI_2 0.1 M in THF, rt, 4 h.

Scheme 44 Application of Mitsonobu reaction and use of SmI_2 for detachment



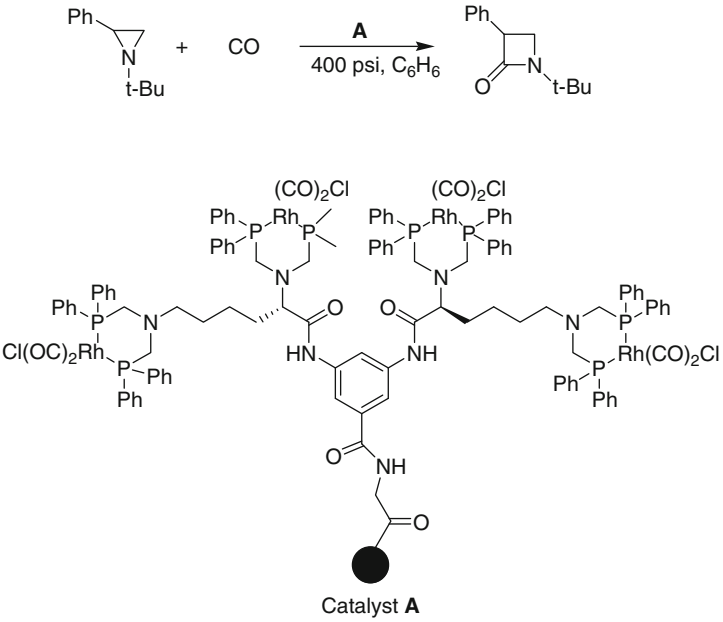
(a) LiOH, THF/H_2O, 24h. (b) HCOOH (assolvent), rt, 6h. (c) Fmoc-Cl, Na_2CO_3, dioxane/water, rt, 12h. (d) **134** , NMP, DMTMM, NMM, 2h. (e) 5 equiv of DEAD, 10 equiv of PPh_3, THF, rt, 24h. (f) Series of Fmoc deprotections with 25% piperidine in DMF followed by couplings using DMTMM in NMP with *N*-Fmoc-Val-OH and *N*-Boc-Ala-OH. (g) SmI_2 0.1 M in THF, rt, 4h.

Scheme 45 Application of Mitsunobu reaction in solid phase synthesis of β-lactam

(Schemes 46 and 47). Variation of the Rh-complexed dendrimers **A** to **B** and generalization with a range of aziridines constituted a generalized and attractive methodology for solid phase β-lactam synthesis.

Chmielewski et al. [208] described a new resin-based chemistry for the straightforward construction of 1-oxacephams, which represent a class of compounds with potential biological activity [209]. The synthetic strategy, outlined in Scheme 48, began with commercially available Wang resin **157** utilizing the cyclization/cleavage approach. The 1-oxacephams **169** and **170** were obtained in good overall yield and high diastereomeric purity was obtained by the cyclization/cleavage step from the corresponding resins **167** or **168** with $BF_3.Et_2O$ in CH_2Cl_2. The good yield and purity of the products, and simple procedure for both reaction sequences make this a very attractive method for the synthesis of 1-oxacephams.

Mata et al. also described a new and robust protocol for the solid-phase synthesis of 2β-methyl substituted penam derivatives using Merrifield resin as support [210]. The work begins with immobilization of 6,6-dibromopenicillanic acid (**171**) onto Merrifield resin followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) to obtain the resin-bound sulfoxide (**173**). The key-step involves the thermal rearrangement of the corresponding penicillin sulfoxide (Scheme 49).

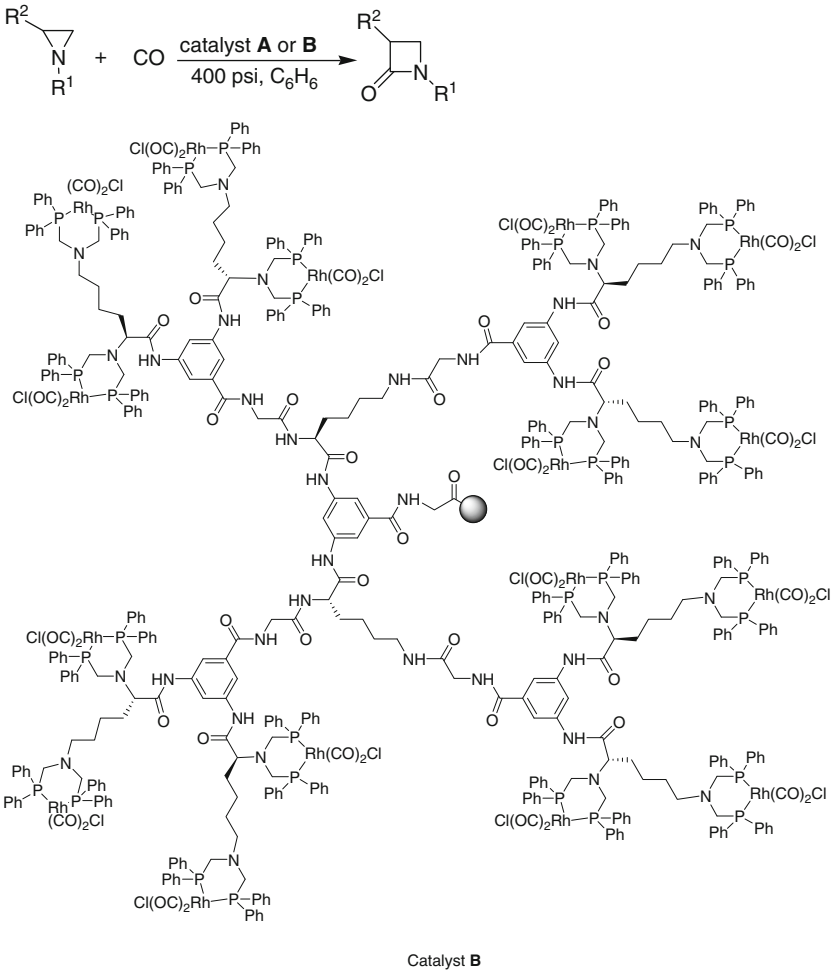


Scheme 46 Carbonylative ring expansion of 1-*tert*-Butyl-2-phenylaziridine using Rh-complexed dendrimers

An efficient and convenient solid-phase method for the synthesis of 2β-methyl substituted penicillins using commercially available resins was developed by Mata et al. [211]. Functionalization of the Merrifield and Wang resin bound penam derivatives was performed by penicillin sulfoxide rearrangement and the products were released from the supports under mild conditions. Merrifield (**178**) and Wang (**179**) resins were selected as polymer supports for the immobilization of penicillins and it was found that both could be used to tether the 6,6-dibromopenicillanic acid (**177**) starting material. However, potassium fluoride in DMF or DCC with catalytic amount of DMAP was used respectively for coupling with resins. The Merrifield resin-bound penicillin **180(M)** and the Wang resin-bound compound **180(W)** were then subjected to solid phase oxidation using *m*-chloroperbenzoic acid followed by mild cleavage conditions, such as $AlCl_3$ and 10% trifluoroacetic acid (Schemes 50 and 51).

Synthesis of thietane-fused β-lactam was reported by Sakamoto et al. [212] involving solid-state photoreaction of *N*-(α,β-unsaturated carbonyl) thiobenzanilide demonstrating a single-step photochemical route to β-lactam, as outlined in Scheme 52.

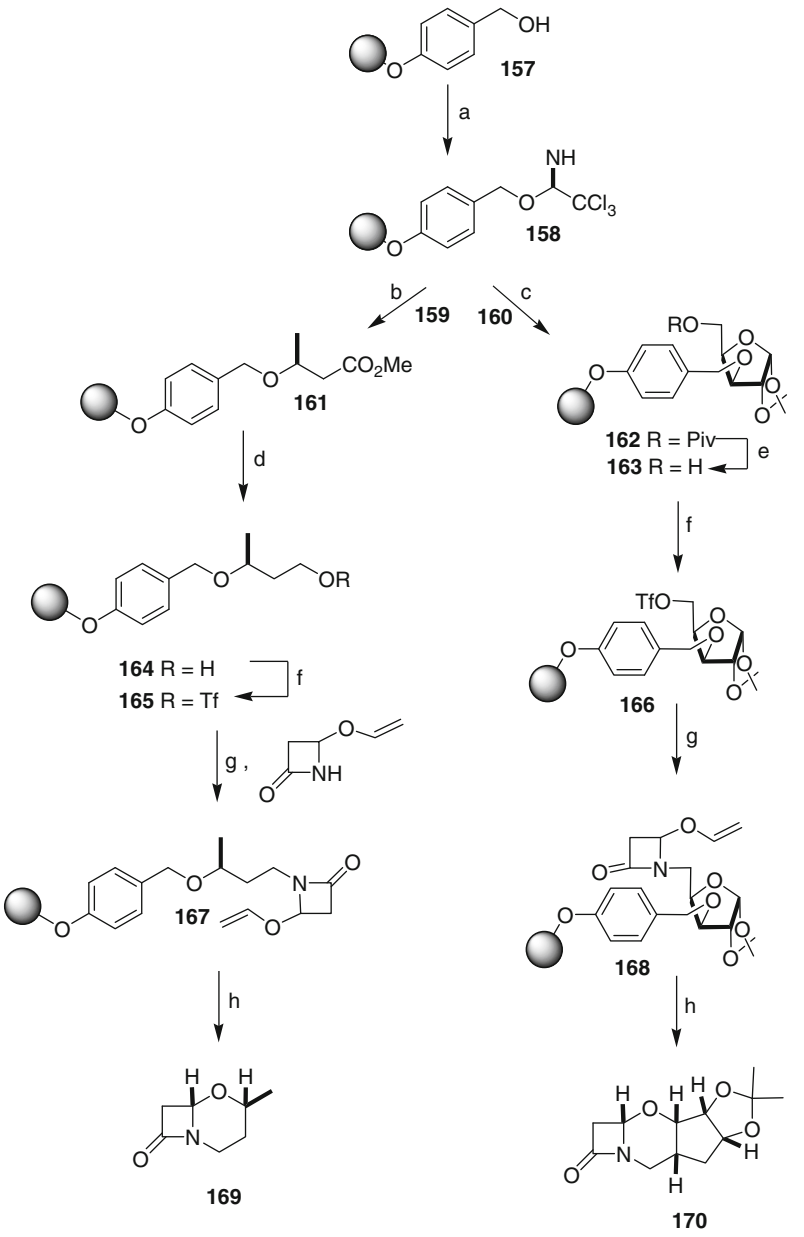
A series of piperidine containing *N*1 activated C4-carboxy azetidinone tryptase inhibitors was prepared by Sutton et al. [213] adopting solid-phase technology. Wang resin was used to attach with the carboxyl group of the β-lactam moiety and removal from the resin surface was achieved as usually by 20% TFA in CH_2Cl_2.



Scheme 47 Carbonylative ring expansion of aziridines using Rh-complexed dendrimers

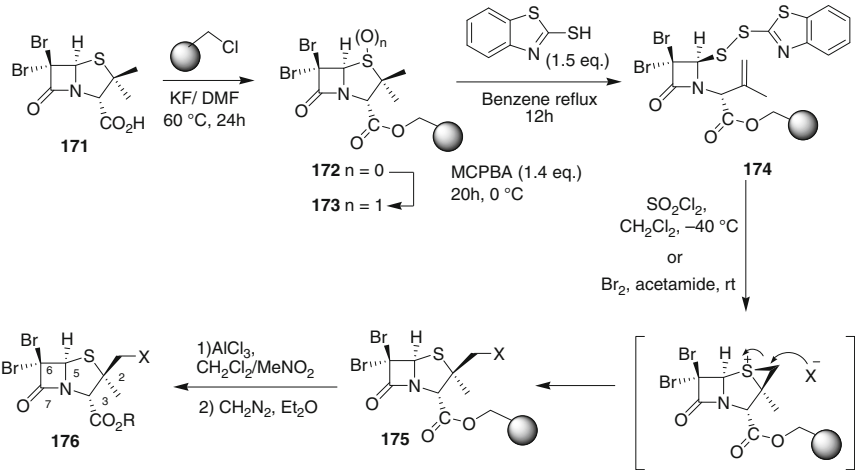
The preparation of the azetidinone core and the coupling to resin is outlined in Scheme 53.

The first expeditious solid-phase procedure for the preparation of optically active quaternary *cis*-β-lactams with an innovative substitution pattern is reported by González-Muñiz et al. [214]. They describe an operationally simple four-step procedure for the solid-phase synthesis of chiral (3*S*,4*S*)-1,3,4,4-tetrasubstituted β-lactams. Taking into account the recurrence of 1,3,4-trisubstituted pattern in bioactive monocyclic β-lactams, the development of an environment friendly method for the synthesis of this 1,3,4,4-analogues may be of major interest. The key step to the four-member ring formation is the enantioselective phosphazene base-assisted cyclization of the resin-bound *N*-(alkyl)-*N*-[(*S*)-2-chloropropionyl]

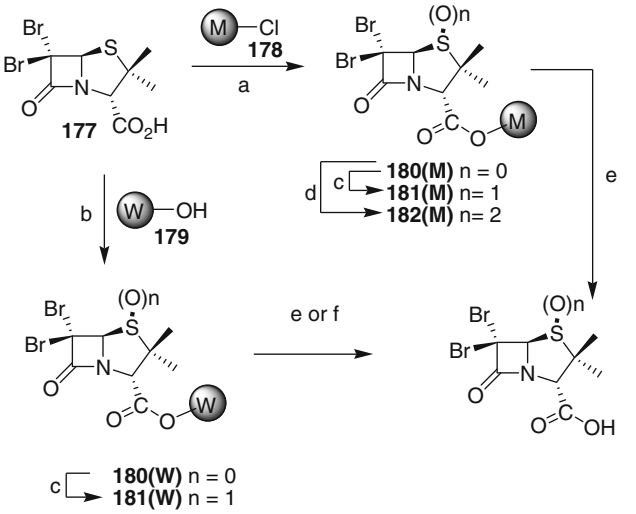


a)CCl_3CN, DBU, CH_2Cl_2 , 20 °C, 3 h; b) methyl (S)-3-hydroxybutyrate (**159**), $BF_3.Et_2O$, CH_2Cl_2/cyclohexane 1/1, 20 °C, 5 min; c) 1,2-O-isopropylidene-5-O-pivaloyl-a-d-xylofuranose (**160**), $BF_3.Et_2O$, CH_2Cl_2/cyclohexane 1/1, 20 °C, 5 min; d) DIBAL-H, THF, 20 °C, 4 h; e) MeONa, MeOH, 20 °C, 2 h; f) Tf2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h; g) nBuLi, Bu_4NHSO_4, THF, -70 °C- 20 °C, 12 h; h) $BF_3.Et_2O$, CH_2Cl_2, 20 °C, 3 h. Piv.=pivaloyl, DBU.=1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H.=diisobutylaluminum hydride.

Scheme 48 Solid-phase synthesis of 1-oxacephams



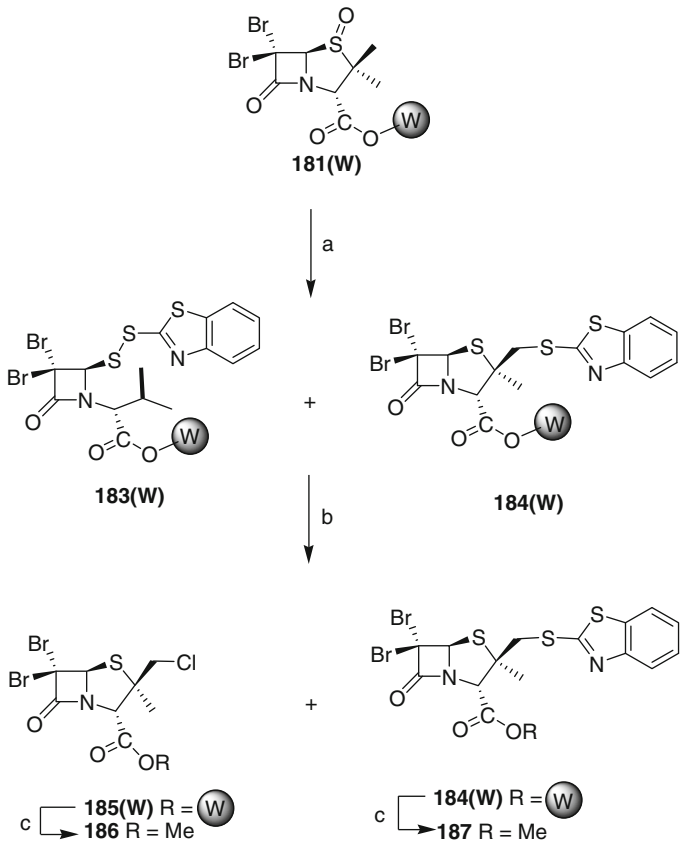
Scheme 49 Solid-phase synthesis of 2-β-methyl substituted penam derivatives



(a) 3, KF, DMF, 60 °C, 24 h; (b)**179**, DCC, DMAP (cat.), CH_2Cl_2–DMF, r.t., 4 h; (c) MCPBA (1.4equiv), CH_2Cl_2, 0 °C, 20 h; (d) MCPBA (5 equiv), CH_2Cl_2, r.t., 96 h; (e) $AlCl_3$, $CH_2Cl_2/MeNO_2$, 0 °C, 30 min; (f) 10% TFA in CH_2Cl_2, r.t., 30 min.

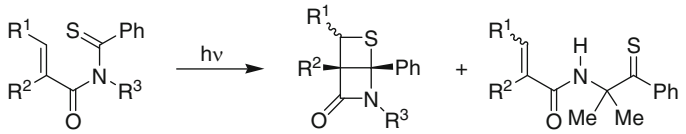
Scheme 50 Solid phase synthesis of penicillin using Merrifield resin and Wang resin

amino acid derivatives. The route does not require any chiral auxiliary or catalyst, since the high enantioselectivity which is obtained is solely directed by the configuration of 2-chloroalkanoyl substituent. This also permits different configurations of



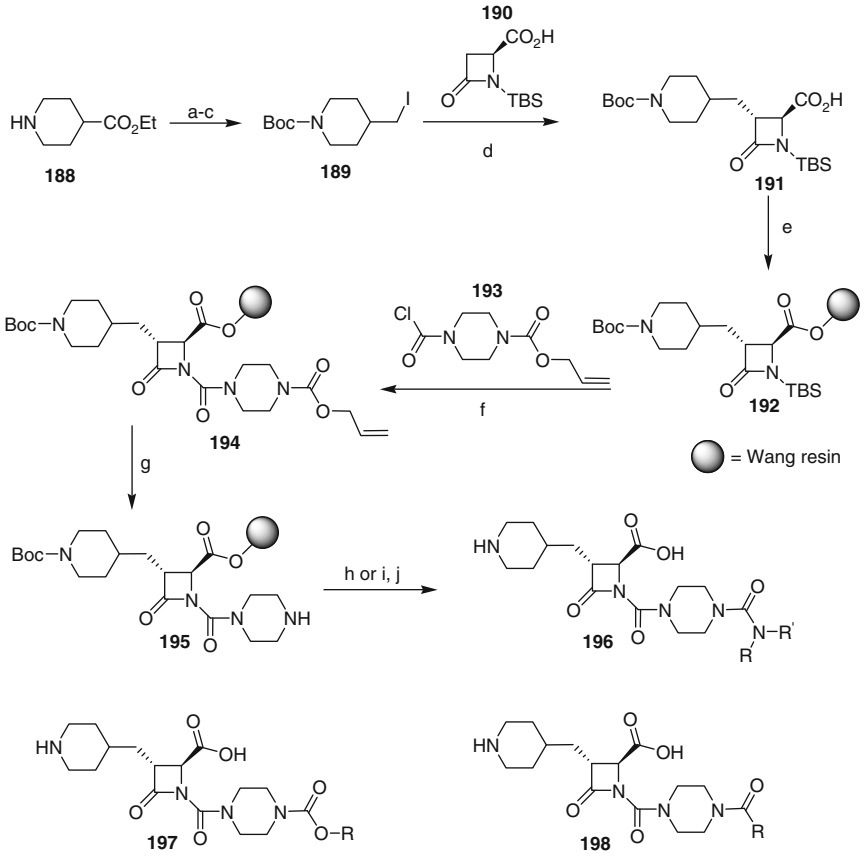
(a) 2-MBT (4 equiv), toluene, reflux, 4 h; (b) Cl_2SO_2, CH_2Cl_2,–40 °C;
(c) (i) 10% TFA in CH_2Cl_2, r.t., 30 min; (ii) CH_2N_2, Et_2O.

Scheme 51 Solid phase synthesis of penicillin using Wang resin



Scheme 52 Synthesis of thietane-fused β-lactam

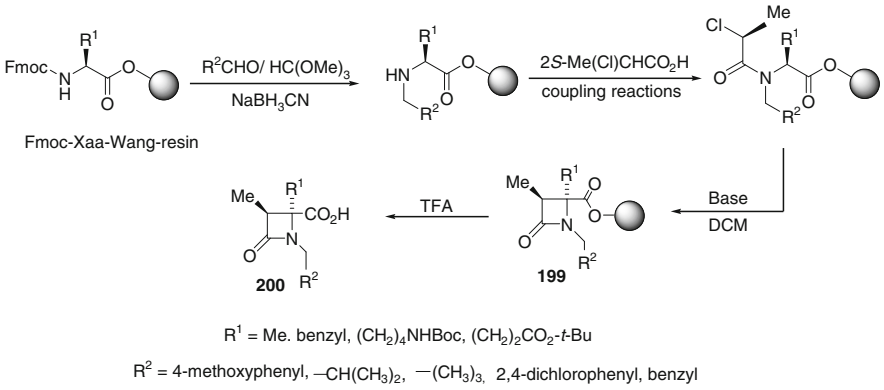
the final β-lactam just by changing the configuration of the 2-chloroalkyl carboxylic acid incorporated in second step. This procedure is highly notable compared to other approaches for the synthesis of highly substituted β-lactams (Scheme 54).



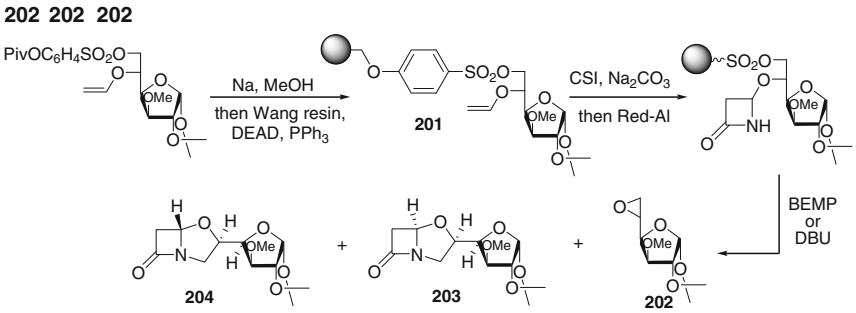
(a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 98%; (b) LiAlH4, THF, 0 °C, 94%; (c) (i) Ph_3P, imidazole, CH_2Cl_2, (ii) I_2, 0 °C, 74%; (d) (i) LDA, THF, -78 to -20 °C, (ii) add compound 7, -78 to -20 °C, 43%; (e) WangResin, MSNT (1-mesitylene-2 sulfonyl)-3-nitro- 1H-1,2,4-triazole), N-methyl-imidazole, CH_2Cl_2, THF; (f) compound 5, Et_3N, DMAP, CH_2Cl_2; (g) $Pd(Ph_3P)_4$, $PhSiH_3$, CH_2Cl_2; (h) isocyanate or chloroformate, Et_3N, DMAP, CH_2Cl_2; (i) carboxylic acid, DIC, HOAT, CH_2Cl_2–dimethylacetamide (1:1); (j) 20% TFA in CH_2Cl_2.

Scheme 53 Preparation of *N*1 activated C4-carboxy azetidinone tryptase inhibitors using Wang resin

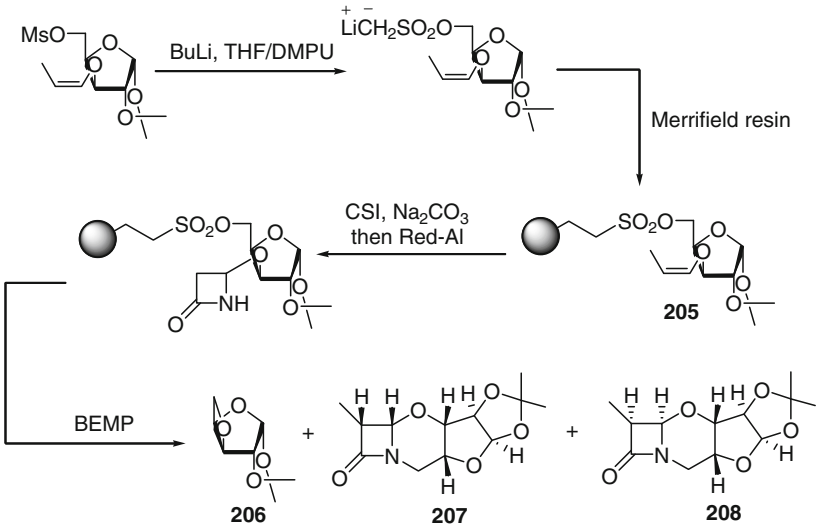
A survey of the literature reports regarding the synthesis of β-lactam using carbohydrate precursors has recently been published by Furman et al. [215]. They have shown that the carbohydrates were used either as chiral tools or chiral auxiliaries. A few solid phase approaches have been outlined in the survey using the vinyl ether bound to the polymeric support through a sulfonyl linker. Two alternative modes of attachment of the vinyl ethers to the resin have been reported.



Scheme 54 A solid-phase synthetic approach showing diversity incorporated at R^1 and R^2



Scheme 55 Vinyl ether linked through Wang resin followed by cleavage to yield β-lactam



Scheme 56 Vinyl ether linked through Merrifield resin followed by cleavage to yield β-lactam

The first one (Scheme 55) uses the *p*-oxyphenylsulfonyl linker attached to the Wang resin by the Mitsunobu procedure [216, 217] whereas the second one (Scheme 56) utilizes alkylation of the lithium salt of a mesylate [218] with the terminal of the Merrifield resin [216, 219].

7 Conclusion

In conclusion, the present review on the synthesis of β-lactams and analogues performed on solid surface covers several intelligent approaches. Although various resins have been employed, Wang resin and application of Staudinger [2+2] cycloaddition reaction have remained the major choice so far. Both unsubstituted and substitutions with different functional groups at various positions of β-lactams have been synthesized using solid phase technology. It may be expected that other solid phase approaches involving different resins would be developed in the coming years.

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References

1. Fleming A (1929) Br J Exp Pathol 10:226
2. Mandell GL, Petri WA, Jr (1996) In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman, A (eds) Goodman & Gilman's the pharmacological basis of therapeutics. McGraw-Hill, New York
3. Manhas MS, Bose AK (1971) β-Lactams: natural and synthetic. Wiley, New York
4. Page MI (1987) In: Bethell D (ed) Advances in physical organic chemistry. Academic Press, London
5. Yoakim C, Ogilvie WW, Cameron DR, Chabot C, Guse I, Hache´ B, Naud J, O'Meara JA, Plante R, De´ziel R (1998) J Med Chem 41:2882
6. Linder MR, Podlech J (1999) Org Lett 1:869
7. Abell AD, Gardiner J (1999) J Org Chem 64:9668
8. Palomo C, Aizpurua JM, Benito A, Galarza R, Khamrai UK, Vasquez J, de Pascual-Teresa B, Nieto PM, Linden A (1999) Angew Chem Int Ed 38:3056
9. Wright AJ (1999) Mayo Clin Proc 74:290
10. Konaklieva MI (2002) Curr Med Chem: Anti-Infect Agents 1:215
11. Singh R, Micetich RGI (2000) Drugs 3:512 As recent examples of beta-lactam inhibitors of HLE see
12. Clemente A, Domingos A, Grancho AP, Iley J, Moreira R, Neres J, Palma N, Santana AB, Valente E (2001) Bioorg Med Chem Lett 11:1065
13. Koteva KP, Cantin AM, Neugebauer WA, Escher E (2001) Can J Chem 79:377
14. Cainelli G, Galletti P, Garbisa S, Giacomini D, Sartor L, Quintavalla A (2003) Bioorg Med Chem 11:5391
15. Kazi A, Hill R, Long TE, Kuhn DJ, Turos E, Dou QP (2004) Biochem Pharmacol 67:365

16. World Health Organization. Overcoming antimicrobial resistance. WHO Report on Infectious Diseases, (2000). www.who.int/infectiousdisease-report/2000/index.html
17. Power JH (2003) Curr Opin Infect Dis 16:547
18. Niccolai D, Tarsi L, Thomas RJ (1997) J Chem Soc Chem Commun:2333
19. Chu DTW, Plattner JJ, Katz L (1996) J Med Chem 39:3853
20. Wilmouth RC, Kasamally S, Westwood NJ, Sheppard RJ, Claridge TD, Alpin RT, Wright PA, Pritchard GJ, Schofield CJ (1999) Biochemistry 38:7989
21. Beauve C, Bouchet M, Touillaux R, Fastrez J, Marchand-Brynaert J (1999) Tetrahedron 55:13301
22. Mascaretti OA, Boschetti CE, Danelon GO, Mata EG, Roveri OA (1995) Curr Med Chem 1:441
23. Kai H, Iwamoto K, Chatani N, Murai S (1996) J Am Chem Soc 118:7634
24. Karupaiyan K, Srirajan V, Deshmukh ARAS, Bhawal BM Tetrahedron Lett 38:4281
25. Singh GS, Singh T, Lakhan R (1997) Indian J Chem 36B:951
26. Barrett AGM, Baugh SPD, Gibson VC, Giles MR, Marshall EL, Procopiou P (1997) Chem Commun:155
27. Barrett AGM, Baugh SPD, Braddock DC, Flack K, Gibson VC, Giles MR, Marshall EL, Procopiou P, White AJP, Williams DJ (1998) J Org Chem 63:7893
28. Shindo M, Oya S, Sato Y, Shishido K (1998) Heterocycles 49:113
29. Cainelli G, Galletti P, Giacomini D (1998) Synlett:611
30. Anklam S, Liebscher J (1998) Tetrahedron 54:6369
31. Podlech J, Steurer S (1999) Synthesis:650
32. Lindler MR, Podlech J (1999) Org Lett 1:869
33. Rossi E, Abbiati G, Pini E (1999) Tetrahedron 55:6961
34. Croce PD, Ferraccioli R, La Rosa C (1999) Tetrahedron 55:201
35. De Risi C, Pollini GP, Veroneze AC, Bertolasi V (1999) Tetrahedron Lett 40:6995
36. Palomo C, Aizpurua JM, Ganboa I, Oirabide M (1999) Eur J Org Chem 3223
37. Tomioka K, Fujieda H, Hayashi S, Hussain MA, Kambara T, Nomura Y, Kanai M, Koga K (1999) Chem Commun:715
38. Naskar D, Roy S (1999) J Chem Soc Perkin Trans 1:2435
39. Homsi F, Rouszeau G (1999) J Org Chem 64:81
40. Trias J (2001) Curr Opin Microbiol 4:520
41. Ratcliffe RW, Albers-Schonberg G (1982) In: Morin RB, Gorman M (eds) Chemistry and biology of β-lactam antibiotics, vol 2. Academic, New York, For reviews on the synthesis of β-lactams
42. Carruthers W (1990) Cycloaddition reactions in organic synthesis. Pergamon Press, Oxford
43. Southgate R, Branch C, Coulton S, Hunt E (1993) In: Lukacs G (ed) Recent progress in the chemical synthesis of antibiotics and related microbial products, vol 2. Springer, Berlin
44. Palomo C, Aizpurua JM, Gracenea JJ, García-Granda S, Pertierra P (1998) Eur J Org Chem 2201
45. Singh GS (2003) Tetrahedron 59:7631
46. Brown AG, Roberts SM (eds) (1985) Recent advances in the chemistry of β-lactam antibiotics. The Royal Society of Chemistry, London
47. Flynn EH (1972) Cephalosporins and penicillins: chemistry and biology. Academic Press, New York
48. Singh GS (2004) Mini Rev Med Chem 4:93
49. Singh GS (2004) Mini Rev Med Chem 4:69
50. Hwu J, Ethiraj K, Hakimelahi GH (2003) Mini Rev Med Chem 3:305
51. Sader H, Gales AC (2001) Drugs 61:553
52. Ojima I, Delaloge F (1997) Chem Soc Rev 26:377
53. Alcaide B, Almendros P (2001) Chem Soc Rev 30:226
54. Cheng J, Deming TJ (2001) J Am Chem Soc 123:9457

55. Eldred SE, Pancost MR, Otte KM, Rozema D, Stahl SS, Gellman SH (2005) Bioconjugate Chem 16:694
56. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2004) Curr Med Chem 11:1837
57. Ojima I (1995) Acc Chem Res 28:383
58. Alcaide B, Almendros P (2002) Synlett 381
59. Page MI (ed) (1992) The chemistry of β-lactams. Chapman Hall, New York
60. Sheehan JC, Henery-Logan KR (1957) J Am Chem Soc 79:1262
61. McGarvey GJ, Kimura MJ (1985) J Org Chem 50:4655
62. Sheehan JC, Bose AK (1950) J Am Chem Soc 72:5158
63. Bachmann BO, Li R, Craig A, Townsend CA (1998) Proc Natl Acad Sci 95:9082
64. Floyd DM, Fritz AW, Pluscec J, Weaver ER, Cimarusti CM (1982) J Org Chem 47:5160
65. Hegedus LS (1995) Acc Chem Res 28:299
66. Lynch JE, Riseman SM, Laswell WL, Tschaen DM, Volante RP, Smith GB, Shinkai I (1989) J Org Chem 54:3792
67. Hart DJ, Ha DC (1989) Chem Rev 89:1447
68. Gilman H, Speeter M (1943) J Am Chem Soc 65:2255
69. Benaglia M, Cinquini M, Cozzi F (2000) Eur J Org Chem: 563
70. Fujieda H, Kanai M, Kambara T, Iida A, Tomioka K (1997) J Am Chem Soc 119:2060
71. Wipf P (ed) (2005) Reagents for high-throughput solid-phase and solution-phase organic synthesis. Wiley, Chichester, U.K. and references therein
72. Dondoni A, Massi A, Sabbatini S, Bertolasi V (2004) Adv Synth Catal 346:1355
73. Gordeev MF, Gordon EM, Patel DV (1997) J Org Chem 62:8177
74. Harris PA (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II, vol I. Elsevier Science Inc, Oxford, 1009
75. Mergler M, Tanner R, Gosteli J, Grogg P (1998) Tetrahedron Lett 29:4005
76. Molteni V, Annunziata R, Cinquini M, Cozzi F, Benaglia B (1998) Tetrahedron Lett 39:1257
77. Annunziata R, Benaglia M, Cinquini M, Cozzi F (2000) Chem Eur J 6:133
78. Singh R, Nuss JM (1999) Tetrahedron Lett 40:1249
79. Georg GI (ed) (1993) The organic chemistry of β-lactams. VCH Publishers, New York
80. Ruhland B, Bhandari A, Gordon EM, Gallop MA (1996) J Am Chem Soc 118:253
81. Georg GI, Ravikumar VT (1993) In: Georg GI (ed) The organic chemistry of β-lactams. Verlag Chemie, New York, 295
82. Ojima I (1993) In: Georg GI (ed) The organic chemistry of β-lactams. Verlag Chemie, New York, 197
83. Look GC, Murphy MM, Campbell DA, Gallop MA (1995) Tetrahedron Lett 36:2937
84. Pei Y, Houghten RA, Kiely JS (1997) Tetrahedron Lett 38:3349
85. Houghten RA (1985) Proc Natl Acad Sci USA 82:5131
86. Meyers HV, Dilley GJ, Durgin TL, Powers TS, Winssinger NA, Zhu H, Pavia MR (1995) Mol Divers 1:13
87. Delpiccolo CML, Mata EG (2002) Tetrahedron: Asymmetry 13:905
88. Guillier F, Orain D, Bradley M (2000) Chem Rev 100:2091
89. Rink H (1987) Tetrahedron Lett 28:3787
90. Sieber P (1987) Tetrahedron Lett 28:2107
91. Albericio F, Kneibcordonier N, Biancalana S, Gera L, Masada RI, Hudson D, Barany G (1990) J Org Chem 55:3730
92. Mergler M, Nyfeler R, Tanner R, Gosteli J, Grogg P (1988) Tetrahedron Lett 29:4009
93. Jensen KJ, Alsina J, Songster MF, Vagner J, Albericio F, Barany G J Am Chem Soc 120:5441
94. Brown DS, Revill JM, Shute RE (1998) Tetrahedron Lett 39:8533
95. Chan WC, White PD, Beythien J, Steinauer R (1985) Chem Commun:589
96. Gordon KH, Balasubramanian S (2001) Org Lett 3:53
97. Kamiya T, Aoki H, Mine Y (1982) In: Morin RB, Gorman M (eds) Chemistry and biology of β-lactam antibiotics, vol 2. Academic Press, New York, 166

98. Koster WH, Cimarusti CM, Sykes RB (1982) In: Morin RB, Gorman M (eds) Chemistry and biology of β-lactam antibiotics, vol 3. Academic Press, New York 339
99. Fukuyama T, Frank RK, Jewell CF (1980) J Am Chem Soc 102:2122
100. Kronenthal DR, Han CY, Taylor MK (1982) J Org Chem 47:2765
101. Broxton TJ, Bunnett JF, Paik CH (1977) J Org Chem 42:643
102. Delpiccolo CML, Fraga MA, Mata EG (2003) J Comb Chem 5:208
103. Delpiccolo CML, Mata EG (2004) Tetrahedron Lett 45:4085
104. Delpiccolo CML, Me´ndez L, Fraga MA, Mata EG (2005) J Comb Chem 7:331
105. Evans DA, Sjogren EB (1985) Tetrahedron Lett 32:3783
106. Testero SA, Mata EG (2006) Org Lett 8:4783
107. Rano TA, Chapman KT (1995) Tetrahedron Lett 36:3789
108. Nam NH, Sardari S, Parang K (2003) J Comb Chem 5:479
109. Me´ndez L, Testero SA, Mata EG (2007) J Comb Chem 9:189
110. Furla´n RLE, Mata EG, Mascaretti OA (1996) Tetrahedron Lett 37:5229
111. Furla´n RLE, Mata EG, Mascaretti OA (1998) J Chem Soc Perkin Trans 1:355
112. Furla´n RLE, Mata EG, Mascaretti OA, Peña C, Coba MP (1998) Tetrahedron 54:13023
113. Nicolaou KC, Estrada AA, Zak M, Lee SH, Safina BS (2005) Angew Chem Int Ed 44:1378
114. Mendez L, Testero SA, Mata EG (2007) For hydrolysis of polymer-supported esters by TMTOH. Tetrahedron Lett 48:1757
115. Georg GI, Mashava PM, Guan X (1991) Tetrahedron Lett 32:581
116. Matsui S, Hashimoto Y, Saigo K (1998) Synthesis 1161
117. Saul R, Kopf J, Köll P (2000) Tetrahedron: Asymmetry 11:423
118. Hafez AM, Taggi AE, Wack H, Drury WJ III, Lectka T (2000) Org Lett 2:3963
119. Flynn DL, Crich JZ, Devraj RV, Hockerman SL, Parlow JJ, South MS, Woodard S (1997) J Am Chem Soc 119:4874
120. Tidwell TT (1995) Ketenes. Wiley, New York
121. Drury WJIII, Ferraris D, Cox C, Young B, Lectka T (1998) J Am Chem Soc 120:11006
122. Ferraris D, Young B, Dudding T, Lectka T (1998) J Am Chem Soc 120:4548
123. Tschaen DH, Turos E, Weinreb SM (1984) J Org Chem 49:5058
124. Taggi AE, Hafez AM, Wack H, Young B, Drury WJIII, Lectka T (2000) J Am Chem Soc 2000(122):7831
125. O'Donnell MJ, Delgado F, Hostettler C, Schwesinger R (1998) The p*K*a of the conjugate acid of BEMP in DMSO is 16.2. Tetrahedron Lett 39:8775
126. Schwesinger R, Willaredt J, Schlemper H, Keller M, Schmitt D, Fritz H (1994) Chem Ber 127:2435
127. Kim BM, Sharpless KB (1990) Tetrahedron Lett 31:3003
128. Pini D, Petri A, Nardi A, Rosini C, Salvadori P (1992) Tetrahedron Lett 32:5175
129. Gordon K, Bolger M, Khan N, Balasubramanian S (2000) Tetrahedron Lett 41:8621
130. Palomo C, Cossio FP, Cuevas C, Lecea B, Mielgo A, Roman P, Luque A, Martinezripoll M (1992) J Am Chem Soc 114:9360
131. Ruhland B, Bombrun A, Gallop MA (1997) J Org Chem 62:7820
132. Roy IL, Mouysset D, Mignani S, Vuilhorgne M, Stella L (2003) Tetrahedron 59:3719
133. Dasgupta SK, Banik BK (2002) Tetrahedron Lett 43:9445
134. Schunk S, Enders D (2000) Org Lett 2:907
135. Overman LE, Osawa T (1985) J Am Chem Soc 107:1698
136. Bräse S, Enders D, Köbberling J, Avemaria F (1998) Angew Chem Int Ed 37:3413
137. Gluchowski C, Cooper L, Breigbreiter DE, Newcomb M (1980) J Org Chem 45:3413
138. Schunk S, Enders D (2002) J Org Chem 67:8034
139. Van der Steen FH, Van Koten G (1991) Tetrahedron 47:7503
140. Fujisawa T, Shimizu M (1996) Rev Heteroatom Chem 15:203
141. Cainelli G, Gaicomini D, Panunzio M, Martelli G, Spunta G (1987) 4-Oxo- and 4-thioxo-substituted β-lactams. Tetrahedron Lett 28:3593

142. Battaglia A, Cainelli G, Giacomini D, Martelli G, Panunzio M (1987) Tetrahedron Lett 28:4347
143. Hart DJ, Kanai K-I, Thomas DG, Yang T-K (1983) N-unsubstituted β-lactams. J Org Chem 48:289
144. Ha D-C, Hart DJ, Yang T-K (1984) J Am Chem Soc 106:4819
145. Young JK, Nelson JC, Moore JS (1994) J Am Chem Soc 116:10841
146. Bräse S, Dahmen S (2000) Chem Eur J 6:1899
147. Keumi T, Umeda T, Inoue Y, Kitajima H (1989) Bull Chem Soc Jpn 62:89
148. Kidwai M, Venkataramanan R, Kohli S (2000) Synth Commun 30:989
149. Meloni MM, Taddei M (2001) Org Lett 3:337
150. Miller MJ, Mattingly PG, Morrison MA, JF K Jr (1980) J Am Chem Soc 102:7026
151. Mellor SL, McGuire C, Chan WC (1997) Tetrahedron Lett 38:3311
152. Falchi A, Giacomelli G, Porcheddu A, Taddei M (2000) 4-[4,6-Dimethoxy-(1,3,5)-triazin-2-yl]-4-methyl-morpholinium chloride (DMTMM): a valuable alternative to PyBOP for solid phase peptide synthesis. Synlett 277
153. Mahadevan V, Getzler YDYL, Coates GW (2002) Angew Chem Int Ed 41:2781
154. Khumtaveeporn K, Alper H (1995) Acc Chem Res 28:414
155. Alper H, Urso F, Smith DJH (1983) J Am Chem Soc 105:6737
156. Calet S, Urso F, Alper H (1989) J Am Chem Soc 111:931
157. Tanner D, Somfai P (1993) Bioorg Med Chem Lett 3:2415
158. Piotti ME, Alper H (1996) J Am Chem Soc 118:111
159. Kamiya Y, Kawato K, Ohta H (1980) Chem Lett 1549
160. Shimizu I, Maruyama T, Makuta T, Yamamoto A (1993) Tetrahedron Lett 34:2135
161. Wang MD, Calet S, Alper H (1989) J Org Chem 54:20
162. Leadbeater NE, Marco M (2002) Chem Rev 102:3217
163. McNamara CA, Dixon MJ, Bradley M (2002) Chem Rev 102:3275
164. de Miguel YR, Brule E, Margue RG (2001) J Chem Soc Perkin Trans 1 3085
165. Sandee AJ, Reek JNH, Kamer PCJ, van Leeuwen PWNM (2001) J Am Chem Soc 123:8468
166. de Miguel YR (2000) J Chem Soc Perkin Trans 1 4213
167. Lindner E, Schneller T, Auer F, Mayer HA (1999) Angew Chem Int Ed 38:2154
168. Nozaki K, Itoi Y, Shibahara F, Shirakawa E, Ohta T, Takaya H, Hiyama T (1998) J Am Chem Soc 120:4051
169. McClenaghan ND, Passalacqua R, Loiseau F, Campagna S, Verheyde B, Hameurlaine A, Dehaeh W (2003) J Am Chem Soc 125:5356 For selected references on dendrimers, see
170. Ong W, Kaifer AE (2003) Angew Chem Int Ed 42:2164
171. Maraval V, Pyzowski J, Caminade A-M, Majoral J-P (2003) J Org Chem 68:6043
172. Enoki O, Imaoka T, Yamamoto K (2003) Org Lett 5:2547
173. Percec V, Glodde M, Bera TK, Miura Y, Shiyanovskaya I, Singer KD, Balagurusamy VSK, Heiney PA, Schnell I, Rapp A, Spiess H-W, Hudson SD, Duan H (2002) Nature 419:384
174. Wimmer N, Marano RJ, Kearns PS; Rakoczy EP, Toth I (2002) Bioorg Med Chem Lett 12:2635
175. Grayson SM, Frechet JMJ (2001) Chem Rev 101:3819
176. Newkome GR, Moorefield CN, Vogtle F (1996) Dendritic molecules: concepts, synthesis, perspectives. VCH, Weinheim
177. King ASH, Twyman LJ (2002) J Chem Soc Perkin Trans 1 2209
178. van Heerbeek R, Kamer PCJ, Van Leeuwen PWNM, Reek JNH (2002) Chem Rev 102:3717
179. Twyman LJ, King ASH, Martin IK (2002) Chem Soc Rev 31:69
180. Astruc D, Chardac F (2001) Chem Rev 101:2991
181. Oosterom GE, Reek JNH, Kamer PCJ, van Leeuwen PWNW (2001) Angew Chem Int Ed 40:1828
182. Crooks RM, Zhao M, Sun L, Chechik V, Yeung LK (2001) Acc Chem Res 34:181
183. Reetz MT, Lohmer G, Schwickardi R (1997) Angew Chem Int Ed 36:1526

184. Knapen JWJ, van der Made AW, de Wilde JC, van Leeuwen PWNM, Wijkens P, Grove DM, van Koten G (1994) Nature 372:659
185. Chen Y-C, Wu T-F, Deng J-G, Liu H, Cui X, Zhu J, Jiang Y-Z, Choi MCK, Chan ASC (2002) J Org Chem 67:5301
186. Mizugaki T, Murata M, Ooe M, Ebitani K, Kaneda K (2002) Chem Commun:52
187. Reetz M, Giebel D (2000) Angew Chem Int Ed 39:2498
188. Albrecht M, Hovestad NJ, Boersma J, van Koten G (2001) Chem-Eur J 7:1289
189. Kleij AW, Gossage RA, Jastrzebski JTBH, Boersma J, van Koten G (2000) Angew Chem Int Ed 39:176
190. Kleij AW, Gossage RA, Klein Gebbink RJM, Brinkmann N, Reijerse EJ, Kragl U, Lutz M, Spek AL, van Koten G (2000) J Am Chem Soc 122:12112
191. Deng G-J, Fan Q-H, Chen X-M, Liu D-S, Chan ASC (2002) Chem Commun:1570
192. Oosterom GE, Steffens S, Reek JNH, Kamer PCJ, van Leeuwen PWNM (2002) Top Catal 19:61
193. Chechik V, Crooks RM (2000) J Am Chem Soc 122:1243
194. Fan Q-H, Chen Y-M, Chen X-M, Jiang D-Z, Xi F, Chan ASC (2000) Chem Commun 789
195. Zhao M, Crooks RM (1999) Angew Chem Int Ed 38:364
196. Zeng H, Newkome GR, Hill CL (2000) Angew Chem Int Ed 39:1772
197. Francavilla C, Bright FV, Detty MR (1999) Org Lett 1:1043
198. Bhyrappa P, Young JK, Moore JS, Suslick KS (1996) J Am Chem Soc 118:5708
199. Dahan A, Portnoy M (2003) Org Lett 5:1197
200. Alper H, Arya P, Bourque SC, Jefferson GR, Manzer LE (2000) Can J Chem 78:920
201. Maraval V, Laurent R, Caminade A-M, Majoral J-P (2000) Organometallics 19:4025
202. Chung Y-M, Rhee H-K (2002) Chem Commun 238
203. Sellner H, Faber C, Rheiner PB, Seebach D (2000) Chem-Eur J 6:3692
204. Sellner H, Seebach D (1999) Angew Chem Int Ed 38:1918
205. Hu Q-S, Pugh V, Sabat M, Pu L (1999) J Org Chem 64:7528
206. Lu S-M, Alper H (2004) J Org Chem 69:3558
207. Lu S-M, Alper H (2003) J Am Chem Soc 125:13126
208. Furman B, Thürmer R, Kałuża Z, Łysek R, Voelter W, Chmielewski M (1999) Angew Chem Int Ed 38:1121
209. Neu HC (1992) In: Page MI (ed) The chemistry of β-lactams. Blackie, Glasgow, pp 101–128
210. Delpiccolo CML, Mata EG (1999) Tetrahedron: Asymmetry 10:3893
211. Boggián DB, Mata EG (2006) Synthesis:3397
212. Sakamoto M, Takahashi M, Mino T, Fujita T (2001) Tetrahedron 57:6713
213. Sutton JC, Bolton SA, Davis ME, Hartl KS, Jacobson B, Mathur A, Ogletree ML, Slusarchyk WA, Zahler R, Seiler SM, Bisacchi GS (2004) Bioorg Med Chem Lett 14:2233
214. Pérez-Faginas P, Teresa Aranda M, Coady L, Teresa García-López M, González-Muñiz R (2008) Adv Synth Catal 350:2279
215. Furman B, Kału˙za Z, Stencel A, Grzeszczyk B, Chmielewski M (2007) Top Heterocycl Chem 7:101
216. Furman B, Łysek R, Matyjasek Ł, WojtkielewiczW, Chmielewski M (2001) Synth Commun 31:2795
217. Furman B, Cierpucha M, Grzeszczyk B, Matyjasek L, Chmielewski M (2002) Eur J Org Chem 2377
218. Musicki B, Widlanski TS (1990) J Org Chem 55:4231
219. Łysek R, Grzeszczyk B, Furman B, Chmielewski M (2004) Eur J Org Chem:4177

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Computational Studies on the Synthesis of β-Lactams via [2+2] Thermal Cycloadditions

Ana Arrieta, Begoña Lecea, and Fernando P. Cossío

Abstract The main computational studies on the formation of β-lactams through [2+2] cycloadditions published during 1992–2008 are reported with special emphasis on the mechanistic and selectivity aspects of these reactions. Disconnection of the N1-C2 and C3–C4 bonds of the azetidin-2-one ring leads to the reaction between ketenes and imines. Computational and experimental results point to a stepwise mechanism for this reaction. The first step consists of a nucleophilic attack of the iminic nitrogen on the sp-hybridized carbon atom of the ketene. The zwitterionic intermediate thus formed yields the corresponding β-lactam by means of a four-electron conrotatoty electrocyclization. The steroecontrol and the periselectivity of the reaction support this two-step mechanism. The [2+2] cycloaddition between isocyanates and alkenes takes place via a concerted (but asynchronous) mechanism that can be interpreted in terms of a $[_{\pi}2_{s} + (_{\pi}2_{s} + _{\pi}2_{s})]$ interaction between both reactants. Both the regio and the stereochemistry observed are compatible with this computational model. However, the combination of solvent and substituent effects can result in a stepwise mechanism.

Keywords β-lactams · ab initio calculations · Alkenes · Imines · Isocyanates · Ketenes · Ketenimines · Semiempirical calculations

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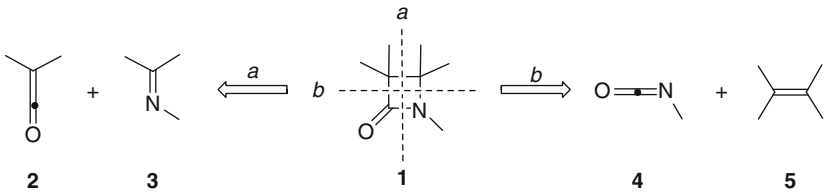
Contents

Abbreviations

AM1	Austin Model 1
B3LYP	Hybrid three-parameter functional derived by Becke, Lee, Yang and Parr
CASSCF	Completely active space self-consistent field
CI-HE	Configuration interaction-half electron method
DFT	Density-functional theory
ECP	Effective core potential
MNDO	Minor neglect of differential overlap
MO	Molecular orbital
MP*n*	n^{th} order Møller-Plesset expansion
PCM	Polarization continuum model
PM3	Third parametrization of MNDO
RHF	Restricted Hartree-Fock
SCF	Self-consistent field
SCRF	Self-consistent reaction field
UHF	Unrestricted Hartree-Fock
ZPVE	Zero-point vibrational energy

1 Introduction

Given the importance of β-lactams in heterocyclic and medicinal chemistry [1–3], many different methods for the synthesis of these compounds have been developed [4, 5]. Among them, those involving [2+2] cycloadditions are of special relevance because of the convergent nature of these methodologies, the readily accessible reagents required, and the wide range of β-lactams thus available [6–9].



Scheme 1 [2+2] disconnections of the β-lactam ring

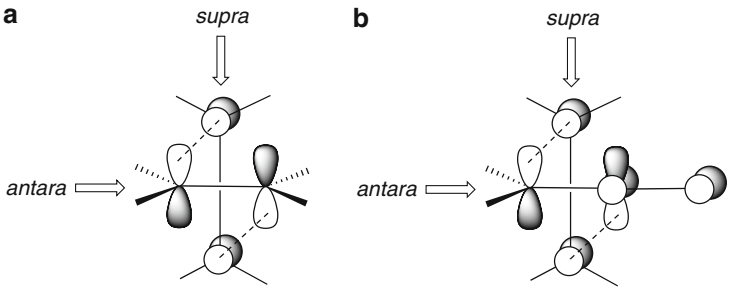
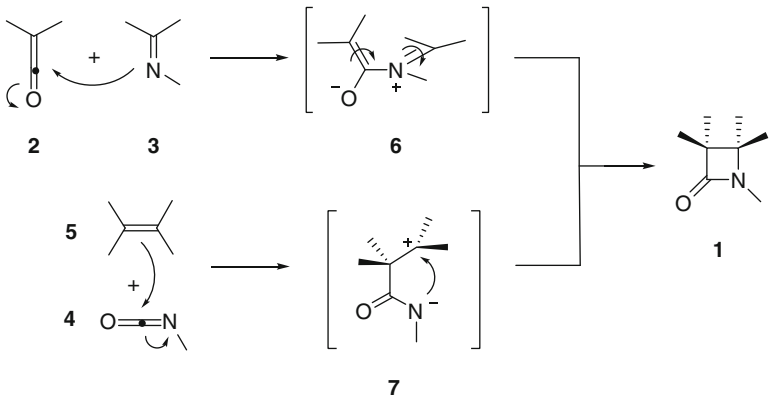


Fig. 1 $[_{\pi}2_{s}+_{\pi}2_{a}]$ Mechanisms in the [2+2] cycloaddition involving π-systems (**a**) and cumulenes (**b**)

Two possible [2+2] cycloadditions can be envisaged for the synthesis of β-lactams (Scheme 1). Interestingly, the same fragmentations have been observed in the mass spectra of these compounds [10, 11]. One possibility consists of the [2+2] cycloaddition between ketenes (**2**) and imines (**3**) to yield β-lactams (**1**). This reaction has been explored experimentally and it is also known as the Staudinger reaction between ketenes and imines [12–15]. In an alternative approach, the [2+2] cycloaddition between alkenes (**5**) and isocyanates (**4**) leads to β-lactams (**1**). This reaction has been less extensively used, but it has proven to be useful in the chemical synthesis of interesting compounds [16–19].

The [2+2] cycloadditions can be concerted under thermal conditions provided that the interaction between the π-systems takes place in a *supra-antara* mode (Fig. 1). This $[_{2}\pi_{s} + _{2}\pi_{a}]$ mechanism [20] is sterically very demanding and, therefore, it should be facilitated by cumulenes possessing *sp*-hybridized electrophilic carbon atoms. This makes ketenes and isocyanates suitable candidates for concerted symmetry-allowed thermal [2+2] cycloadditions. However, the presence of heteroatoms in both possible [2+2] reactions leads in turn to different stepwise mechanisms in which the electrophilic nature of the *sp*-hybridized carbon atoms of ketenes and isocyanates plays a crucial role (Scheme 2). According to these mechanisms, zwitterionic intermediates (**6**) and (**7**) are plausible via formation of C–N or C–C bonds, respectively.

All these concerted and stepwise mechanisms as well as the regio and stereochemical issues associated with these reactions pose complex mechanistic problems and make computational chemistry a suitable tool to analyze the different



Scheme 2 Stepwise mechanisms in the reaction between ketenes and imines or isocyanates and alkenes to form β-lactams

reaction paths as well as to predict the stereochemical and regiochemical outcomes. In this review, the main contributions in this field during the 1992–2008 time span will be presented, although references to previous work will also be included when necessary. The aim of this review has not been to address a theoretical audience but organic chemists interested in the mechanistic aspects of these reactions.

2 The Reaction Between Ketenes and Imines and Related Transformations

2.1 Reaction Between Ketenes and Imines

2.1.1 General Mechanism

Since the pioneering work of Boyd et al. [21], many studies have analyzed the Staudinger reaction. Although early ab initio works [22, 23] performed at the RHF/3-21G levels of theory predicted concerted but asynchronous mechanisms, these early claims were questioned on the basis of computational [24] and experimental arguments. Thus, Sordo et al. [25] and our group [26] concluded that the Staudinger reaction between ketenes and imines takes place via stepwise mechanisms, based on ab initio [25] and semiempirical [26] calculations at the AM1 level of theory [27]. According to this description of the mechanisms, the reaction starts with a nucleophilic attack of the iminic nitrogen atom on the *sp*-hybridized atom of the ketene to yield a zwitterionic intermediate. The chief features of the first transition structure associated with the reaction between ketene and methanimine as well as that corresponding to the zwitterionic intermediate can be found in Fig. 2.

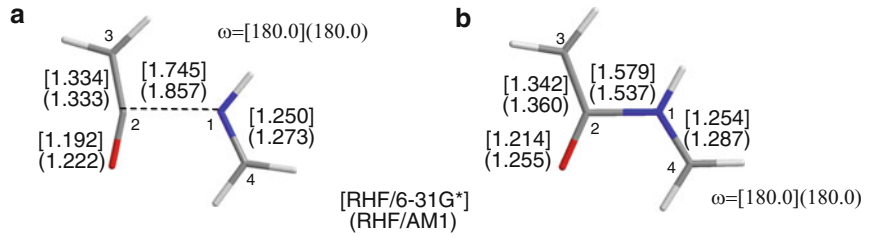
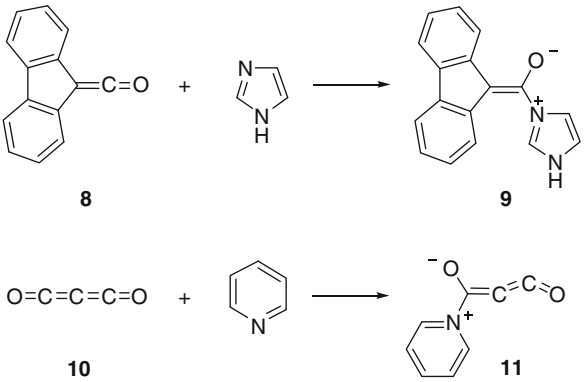
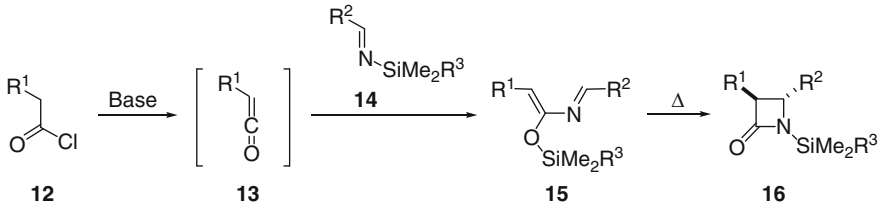


Fig. 2 Optimized geometric features of the first transition structure (**a**) and the intermediate (**b**) corresponding to the reaction between ketene and methanimine. Bond distances and angles are given in Å and deg., respectively. ω denotes the dihedral angle between the C4, N1, C2 and C3 atoms



Scheme 3 Zwitterionic intermediates associated with the interaction between ketenes and nitrogen containing heterocycles



Scheme 4 Stepwise mechanism corresponding to the reaction between ketenes and *N*-silyl imines

It is interesting to note that, under special conditions, these zwitterionic intermediates have been isolated (Scheme 3). Thus, the interaction of ketene (**8**) with imidazole showed an intermediate whose IR properties were attributed to zwitterion (**9**) [28]. More recently, Wentrup et al. [29] have calculated the stability of the complex formed by C_3O_2 (**10**) and pyridine and have found that at the B3LYP/6-31G* level at least a dielectric medium of relatively large dielectric permitivity ($\varepsilon = 40$) is required to yield the zwitterionic intermediate (**11**). This result is in line

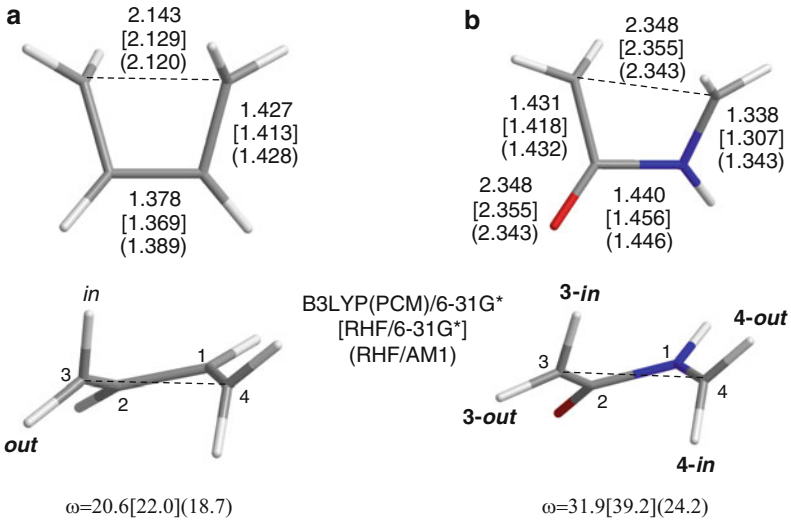


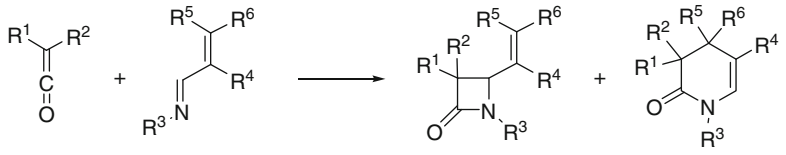
Fig. 3 Optimized geometric features of the transition structure associated with the cyclobutene-1,3-butadiene interconversion (**a**) and with the second transition structure of the reaction between ketene and methanimine to yield azetidin-2-one. Bond distances and angles are given in Å and deg., respectively. ω denotes the dihedral angle between the C4, N1, C2, and C3 atoms

with the difficulties found in the isolation of other zwitterionic intermediates of type (**6, 9, 11**). There is an exception, however. Panunzio et al. [30–33] have isolated 3-aza-1,3-dienes (**15**) in the reaction between ketenes (**13**) and *N*-silyl imines (**14**) (Scheme 4). These intermediates were fully characterized and transformed into the corresponding *N*-silyl-β-lactams (**16**). Therefore, 3-aza-1,3-dienes (**15**) can be considered as neutral isolable equivalents of zwitterionic intermediates (**6**). Given the preparative and mechanistic interest of this reaction, it has been studied computationally in detail (vide infra).

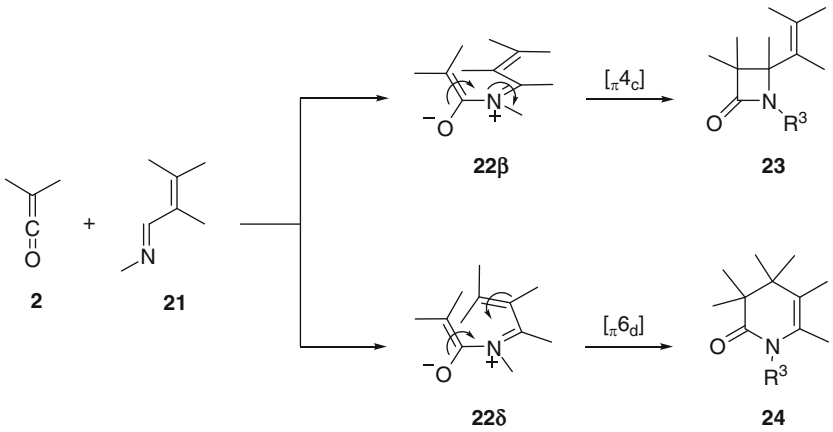
Intermediates (**6**) can yield to the corresponding β-lactams via conrotatory electrocyclic closures (Fig. 3). The main features of these transition structures closely resemble those found for the thermal electrocyclic ring opening of cyclobutenes [34].

As a consequence, it has been proposed [35, 36] that the torquoelectronic model developed by Houk [35–37] for this latter reaction can be extended to the Staudinger reaction between ketenes and imines. This model relies on the non-equivalent positions of the substituents in the conrotatory transition structures, as shown in Fig. 3. In these transition structures the *outward* and *inward* positions are not equivalent, which has profound consequences on the stereochemical outcome of the reaction (vide infra).

It is important to note that inclusion of solvent effects in the calculation of the mechanism is very important in order to reproduce correctly the reaction profile. Thus, if the electrostatic part of the free energy of solvation (ΔA_{solv}) is calculated in the form



Scheme 5 [2+2] and [4+2] periselectivity in the reaction between ketenes and α,β-unsaturated imines



Scheme 6 Stepwise mechanisms associated with the reaction between ketenes and α,β-unsaturated imines

$$\Delta A_{solv} = -\frac{1}{2}\sum_{l,l'}\sum_{m,m'} M_l^m f_{ll'}^{mm'} M_{l'}^{m'} \tag{1}$$

where M_l^m is a component of the multipole moment of order l and $f_{ll'}^{mm'}$ are the SCRF factors, it has been found that at the MP2/6-31G* level the main contribution corresponds to the dipole term (l = 1), although higher multipoles have substantial contributions (l = 2,3), specially for the zwitterionic intermediate [38]. A more detailed study [39] (up to MP4/6-31G* level) showed the importance of solvent effects to stabilize the zwitterionic intermediate, as well as the relevance of ZPVE corrections. It is noteworthy that semiempirical calculations in the gas phase (RHF/AM1) give similar potential energy surfaces to those obtained by ab initio methods included solvation effects [40].

2.1.2 Periselectivity

When imines derived from α,β-unsaturated aldehydes react with ketenes, formal [2+2] and [4+2] cycloadditions are possible [11, 41] (Scheme 5). Although a $[\pi 2_s + \pi 4_s]$ concerted (but not necessarily synchronous) mechanism is conceivable,

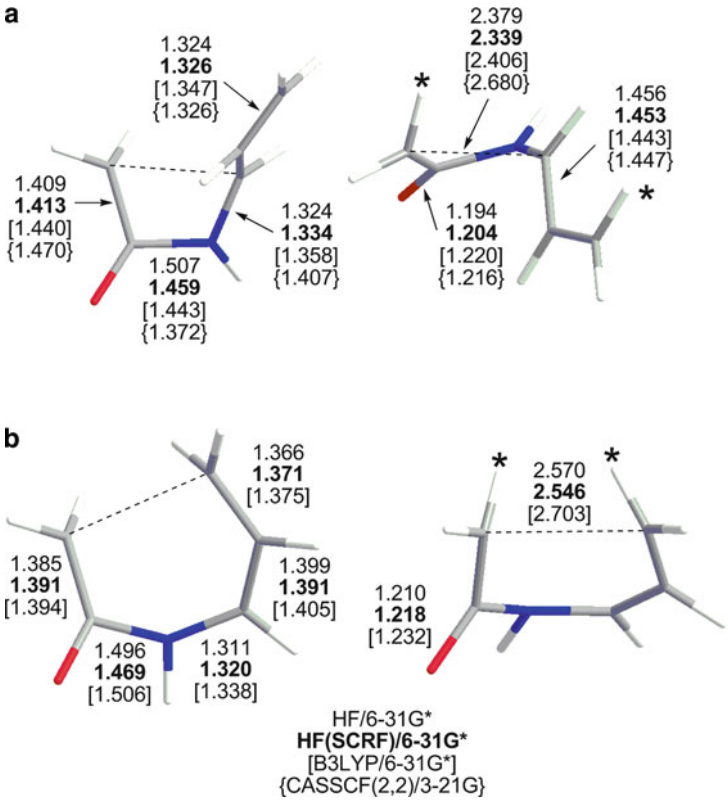
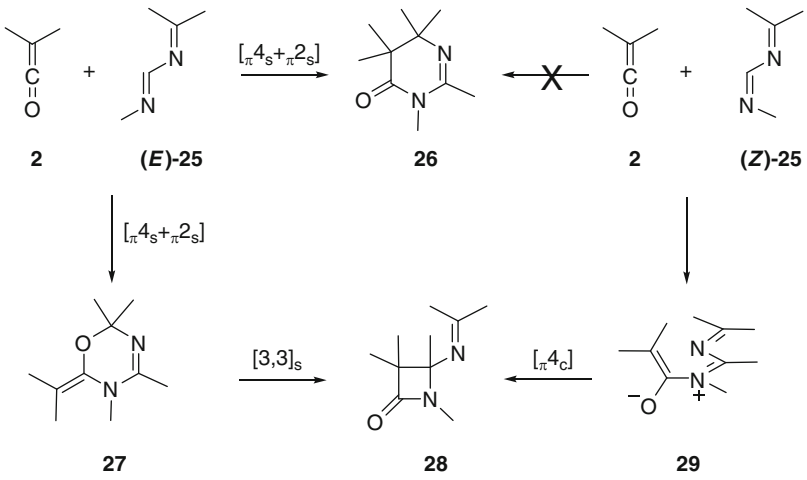


Fig. 4 Optimized geometric features of the electrocyclic transition structures associated with the conrotatory (**a**) and disrotatory (**b**) ring closure of the zwitterionic intermediates resulting from the interaction between ketene and prop-2-en-1-imine. Bond distances are given in Å

both semiempirical RHF/AM1 [42] and SCF-MO [43] calculations suggest that both [2+2] and [4+2] reactions are stepwise.

Thus, nucleophilic attack of the nitrogen of the α,β-unsaturated imine (**21**) (Scheme 6) on the electrophilic carbon atom of ketenes (**2**) leads to the formation of zwitterionic intermediates (**22**) in the β and δ conformations. The thermally allowed $[_{\pi}4_{c}]$ reaction (**22**β) leads to the formation of β-lactams (**23**), whereas the $[_{\pi}6_{d}]$ electrocyclization of (**22δ**) leads to the formation of the corresponding δ-lactams (**24**) (Scheme 6).

Figure 4 shows the main geometric features of the transition structures associated with the $[_{\pi}4_{c}]$ and $[_{\pi}6_{d}]$ steps in the reaction between ketene and prop-2-en-1-imine. Experimental and computational studies [42, 43] showed that the periselectivity of this reaction is very sensitive to substituent effects. Thus, in general disubstituted ketenes and/or imines possessing bulky substituents at the β-position favor the formation of [2+2] cycloadducts because of severe steric



Scheme 7 Mechanisms of the reaction between ketenes and 1,3-diazabuta-1,3-dienes

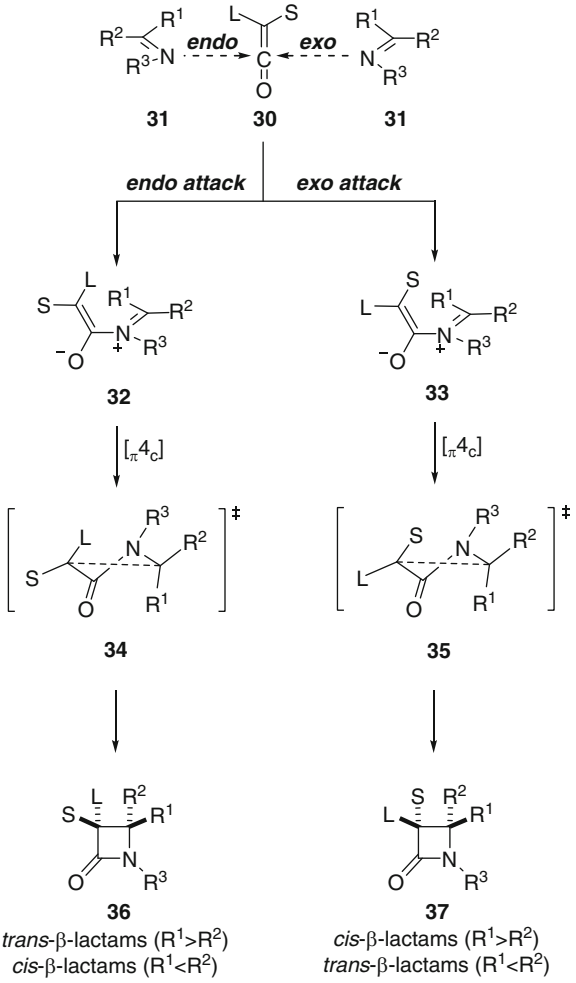
interactions in the *inward* positions of the disrotatory transition states. (These positions are highlighted with asterisks in Fig. 4).

The reaction between ketenes and 1,3-diazabuta-1,3-dienes [44–48] has also been studied computationally [48]. According to the MP2/6-31G* + ΔZPVE results obtained by Bharatam et al. in the gas phase, there are at least three reaction paths leading to the [2+2] and [4 + 2] cycloadducts.

Thus, ketenes (**2**) can react as dienophiles with (E)-1,3-diazabuta-1,3-dienes (E)-(**25**) to yield either [4 + 2] cycloaducts (**26**) or (**27**) depending on the participation of the C = C or C = O moieties of the ketenes (Scheme 7). Claisen rearrangement of 3,6-dihydro-2-methylene-2*H*-1,3,5-oxadiazines (**27**) yields the β-lactams (**28**). Alternatively, reaction between ketenes (**2**) and (Z)-1,3-diazabuta-1,3-dienes (Z)-(**25**) leads to the usual zwitterionic intermediates (**29**), whose conrotatory electrocyclation leads to β-lactams (**28**). No computational data including solvent effects have been reported for these reactions.

2.1.3 Stereoselectivity

Despite its formal simplicity, the stepwise mechanism of the reaction between ketenes and imines raises a complex stereochemical situation since ketenes can be unsymmetrically substituted and imines can exist in either (E)- or (Z)-configurations [49]. As far as the first step of the reaction is concerned, the nucleophilic attack of the nitrogen atom of the imine can occur through the less hindered *exo* face, namely that which has the shortest substituent, or through the *endo* face, which incorporates the largest substituent (Scheme 8). In principle, the *exo* attack leads to second transition structures that exhibit the largest substituents at the 3-out position.



Scheme 8 Stereochemistry of the reaction between ketenes and imines

According to the torquoelectronic theory [34–37], this should result in less energetic transition structures if the largest substitution is electron-releasing. In contrast, if this substituent is electron-withdrawing, the 3-*inward* position should be favored. This prediction was verified by computational studies carried out both in the gas phase and in dichloromethane solution. Table 1 shows some significant results [50–52].

According to this scheme, the Staudinger reaction between (E)-imines and ketenes should yield preferentially the kinetic *cis*-β-lactams, provided that the first step takes place via an *exo* attack, which leads to a second transition state in which the L substituent occupies the 3-out position (Scheme 8). Using the same argument, (Z)-imines should yield *trans*-β-lactams as main cycloadducts [26].

Table 1 Torquoelectronic effects[a] in the transition structures associated with the conrotatory ring closure of monosubstituted ketenes

R	R^1	R^2	R^3	ΔE_{in-out}	
				$\varepsilon = 1.00$	$\varepsilon = 0.93$
OH	H	H	H	12.1[b]	14.0[b]
CH_3	H	H	H	9.2[b]	9.0[b]
CH_3	CH_3	H	H	7.2[c]	7.6[c]
CH_3	H	CH_3	H	5.6[c]	7.2[c]
Cl	H	H	H	12.7[d]	
Cl	CH_3	H	H	8.2[c]	11.6[c]
Cl	H	CH_3	H	6.8[c]	9.1[c]
Cl	$CH = CH_2$	H	CH_3	9.5[c]	10.7[c]
Cl	H	$CH = CH_2$	CH_3	8.3[c]	9.8[c]
CN	H	H	H	2.4[b]	4.0[b]
BH_2	H	H	H	−12.5[b]	−11.5[b]

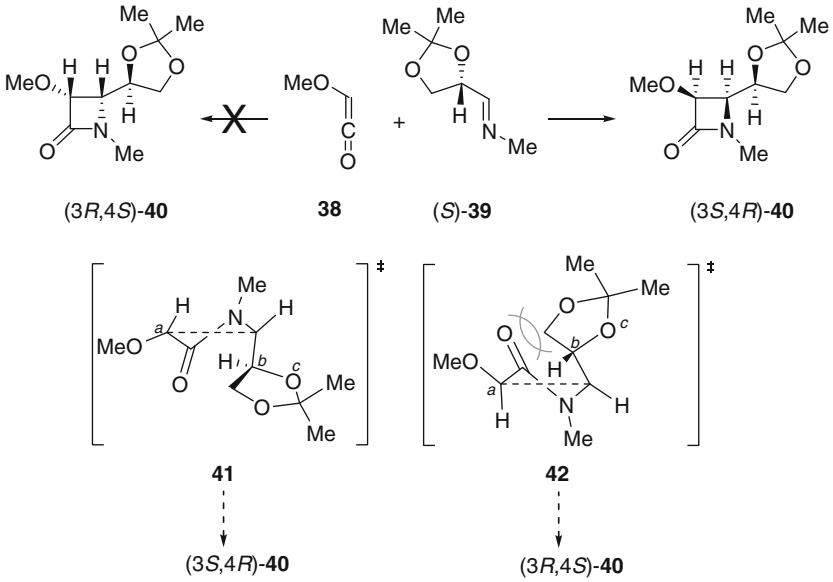
[a]Measured as the difference in energy between the transition structures incorporating the substituent R in an inward and outward position
[b]Data taken from [51] and computed at the MP2(SCRF)/6-31G*//RHF/6-31G* level
[c]Data taken from [52] and computed at the B3LYP(SCRF)/6-31G* level
[d]Data taken from [50] and computed at the MP2/6-31G*//RHF/6-31G* level

Hegedus et al. analyzed this model in detail and concluded that, in general, it agrees with the experimental evidence available [53].

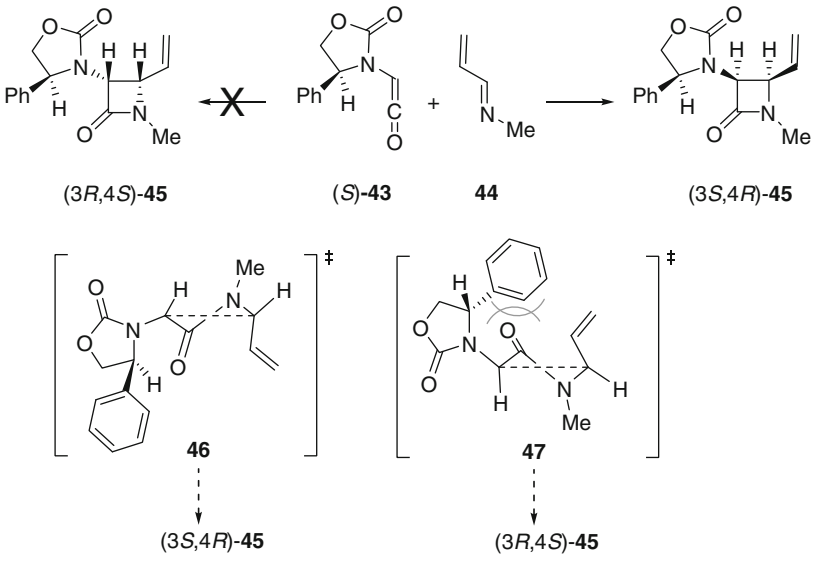
There are some examples on diastereoslective reactions between ketenes and imines [54–61]. However, the number of computational studies dealing with these reactants is scarce [59, 62–64]. As an example of Staudinger reaction in which the chirality source is at the C4 position of the ring being formed, our group studied the reaction between methoxyketene (**38**) and imine (S)-(**39**) derived from (S)-α-alkoxyaldehydes to yield the corresponding *cis*-β-lactam (3S,4R)-(**40**) (Scheme 9).

The RHF/AM1 transition structure (**41**) was found to be 1.5 kcal mol^{-1} more stable than the saddle point (**42**), in good agreement with the experimental findings [62]. This large stereocontrol was attributed to the two-electron interaction between the p-AO of the C_A atom and the C_B-O_C subunit, which acts as σ-acceptor. In the case of transition structure (**42**), this conformation leads to a steric congestion between the 1,3-dioxolaryl group and the β-lactam ring being formed, thus resulting in a less stable structure (Scheme 9).

The reaction between Evans-Sjögren ketene (**43**) and the model (E)-imine (**44**) was also studied at the RHF/AM1 level (Scheme 10). The calculations indicated that in this case the dominant conformation is dictated by the *anti* orientation of the carbonyl groups of the oxazolidinone and azetidine rings [62]. In this case, the transition structure (**47**), which incorporates a destabilizing interaction between the phenyl group and the β-lactam being formed, was calculated to be 4.9 kcal mol^{-1} higher in energy than saddle point (**46**). Therefore, exclusive formation of *cis*-β-lactam (3S,4R)-(**45**) is predicted in good agreement with the experimental results [54].



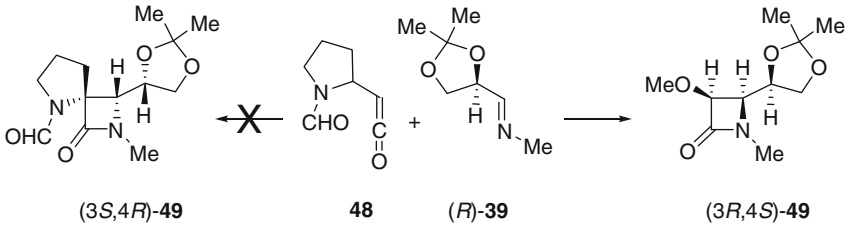
Scheme 9 Stereochemistry of the reaction between methoxyketene (**38**) and imine (S)-(**39**)



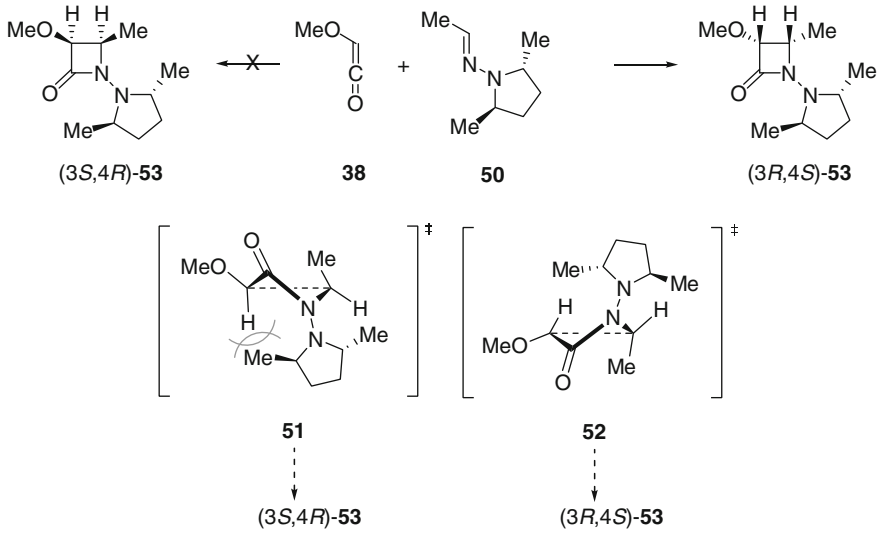
Scheme 10 Stereochemistry of the reaction between ketene (S)-(**43**) and imine (**44**)

González et al. [63] investigated the model reaction between ketene (**48**) and imine (R)-(**39**) to yield β-lactam (3R,4S)-(**49**) (Scheme 11). These authors found that, at the B3LYP/6-31 + G* level of theory, only cycloadducts (3R,4S)-(**49**) should be observed.

Studies on imines possessing chiral groups at the nitrogen atom are scarce, mainly because of the lower stereocontrol usually achieved under these conditions. A recent exception consists of the computational study of the reaction between methoxyketene (**38**) and (E)-hydrazone (**50**) (Scheme 12) [64] to yield β-lactams (**53**). The second transition structures leading to the (3R,4S) and (3S,4R)-cycloadducts possess 3-*outward* methoxy groups and 4-*inward* methyl groups. However, in transition structure (**51**) there is a strong steric interaction between the C_2-symmetric (R,R)-pyrrolidine moiety and the β-lactam ring being formed, thus resulting in the experimentally observed almost exclusive formation of cycloadducts (3R,4S).



Scheme 11 Stereochemistry of the reaction between ketene (**48**) and imine (R)-(**39**)

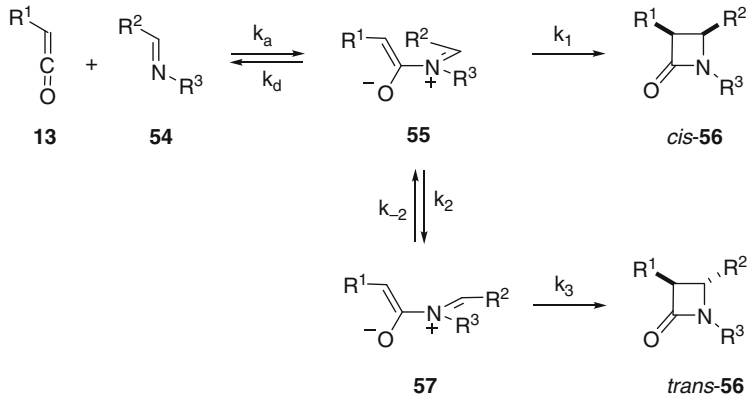


Scheme 12 Stereochemistry of the reaction between methoxyketene (**38**) and (E)-hydrazone (**50**)

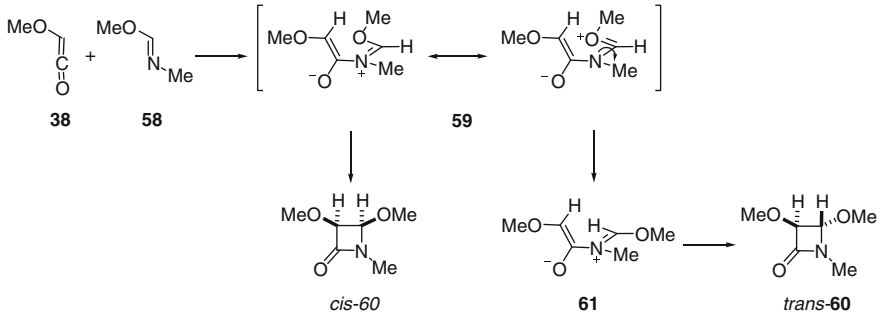
Very recently, an experimental study reported by Xu et al. [65] has highlighted the importance of the isomerization pathways in the reaction between ketenes and imines. According to this analysis, the *cis*/*trans* ratio is closely related to the rate constants of the direct ring closure (k_1) and the isomerization of the zwitterionic intermediate (**58**) (k_2), as indicated in (2) and Scheme 13.

$$\frac{[cis-59]}{[trans-59]} = \frac{k_1 \int [58]dt}{k_2 \int [58]dt - [60]} \approx \frac{k_1}{k_2} \tag{2}$$

A similar scheme was investigated at the RHF/AM1 level for the reaction between methoxyketene (**38**) and methyl methylimidoformiate (**58**) [66]. The computational results showed that at the 3x3CI-HE/AM1 level the rotation about the N1-C4 bond in zwitterionic intermediate (**59**) to form the intermediate (**61**) was favored over direct formation of the cycloadduct *cis*-**60**, thus resulting in the exclusive formation of *trans*-**60**, in good agreement with the experimental evidence on related imidates [67] (Scheme 14).



Scheme 13 Formation of *cis*- and *trans*-β-lactams (**56**) via zwitterionic intermediates (**55**) and (**57**)



Scheme 14 Formation of *cis*- and *trans*-β-lactams (**60**) via zwitterionic intermediates (**59**) and (**61**)

More recently, we have found that the role of the isomerization pathways in the reaction between ketenes and imines can be extended to the (E)/(Z) isomerization of imines themselves [68]. Thus, the stereocontrol observed in the reaction between methoxyketene **41** and (E)-imines (**62a,b**) was attributed to the competition between the energy barriers associated with the formation of intermediates (**63a,b**) and (**65a,b**) and the energies of activation corresponding to the isomerisation of (E)-imines (**62a,b**). Inclusion of isomerisation processes involving both imines (**62a,b**) and zwitterionic intermediates (**63a,b**) and (**65a,b**) led to a more complex kinetic analysis. As the final steps leading to β-lactams (**64**) can be considered irreversible, the formation of both *cis*- and *trans*-(**64**) can be described by (3) and (4):

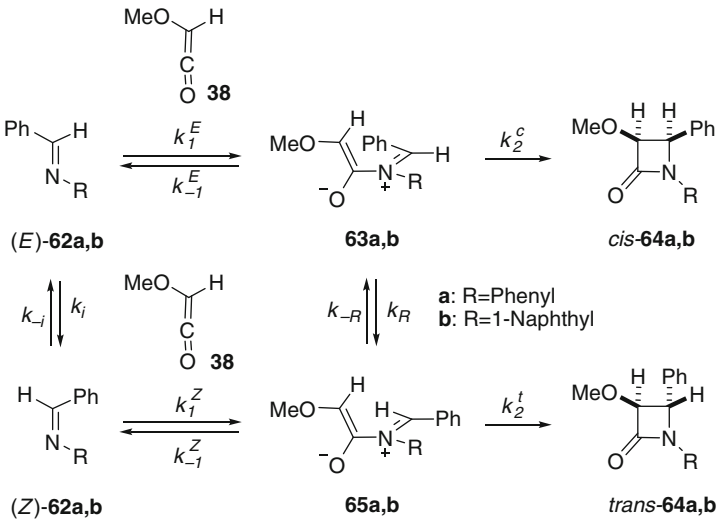
$$\frac{d}{dt}[cis-64] = k_1^c[63] \tag{3}$$

$$\frac{d}{dt}[trans-64] = k_2^t[65] \tag{4}$$

The concentration of intermediates (**63**) and (**65**) (Scheme 15) is determined by (5):

$$-\frac{d}{dt}A = KA \tag{5}$$

where K is the matrix of reactants and reaction intermediates (6) and K is the rate matrix (7):



Scheme 15 Formation of *cis*- and *trans*-β-lactams (**64a,b**) via zwitterionic intermediates (**63a,b**) and (**65a,b**)

$$A = \begin{pmatrix} [(E)-62] \\ [(Z)-62] \\ [63] \\ [64] \end{pmatrix} \tag{6}$$

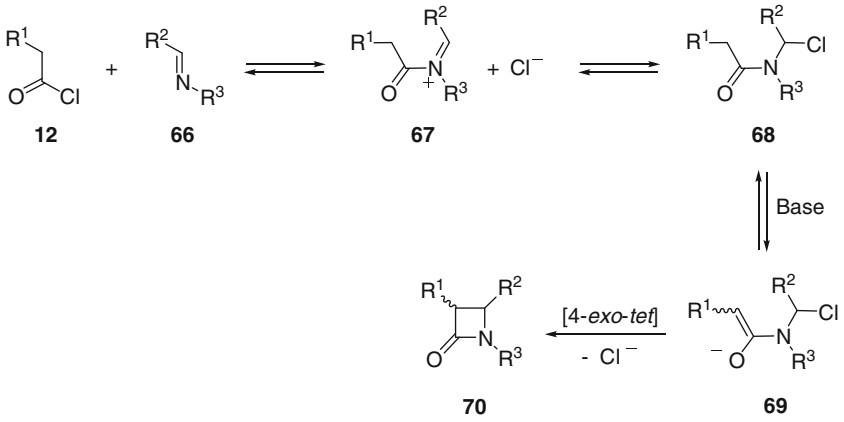
$$K = \begin{pmatrix} k_i + k_1^E[38] & -k_i & -k_{-1}^E & 0 \\ -k_i & k_{-1} + k_1^Z[38] & 0 & -k_{-1}^Z \\ -k_1^E[38] & 0 & k_{-1}^E + k_R + k_2^c & -k_{-R} \\ 0 & -k_1^Z[38] & -k_R & k_{-1}^Z + k_{-R} + k_2^t \end{pmatrix} \tag{7}$$

Numerical simulations on (3)–(7) [68] led to results similar to those found experimentally. Thus, at the B3LYP(PCM)/6-31 + G*//B3LYP(PCM)/6-31G* + ΔZPVE level of theory, the isomerization barrier corresponding to the $(E) \rightarrow (Z)$ transformation of imine (**62a**) (R = Ph) was found to be larger than the activation energy associated with the formation of zwitterion (**63a**). This results in the formation of cycloadduct *cis*-(**64a**) as the only stereoisomer. In contrast, the situation was reversed in the case of (E)-N-benzylidenenaphtalene-1-amine (**62b**). In this case, it was calculated that the activation barrier leading to the formation of (**63b**) was higher than that leading to the isomerisation of (E)-(**62b**) to the more nucleophilic imine (Z)-(**62b**). This resulted in the exclusive formation of β-lactam *trans*-(**64b**) via intermediate (**65b**). These results were in good agreement with previous experimental findings [69, 70].

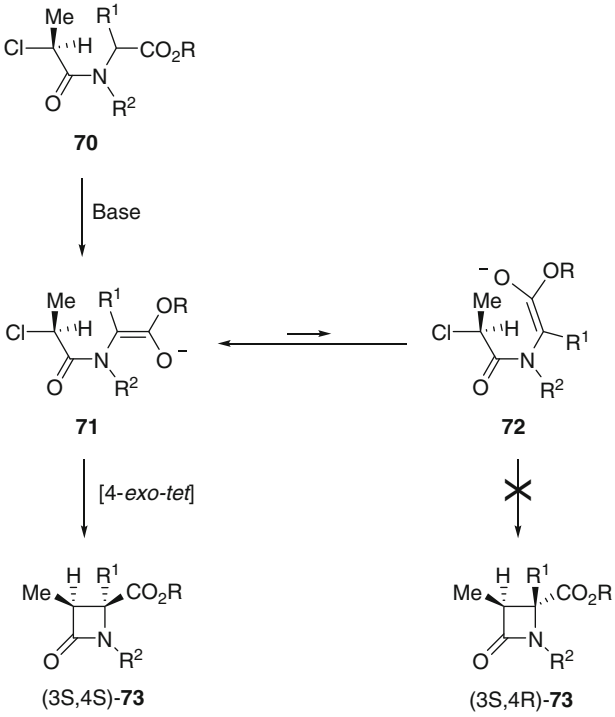
Another important issue of this reaction is the variable stereochemical outcome obtained depending upon the solvent used, the temperature, and the sequence of addition of the reactants. These aspects have been carefully studied experimentally by Xu et al. [71–73] in a brilliant series of papers. In particular, since one method for the generation of ketenes consists of the reaction between acyl chlorides (**12**) and bases (usually tertiary bases such as triethylamine), the direct reaction between compounds (**12**) with imines (**66**) was investigated at the B3LYP/6-31G* level of theory [52]. Under these conditions, it was calculated that formation *trans*-β-lactams (**70**) from enolates (**69**) is preferred, in agreement with the experimental results [74–76] and with the careful analysis of Xu et al. [72] (Scheme 16).

In a complementary approach, the stereocontrolled [4-*exo*-tet] cyclization of enolates (**71**) in which the nucleophilic species attack from the C4-position of the **β**-lactam ring to be formed has been reported [77] (Scheme **17**). B3LYP/6-311++G** calculations showed that the enolates (**71**) are preferred with respect to enolates (**72**) thus resulting in the formation of **β**-lactams (3S,4)-(**73**).

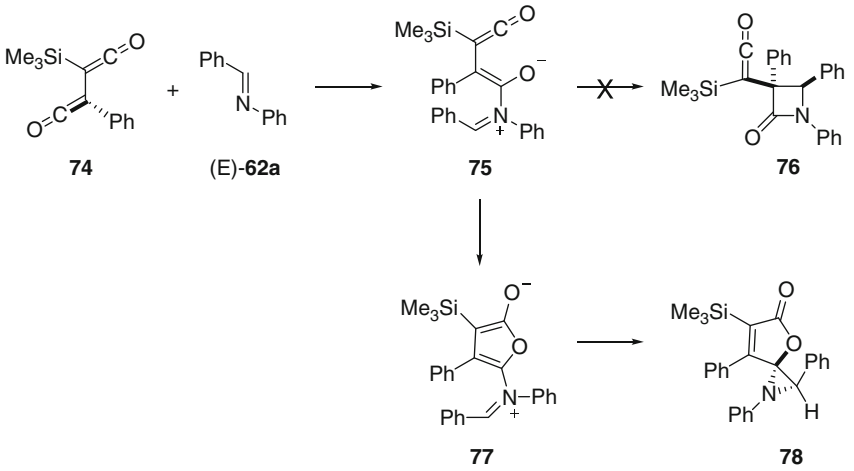
Bisketenes can provide different reaction paths in the reaction with imines (Scheme 18). For example, bisketene (**74**) does not form β-lactam species like (**76**). Instead, DFT computations [78] indicate that zwitterionic intermediate (**75**) leads to the furane intermediate (**77**) whose cyclization yields aziridine (**78**). 1,2-, 1,3- and 1,4-bisketenyl benzene react normally to yield mainly bis (β-lactams) [78].



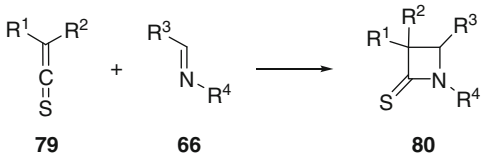
Scheme 16 Formation of β-lactams (**70**) form the direct reaction between acyl chlorides (**12**) and aldimines (**66**)



Scheme 17 Formation of β-lactam (3S,4S)-(**73**) via [4-*exo*-tet] cyclization of intermediate (**71**)



Scheme 18 Formation of bicyclic compound (**78**) in the reaction between bisketene (**74**) and imine (E)-(**62a**)



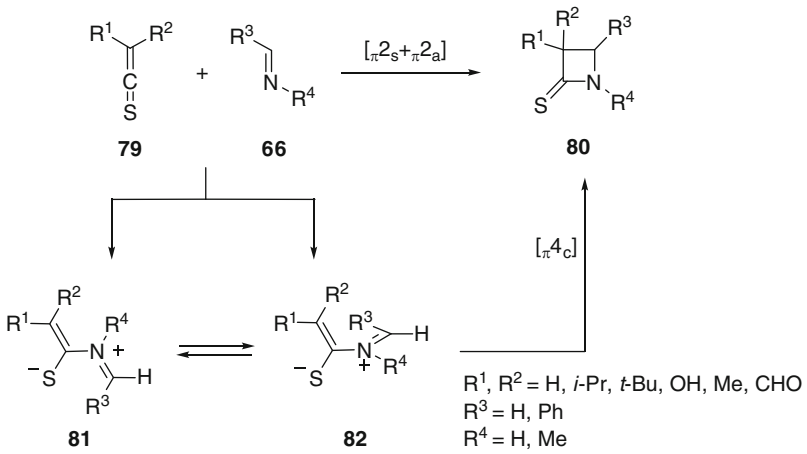
Scheme 19 Formation of β-thiolactams from thioketenes and imines

2.2 *Reaction Between Thioketenes and Imines*

Sordo et al. [79] investigated computationally the reaction between thioketenes (**79**) and imines to yield β-thiolactams (**80**) (Scheme 19), a reaction investigated experimentally by Schaumann [80].

Several model reactions were studied by Sordo et al. at the MP2/6-31G*//RHF/6-31G*, B3LYP/6-31G*, and RHF/6-31G*//RHF/3-21G* levels of theory, both in the gas phase and in anisole ($\varepsilon = 4.33$) and *N*,*N*-dimethylformamide ($\varepsilon = 37.0$) solution, using SCRF procedures. Under these conditions, both concerted [$_{\pi}2_{s} + {}_{\pi}2_{a}$] and stepwise mechanisms were found, although only the latter were obtained in solution (Scheme 20).

According to the computational results, the stereochemical outcome of the reaction is determined by electronic effects related to the torquoelectronic model [34–37] rather than by steric effects. In contrast, the stereochemical outcome was not very sensitive to solvent polarity.



Scheme 20 Concerted and stepwise mechanisms for the reaction between thioketenes and imines

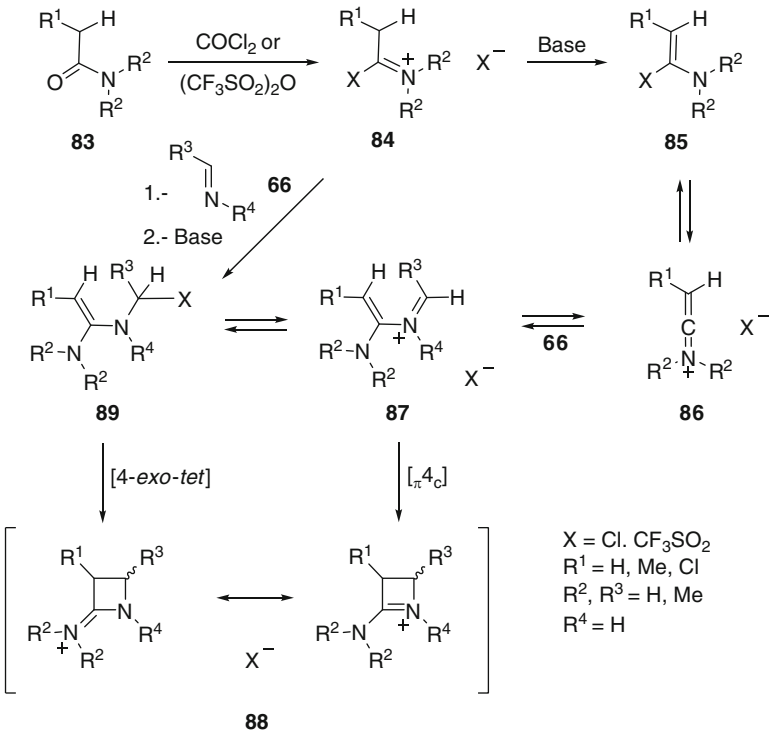
2.3 Reaction Between Ketenimines and Imines

This transformation is in general not easily achieved and therefore, the first versions of this reaction involved the much more electrophilic keteniminium salts [81–83], usually generated from carboxamides (Scheme 21).

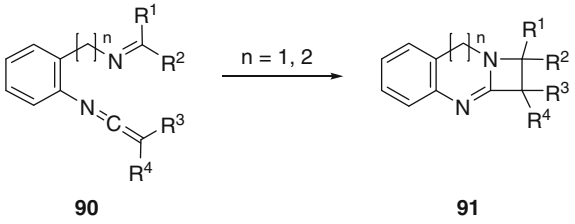
The reaction profiles involving reactants, intermediates, and products shown in Scheme 21 were calculated at the RHF/6-31G*, MP2/6-31G*, B3LYP/6-31G*, and B3LYP(SCRF)/6-31G* levels of theory [84]. It was found that all the possible reaction paths are stepwise and involve the sequential formation of the N1-C2 and C3–C4 bonds. When the reaction takes place via intermediates (**87**), the second step consists of a electrocyclic ring closure to yield the products (**88**) (Scheme 21). However, when chloroenamines (**84**) (X = Cl) are used as precursors of the keteneimine ions, the step involving the formation of the C3–C4 bond can consist of an intramolecular S_N2 reaction of type [4-*exo*-tet], thus yielding mainly the *trans*-cycloadducts (**88**) with low stereocontrol. These results are in good agreement with the experimental data available.

The reaction between ketenimines and imines was found to be much more difficult to accomplish [85, 86]. However, Alajarín et al. [87, 88] discovered that the intramolecular version of the reaction proceeded smoothly and several previously unknown azeto[2,1-b] quinazolines (**91**)] were proposed (Scheme 22).

Computational studies [89] on the model reactions shown in Scheme 22 at the RHF/6-31G*, MP2/6-31G*, B3LYP/6-31G* in vacuo and including solvent effects via SCRF methods showed that both processes take place via stepwise mechanisms similar to those found for the reaction between ketenes and imines. In both cases the nucleophilic attack of the iminic moiety was the rate-limiting step, the electrocyclic ring closure of intermediates (**93**, **96**) being much faster. However, the first

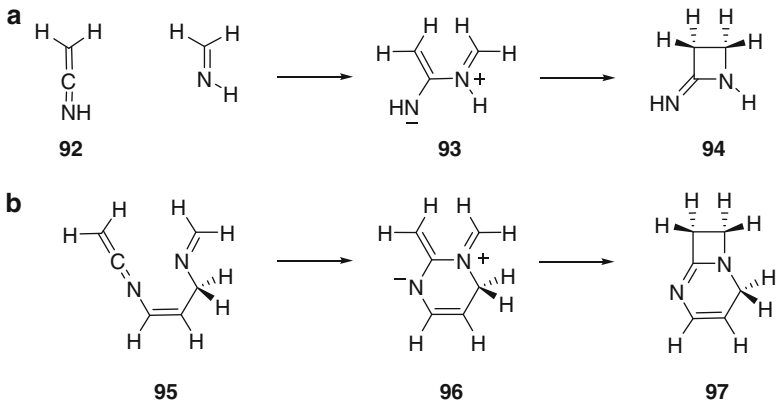


Scheme 21 Possible reaction mechanisms for the reaction between imines (**66**) and ketenimi-nium salts

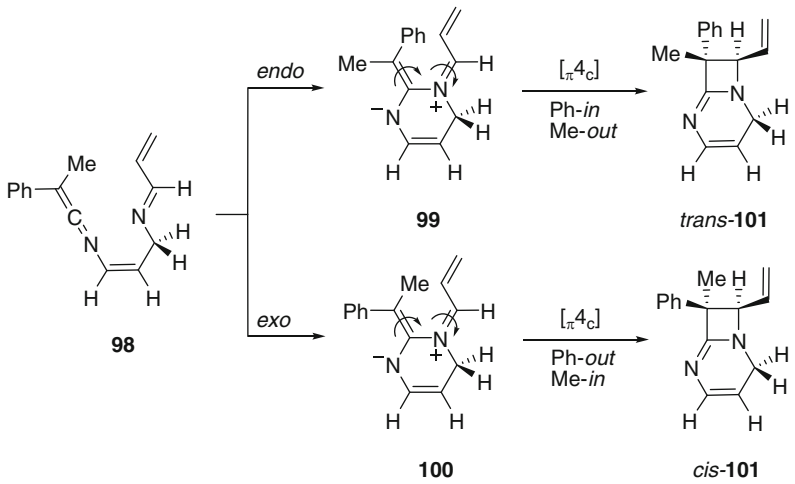


Scheme 22 Intramolecular reaction between neutral ketenimines and imines

activation energy of reaction *a* (Scheme 23) was found to be 4.4 kcal mol^{-1} (B3LYP(SCRF)/6-31G* results) higher than that computed for reaction *b*, in line with the experimental findings [87, 88]. In the same study, the stereochemical outcome of the model reaction depicted in Scheme 24 was analyzed. It was found that at the B3LYP(SCRF)/6-31G*//RHF/3-21G* level the energies associated with the conrotatory electrocyclizations of intermediates (**99**) and (**100**) were very similar. Therefore, the obtention of cycloadducts equivalent to *cis*-(**101**) was attributed to the preferential *exo* attack in reactant (**98**), thus surpassing the torquoelectronic effects operating in the second step of the reaction.



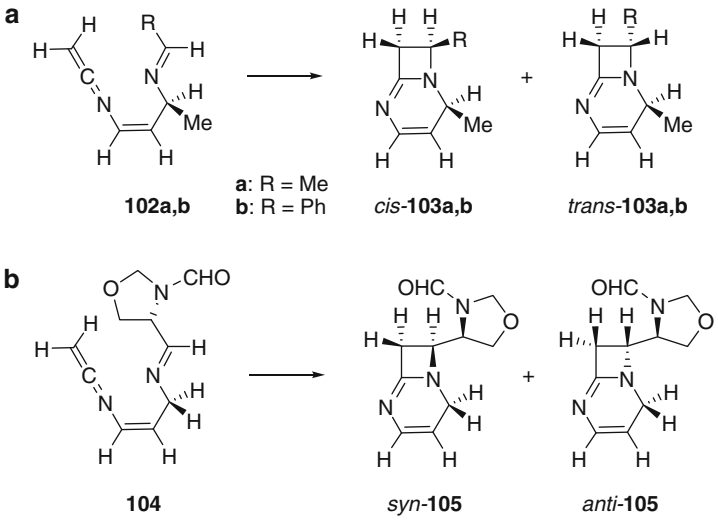
Scheme 23 Model reactions for the computational study of intermolecular (a) and intramolecular (b) reaction between ketenimines and imines



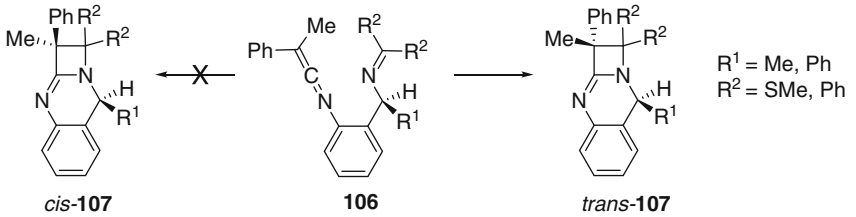
Scheme 24 Formation of *cis*- and *trans*-(**101**) from precursor (**98**)

The stereochemical outcome of these reactions was also studied computationally by introducing several chirality sources at different positions [90], as shown in Scheme 25.

The results obtained from reaction (a) in Scheme 25 at the B3LYP(SCRF)/6-31G* level showed a complete preference for *cis*-(**103a, b**) in good agreement with the experimental results obtained for related systems. The key element for the diastereoselectivity was the equatorial orientation of the methyl group of (**102a, b**) in the two transition structures, whereas in the case of *trans*-(**103a, b**) this methyl group occupies the axial position. This efficient diastereocontrol suggested that it could be exploited in systems such as that represented in Scheme 26 [91].



Scheme 25 Chiral induction in the intramolecular reaction of ketenimines (**102a,b**) and (**104**)



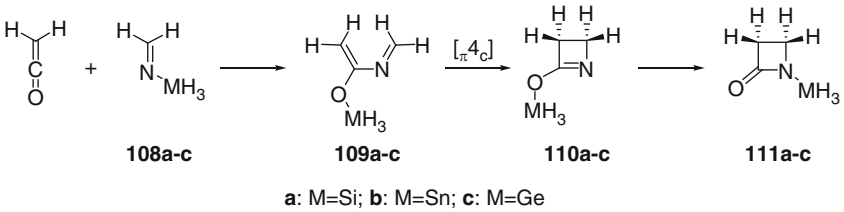
Scheme 26 Remote chiral induction in the intramolecular reaction of ketenimine (**106**)

The computational prediction was confirmed since only cycloadducts *trans*-(**107**) were obtained in the experimental study.

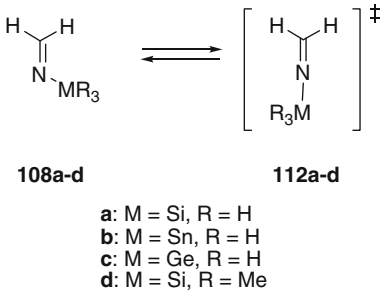
2.4 Reactions Involving Metalated Ketenes and/or Imines

As we have indicated previously, the reaction between ketenes and *N*-silyl imines was described by Pannunzio et al. [30–33] and constitutes an interesting version of the Staudinger reaction between ketenes and imines because of the isolation of the intermediate of silyloxyazadienes. Given its interest, this reaction has been studied by different groups [92–94].

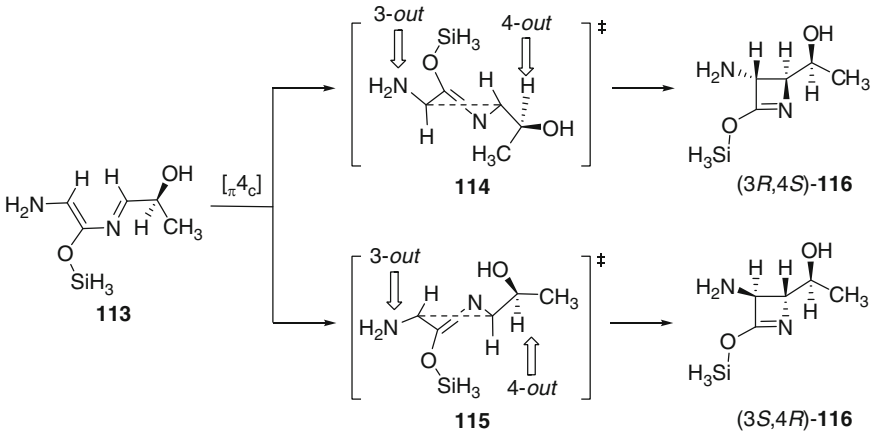
The parent reaction between ketene and *N*-silyl, *N*-stannyl and *N*-germanylimines (**108a,c**) has been studied at B3LYP/6-31G*, MP2/6-31G*, and B3LYP/6-311+G(d,p)&ECP levels of theory, both in the gas phase and in solution using



Scheme 27 Model reactions between ketene and *N*-MH_3 containing imines (**108a-c**) to form β-lactams (**111a-c**)



Scheme 28 Transition structures (**112a-d**) corresponding to the degenerate isomerization of imines (**108a-d**)



Scheme 29 Formation of intermediates (**116**) via conrotatory electrocyclization of homochiral azadiene (**113**)

SCRF methods [92–94] (Scheme 27). It was found that the first step of the reaction takes place with a concomitant N-O displacement of the MH_3 moiety, thus yielding neutral azadienic intermediates (**109**), whose electrocyclic conrotatory reaction yields cycloadducts (**110**). The N-substituted-β-lactams (**111**) are formed via another O-N pseudopericyclic displacement of the MH_3 unit.

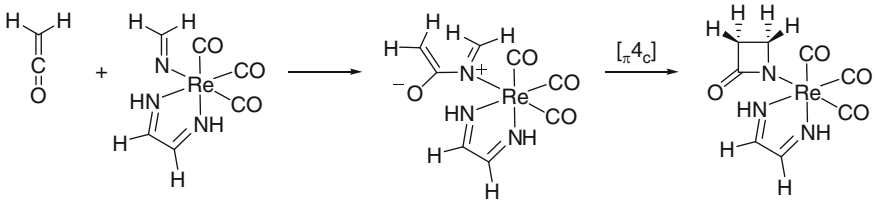
It is important to note that in imines (**108a-d**) (Scheme 28) the isomerization barrier was found to be significantly lower than the activation barrier leading to intermediates (**109**) [92–94]. This suggests that *trans*-β-lactams will be formed in all cases as sole or major products, in good agreement with the experimental evidence [30–33].

Finally, the effect of chiral groups at the 4-*out* position in the conrotatory transition structures (**114**, **115**) was studied at the B3LYP/6-31G* level. It was found that both transition structures are almost isoenergetic, thus showing that in electrocyclic conrotatory transition structures the 4-*outward* disposition is much less efficient as a source of chirality, a result already observed by Pannunzio et al. in their experimental studies [32, 33] (Scheme 29).

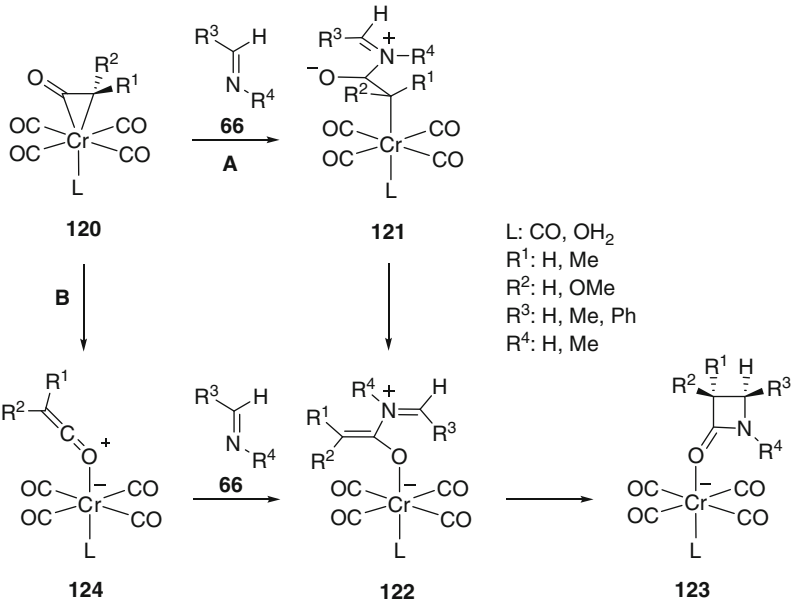
Another interesting example of the [2+2] reaction involving *N*-metalated imines has been reported by Pérez et al. [95]. In this reaction, the nucleophilic part is an *N*-Rhenaimine, whose simplified computational model is the structure (**117**) reported in Scheme 30. Calculations at the B3LYP/6-31G + G*(ECP) level of theory, revealed the known stepwise mechanism. However, the activation energy associated with the formation of the N1-C2 bond was found to be of only 3.1 kcal mol^{-1} whereas the computed activation energy of the conrotatory ring closure of (**118**) was 15.2 kcal mol^{-1}. Thus, calculations indicate an enhancement of the nucleophilicity of the imine (**117**) with respect to nonmetallic analogues.

Hegedus et al. discovered that irradiation of chromium–carbene complexes resulted in a photoinsertion of CO into the Cr–carbene bond to form Cr–ketene complexes [96, 97]. This opened novel routes to the preparation of valuable compounds via Cr–ketene chemistry. Among them, the reaction of metallated ketenes with imines was intensively explored [98–100]. Within this context, the reaction between several model Cr–ketenes (**120**) and imines was explored at the B3LYP/6-31G*&ECP level of theory [101, 102]. The mechanisms thus obtained are reported in Scheme 31.

It was found that one possible mechanism, denoted as (A) in Scheme 31, consists of the nucleophilic attack of imine (**66**) in the chromacyclopropanone complex (**120**) to yield intermediate (**121**). Isomerization of this [Cr]-C complex leads to [Cr]-O zwitterionic intermediate (**122**), whose electrocyclic reaction yields O-coordinated β-lactam (**123**). Alternatively, isomerization of (**120**) to the O-complexed ketene (**124**) permits the direct formation of zwitterionic intermediate



Scheme 30 Model reaction between ketene and *N*-metalated imine (**117**)

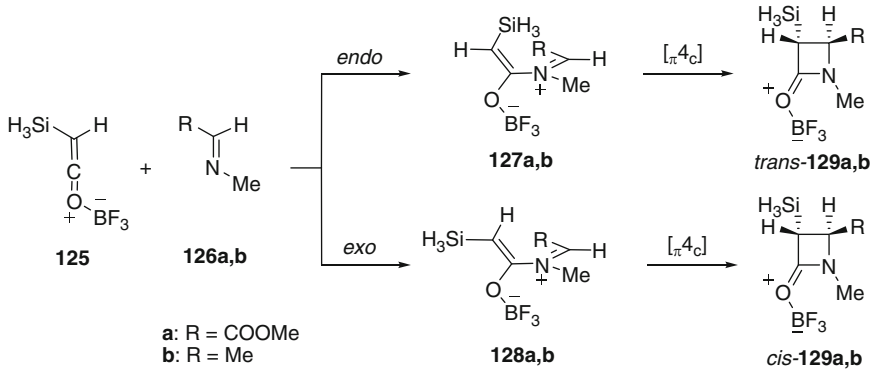


Scheme 31 Reaction between metalated ketenes (**120**) and (**124**) and imines (**66**) to yield coordinated β-lactams (**123**)

(**122**) (Scheme 31, Mechanism B). It was demonstrated that the experimental findings are better reproduced by Mechanism B [102].

2.5 Catalytic Versions of the [2+2] Cycloaddition Between Ketenes and Imines

The development of catalytic versions of the [2+2] version between ketenes and imines has attracted considerable attention in recent years because of the possibility of introducing chirality in the resulting cycloadducts in a very efficient manner [5, 6]. However, the number of computational papers dealing with this version of the reaction is scarce. Thus, Pons, Sordo et al. [103] studied at the B3LYP(PCM)/6-311 + G(d,p) level the reaction of ketene (**125**) with imines (**126a,b**) in the presence of BF_3 (Scheme 32). These authors found that the most likely mechanism involves the coordination of the Lewis acid with the ketene to yield a stepwise mechanism, which is led by the *endo* and *exo* attacks to the formation of *trans*- and *cis*-cycloadducts (**129a,b**) via intermediates (**127a,b**) and (**128a,b**), respectively. A factor that complicates the efficiency of the reaction is the interaction between the Lewis acid and the imine, thus resulting in stable intermediates that make difficult the completion of the cycloaddition and the catalytic cycle.



Scheme 32 Reaction between ketene (**125**) and imines (**126a, b**) to yield *cis*- and *trans*-β-lactams (**129a, b**)

Another more efficient catalytic version of the reaction consists of the interaction of ketones with chiral amines [6] to form enolate-like intermediates that are able to react with electrophilic imines. It has been postulated that this reaction takes place via the catalytic cycle depicted in Scheme 33. The chiral amine (**130**) attacks the sp-hybridized carbon atom of ketene (**2**) to yield intermediate (**131**). The Mannich-like reaction between (**131**) and the imine (**2**) yields the intermediate (**132**), whose intramolecular addition–elimination reaction yields the β-lactam (**1**) and regenerates the catalyst (**130**). In spite of the practical interest in this reaction, little work on its mechanism has been reported [104, 105]. Thus, Lectka et al. have performed several MM and B3LYP/6-31G* calculations on structures such as (**131a-c**) in order to ascertain the nature of the intermediates and the origins of the stereocontrol (Scheme 33). According to their results, conformations like those depicted in Scheme 33 for intermediates (**131**) account for the chiral induction observed in the final cycloadducts.

3 The [2+2] Cycloaddition Between Isocyanates and Alkenes

3.1 General Mechanism

As in the case of the reaction between ketenes and imines, the [2+2] cycloaddition between isocyanates and alkenes [106, 107] can take place via concerted and stepwise mechanisms. However, with the exception of highly nucleophilic alkenes (vide infra), concerted mechanisms were postulated, since isocyanates are suitable candidates to act as antarafacial partners in thermal [2+2] cycloadditions (Fig. 1). Aside from the $[_{\pi}2_{s} + {}_{\pi}2_{a}]$ mechanism, in principle $[_{\pi}2_{s} + ({}_{\pi}2_{s} + {}_{\pi}2_{s})]$ [108] and $[_{\pi}2_{s} + ({}_{\pi}2_{s} + {}_{w}2_{s})]$ [109] mechanisms can be envisaged (Fig. 5).

Scheme 33 General catalytic cycle for the reaction between ketenes and imines to yield β-lactams via zwitterionic intermediates (**131a-c**) and (**132**)

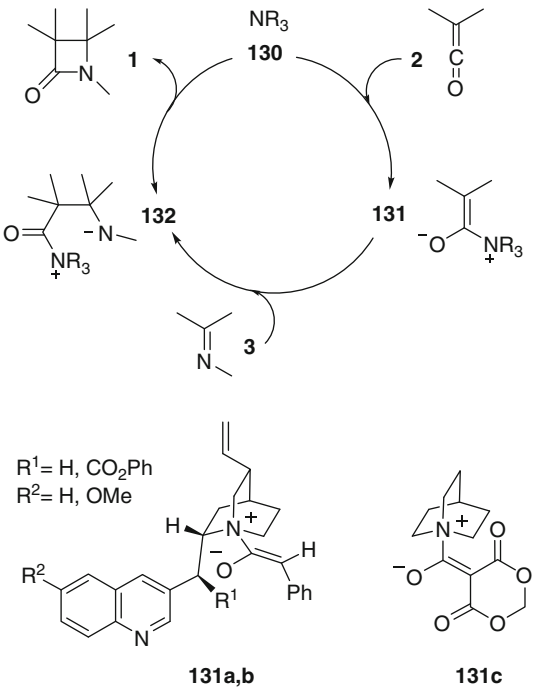
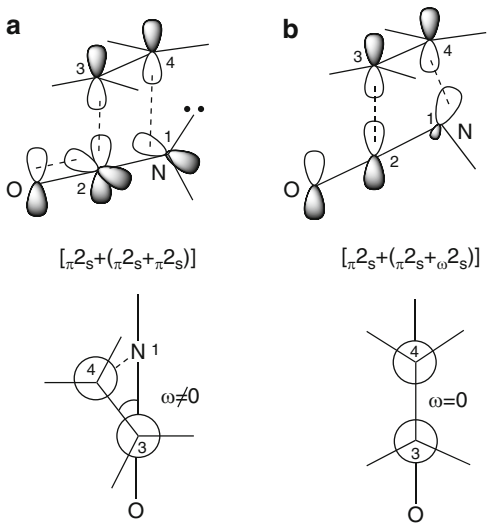


Fig. 5 Possible concerted mechanisms for the reaction between alkenes and isocyanates



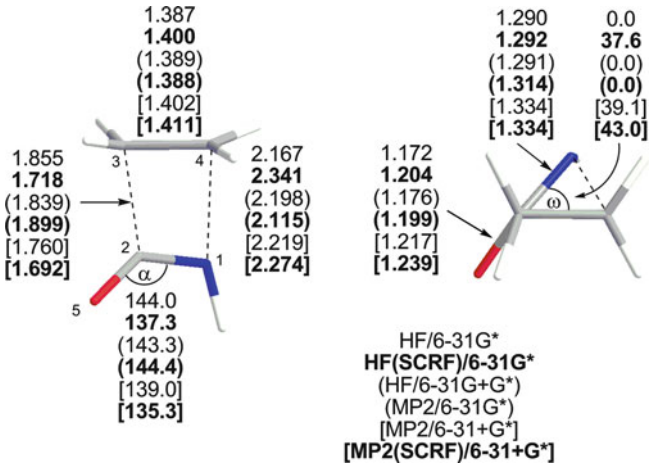


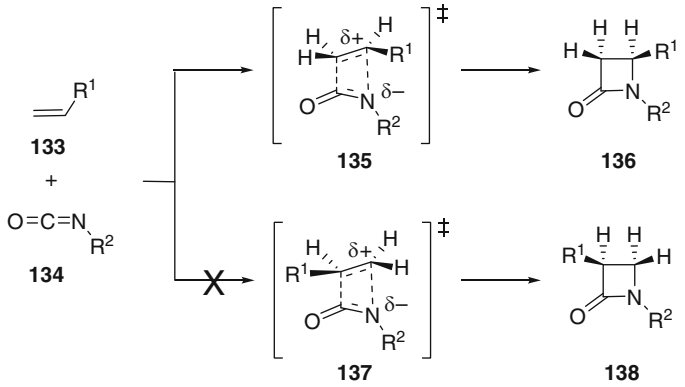
Fig. 6 Different geometries for the transition structure associated with the reaction between ethylene and isocyanic acid. Bond distances and angles are in Å and deg., respectively. α Denotes the bond angle determined by N1, C2, and O5 atoms. ω Stands for the dihedral angle formed by N1, C2, C3, and C4 atoms

If we consider the $[_{\pi}2_s + (_{\pi}2_s + {}_{\pi}2_s)]$ mechanism, then the lateral overlap between N1 and C4 pAOs leads to a C_1-symmetric transition structure and a nonzero value for the ω = N1-C2-C3-C4 dihedral angle (Fig. 5), as well as to larger N1-C4 distances. In contrast, the $[_{\pi}2_s + (_{\pi}2_s + {}_{\omega}2_s)]$ interaction leads to a C_s transition state for the reaction between ethylene and isocyanic acid. Both geometries were found for this reaction at different theoretical levels [109–111] (Fig. 6). Thus, at the RHF level the transition structure was found to be C_s-symmetric [110, 111], whereas the RHF(SCRF, MP2 and MP2(SCRF) leads to ω values of ca. 40 deg. Thus, inclusion of solvent effects and/or electron correlation favor the $[_{\pi}2_s + (_{\pi}2_s + {}_{\pi}2_s)]$ mechanism. This behavior was also observed with substituted alkenes [109].

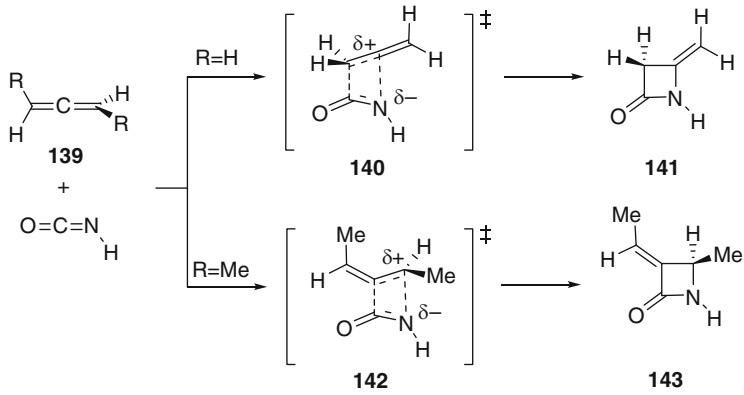
Williams and Whitehead [112] reported a computational study on this reaction using semiempirical methods. They found that MNDO and AM1 geometries corresponding to these reactions are significantly different from ab initio geometries, whereas PM3 activation energy barriers were found to be in better agreement.

3.2 Regiochemistry and Sterochemistry

The regiochemistry of the reaction has been studied computationally (Scheme 34) [109]. It was found that the asynchronicity and the polar nature of the transition structures favor the formation of the 4-substituted cycloadducts (**136**) via transition structures (**135**) when electron-releasing groups are present. The alternative transition structures (**137**) were calculated to be of much higher energy.



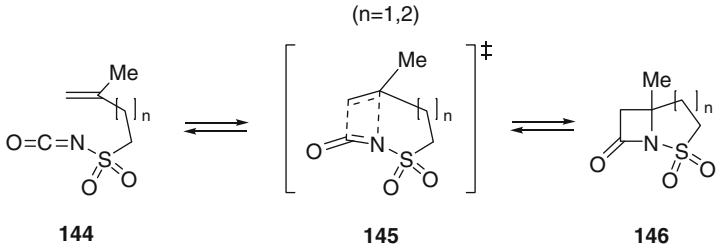
Scheme 34 Formation of 4- and 3-substituted β-lactams via concerted [2+2] cycloaddition between alkenes (**133**) and isocyanates (**134**)



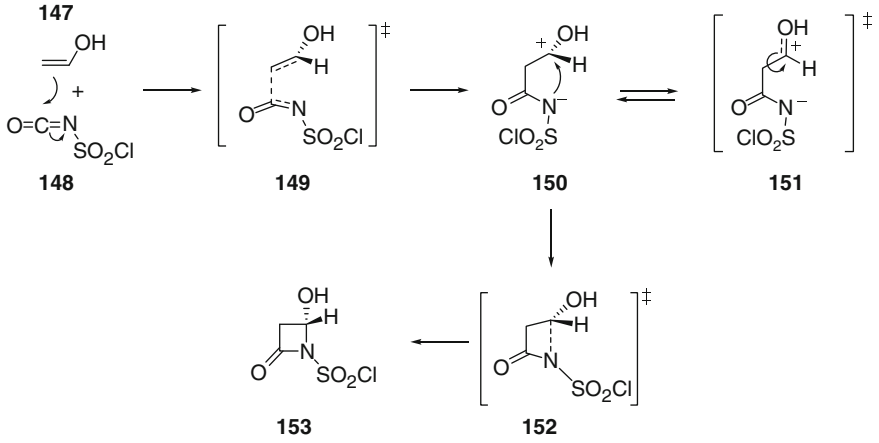
Scheme 35 Regiochemistry of the reaction between allenes (**139**) and isocyanic acid

The reaction between isocyanic acid and allenes was also studied and showed different regiochemistries depending on the substitution pattern (Scheme 35). Thus, in the simplest case (not studied experimentally), the formation of the 4-substituted cycloadduct (**141**) is predicted to be strongly favored, mainly because of the lower distortion of the allenic moiety at the transition structure (**140**). In contrast, substituted allenes such as 1,3-dimethylallene form the 3-alkylidene derivative (**143**) via a more stabilized transition structure like (**142**), in good agreement with the experimentally observed regiochemistry[113–115].

Some intramolecular [2+2] cycloadditions of sulfonyl isocyanate-olefins have been studied by Metz et al. [116]. These authors found that the intramolecular reaction depicted in Scheme 36 was calculated to be endergonic at the B3LYP/6-31G* and B3LYP(PCM)/6-31G* levels, the corresponding free activation energies being in the



Scheme 36 Intramolecular [2+2] cycloaddition between alkenes and isocyanates via transition structures (**145**)

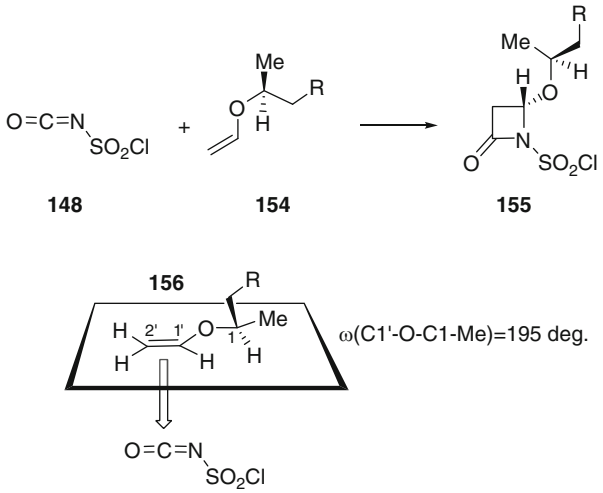


Scheme 37 Stepwise mechanism computed for the reaction between ethenol (**147**) and chlorosulfonyl isocyanate (**148**)

range 43.0–50.1 kcal mol^{-1}, thus explaining the failure in the obtention of cycloadducts (**146**) by reaction of isocyanates (**144**) in refluxing benzene.

The stereochemistry of the reaction between alkenes and isocyanates has been studied experimentally [117] and computationally [109]. It was found that the concerted nature of the reaction should result in retention of configuration of the starting olefin. However, in one case in which a strong π-donor was present it was possible to characterize a stepwise mechanism (Scheme 37). Reaction between vinyl alcohol (**147**) and chlorosulfonyl isocyanate (**148**) was calculated to proceed at the MP2(SCRF)/6-31G*//RHF(SCRF)/6-31G* level via zwitterionic intermediate (**150**), whose rotation about the C4-OH bond through transition structure (**151**) opens the possibility of a loss of stereoselectivity in this kind of reactions, a phenomenon observed in some cases in the reaction between (**148**) and vinyl ethers [118].

Although the reaction profiles of the reaction between isocyanates and chiral alkenes has not been studied computationally, some proposals have been made



Scheme 38 Formation of chiral β-lactams (**155**) from chlorosulfonyl isocyanate (**148**) and homochiral enol ethers (**154**)

based on early transition structures expected when a good matching between the nucleophilic character of the alkene and the electrophilicity of the isocyanate is achieved. Thus Chmielewski et al. [119] have proposed that the excellent stereocontrol observed in the reaction between (**148**) and chiral enol ethers (**154**) can be attributed to the minimum-energy (and NOE-compatible) conformations of type (**156**) (Scheme 38).

4 Concluding Remarks

The mechanistic studies carried out on the [2+2] cycloaddition reactions leading to the formation of β-lactams constitute a fruitful example of synergy between theory and experiment.

There is a general agreement on the stepwise nature of the [2+2] cycloaddition between ketenes and imines. The first step consists of a nucleophilic attack of the iminic lone pair on the *sp*-hybridized atom of the ketene to form a zwitterionic intermediate. The subsequent four-electron conrotatory electrocyclization leads to the corresponding β-lactam. The final stereochemical outcome of the reaction depends on the combination of the following features: (1) *endo*/*exo* attack of the imine on the ketene; (2) *inward*/*outward* disposition of the substituents at the conrotatory transition structure; and (3) relevance of the isomerization pathways, including those of the starting imines.

In contrast, the [2+2] cycloaddition between alkenes and isocyanates is in general concerted (although highly asynchronous) and consists of $[{}_{\pi}2_{s} + ({}_{\pi}2_{s} + {}_{\pi}2_{s})]$ mechanism rather than a $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ process. The polarity of the transition

state of this reaction determines the regiochemistry of the reaction, the most important ERG occupying the 4-position of the β-lactam ring in formation. In some cases where there are strong π-donating groups, solvent and substituent effects can lead to a stepwise mechanism.

Further explorations on these reactions should lead to novel β-lactam rings showing interesting properties. We think that, in these developments, computational chemistry will be useful not only to *explain* but also to *predict* the behavior of novel substituents or catalysts.

References

1. Georg GI (1993) The organic chemistry of β-lactams. VCH, New York
2. Katritzky AR, Rees CW, Scriven EFV (eds) (1996) Comprehensive heterocyclic chemistry II. Vol. 1B. Pergamon, New York, pp 507–720
3. Bruggink A (ed) (2001) Synthesis of β-lactams antibiotics. Chemistry, biocatalysis and process integration. Kluwer, Dordrecht
4. Singh GS (2003) Tetrahedron 59:7631
5. Magriotis PA (2001) Angew Chem Int Ed 40:23
6. France S, Weatherwax A, Taggi AE, Lectka T (2004) Acc Chem Res 37:592
7. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (1999) Eur J Org Chem 3223
8. Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2004) Curr Med Chem 11:1837
9. Gómez-Gallego M, Mancheño MJ, Sierra MA (2000) Tetrahedron 56:5743
10. Audier HE, Fétizon M, Kagan HB, Luche JL (1967) Bull Soc Chim Fr 2297
11. Palomo C, Cossío FP, Odriozola JM, Oiarbide M, Ontoria JM (1991) J Org Chem 56:4418
12. Staudinger H (1908) Liebigs Ann Chem 356:51
13. Tidwell TT (2006) Ketenes II. Wiley, Hoboken, pp 500–513
14. Fu N, Tidwell TT (2008) Tetrahedron 64:10465
15. Cossío, FP, Arrieta A., Sierra MA (2008) Acc Chem Res 41:925
16. Graf R (1963) Ann 661:111
17. Moriconi EJ, Kelly JF (1986) J Am Chem Soc 88:3657
18. Oligaruso MA, Wolfe JF (1993) In: Patai S, Rappoport Z (eds) Synthesis of lactones and lactams. Wiley, Chichester, pp 162–168
19. Borsuk K, Kazimierski A, Solecka J, Urbanczyk-Lipkowska Z, Chmieleswski M (2002) Carbohydrate Res 337:2005
20. Woodward RB, Hoffmann R (1969) Angew Chem Int Ed Engl 8:781
21. Cooper RDG, Daugherty BW, Boyd DB (1987) Pure Appl Chem 59:485
22. Fang DC, Fu XY (1992) Int J Quantum Chem 43:669
23. Xu ZF, Fang DC, Fu XY (1994) J Mol Struc (Theochem) 305:191
24. Assfeld X, Lopez R, Ruiz-Lopez MF, González J, Sordo TL, Sordo JA (1995) J Mol Struct (Theochem) 331:1
25. Sordo JA, González J, Sordo TL (1992) J Am Chem Soc 114:6249
26. Cossío FP, Ugalde JM, Lopez X, Lecea B, Palomo C (1993) J Am Chem Soc 115:995
27. Venturini A, González J (2002) J Org Chem 67:9089
28. Pancasky J, Chang JS, Brown DW, Schwarz WJ (1982) J Org Chem 47:2233
29. Couturier-Tamburelli I, Aycard J-P, Wong MW, Wentrup C (2000) J Phys Chem A 104:3466
30. Bandini E, Martelli G, Spunta G, Bongini A, Pannunzio M (1996) Tetrahedron Lett 37:4409
31. Bandini E, Martelli G, Spunta G, Bongini A, Pannunzio M (1996) Synlett 1017
32. Bandini E, Favi G, Martelli G, Pannunzio M, Piersanti G (2000) Org Lett 2:1077
33. Pannunzio M, Bongini A, Tamanini E, Campana E, Martelli G, Vicennati P, Zanardi I (2003) Tetrahedron 59:9577

34. Dolrier WR Jr, Korionak H, Houk KN, Sheu C (1996) Acc Chem Res 29:471
35. Kirmse W, Rondan NG, Houk KN (1984) J Am Chem Soc 106:7989
36. Rondan NG, Houk KN (1985) J Am Chem Soc 107:2099
37. Niwayama S, Kallel EA, Spellmeyer DC, Sheu C, Houk KN (1996) J Org Chem 61:2813
38. Assfeld X, Sordo JA, González J, Ruiz-López MF, Sordo TL (1993) J Mol Struct (Theochem) 287:193
39. Assfeld X, Ruiz-López MF, González J, López R, Sordo JA, Sordo TL (1994) J Comput Chem 15:479
40. Barcza MV, Carneiro JW de M, Serra AA, Barboza JCS (1997) J Mol Struct (Theochem) 394:281
41. Moore HW, Hughes G, Srinivasachar K, Fernandez M, Nguyen NV, Schoon D, Tranne A (1985) J Org Chem 50:4231
42. Arrrastia I, Arrieta A, Ugalde JM, Cossío FP, Lecea B (1994) Tetrahedron Lett 35:7825
43. Lecea B; Arrastia I, Arrieta A, Roa G, Lopez X, Arriortua MI, Ugalde JM, Cossío FP (1996) J Org Chem 61:3070
44. Rossi E, Abbiati G, Pini E (1997) Tetrahedron 44:14107
45. Mazumdar SN, Mahanan MP (1991) Tetrahedron 47:1473
46. Mazumdar SN, Mukherjee S, Sharma AK, Sengupta D, Mahajan MP (1994) Tetrahedron 50:7579
47. Dey PD, Sharma AK, Bharatam PV, Mahajan MP (1997) Tetrahedron 53:13829
48. Bharatam PV, Kumar RS, Mahajan MP (2000) Org Lett 2:2725
49. Hegedus LS, Montgomery J, Narukawa Y, Snustad DC (1991) J Am Chem Soc 113:5748
50. López R, Sordo TL, Sordo JA, González J (1993) J Org Chem 5A:7036
51. López R, Suárez D, Ruiz-López MF, González J, Sordo JA, Sordo TL (1995) J Chem Soc Chem Commun:1677
52. Arrieta A, Lecea B, Cossío FP (1998) J Org Chem 63:5869
53. Dumas S, Hegedus LS (1994) J Org Chem 59:4967
54. Evans DA, Sjögren EB (1985) Tetrahedron Lett 31:6317
55. Jackson BG, Gardner EB, Heath PC (1990) Tetrahedron Lett 31:6317
56. Muller M, Bur D, Tschamber T, Streith J (1991) Helv Chim Acta 74:767
57. Boger DL, Myers JB Jr (1991) J Org Chem 56:5385
58. Palomo C, Cossío FP, Cuevas C, Lecea B, Mielgo MA, Román P, Luque A, Martinez-Ripoll M (1992) J Am Chem Soc 114:9360
59. Hubschwerlen C, Schmid G (1983) Helv Chim Acta 66:2206
60. Banik BK, Manhas MS, Kaluza Z, Barakat KJ, Bose AK (1992) Tetrahedron Lett 33:3603
61. Evans DA, Williams JM (1988) Tetrahedron Lett 29:5065
62. Cossío FP, Arrieta A, Lecea B, Ugalde JM (1994) J Am Chem Soc 116:2085
63. Macías A, Alonso E, del Pozo C, Venturini A, González J (2004) J Org Chem 69:7004
64. Martín-Zamora E, Ferrete A, Llera JM, Muñoz JM, Pappalardo RR, Fernández R, Lassaletta JM (2004) Chem Eur J 10:6111
65. Jiao L, Liang Y, Xu JX (2006) J Am Chem Soc 128:6060
66. Arrieta A, Ugalde JM, Cossío FP, Lecea B (1994) Tetrahedron Lett 35:4465
67. Bose AK, Chiang YH, Manhas MS (1972) Tetrahedron Lett 4091
68. Banik BK, Lecea B, Arrieta A, de Cózar A, Cossío FP (2007) Angew Chem Int Ed 46:3028
69. Banik BK, Becker FF (2000) Tetrahedron Lett 41:6551
70. Banik I, Hackfield L, Banik BK (2003) Heterocycles 59:505
71. Liang Y, Jiao L, Zhang S, Xu J (2005) J Org Chem 70:334
72. Wang Y, Liang Y, Jiao J, Du D-M, Xu J (2006) J Org Chem 71:6983
73. Li B, Wang Y, Du D-M, Xu J (2007) J Org Chem 72:990
74. Arrieta A, Lecea B, Palomo C (1987) J Chem Soc Perkin Trans I 845
75. Bose AK, Anjaneyulu B, Bhattacharaya SK, Manhas MS (1967) Tetrahedron 23:4769
76. Oshiro Y, Komatsu M, Vesaka M, Agawa T (1984) Heterocycles 22:549

77. Pérez-Faginas P, Alkorta I, García-López MI, González-Muñiz R (2008) Tetrahedron Lett 49:215
78. Allen AD, Godoy J, Fu N, Nagy M, Spadaro S, Tidwell TT, Vukovic S (2008) J Am Chem Soc 130:2386
79. López R, Suárez D, Sordo TL, Ruiz-López MF (1998) Chem Eur J 4:328
80. Schaumann E (1976) Chem Ber 109:906
81. De Poortere M, Marchand-Brynaert J, Ghosez L (1974) Angew Chem Int Ed Engl 13:267
82. Ghosez L, Bogdan S, Cérésiat M, Frydrych C, Marchand-Brynaert J, Moya-Portuguez M, Huber I (1987) 59:393
83. Ghosez L, Marchand-Brynaert J (1991) In: Trost BM, Fleming I, Paquette LA (eds) Comprehensive organic synthesis. Pergamon Press, Oxford, pp 85–122
84. Arrieta A, Cossío FP, Lecea B (1999) J Org Chem 64:1831
85. Van Camp A, Grossens D, Moya-Portuguez M, Marchand-Brynaert J, Ghosez L (1980) Tetrahedron Lett 21:3081
86. Arnold B, Regitz M (1979) Angew Chem Int Ed Engl 18:320
87. Alajarín M, Molina P, Vidal A (1996) Tetrahedron Lett 37:8945
88. Alajarín M, Molina P, Vidal A, Tovar F (1997) Tetrahedron 53:13449
89. Alajarín M, Vidal A, Tovar F, Arrieta A, Lecea B, Cossío FP (1999) Chem Eur J 5:1106
90. Cossío FP, Arrieta A, Lecea B, Alajarín M, Vidal A, Tovar F (2000) J Org Chem 65:3633
91. Alajarín M, Vidal A, Tovar F, Ramírez de Arellano MC, Cossío FP, Arrieta A, Lecea B (2000) J Org Chem 65:7512
92. Arrieta A, Cossío, FP, Lecea B (2000) J Org Chem 65:8458
93. Bongini A, Pannunzio M, Piersanti G, Bandini E, Martelli G, Spunta G, Venturini A (2000) J Org Chem 65:2379
94. Campomames P, Menéndez MI, Sordo TL (2005) J Phys Chem A 109:11022
95. Hevia E, Pérez J, Riera V, Miguel D, Campomames P, Menéndez MI, Sordo TL, García-Granda S (2003) J Am Chem Soc 125:3706
96. McGuire MA, Hegedus LS (1982) J Am Chem Soc 104:5538
97. Hegedus LS (1997) Tetrahedron 53:4105
98. Hegedus LS, de Weck G, D'Andrea S (1988) J Am Chem Soc 110:2122
99. Hegedus LS (1995) In: Abel EW, Stone FGA, Wilkinson G (eds) Comprehensive organometallic chemistry II, vol 12. Pergamon Press, Oxford, p 549
100. Hegedus LS (1995) Acc Chem Res 28:299
101. Arrieta A, Cossío FP, Fernández I, Gómez-Gallego M, Lecea B, Mancheño MJ, Sierra MA (2000) J Am Chem Soc 122:11509
102. Fernández I, Sierra MA, Mancheño MJ, Gómez-Gallego M, Cossío FP (2008) J Am Chem Soc 130:13892
103. Pelotier B, Rajzmann M, Pons J-M, Campomames P, López R, Sordo TL (2005) Eur J Org Chem 2599
104. Taggi AE, Hafez AM, Wack H, Young B, Ferraris D, Lectka T (2002) J Am Chem Soc 124:6626
105. Taggi AE, Hafez AM, Dudding T, Lectka T (2002) Tetrahedron 58:8351
106. Graf R (1968) Angew Chem Int Ed Engl 7:172
107. Moriconi EJ, Crawford WC (1968) J Org Chem 33:370
108. Pasto DJ (1979) J Am Chem Soc 101:37
109. Cossío FP, Roa G, Lecea B, Ugalde JM (1995) J Am Chem Soc 117:12306
110. Cossío FP, Lecea B, Lopez X, Roa G, Arrieta A, Ugalde JM (1993) J Chem Soc Chemm Commun 1450
111. Fang D-C, Xu Z-F, Fu X-Y (1995) J Mol Struc (Theochem) 333:159
112. Williams CI, Whitehead MA (1999) J Mol Struc (Theochem) 491:93
113. Buynak JD, Rao MN, Pajouhesh H, Chandrasekran RY, Finn K (1985) J Org Chem 50:4245
114. Lysek R, Furman B, Kaluza Z, Frelek J, Suwinska K, Urbanczyk-Lipowska Z, Chmielewski M (2000) Tetrahedron:Asymmetry 11:3131

115. Lysek R, Krajewski P, Urbanczyk-Lipowska Z, Furman B, Kaluza Z, Kozerski L, Chmielewski M (2000) J Chem Soc Perkin Trans 2:61
116. Freitag D, Drees M, Goutal S, Strassner T, Metz P (2005) Tetrahedron 61:5615
117. Furman B, Borsuk K, Kaluza Z, Lysek R, Chmielewski M (2004) Curr Org Chem 8:463
118. Effenberger F, Kiefer G (1967) Angew Chem Int Ed Engl 6:951
119. Furman B, Krajewski P, Kaluza Z, Thürmer R, Voelter W, Kozerski L, Williamson M, Chmielewski M (1999) J Chem Soc Perkin Trans 2:217

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Novel Anticancer β-Lactams

Bimal K. Banik, Indrani Banik, and Frederick F. Becker

Abstract Stereocontrolled synthesis of racemic and chiral novel β-lactams using polyaromatic imines has been accomplished. Domestic and automated microwave-induced reactions have been investigated for the preparation of these types of β-lactams. A preliminary mechanism of this reaction has been advanced. Formation of *trans*-β-lactams has been explained through isomerization of the enolates formed during the reaction of acid chloride with imines in the presence of tertiary base. A donor–acceptor complex pathway has been believed to be involved in the formation of *cis*-β-lactams. The effect of a *peri* hydrogen has been found to be significant in controlling the stereochemistry of the β-lactams. Structure–activity relationship has identified β-lactams with anticancer activity. The presence of an acetoxy group has proven very important for anticancer activity. The preparation and mechanism of action of several other new anticancer β-lactams have also been explored.

Keywords β-Lactams · Anticancer agents · Mechanism of action · Staudinger reaction

Contents

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Abbreviations

DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
h	Hour (s)
IC_{50}	Cell growth inhibition at 50% concentration
NMR	Nuclear magnetic resonance
PAH	Polyaromatic hydrocarbon
SN^2	Substitution nucleophilic bimolecular

1 Introduction

The β-lactams have had a variety of clinical applications. In addition to penicillins and cephalosporins, a number of biologically relevant enzymes have been targeted by these types of compounds [1–4]. The usefulness of effective β-lactam antibiotics and β-lactamase inhibitors has motivated chemists and scientists to design and synthesize new β-lactams [5]. β-Lactams have also served as starting compounds in the synthesis of various heterocyclic compounds of biological importance [6–10]. Hydroxy β-lactam derivatives have been the key materials in the semi-synthesis of paclitaxel (Taxol) and docetaxel (Taxotere) [11]. The medicinal application of β-lactams as therapeutic agents for lowering plasma cholesterol levels has been published [12–15]. Synthetic and biological studies of human leukocyte elastase inhibitory mechanisms of these classes of compounds have also been reported [16]. A few remarkable developments, such as catalytic asymmetric [17–21] and polymer-supported [22–29] synthesis of β-lactams, have been realized in recent years.

On this basis of several developments, the searches for clinically useful β-lactams that are antibacterial and have other medicinal values have become the focus of intense investigations [30–34].

Various methods for the synthesis of β-lactams [35–52] and several biologically active compounds have been demonstrated by our group ([53–60]; also see [61]; [62–74]). In continuation of our research in this area, we reported stereocontrolled synthesis of novel anticancer β-lactams starting from imines, with pendent polyaromatic substituents [69–74]. Although chemistry of β-lactam as antibiotics is very rich, studies on these as anticancer agents have been very poor. Recently, a few other groups demonstrated the synthesis and studied the mechanism of action of anticancer β-lactams. In spite of the notable developments in the area of anticancer research, novel compounds with less toxicity are required. Based on our and others work, we realize that novel β-lactams can be identified as anticancer agents that may have less toxicity but increased activity against cancer cells.

Analyzing the structures of the products and moderate anticancer activities of some of our compounds, it had come to our attention that more potent but less toxic analogues could be made by adopting principle of cyclic and noncyclic version of organic compounds. Structures **1** and **2** suggested that a ring closure reaction using N_1 and C_4 would result in β-lactam **3**. On this basis, it was envisioned that β-lactam **3** of the general structure as shown in Fig. 1 would work as a conformationally constrained analogue of our open-chain compounds (**1** and **2**) that had shown anticancer activity against various cancer cell lines in vitro. The initial target for this study was to prepare substituted amines and amides with polyaromatic substituents, with the goal of investigating such compounds for potential anticancer activity. Based on the promising data on amides, it was then decided to extend the scope of study by including β-lactams.

It has been confirmed that conformationally constrained molecules have a greater effect on biological properties when compared to the relatively flexible open-chain compounds in many cases (e.g., see [75–82]; for a few examples, see [83–92]). For example, UAB-8, a conformationally constrained analogue of

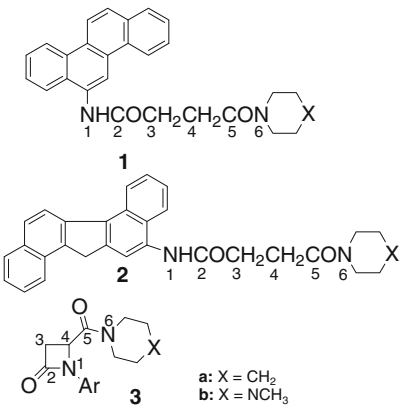


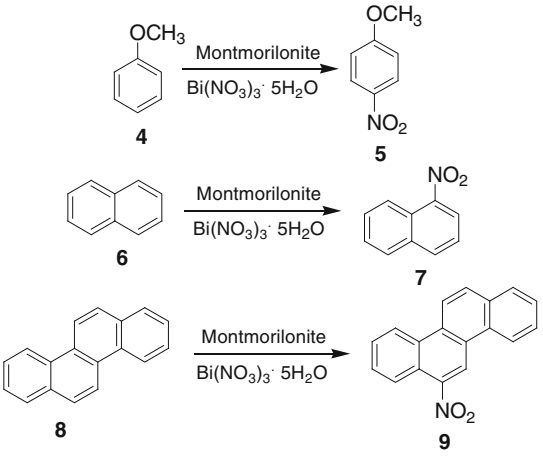
Fig. 1 Conformationally restricted compounds

retinoic acid, had favorable toxicological properties relative to the nonrestricted structures. Tricyclic indole analogues of melatonin demonstrated superiority of the *cis*-constrained isomer over *trans*-constrained isomer as an agonist. Phenalene derivatives appeared to be promising restricted ligands for melatonin receptors. Anesthetic steroids that modulate $GABA_A$ receptors were investigated. The discovery of conformationally constrained Taxol analogues was reported. Conformationally restricted compounds that were more effective include antibiotic linezolide and nicotine derivatives.

On the basis of these experiments, we anticipated that conformationally constrained analogues of our open chain diamides (**1** and **2**) may increase activity against cancer cell lines. In β-lactam chemistry, this kind of hypothesis had been tested, and it was established that certain β-lactams are more effective at lowering cholesterol in human plasma when compared to open-chain substrates [12–15]. Therefore, preparation of β-lactams of type **3** and related compounds was necessary to investigate a comparative study with diamides **1** and **2**.

2 Preparation of Starting Compounds

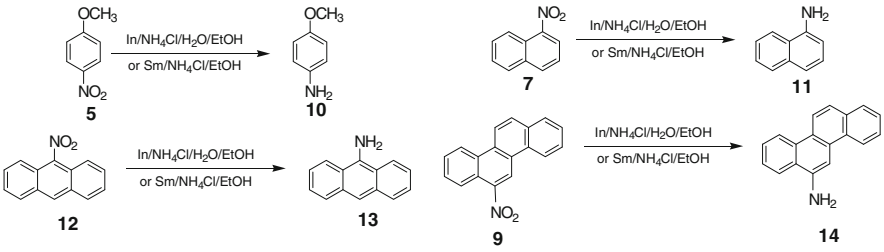
Many polycyclic aromatic amines and aldehydes are commercially available, but their supply is very limited. Preparation of these starting materials is necessary for studying the β-lactam formation reaction [93]. Nitro compounds are the precursors for the amines. An important task was to prepare polycyclic aromatic nitro compounds, particularly those of chrysene, phenanthrene, pyrene, and dibenzofluorene in good yield. Nitration of these hydrocarbons with concentrated nitric acid in sulfuric acid is a widely used reaction for this purpose. Our research culminated in facile synthesis of polyaromatic nitro derivative **9** starting from polyaromatic hydrocarbons (PAHs) **8** through the use of bismuth nitrate impregnated with clay (Scheme 1) ([94, 95]; for some examples of bismuth nitrate-catalyzed reactions



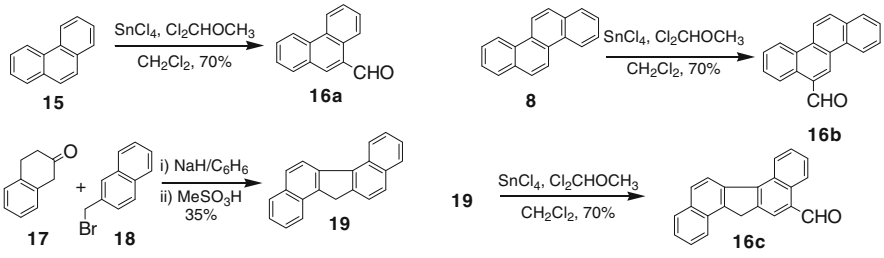
Scheme 1 Synthesis of polyaromatic nitro compounds

from our laboratory, see [66, 96–104]). The advantages of this method over the classical methods are numerous.

Several methods can be used to prepare polyaromatic amines from polyaromatic nitro compounds. Catalytic hydrogenation, catalytic transfer hydrogenation, and several new methods have been found to be suitable for the reduction of polyaromatic nitro compound **9** to polyaromatic amine **14**. However, these methods were not suitable with PAH derivatives. Indium- ([105, 106]; for some examples of indium-induced reactions from our laboratory, see [107–109]) and samarium-induced ([105–111]; for some examples of samarium-induced reactions from our laboratory, see [112–121]) reduction methods offered good opportunities to achieve this goal. For example, the indium-induced reaction was performed in water in the presence of ammonium chloride, while the samarium-induced reaction elicited a product within a few minutes of using ultrasound (Scheme 2). The indium-induced method was accomplished in 10 g scale. Synthesis of polyaromatic aldehydes, particularly phenanthrene **16a**, chrysene **16b**, and dibenzofluorene **16c**, was performed using a previously described method [93] from their respective hydrocarbons **15**, **8**, and **19**. Synthesis of dibenzofluorene hydrocarbon **19** was achieved following one-pot method by reacting β-tetralone **17** and naphthyl bromide **18** in the presence of sodium hydride and subsequent acid-induced reaction (Scheme 3). This process included alkylation, cyclodehydration, and aromatization in a one-pot operation.



Scheme 2 Synthesis of aromatic amino compounds



Scheme 3 Synthesis of dibenzofluorene

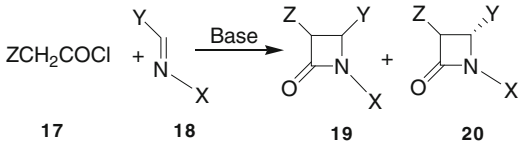
3 Synthesis of Novel β-Lactams with Polyaromatic Imines

The Staudinger reaction has been extensively studied for the synthesis of monocyclic β-lactams (Scheme 4, e.g., **19** and **20**) [37]. An imine **18**, a tertiary base (triethylamine), and acid chloride **17** (or equivalent) are required for this reaction.

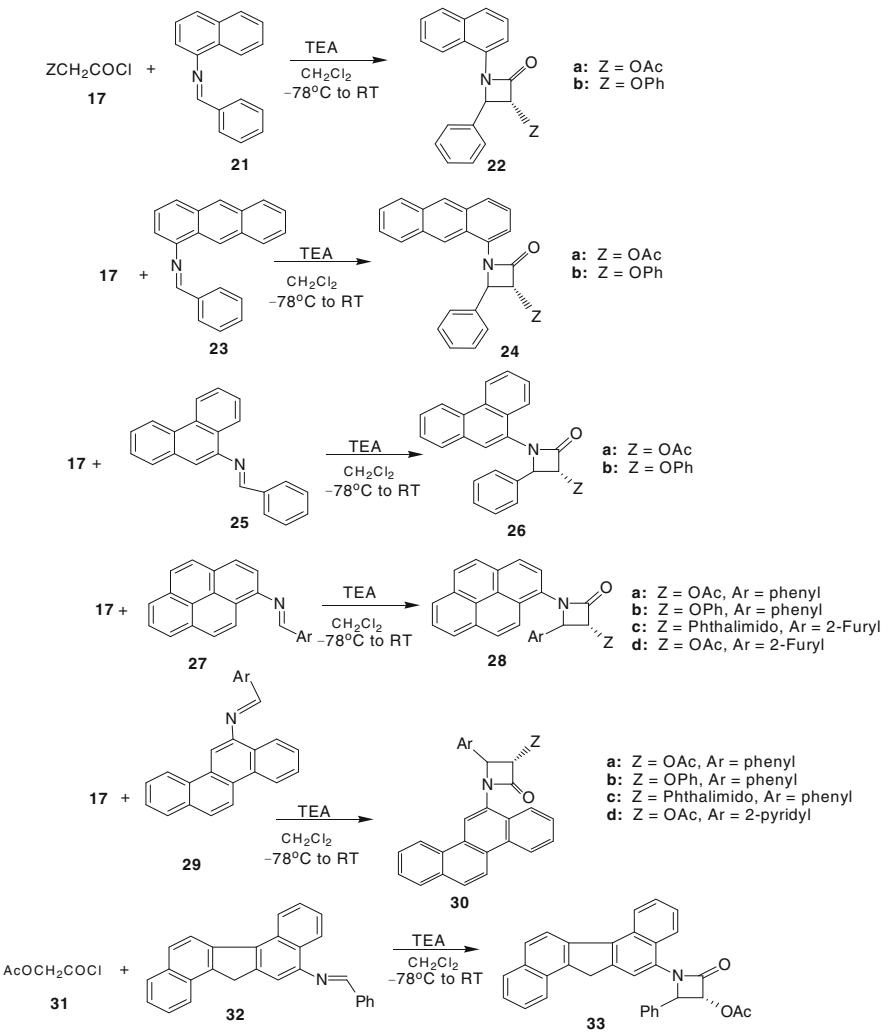
The stereochemistry of the resulting β-lactams may vary depending upon the conditions (Scheme 5). The reaction of acyloxy, alkoxy, and nitrogen-containing acid chloride with diaryl imines produces *cis*-β-lactams under Staudinger reaction conditions [122]. In contrast, reaction of polyaromatic imines (**21**, **23**, **25**, **27**, **29**, and **36**) with acetoxy, phenoxy, and phthalimido acid chloride in the presence of triethyl amine at −78°C to room temperature produced exclusively *trans*-β-lactams (**22**, **24**, **26**, **28**, **30**, and **33**). *cis*-β-Lactams were expected according to the literature results [122]. The *trans* stereochemistry of the products was deduced from the nuclear magnetic resonance (NMR) data. The coupling constant of the C_3 and C_4 hydrogens in the *cis*-compounds is higher than that of in the *trans*-products. Isomeric polyaromatic imines (**34**, **36**, and **38**) in which the aromatic groups were interchanged produced exclusively *cis*-β-lactams (**35**, **37**, and **39**) (Scheme 6). However, imine **40** derived from cinnamaldehyde and 1-amino pyrene also afforded *cis* β-lactam **41** as the only product (Scheme 7).

To investigate the reaction in more detail, isomeric naphthalenyl and anthracenyl imines were employed in the Staudinger reaction. The 1-substituted compounds (**21** and **23**) produced only the *trans* isomers (**22** and **24**). However, the 2-substituted compounds (**42** and **45**) produced a mixture of *cis* (**44** and **47**) and *trans* isomers (**43** and **46**) in a ratio of 1:1 (Scheme 8). The reason for this observation is not clear. The *peri* hydrogen in **21** and **23** was closer to the imine bond than it was in **42** and **45**. Further research is necessary to define the role of the *peri* hydrogen in this type of reaction.

The preparation of β-lactams using the Staudinger reaction was discovered more than a century ago. Notably, the formation of *trans*-β-lactams as seen in the present investigation had not been described in the literature [37]. A few previous studies were performed toward the preparation of *trans* β-lactams. For example, synthesis of some *trans*-β-lactams was achieved using microwave irradiation and by changing the order in which the reagents were added [123–127]. Furthermore, *trans* β-lactams were formed as the only isolated products using cyclic imines. Structurally, those cyclic imines were completely different than the polyaromatic imines. Since microwave-irradiation was helpful in achieving the synthesis of *trans*-β-lactams, it was decided to test this approach.



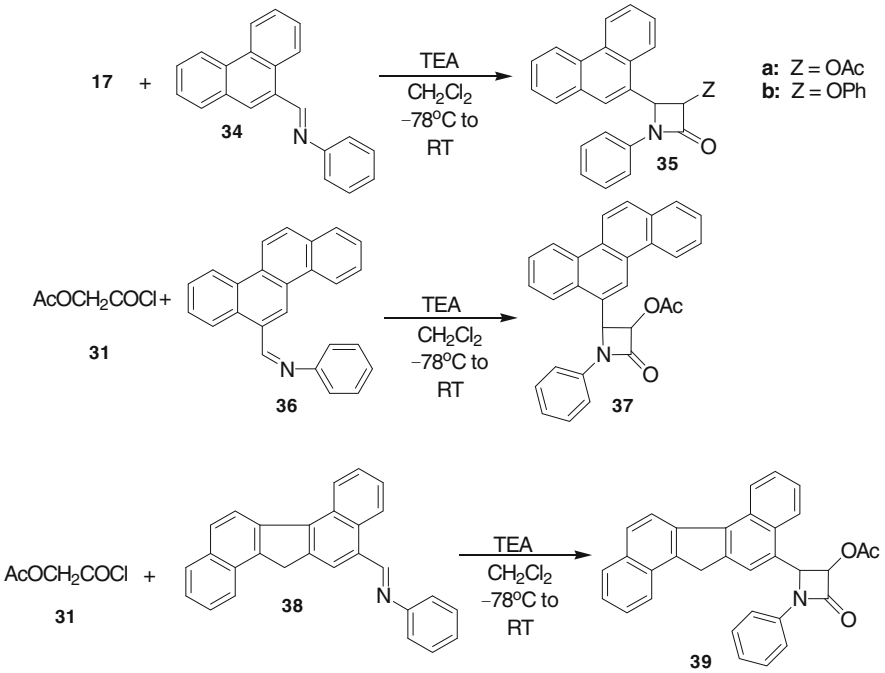
Scheme 4 Synthesis of β-lactam



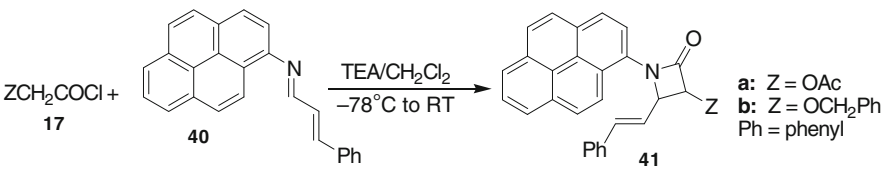
Scheme 5 Synthesis of β-lactams

4 Microwave-Induced Synthesis of β-Lactams

The use of domestic microwave and automated oven in organic synthesis is well established (Microwave activation has become a very popular and useful technology in organic and medicinal chemistry. For some recent examples, see [128–131]). This is particularly very noteworthy because of the unconventional set up necessary for conducting the reaction. Microwave irradiation of a solution of imines **21**, **23**, and **29** with acetoxyacetyl chloride in chlorobenzene using a domestic and



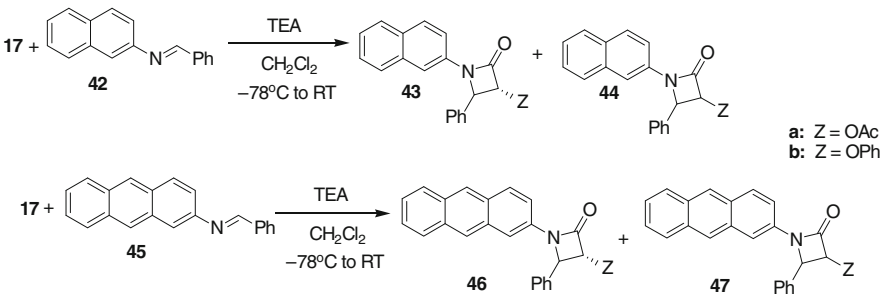
Scheme 6 Synthesis of β-lactams



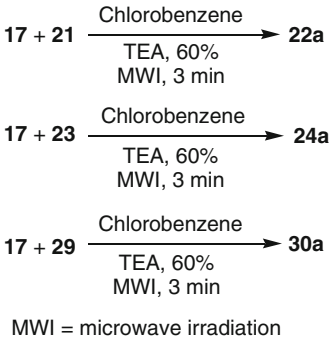
Scheme 7 Synthesis of β-lactams

automated microwave oven afforded *trans* β-lactams **22a**, **24a**, and **30a**, respectively (Scheme 9).

When irradiated in a microwave oven using chlorobenzene and triethylamine, *cis* β-lactams **44** and **47** did not isomerize to *trans* β-lactams **43** and **46**. These experiments clearly established that there is no isomerization of the *cis* β-lactams to the more stable *trans* β-lactams during reaction of imines with acid chlorides at a high temperature and under microwave irradiation. Irradiation of **21**, **23**, and **29** with **17** under identical conditions afforded the *trans* product **22a**, **24a**, and **30a** as the only isomers. Therefore, the present study clearly indicated that microwave irradiation can accelerate the synthesis of β-lactams (e.g., see [132–139]). No



Scheme 8 Synthesis of β-lactams



Scheme 9 Synthesis of β-lactams by microwave irradiation

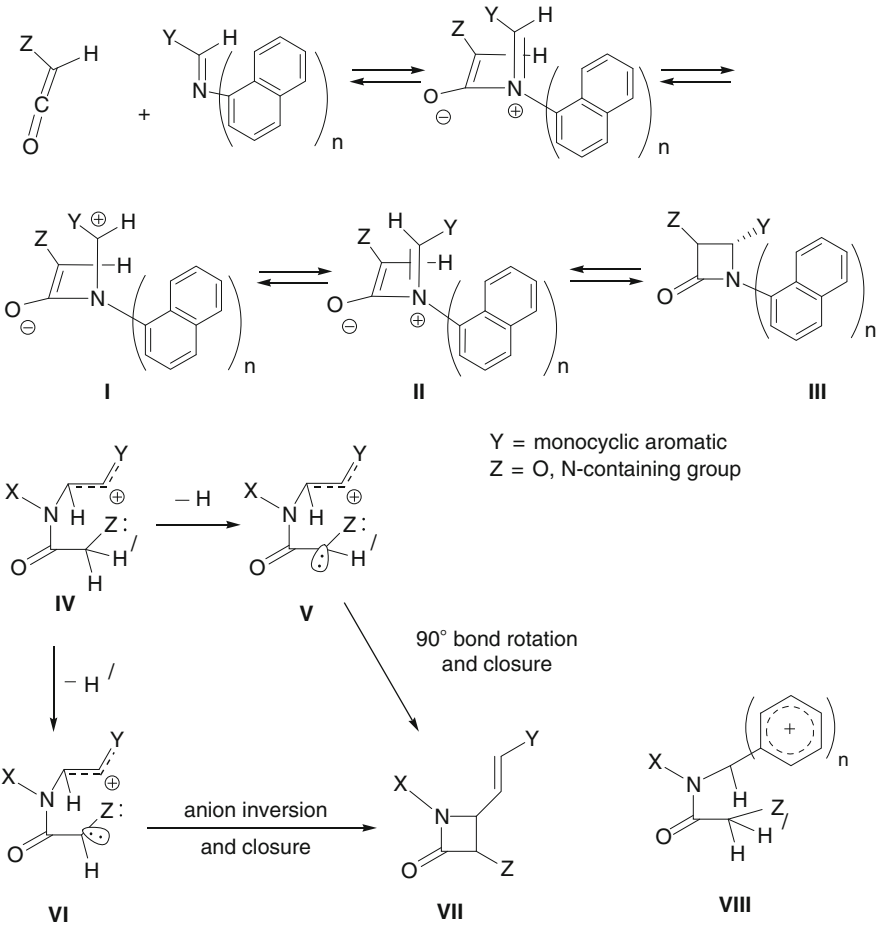
differences in the yields of the products could be detected in the domestic and automated microwave oven.

5 Mechanism of β-Lactam Formation with Polyaromatic Imines

The mechanism of β-lactam formation has been investigated extensively. But the rationale for the observed diastereoselectivity in certain cases remains unknown. It has been demonstrated that the stereoselectivity depends on the structure of the imine, acid-chloride, order of addition of the reagents, solvent, temperature, bases, and many other conditions. In many cases, *cis* β-lactam was found to be the exclusive or major product when acid chloride (equivalent) was added drop-wise at low-to-room temperature to the solution of imines and a base. However, a *trans* β-lactam was the major or exclusive product obtained when a tertiary base was slowly added to the imine and acid chloride (equivalent) solution at high temperature. Georg and Ravikumar established a few rules regarding stereoselectivity in the formation of β-lactam rings [122]. Computer-assisted calculations were advanced to explain the stereochemical preferences [140–144]. Cossio et al. [140–143] and

Sordo et al. [144] explained the stereoselectivity on the basis of torquoelectronic effects. Low-temperature infrared spectroscopy was also used to identify the reactive intermediates [145]. Two mechanisms were proposed to explain the product distribution in the β-lactam formation reaction. The ketene mechanism was observed in a low temperature infrared spectroscopy study [145], while the acylation of imine mechanism was believed to be involved in some [122]. Both mechanisms were supported by evidences. It had been hypothesized that cycloaddition of the imine occurs from the least hindered side of the ketene, and this process generates zwitterionic intermediates; conrotatory cyclization of these intermediates then produce *cis*- and *trans*-β-lactams. Acylation of the imine by the acid chloride to form *N*-acyliminium chloride also produced zwitterionic intermediates (Scheme 10).

The formation of a *trans*-isomer could be explained through isomerization of the enolates (**I–II**). The electron-withdrawing polyaromatic group at the nitrogen had



Scheme 10 Mechanism of β-lactam formation reaction

stabilized the iminium ion. This process allowed rotation of the bond (**I–II**) and resulted in formation of *trans*-β-lactam **III**. This mechanism was supported by an observation reported by Just et al. [146]. In contrast, the exclusive formation of a *cis*-β-lactam with a polyaromatic group and cinnamyl at C_4 prompted to propose a hypothesis previously described by Doyle et al. [147]. An extended conjugation of the cinnamyl and polyaromatic system may stabilize the acyliminium ion **IV**. The presence of the cinnamyl or polyaromatic system at C_4 may outweigh the contribution of the N-polyaromatic system, resulting in *cis*-β-lactam formation. Subsequent proton abstraction from complex **IV** would lead to *cis*-β-lactam **VII** through **V** (90° bond rotation and closure) or **VI** (anion inversion and closure). This suggestion was further strengthened by the possible formation of donor–acceptor complex **VIII** proposed by Bose et al. [148]. This complex formation effectively stabilized the transition state of the reaction. Cossio et al. [140] described that the SN_2 intramolecular mechanism favored the preferential or exclusive formation of *trans* β-lactams, particularly when the reactions were allowed to take place in the absence of a tertiary base in the initial stages of the reaction. The use of diisopropylethyl amine as the base could not improve the yield of products with polyaromatic systems. However, the stereochemistry of the products remained identical. Lassaletta et al. ([149]; for a similar and elegant contribution, also see [150]) explained the stereoselectivity of *trans* β-lactam formation following steric factors. It had been postulated that the isomerization of the imine bond prior to ring closure is a result of severe steric interactions between *N*-benzyloxycarbonyl-*N*-benzylamnio group and the alkyl group of hydrazone. This mechanism explained *trans*-selectivity, but could not explain the formation of *cis*-isomers with similar types of compounds. Formation of a mixture of *cis*- and *trans*- isomers with naphthalenyl and anthracenyl imines could not be explained using the mechanisms described earlier [140–150]. If the electron withdrawal properties or the steric crowding of the N-polyaromatic systems were solely responsible for the *trans* β-lactam formation, an identical stereochemical distribution would have been observed in the isomeric naphthalenyl and anthracenyl compounds. An examination of the N-polyaromatic systems in which *trans* isomers were the only products revealed a structural similarity. Imines **21** and **23** have a *peri* hydrogen very close to the C=N bond, whereas this *peri* hydrogen is relatively away from the same bond in imines **42** and **45**. A critical role for a *peri* nitrogen atom in the biological activity of a number of carboxamides had been demonstrated. It appeared that stabilization of the positive charge by the extended conjugation is the main contributor in dictating the stereochemistry of the final β-lactams. These results also suggested that it is the nature of the C_4 group that controls the isomeric distribution of the products.

6 Anticancer Activities of the β-Lactams

Several of these β-lactams were tested using nine human cancer cell lines with cisplatin and diamide **1b** as controls. The results are shown in Table 1.

The structure–activity study revealed that, regardless of the configuration of the β-lactams, neither naphthalene (**22**) and anthracene (**24**) nor pyrene derivatives (**28**)

Table 1 *In vitro* cytotoxicity of β-lactams on human cancer cell lines (μM)

Compounds	BRO	MCF-7	MDA-231	OVCAR	SKOV	PC-3	HL-60	K-562	HT-29
Cisplatin	7.66	10.05	12.33	3.99	5.99	4.66	1.66	2.33	16.99
1b	33.64	40.0	12.23	18.11	11.05	27.29	9.41	12.70	16.70
26a	10.48	10.09	12.49	18.0	18.00	9.3	5.21	4.0	10.49
30a	10.84	9.81	11.98	4.17	6.88	16.32	3.64	4.33	5.66
30d	11.00	14.93	14.46	–	9.0	–	2.5	2.5	15.90
22, **24**, **26b, 28**, **30b**, **30c**, **33**, **35, 37, 39**	>20	>20	>20	>20	>20	>20	>20	>20	>20

All the in vitro cytotoxicity assays were performed using MTT assay

demonstrated activity against any of these cancer cell lines. The *trans* acetoxy phenanthrene and chrysene derivatives (**26a**, **30a**, and **30d**) demonstrated reasonable activity. Phenoxy and phthalimido (**26b**, **30b**, and **30c**) β-lactams were inactive. Interestingly, on the breast cancer cell line MCF-7, three compounds (cisplatin, **26a**, and **30a**) had identical activity, while on the colon cancer cell line HT-29, **30a** was three times as active as cisplatin. Differences in cytotoxicity were also confirmed on the ovarian cancer cell line OVCAR, where cisplatin and **30a** had equal activity and **26a** had very little activity. This selectivity of cytotoxicity differences among compounds was very striking.

A number of conclusions can be made from the results of the in vitro studies. It was clear that the minimal structural requirement of the aromatic system for cytotoxicity is at least three aromatic rings in an angular configuration. This was confirmed by the fact that only phenanthrene **26a** and two chrysene derivatives **30a** and **30d** demonstrate cytotoxicity against the tumor cell lines. The other polyaromatic compounds derived from naphthalenes, anthracenes, and pyrene compounds (**22**, **24**, **26b**, **28**, **30b-c**, **35**, and **37**) were inactive. Interestingly, the presence of the acetoxy group proved to be very crucial for anticancer activity. Acetoxy is a well-established leaving group for reactions with a wide range of nucleophiles. This indicated that an enzymatic or other modification at this site is involved in the activation of these compounds (**26a**, **30a**, and **30d**). It was very important to note that only the *trans* β-lactams (**26a** and **30a** vs. **35a** and **37a**) have antitumor activity. Our study supports that certain conformationally restricted compounds, indeed, can demonstrate better activity in biological systems. It has been confirmed that **26a**, **30a**, and **30d** are more active than diamide **1b** in many cancer cell lines in vitro.

7 Asymmetric Synthesis of Anticancer β-Lactam

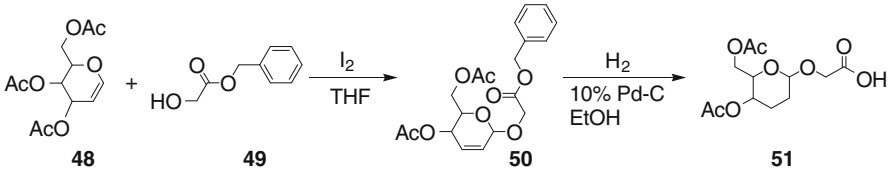
The anticancer activity of our racemic β-lactams has prompted us to devise method for the preparation of the optically active analogues. It is known that an optically active isomer of a racemic compound has better and much selective biological

activity. Tremendous success has been achieved in the cycloaddition of optically active aminoketene with imines. In contrast, the analogous reaction of imines with chiral hydroxyketene equivalents has not been explored systematically. The reaction of achiral alkoxy ketenes with chiral imines derived from optically active α-oxy and α-amino carbonyl compounds had been investigated for the preparation of optically active β-lactams. Asymmetric synthesis of *cis*-hydroxy β-lactam (70% yield) derived from α-*O*-glycoside as the ketene component was reported with diaryl imine. The control of absolute stereochemistry was the most challenging part. The stereochemistry of the anomeric center of the carbohydrate is very crucial. Our hypothesis was to use the glycosides (α- and β-) as the ketene component. We predicted that the absolute stereochemistry of the anomeric center in the ketene component of the carbohydrate would be the most important, although the nature of the other center with different protective groups may play an important role in the formation of the β-lactam ring.

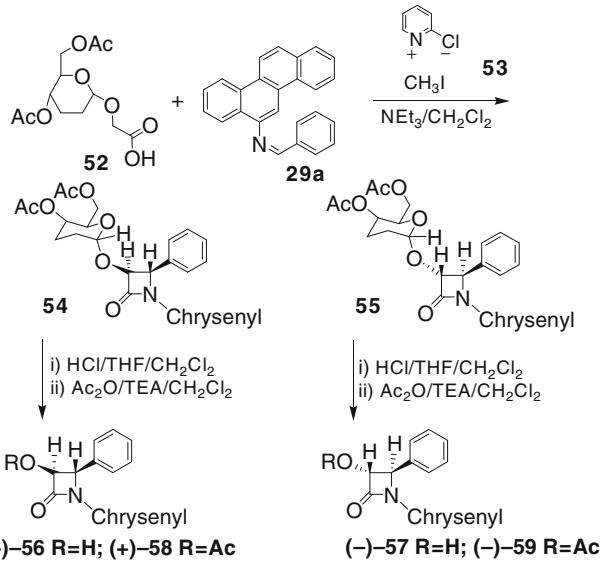
Ferrier rearrangement was used for the preparation of the starting β-glycosides. Reaction of 3, 4, 5-tri-*O*-acetyl D-glucal (**48**) with benzyl glycolate (**49**) in the presence of iodine has produced a glycoside **50**. Hydrogenolysis of the benzyl ester **50** and the hydrogenation of the alkene group had been performed by catalytic hydrogenation to afford acid **51** (Scheme 11).

Reaction of the activated acid **51** with polyaromatic imine **29a** in the presence of triethylamine produced a mixture of diastereomeric O-glycosides of *trans* β-lactams **54** and **55** in a ratio of 45:55. The diasteromers **54** and **55** were separated through column chromatography. Acid-mediated reaction was used to cleave the anomeric bond, and this process produced *trans*-hydroxy β-lactams (+)-**56** and (−)-**57** in excellent yield. The hydroxy compounds were converted to the acetates (+)-**58** and (−)-**59** (Scheme 12). The absolute stereochemistry of the *trans*-acetoxy-β-lactam (+)-**58** and (−)-**59** was confirmed by comparison with known *trans*-β-lactam described earlier [151]. An application of this chemistry was extended to a similar reaction with a β-glycoside. The synthesis of the acid with a β-glycoside bond was performed. Indium-induced reaction of acetobromoglucose (**60**) with **49** afforded an ester **61**. Hydrogenolysis of the benzyl group produced the β-glycoside **62** (Scheme 13).

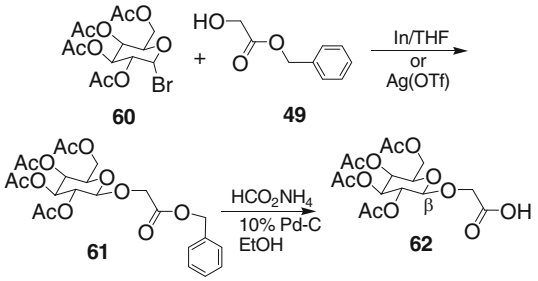
Cycloaddition of the acid **62** with imine **29a** was performed using imine in the presence of *N*-methyl-2-chloropyridiniumiodide (**53**) and triethylamine. NMR analyses of the crude reaction mixture showed the presence of two diasteromeric *trans* β-lactams **63** and **64** in 60:40 ratios. The diaseteromeric O-glycosides after



Scheme 11 Synthesis of starting acid for Staudinger reaction



Scheme 12 Synthesis of chiral anticancer β-lactams

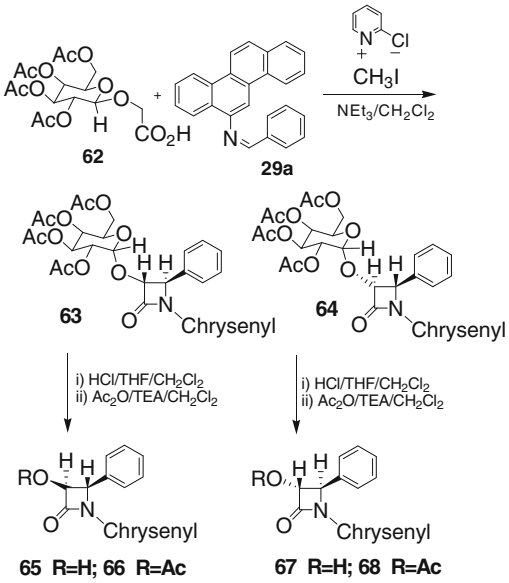


Scheme 13 Synthesis of starting acid for Staudinger reaction

separation was treated with mild aqueous acid to the hydroxy compounds **65** and **67**, and the resulting alcohols were converted to acetates. The absolute stereochemistry of the *trans* acetoxy-β-lactam **66** and **68** was confirmed by a comparison with known *trans* β-lactam as described earlier (Scheme 14).

7.1 In Vitro Cytotoxicity of the Optically Active β-Lactams

These optically active β-lactams were tested using seven human cancer cell lines against cisplatin and racemic β-lactam as controls, and the data is shown in Table 2.



Scheme 14 Synthesis of chiral anticancer β-lactam

Table 2 *In vitro* cytotoxicity of optically active β-lactams on human cancer cell lines (μM)

Compounds	BRO	MDA-231	SKOV-3	PC-3	HL-60	K-562	HT-29
Cisplatin	7.66	12.33	5.99	4.66	1.66	2.33	16.99
(+)-**1**	15.7	8.7	10.00	11.1	0.7	1.1	2.0
(+)-**66** and (+)-**(58)**	6.1	0.8	6.8	1.4	0.7	1.1	0.7
(−)-**68** and (−)-**59**	22.0	8.5	6.1	15.5	5.4	6.0	8.3

The cell growth inhibition data confirmed that, of the optically active β-lactam, **66** and **58** were extremely active (obtained from two different pathways), and the activity of the other optical isomer **68** and **59** (obtained from two different pathways) was reduced compared to the racemic β-lactam **1**.

8 Mechanism of Action

Because of the presence of the cyclic four-membered amide connected to the multicyclic ring systems, an effort to define their mechanism of action would be highly important. Despite a number of synthetic efforts, a relatively small amount of research had been focused on the use of compounds related to PAHs as anticancer agents. Bair et al. [152, 153] reported a close correlation between antitumor activity and the shape of the polyaromatic system. However, his group did not make a definitive correlation between the ability of these compounds to bind to deoxyribonucleic acid (DNA) and their cytotoxic activity. Bair's group developed

benzylic aminopropanediols from a structure–activity relationship study. These amino propanediols were believed to interact with DNA via intercalation and to be topoisomerase II inhibitors. The antitumor activity of two of the most active naphthalimides, amonafide, and mitonafide had been established due to intercalation to DNA. To improve its potency, naphthalene was modified to anthracene to serve as the chromophore. The resulting compound azonafide showed increased cytotoxic activity over naphthalene-based analogues. Not all azonafide derivatives, which had characteristic mechanistic properties when compared with existing classes of DNA intercalators, were localized in the nucleus. Other differences with existing DNA intercalators, such as mitoxantrone, had included a lack of inhibition of topoisomerase II enzymes at equicytotoxic concentrations. Improving cellular cytotoxic potency was adopted by linking two naphthalimide or anthralimide groups with a polyamine bridge. The mechanism of action of β-lactams as different types of biologically active compounds had been studied. However, investigations directed to define the mechanism of action of β-lactams as anticancer agents had not been explored. The active compounds may follow one of these mechanisms as described earlier or it may act on cancer cells through a novel mechanism.

9 Mutagenicity Assays

Mutagenicity assays were performed by BioReliance Corporation as study AA65FL-FM.501.BTA. Compounds **26a** and **30a** were examined using the Salmonella Plate Incorporation, Mutagenicity Assay. The tester strains used were *Salmonella typimurium* histidine auxotrophs TA98 and TA100 [70]. Tester strain TA98 was reverted from auxotrophy to prototrophy by frame shift mutagens. Tester strain TA100 was reverted by mutagens that cause both frame shift and base pair substitution mutations. Both these compounds were exposed separately via the plate incorporation methodology. Each one of the β-lactam was tested at ten dose levels along with appropriate vehicle control and positive controls with tester strains TA98 and TA100 in the presence and absence of Aroclor-induced rat liver S9. All dose levels of test compounds, vehicle control and positive controls, were plated in duplicate. For each compound to be evaluated positive, it must have demonstrated a dose-related increase in the mean revertants per plate for at least one tester strain over a minimum of two increasing concentrations of the test article. Data sets for tester strains TA98 and TA100 were judged to be positive if the increase in mean revertants at the peak of the dose response was equal to or greater than twice the mean vehicle control value.

The results of the mutagenicity assay indicated that neither **26a** nor **30a** demonstrated a positive response with these tester strains at any concentration in either the presence or the absence of Aroclor-induced rat liver S9, indicating that neither of these compounds demonstrate any mutagenicity. This is an important finding in the field of cancer research.

10 Apoptosis

To determine whether exposure to **26a** or **30a** induced DNA cleavage in sensitive and resistant tumor cell lines, the APO-BRDU assay was performed. Compound **30a** demonstrated no significant increase in BRDU insertion into the DNA of HL-60 cells exposed for 24 h. In two identical runs, **26a** also failed to demonstrate an increase in BRDU insertion. These results were striking since, in all of these experiments, concentrations approximately twice that required for the IC_{50} of **26a** and three times greater than that required for **30a** were used. In one of these experiments, MDA-231, a human breast cancer line that was resistant in vitro to the effects of **30a**, was tested for BRDU insertion. As expected from the above experiments, a significant increase was not detected. These results confirmed scanning electron microscopy studies of exposed cells that suggested the lack of alterations in these cancer cell lines, which were associated with the induction of apoptosis in the target cancer cells.

11 Interactions with Topoisomerases

TOPOGEN Inc. has the necessary kits to identify the interaction of organic compounds with topoisomerases. These kits contained reagents required for detection of topoisomerase I and II with DNA markers for detection of enzymatic action and standard topoisomerase inhibitors. The activity of **26a** and **30a** was determined using these systems. No inhibition of either topoisomerase I or topoisomerase II was detected in the HL-60 cancer cell lines using much higher concentration that were required to inhibit the growth of this cell lines in vitro. Therefore, there was no evidence that the active β-lactams had their cytotoxic activity in sensitive cell lines through interaction with DNA or DNA-associated enzyme systems. These compounds failed to increase BRDU insertion into DNA and display inhibitory action toward the two topoisomerase systems. The failure to induce apoptosis was consistent with these findings because in many instances this phenomenon was the putative result of such DNA interactions.

12 Cell Cycle Activity

Cell cycle activity of the active compounds was investigated. Propidium iodine (the marker for DNA content) was used as a marker of the cell cycle. This cytometric determination was calibrated separately and calculated for a related program to evaluate the percentage of cells in each phase of the cell cycle. The treated cells were compared with that of control HL-60 cancer cells for the percentage of cells in each cell cycle compartment over a period of 24 h. HL-60 cells treated with 10 μg

of **30a** demonstrated an increase in the percentage of cells in the G_2 phase that was particularly predominating at 24 h. The average percentage of untreated cells in G_2 was 17.2%, and that of cells treated with **30a** and **26a** was 38.4 and 23.6%, respectively. To determine whether alteration of the cell cycle occurred in a cell line that had repeatedly demonstrated resistance to the in vitro effect of **30a**, the human breast cancer cell line MDA-231 was examined. HL-60 cells treated with **30a** (1 μg) demonstrated a striking increase at 24 h (34.1%), but no increase was detected in MDA-231, which was identical to that in untreated MDA-231 cells (approximately 14%) [70].

13 Anticancer β-Lactams from Other Groups

Parallel to our group, a few other researchers also performed significant studies on anticancer β-lactams. For example, β-lactam derivatives (Fig. 2) induced DNA damage, inhibited DNA replication, and activated the apoptotic death program in human leukemic Jurkat T cells in a time and concentration-dependent manner. Importantly, β-lactam **69** also inhibited proliferation and induced apoptosis in other human solid tumor cell lines (breast, prostate, and head-and-neck). It was believed that induction of apoptosis by **69** is associated with activation of p38 mitogen-activated protein (MAP) kinase, release of mitochondrial cytochrome c, and activation of the caspases. It was reported that apoptosis is blocked by a specific inhibitor to p38 kinase, implicating p38 MAP kinase as the major factor in β-lactam-induced apoptosis [154]. This study was very significant.

Turos and Ping found that two β-lactam analogs (**73** and **74**), both containing a branched-chain system at C_3 of the ring, exhibited potent apoptosis-inducing activity. However, **73** exhibited superior in vitro activity over **74**. (Fig. 3) The β-lactams with these side chains were able to inhibit the growth of mice bearing

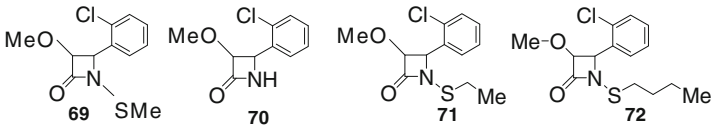


Fig. 2 Structures of a few anticancer β-lactams

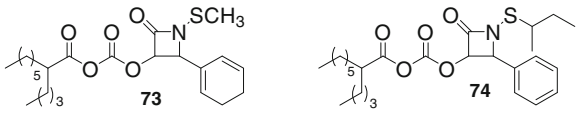


Fig. 3 Structures of a few anticancer β-lactams

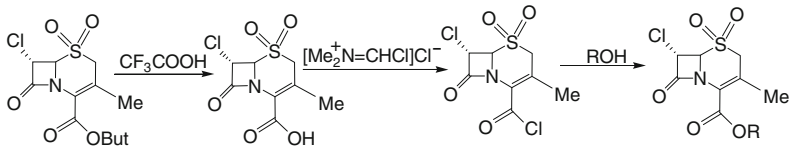
breast cancer xenografts as a result of the induction of DNA damage and apoptosis in tumor tissues [155].

Veinberg et al. reported synthesis and anticancer properties of 7α-chloro-3-methyl-1,1-dioxoceph-3-EM-4-carboxylic acid esters. The tested esters were divided into two groups according to their anticancer effects. Interestingly, the *n*-butyl **(75d)**, 2,2,2-trichloroethyl **(75g)** was characterized by LC_{50} values in the range 10–30 μg/mL and by active generation of nitric oxide radicals in the cell medium. But methyl ester **75a** was characterized by a large cytotoxic effect in relation to both cancer cells and to normal cells. This was also confirmed by low LD_{50} values of 236 and 252 mg/kg for these compounds. It was crucial to note that an increase in the carbon chain in the ester group of compounds **75b**, **75c**, and **75e–g** to 2 or 3 carbon atoms enabled a strengthening of the toxic effect in relation to cancer and a weakening of it in relation to normal cells. Surprisingly, the selectivity developed led to a more than twofold reduction in the toxicity index (Fig. 4).

The results of this study indicated that the modification of the ester group in 7α-chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylic acid is promising in the search of new anticancer substances permitting action both on the cytotoxic effectiveness of compounds and on their selectivity in relation to cancer and normal cells [156].

With the goal of obtaining information on the potential antitumor activity of the new compounds, Ruf et al. synthesized and tested β-lactams at a concentration of 20 < μM in an in vitro screening method with the following human cancer cell lines: 5637 (urinary bladder carcinoma), RT-4 (urinary bladder carcinoma), A-427 (lung carcinoma), LCLC-103H (large cell lung carcinoma) (Fig. 5). While many compounds in this series were inactive, some compounds seem to form the most interesting group, as they exhibited a differentiated behavior [157].

Meegan et al. reported the synthesis of a number of β-lactams and these were evaluated in a series of in vitro assays, which determined their antiproliferative activity in MCF-7 and MDA-MB-231 breast cancer cell lines and also their affinity for the oestrogen receptor (Fig. 6). The cytotoxicity of the β-lactams was determined in the LDH assay to establish that the antiproliferative effects observed were due to cytostasis rather than cellular necrosis. Most of the compounds demonstreated low cytotoxicity, indicating that their action is cytostatic rather than cytotoxic. Cytotoxicity values considerably below that obtained for tamoxifen (13.4%, 10 μM) were observed with a most potent compound (3%, 10 μM in MCF-7 cell



75 a: R=Me, **b:** R=Et, **c:** R=i-Pr, **d:** R=n-Bu, **e:** R=$CH_2CH{=}CH_2$, **f:** R=CH_2CH_2Cl, **g:** R=CH_2CCl_3

Fig. 4 Structures of a few anticancer β-lactams

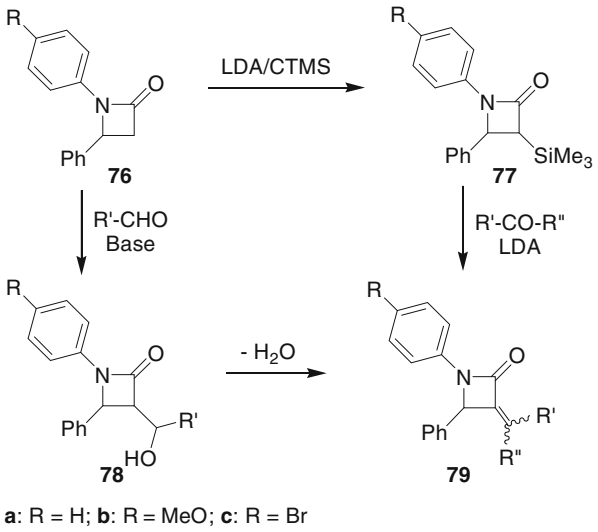


Fig. 5 Structures of a few anticancer β-lactams

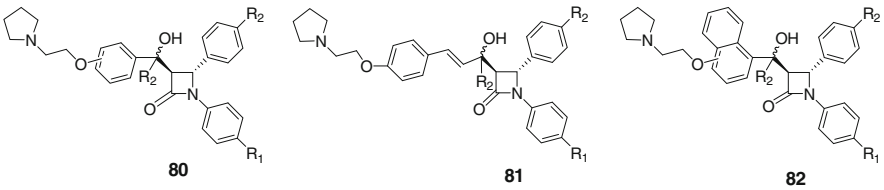


Fig. 6 Structures of a few anticancer β-lactams

line). A few β-lactams also showed low cytotoxicity in MDA-MB-231 cancer cell line [158].

14 Conclusion

We and others have demonstrated facile synthesis of a number of new anticancer active β-lactams. The β-lactam derivatives described herein are unique, and they demonstrate reasonable in vitro antitumor cytotoxicity. The stereochemical outcome of the Staudinger reaction as reported herein may offer our laboratory and others many additional opportunities to use β-lactams in the synthesis of biologically active compounds. Although the mechanism of action of the lead compounds has not been totally established, our research on cell cycle analysis offers intriguing

possibilities. In the absence of effect upon DNA or DNA enzyme-systems, they produced a striking blockade. This "check point" in the cell cycle has attracted a considerable amount of attention recently. Studies are now underway to determine the exact site of this action and to utilize it in an effort to modify our β-lactams to obtain more potent compounds. It is our expectation that novel anticancer β-lactams with high potency and unique mechanism of action will be discovered by other researchers as well.

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References

1. Southgate R, Branch C, Coulton S, Hunt E (1993) Lukacs G (ed) vol 2. Springer, Berlin, p 621
2. Kidwai M, Sapra P, Bhushan KR (1999) Curr Med Chem 6:195–215
3. Bose AK, Manhas MS, Banik BK, Srirajan V (2000) In: Greenberg A, Breneman CM, Liebman JF (eds) The amide linkage: selected structural aspects in chemistry, biochemistry, and material science. Wiley, New York, pp 157−214. Chapter 7 (β-Lactams: Cyclic Amides of Distinction)
4. Banik BK (2004) Curr Med Chem 11:151
5. Buynak J (2004) Curr Med Chem 11:1951–1964
6. Manhas MS, Banik BK, Mathur A, Vincent JE, Bose AK (2000) Tetrahedron Symposium 56:5587–5601
7. Bose AK, Mathur C, Wagle DR, Manhas MS (2000) Tetrahedron. Symposium 56:5603–5619
8. Ojima I (1995) Acc Chem Res 28:383–389
9. Banik BK, Manhas MS, Bose AK (1994) J Org Chem 59:4714–4716
10. Banik BK, Manhas MS, Bose AK (1993) J Org Chem 58:307–309
11. Suffness M (1995) In taxol science and applications. CRC, Boca Raton, FL
12. Clader JW, Burnett DA, Caplen MA, Domalski MS, Dugar S, Vaccaro W, Sher R, Browne ME, Zhao H, Burrier RE, Salisbury B, Davis HR (1996) J Med Chem 39:3684–3693
13. Burnett DA, Caplen MA, Darris HR Jr, Burrier RE, Clader JW (1994) J Med Chem 37:17334–1736
14. Burnett DA (2004) Curr Med Chem 11:1873–1887
15. Clader JW (2004) J Med Chem 47:1–9
16. Finke PE, Shah SK, Fletcher DS, Ashe BM, Brause KA, Chandler GO, Dellea PS, Hand KM, Maycock AL, Osinga DG, Underwood DJ, Weston H, Davies P, Doherty JB (1995) J Med Chem 38:2449–2462, and earlier references
17. Taggi AE, Hafez AM, Wack H, Young B, Drury WJ III, Lectka T (2000) J Am Chem Soc 122:7831–7832
18. Magriotis PA (2001) Angew Chem 113:4507–4509
19. Hodous BL, Fu GC (2002) J Am Chem Soc 124:1578–1579
20. Cordova A, Watanabe S, Tanaka F, Notz W, Barbas CF III (2002) J Am Chem Soc 124:1866–1867
21. France S, Weatherwax A, Taggi AE, Lectka T (2004) Acc Chem Res 37:592–600
22. Ruhland B, Bhandari A, Gordon EM, Gallop MA (1996) J Am Chem Soc 118:253–254
23. Furman B, Thurmer R, Kaluza Z, Lysek R, Voelter W, Chmielewski M (1999) Angew Chem Int Ed 38:1121–1123

24. Gordon K, Bolger M, Khan N, Balasubramanian SA (2000) Tetrahedron Lett 41:8621–8625
25. Schunk S, Enders D (2000) Org Lett 2:907–910
26. Annunziata R, Benaglia M, Cinquini M, Cozzi F (2000) Chem Eur J 6:133–138
27. Gordon KH, Balasubramanian S (2001) Org Lett 3:53–56
28. Schunk S, Enders D (2002) J Org Chem 67:8034–8042
29. Delpiccolo CML, Mata EG (2002) Tetrahedron Asymmetry 13:905–910
30. Mascaretti OA, Boschetti CE, Danelon GO, Mata EG, Roveri O (1995) Curr Med Chem 1:441–470
31. Edwards PD, Bernstein PR (1994) Med Res Rev 14:127–194
32. Sandanayaka VP, Prashad AS, Yang Y, Williamson T, Lin YI, Mansour TS (2003) J Med Chem 46:2569–2571
33. Buynak JD, Rao AS, Fod GP, Carver C, Carver C, Adam G, Geng B, Bachmann B, Shobassy S, Lackey S (1997) J Med Chem 40:3423–3433
34. Bonneau PR, Hasani F, Plouffe C, Malenfant E, Laplante SR, Guse I, Ogilvie WW, Plante R, Davidson WC, Hopkins JL, Morelock MM, Cordingley MG, Deziel R (1999) J Am Chem Soc 121:2965–2973
35. Ghatak A, Becker FF, Banik BK (2000) Heterocycles 53:2769–2772
36. Banik BK, Ghatak A, Becker FF (2000) J Chem Soc Perkin Trans 1:2179–2181
37. Banik BK, Becker FF (2000) Tetrahedron Lett 41:6551–6554
38. Ng S, Banik I, Okawa A, Becker FF, Banik BK (2001) J Chem Res 3:118–119
39. Dasgupta SK, Banik BK (2002) Tetrahedron Lett 43:9445–9447
40. Banik BK, Samajdar S, Banik I (2003) Tetrahedron Lett 44:1699–1701
41. Banik BK, Banik I, Hackfeld L (2003) Heterocycles 59:505–508
42. Banik BK, Adler D, Nguyen P, Srivastava N (2003) Heterocycles 61:101–104
43. Banik BK, Banik I, Samajdar S, Wilson M (2003) Heterocycles 63:283–296
44. Banik BK, Lecea B, Arrieta A, Cozar A, Cossio FP (2007) Angew Chem Int Ed 46:3028
45. Sanchez Rivera G, Bandyopadhyay D, Aguilar H, Salinas I, Banik BK, Molecules (in press)
46. Bandyopadhyay D, Banik BK (2010) Helv Chim Acta (in press)
47. Banik BK, Becker FF (2010) Mol Med Rep 3:315–317
48. Bandyopadhyay D, Xavier M, Banik BK (2009) Heterocycl Comm (in press)
49. Banik BK, Aguilar H (2009) Heterocycl Comm (in press)
50. Sanchez G, Bandyopadhyay D, Jaggi S, Gonzalez CG, Banik BK (2009) Heterocycl Comm 323–326
51. Banik BK, Zegrocka O, Manhas MS, Bose AK (2009) Heterocycles 78:2443–2454
52. Banik BK, Aguilar H, Cordova D (2008) Heterocycles 11:2321–2324
53. Becker FF, Banik BK (1998) Bioorg Med Chem Lett 8:2877–2880
54. Banik BK, Venkatraman MS, Mukhopadhyay C, Becker FF (1998) Tetrahedron Lett 39:7247–7250
55. Becker FF, Mukhopadhyay C, Hackfeld L, Banik I, Banik BK (2000) Bioorg Med Chem 8:2693–2699
56. Banik BK, Ghatak A, Mukhopadhyay C, Becker FF (2000) J Chem Res 108−109
57. Mukhopadhyay C, Becker FF, Banik BK (2001) J Chem Res 1:28–31
58. Banik BK, Becker FF (2001) Bioorg Med Chem 9:593–605
59. Banik BK, Becker FF (2001) Curr Med Chem 8:1513–1533
60. Banik BK (ed) (2001) Curr Med Chem, 8
61. Banik BK, Samajdar S, Banik I (2004) J Org Chem 69:213–216
62. Becker FF, Banik BK (2000) US Patent 6:015,811
63. Becker FF, Banik BK (2001) US Patent 6:84,224
64. Becker FF, Banik BK (2002) US Patent 6:362,200
65. Laali KK, Okazaki T, Sultana F, Bunge SD, Banik BK, Swartz C (2008) Eur J Org Chem 10:1740–1752
66. Banik BK, Cardona M (2006) Tetrahedron Lett 47:7385–7388

67. Landis-Piwowar KR, Chen D, Cui QC, Minic V, Becker FF, Banik BK, Dou QP (2006) Int J Mol Med 17:931–935
68. Banik BK, Mukhopadhya C, Logan C (2007) Synth Comm 37:3895
69. Banik I, Becker FF, Banik BK (2003) J Med Chem 46:12–15
70. Banik BK, Becker FF, Banik I (2004) Bioorg Med Chem 12:2523−2528. (Presented at the American Chemical Society (ACS) National Meeting, Orlando, FL, April 2002, MEDI-213 August 8, 2001)
71. Banik BK, Banik I, Becker FF (2010) Eur J Med Chem 45:846–850
72. Banik BK, Becker FF (2010) Mol Med Report 3:315–318
73. Banik BK, Samajdar S, Becker FF (2010) Mol Med Report 3:319–322
74. Banik BK, Banik I, Becker FF (2005) Bioorg Med Chem 13:3611
75. Lin TH, Rogers TS, Hill DL, Simpson-Herren L, Farnell DR, Kochhar DM, Alam M, Brouillette W, Muccio DD (1996) Toxicol Appl Pharmacol 139:310–316
76. Garratt PJ, Vonhoff S, Rowe SJ, Sugden D (1994) Bioorg Med Chem Lett 4:1559–1564
77. Mathe-Allainmat M, Gaudy F, Sicic S, Dangy-Caye A-L, Shen S, Bremont B, Benatalah Z, Langlois M, Renard P, Delagrange P (1996) J Med Chem 39:3089–3095
78. Anderson A, Boyd AC, Clark JK, Fielding L, Gemmell DK, Hamilton NM, Maidment MS, May V, McGuire R, McPhail P, Sansbury FH, Sundaram H, Taylor R (2000) J Med Chem 43:4118–4125
79. Barboni L, Lambertucci C, Appendino G, Vander Velde DG, Himes RH, Bombardelli E, Wang M, Snyder JP (2001) J Med Chem 44:1576–158
80. Hernandez AI, Balzarini J, Karlsson A, Camarasa MJ, Perez MJ (2002) J Med Chem 45:4254–4263
81. Selvakumar N, Srinivas D, Khera MK, Kumar MS, Mamidi RNVS, Sarnaik H, Charavaryamath C, Rao BS, Raheem MA, Das J, Iqbal J, Rajagopalan R (2002) J Med Chem 45:3953–3962
82. Ullrich T, Krich S, Binder D, Mereiter K, Anderson DJ, Meyer MD, Pyerin M (2002) J Med Chem 45:4047–4054
83. Kaiser M, De Cian A, Sainlos M, Renner C, Mergny JL, Teulade-Fichou MP (2006) Org Biomol Chem 4:1049–1057
84. Wang X, Lou Q, Guo Y, Xu Y, Zhang Z, Liu J (2006) Org Biomol Chem 4:3252–3258
85. Naganawa A, Matsui T, Ima M, Saito T, Murota M, Aratani Y, Kijima H, Yamamoto H, Maruyama T, Ohuchida S, Nakai H, Toda M (2006) Bioorg Med Chem 14:7121–7137
86. Sakashita H, Akahoshi F, Yoshida T, Kitajima H, Hayashi Y, Ishii S, Takashina Y, Tsutsumiuchi R, Ono S (2007) Bioorg Med Chem 15:641–655
87. Mateo C, Lopez V, Medarde M, Pelaez R (2007) Chem Eur J 13:7246–7256
88. Menear KA, Adcock C, Alonso FC, Blackburn K, Copsey L, Drzewiecki J, Fundo A, Le Gall A, Gomez S, Javaid H, Lence CF, Martin NMB, Mydlowski C, Smith GCM (2008) Bioorg Med Chem Lett 18:3942–3945
89. Yamaguchi K, Kazuta Y, Hirano K, Yamada S, Matsuda A, Shuto S (2008) Bioorg Med Chem 16:8875–8881
90. Hacker A, Marton LJ, Sobolewski M, Casero RA Jr (2008) Cancer Chemother Pharmacol 63:45–53
91. Zhang Z, Lockman PR, Mittapalli RK, Allen DD, Dwoskin LP, Crooks PA (2008) Bioorg Med Chem Lett 18:5622–5625
92. Martinez R, Arzate MM, Ramirez-Apan MT (2009) Bioorg Med Chem 17:1849–1856
93. Banik BK, Mukhopadhyay C, Becker FF (2001) Synth Comm 31:2399–2403
94. Samajdar S, Becker FF, Banik BK (2000) Tetrahedron Lett 41:8017–8020
95. Samajdar S, Becker FF, Banik BK (2001) Arkivoc 27−30
96. Samajdar S, Basu MK, Becker FF, Banik BK (2002) Synth Commun 32:1917–1921
97. Samajdar S, Becker FF, Banik BK (2001) Synth Commun 31:2691–2695
98. Srivastava N, Dasgupta S, Banik BK (2003) Tetrahedron Lett 44:1191–94
99. Srivastava N, Banik BK (2003) J Org Chem 68:2109–2114

100. Banik BK, Banik I, Renteria M, Dasgupta S (2005) Tetrahedron Lett 46:2643–2646
101. Banik BK, Reddy A, Dutta A, Mukhopadhyay C (2007) Tetrahedron Lett 48:7392
102. Banik BK, Garcia I, Morales F (2007) Heterocycles 71:919–923
103. Bose A, Sanjoto P, Villareal S, Aguilar H, Banik BK (2007) Tetrahedron Lett 48:3945–3948
104. Rivera S, Bandyopadhyay D, Banik BK (2009) Tetrahedron Lett 50:5445–5448
105. Banik BK, Suhendra M, Banik I, Becker FF (2000) Synth Commun 30:3745–3754
106. Banik BK, Banik I, Becker FF (2004) Organic Synth 81:188–194
107. Banik BK, Samajdar S, Banik BK, Zegrocka O, Becker FF (2001) Heterocycles 55:227–230
108. Banik BK, Banik I, Hackfeld L, Becker FF (2001) Heterocycles 56:467–470
109. Banik BK, Hackfeld L, Becker FF (2001) Synth Commun 31:1581–1586
110. Banik BK, Mukhopadhyay C, Venkatraman MS, Becker FF (1998) Tetrahedron Lett 39:7243–7247
111. Basu MK, Becker FF, Banik BK (2001) Tetrahedron Lett 41:6551–6554
112. Banik BK, Zegrocka O, Banik I, Hackfeld L, Becker FF (1999) Tetrahedron Lett 40: 6731–6734
113. Banik BK, Zegrocka O, Becker FF (2000) J Chem Res 321−322
114. Ghatak A, Becker FF, Banik BK (2000) Tetrahedron Lett 41:3793–3796
115. Basu MK, Becker FF, Banik BK (2000) J Chem Res 406−407
116. Basu MK, Banik BK (2001) Tetrahedron Lett 42:187–191
117. Banik BK (2002) Eur J Org Chem 2431−2444
118. Samajdar S, Banik BK (2003) Chem Indian J 1:230
119. Banik BK (2003) Chem Indian J 1:149
120. Banik BK, Venkatraman MS, Banik I, Basu MK (2004) Tetrahedron Lett 45:4737–4739
121. Banik BK, Banik I, Samajdar S, Cuellar R (2005) Tetrahedron Lett 46:2319–2321
122. Georg GI, Ravikumar VT (1992) In: Georg GI (ed) The organic chemistry of β-lactams. NY, VCH
123. Alcaide B, Vicente-Rodriguez A (1999) Tetrahedron Lett 40:2005–2006
124. Afonso A, Rosenblum SB, Puar MS, McPhail AT (1998) Tetrahedron Lett 39:7431–7434
125. Bolli MH, Marfurt J, Grisostomi C, Boss C, Binkert C, Hess P, Treiber A, Thorin E, Morrison K, Buchmann S, Bur D, Ramuz H, Clozel M, Fischli W, Weller T (2004) J Med Chem 47:2776–2795
126. Endo M, Droghini R (1993) Bioorg Med Chem Lett 3:2483–2486
127. Bose AK, Banik BK, Manhas MS (1995) Tetrahedron Lett 36:213–216
128. Perreux L, Loupy A (2001) Tetrahedron 57:9199–9223
129. Lidstrom P, Tierney J, Wathey B, Westman J (2001) Tetrahedron 57:9225–9287
130. Bose AK, Manhas MS, Ganguly SN, Sharma AH, Banik BK (2002) Synthesis 1578−1591
131. Bose AK, Banik BK, Lavlinskaia N, Jayaraman M, Manhas MS (1997) Chemtech 27:18–24, and references cited therein
132. Bose AK, Manhas MS, Ghosh M, Shah M, Raju VS, Bari SS, Newaz SN, Banik BK, Barakat KJ, Chaudhury AG (1991) J Org Chem 56:6968–6970
133. Banik BK, Manhas MS, Kaluza Z, Barakat KJ, Bose AK (1992) Tetrahedron Lett 33: 3603–3606
134. Banik BK, Manhas MS, Newaz SN, Bose AK (1993) Bioorg Med Chem. Lett 3:2363–2368
135. Bose AK, Banik BK, Barakat KJ, Manhas MS (1993) Synlett 575−577
136. Bose AK, Manhas MS, Banik BK, Robb EW (1994) Res Chem Interm 20:1–20
137. Banik BK, Manhas MS, Robb EW, Bose AK (1997) Heterocycles 405
138. Banik BK, Jayaraman M, Srirajan V, Manhas MS, Bose AK (1997) J Ind Chem Soc 74:951
139. Banik BK, Barakat KJ, Wagle DR, Manhas MS, Bose AK (1999) J Org Chem 64:5746–5753
140. Arrieta A, Lecea B, Cossio FP (1998) J Org Chem 63:5869–5876
141. Cossio FP, Arrieta A, Lecea B, Ugalde JM (1994) J Am Chem Soc 116:2085–2093
142. Cossio FP, Ugalde JM, Lopez X, Lecea B, Palomo C (1993) J Am Chem Soc 115:995–1004
143. Hegedus LS, Montgomery J, Narukawa Y, Snustad DC (1991) JAm Chem Soc 113:5784–5791
144. Lopez R, Sordo TL, Sordo JA, Gonzalez J (1993) J Org Chem 58:7036–7037

145. Lynch JE, Riseman SM, Laswell WL, Tschaen DM, Volante RP, Smith G, Shinkai I (1989) J Org Chem 54:3792–3796
146. Just G, Ugolini A, Zamboni R (1979) Synth Commun 9:117–121
147. Doyle TW, Belleau B, Luh BY, Ferrari CF, Cunningham MP (1977) Can J Chem 55:468–507
148. Bose K, Chiang YH, Manhas MS (1972) Tetrahedron Lett 13:4091–4094
149. Diez E, Fernandez R, Marques-Lopez E, Martin-Zamora E, Lassaletta JM (2004) Org Lett 6:2749–2752
150. Fernandez R, Ferrete A, Lassaletta JM, Llera JM, Martin-Zamora E (2002) Angew Chem Int Ed 41:831
151. Banik BK, Manhas MS, Bose AK (1997) Tetrahedron Lett 38:5077–5080
152. Bair KW, Andrews CW, Tuttle RL, Knick VC, Cory M, McKee DD (1991) J Med Chem 34:1983–1990
153. Harvey RG, Pataki J, Cortez C, DiRaddo P, Yang C (1991) J Org Chem 56:1210
154. Smith DM, Aslamuzzaman K, Smith L, Long TE, Heldreth B, Turos E, Ping Dou Q (2002) Mol Pharmacol 66:1349
155. Frezza M, Garay J, Chen D, Cui C, Turos E (2008) Ping Dou Q. Int J Mol Med 21:689–690
156. Vorona M, Veinberg G, Shestakova I, Kanepe I, Potorchina I (2007) Chem Heterocycl Compd 43:213
157. Ruf S, Neudert G, Gürtler S, Grünert R, Bednarski PJ, Otto HH (2008) Monatsh Chem 139:848–849
158. Meegan MJ, Carr M, Knox AJS, Zisterer DM, Lloyd DG (2008) J Enzyme Inhib Med Chem 23:679–682

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