

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

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Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BSA	<i>N,O</i> -Bis(trimethylsilyl)acetamide
Bu	Butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Cbz	Benzyloxycarbonyl
d	Day(s)
DCC	<i>N,N</i> -Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DIBALH	Diisobutylaluminum hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
h	Hour(s)
HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluranium tetrafluoroborate
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
MCPBA	<i>m</i> -Chloroperoxybenzoic acid
Me	Methyl
MIC	Minimal inhibitory concentration
min	Minute(s)
mL	Milliliter(s)
Ms	Mesityl
NCS	<i>N</i> -Chlorosuccinimide

NMP	<i>N</i> -Methylpyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
Nu	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
<i>i</i> -Pr	Isopropyl
PTC	Phase transfer catalyst
<i>p</i> -TSA	<i>p</i> -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], sulbactam [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).

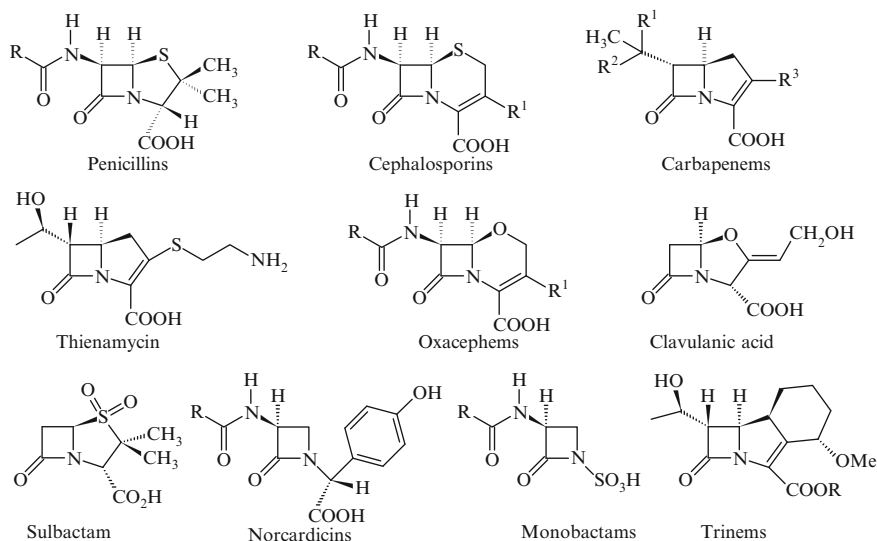


Fig. 1 β -Lactam antibiotics

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 inducers [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 stereoselective 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. Chmielewski 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 configured β -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

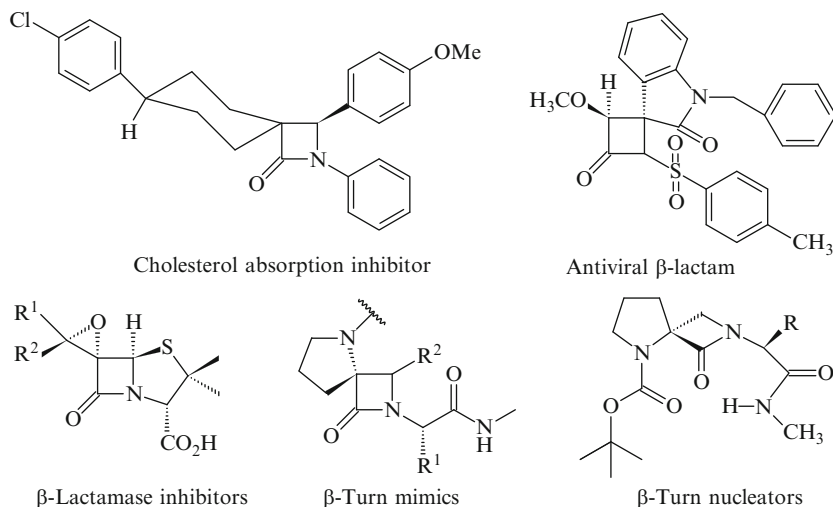
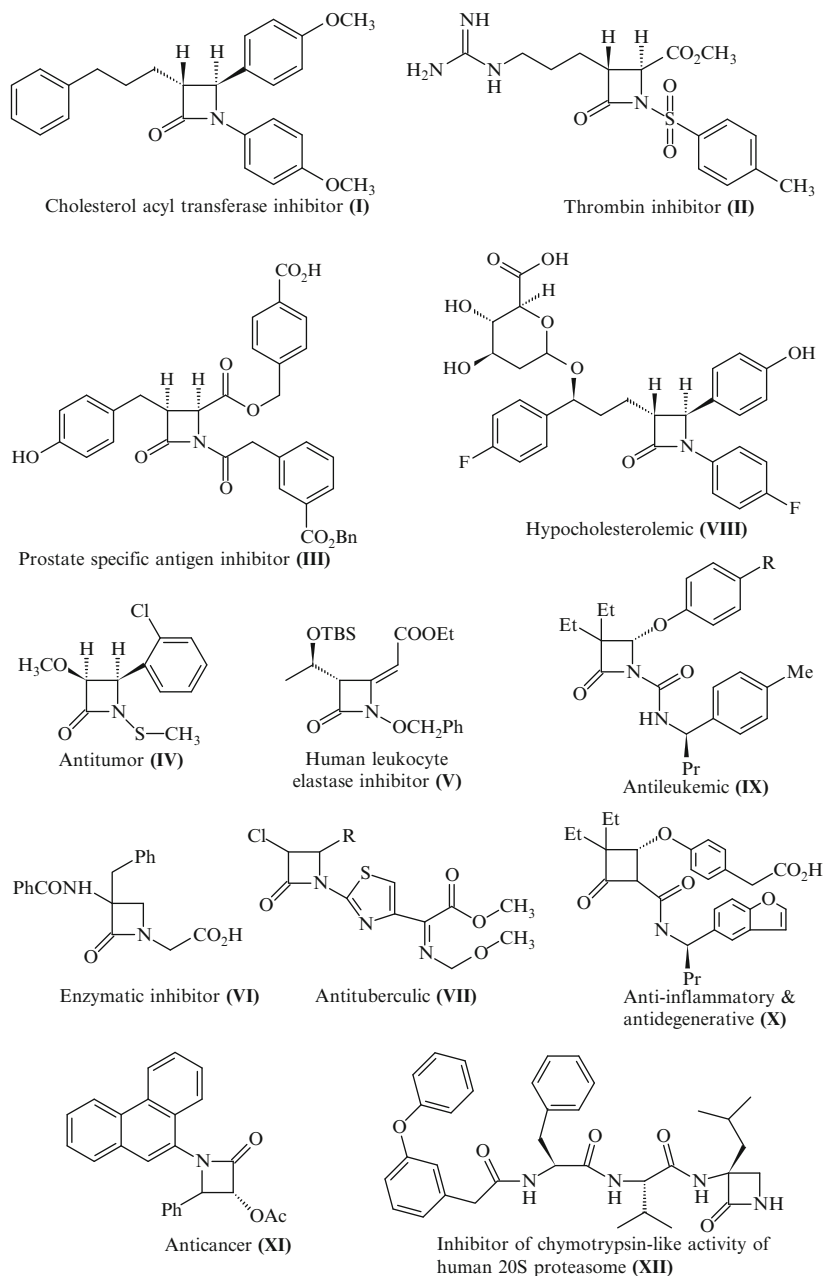


Fig. 2 Biologically active spirocyclic β -lactams

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 like **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).

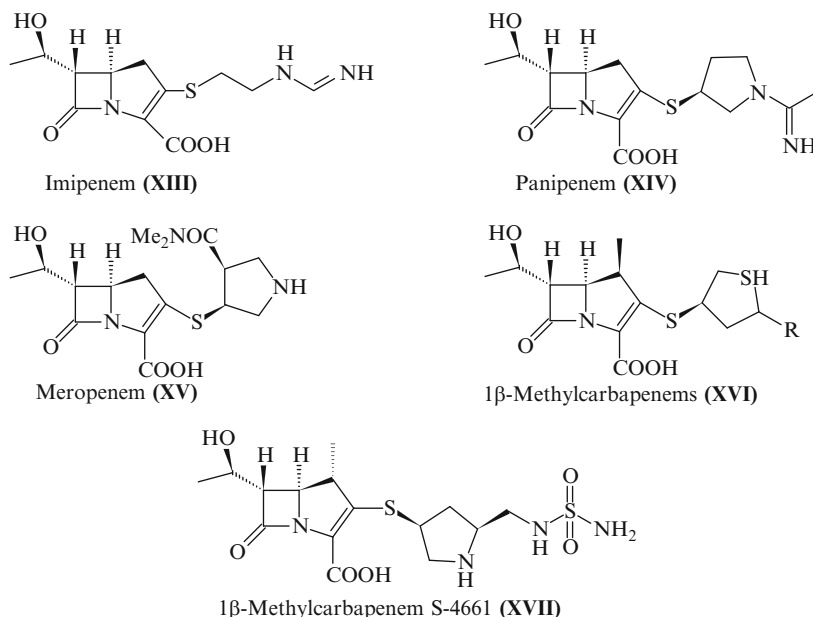
**Fig. 3** Biologically active monocyclic β -lactams

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.

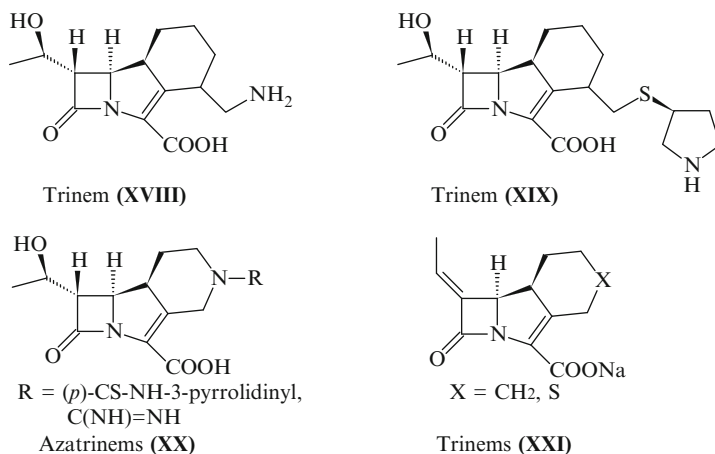
Currently, bicyclic β -lactams such as, imipenem (XIII), panipenem (XIV), and meropenem (XV) have been shown to exhibit broad antimicrobial spectrum and potent bactericidal activity [64–66].

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

Tricyclic- β -lactams: Antibacterial and β -lactamase inhibitorsFig. 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 $\mu\text{g mL}^{-1}$). However, tricyclic β -lactam **XIX** having pyrrolidinylthiomethyl moiety exhibit the most potent anti-MRSA activity (MIC = 1.5 $\mu\text{g mL}^{-1}$) 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-azatrinem (**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.

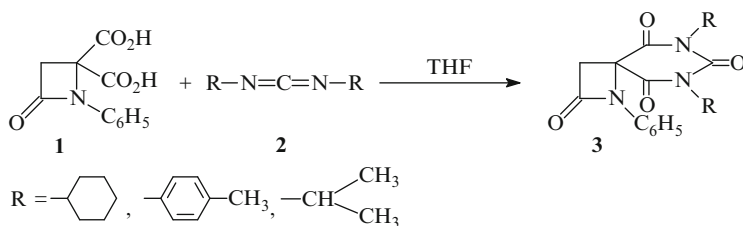
The synthesis of β -lactams having a small fused ring is of interest since the large strain of the ring should substantially alter the reactivity of β -lactams. Several approaches for the synthesis of spiro- β -lactams have been described in literature.

3.1 Synthesis

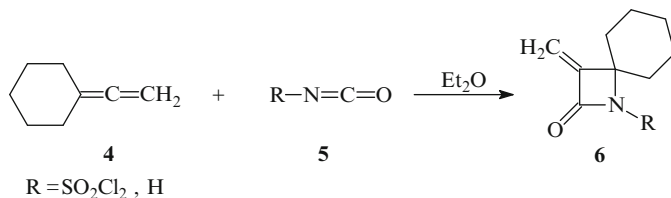
Bose et al. [74] have investigated the novel synthetic route for the preparation of spirobarbiturates—a class of compounds known for their interesting physiological activity. The synthesis of spiro- β -lactams **3** (Scheme 1) was achieved by the reaction of 4,4-dicarboxy-*N*-phenylazetidin-2-one **1** 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 cyclohexylidenephénylamine **8** in the presence of triethylamine and dichloromethane. Azidoacetyl chloride was found to be even more reactive

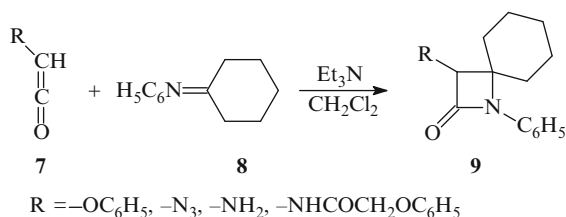


Scheme 1 Preparation of spirobarbiturates using 4,4-dicarboxy-*N*-phenylazetidin-2-one and carbodiimides

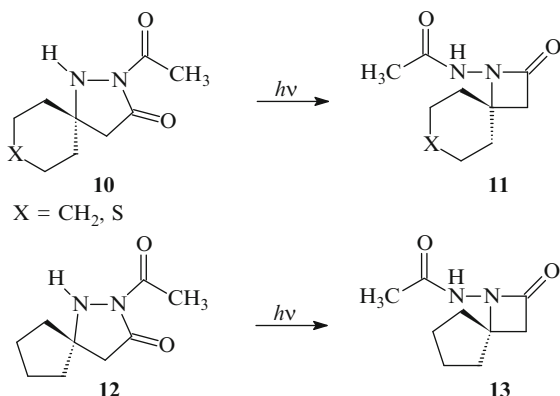


Scheme 2 Synthesis of spiro- β -lactams by 1,2-dipolar cycloaddition

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



Scheme 4 Photochemical synthesis of spirocyclic- β -lactams



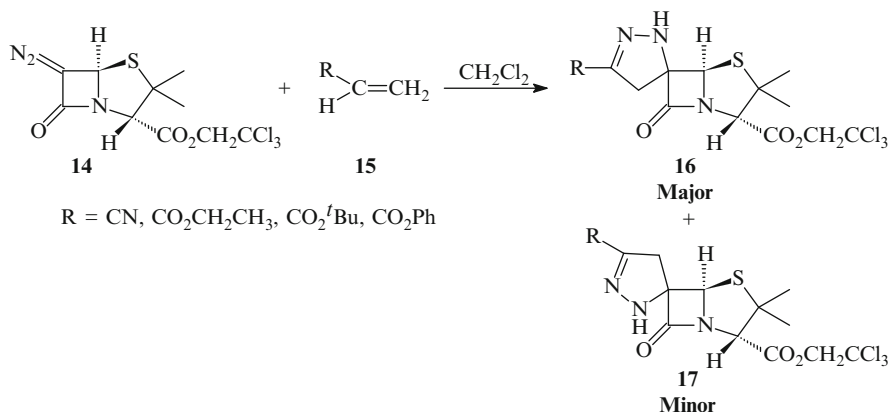
than phenoxyacetyl chloride in the cycloaddition reaction, giving azido β -lactam in 54% yield. The azide group was easily reduced by catalytic hydrogenation in the presence of Adam's catalyst. Acylation with phenoxyacetyl chloride of the amine group readily transformed it into α -amido-spiro- β -lactam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

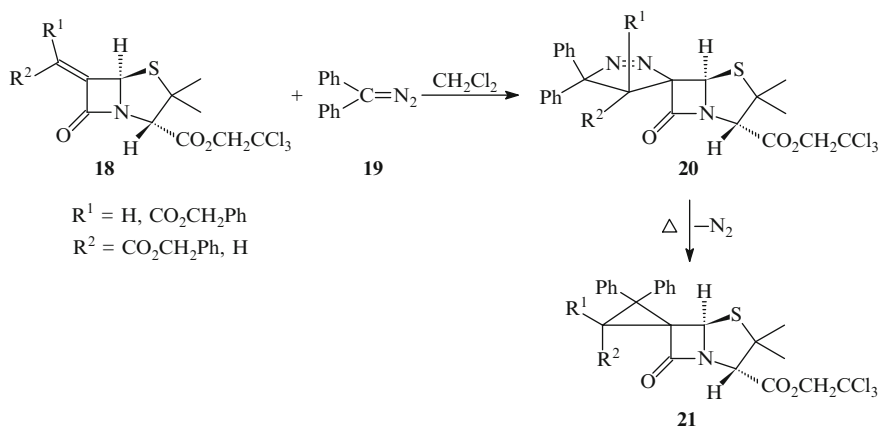
Novel spiropenicillins (Scheme 5) have also been prepared by Sheehan et al. [78]. β,β,β -Trichloroethyl-6-diazopenicillanate **14** reacts with acrylonitrile, ethyl acrylate, and *t*-butyl acrylate to give isomeric compounds **16** and **17**. The preferred mode of addition is from the sterically less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

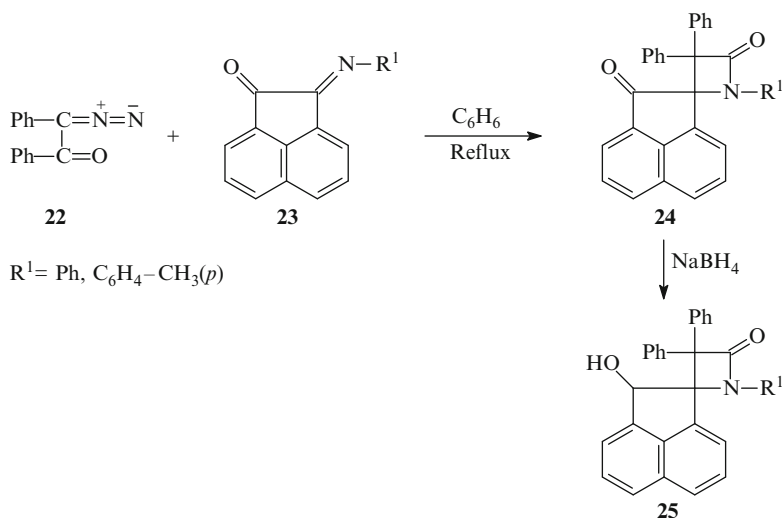


Scheme 6 Use of diphenyldiazomethane in preparation of spiroenicillians

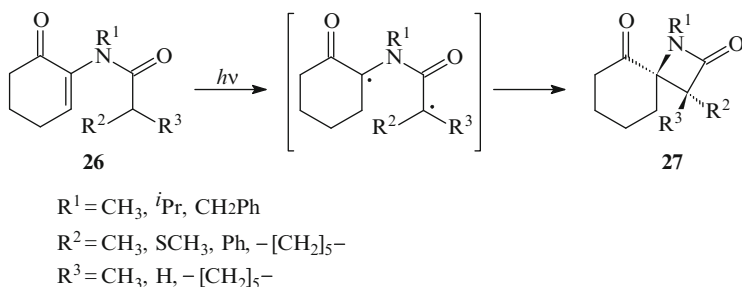
been found to be unaffected either by hydrolysis or treatment with sodium borohydride and could be used as precursors for the introduction of other desired functionalities.

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-phenyliminoacenaaphthenone

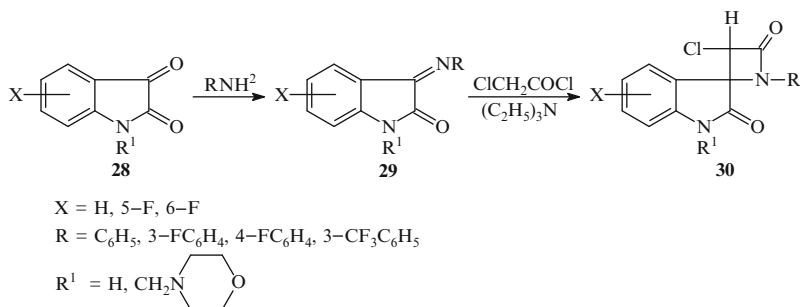


Scheme 8 Photochemical entry to spiro- β -lactams

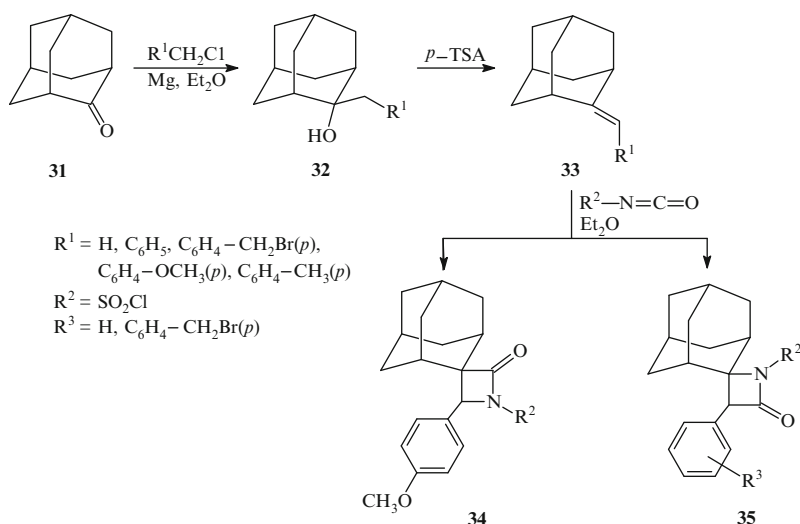
28 resulting in the formation of the intermediate Schiff's bases **29** which on cycloaddition with chloroacetyl chloride gave the spiro- β -lactams **30**.

Georgiev et al. [82] have described the preparation of novel adamantane-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*-methyladamantanylnitrone **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

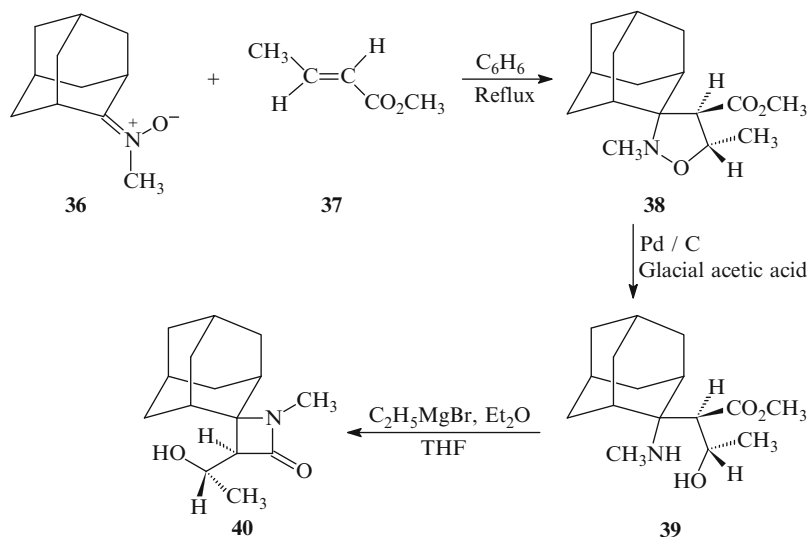


Scheme 10 Preparation of adamantane-spiroheterocyclic β -lactams

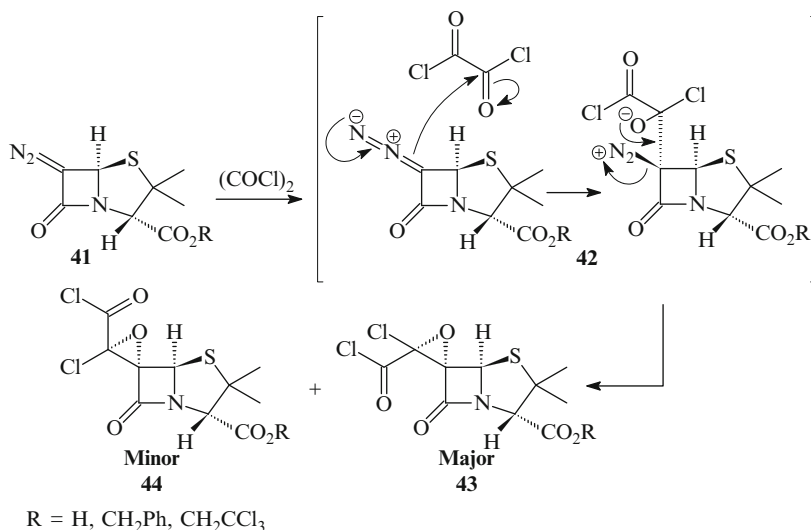
provide the aminoalcohol ester **39**. Subsequent treatment of compound **39** with ethyl magnesium bromide furnished spiro- β -lactam **40** (Scheme 11).

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.

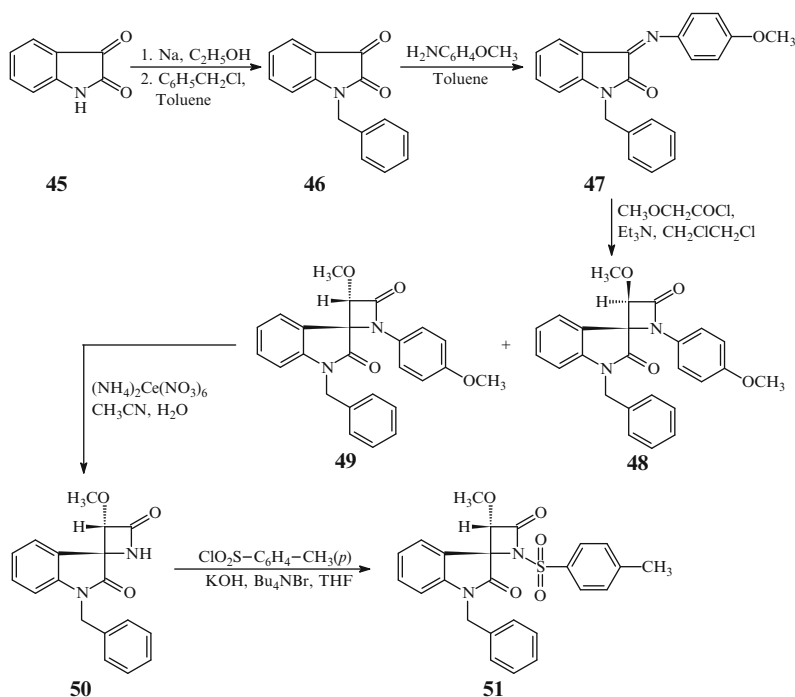


Scheme 11 Parallel synthesis of spiro- β -lactams using *N*-methyladamantanylnitrone



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-proteinases ($\text{IC}_{50} = 20 \mu\text{g mL}^{-1}$). All picornaviruses studied produced a 3C-proteinase, which is required for the virus to undergo maturation.

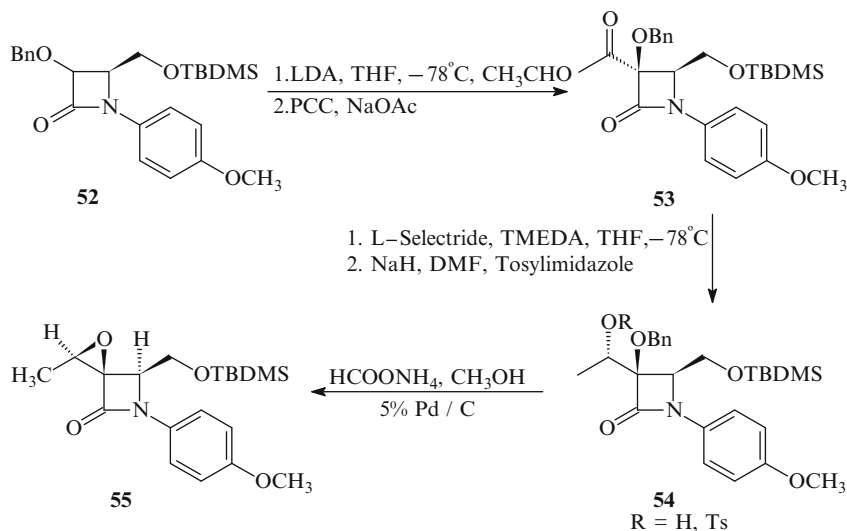


Scheme 13 Synthesis of antiviral spiroindolinone- β -lactams

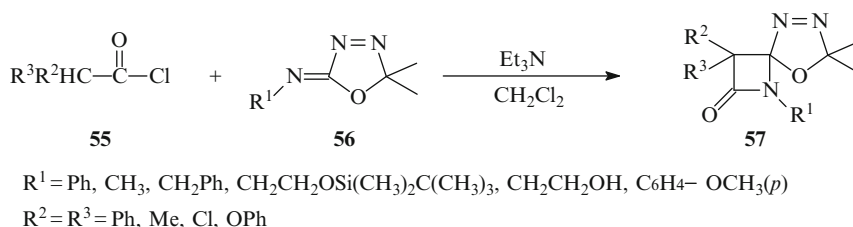
The synthesis of antiviral spiro- β -lactam **51** begins with the benzylation of isatin **45** to give 1-benzylisatin **46**, which affords Schiff's base **47** on reaction with anisidine in ethanol. The Schiff's base **47** on treatment with methoxyacetyl chloride by the chloride-imide cycloaddition [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-benzyloxyazetidin-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 debenylation-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.



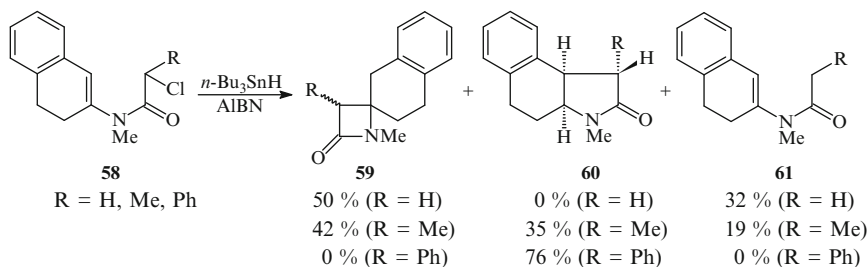
Scheme 14 Stereospecific synthesis of 3-spiro-epoxyazetidin-2-ones



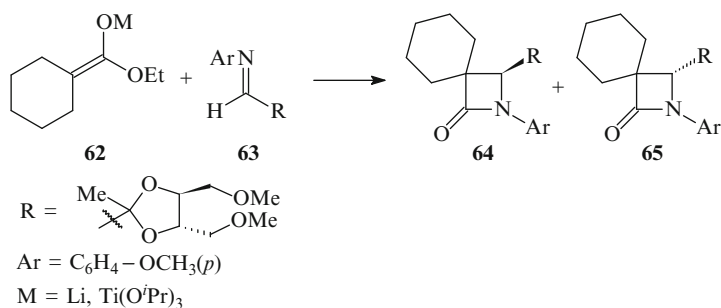
Scheme 15 General strategy for the synthesis of spiro- β -lactam oxadiazolines

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 -chloroacetamide. They found that *n*-Bu₃SnH 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 congestion 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, substituents 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**.



Scheme 16 Preparation of spiroazetidin-2-ones through $n\text{-Bu}_3\text{SnH}$ mediated cyclization of α -chloroacetamide

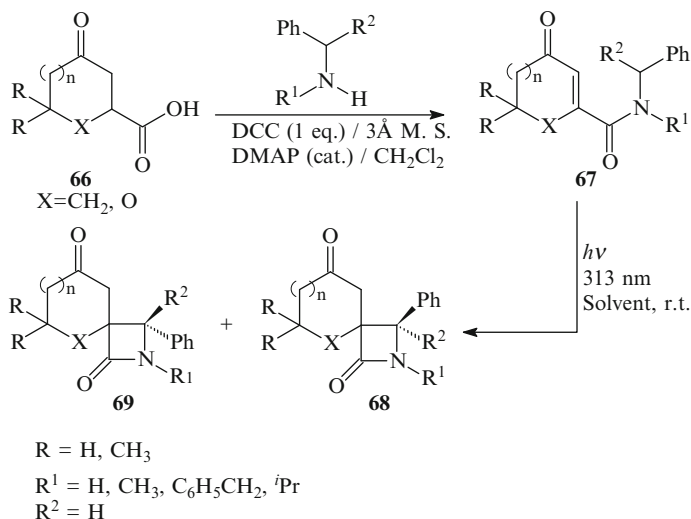


Scheme 17 Stereodivergent synthesis of spiro- β -lactams using ester enolates and chiral imines

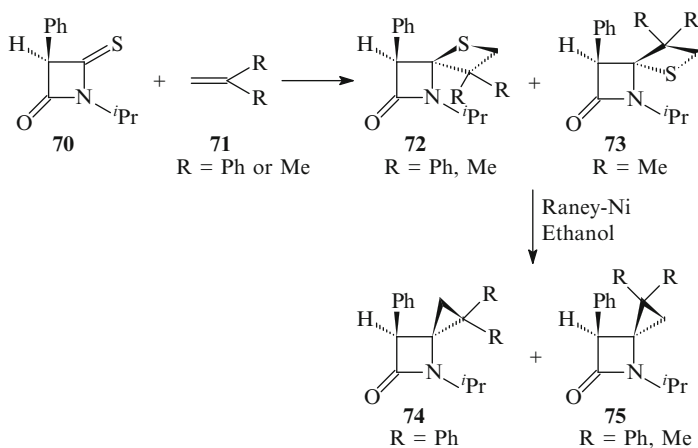
Fujisawa et al. [89] have reported the stereodivergent synthesis of spiro- β -lactams **64**, **65** (Scheme 17) by reaction of lithium or titanium ester enolates **62** with single chiral imines **63** by taking advantage of different coordination states of the enolate metals. Almost complete reversal 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 oximides **67** to spiranic β -lactams **68**, **69** by intramolecular hydrogen abstraction under photochemical activation. Starting oximides **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



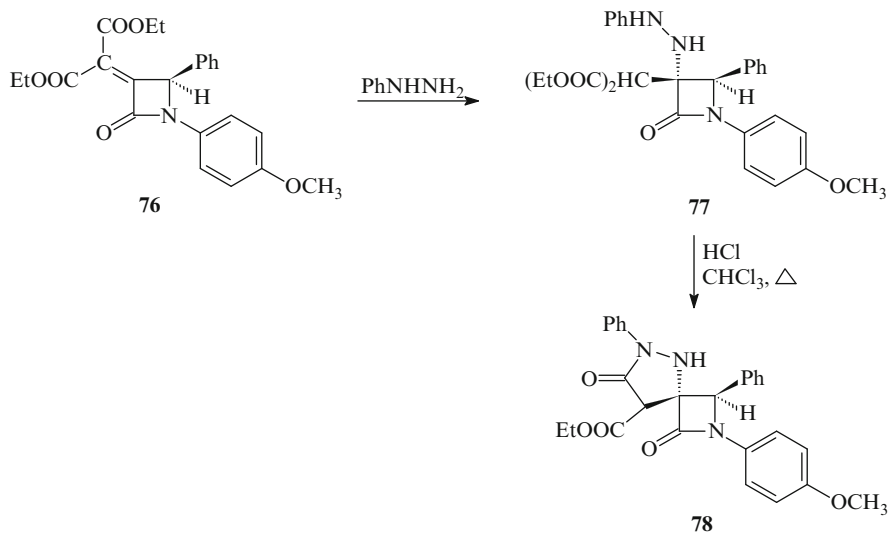
Scheme 18 Photochemically induced diastereoselective route to spiro- β -lactams



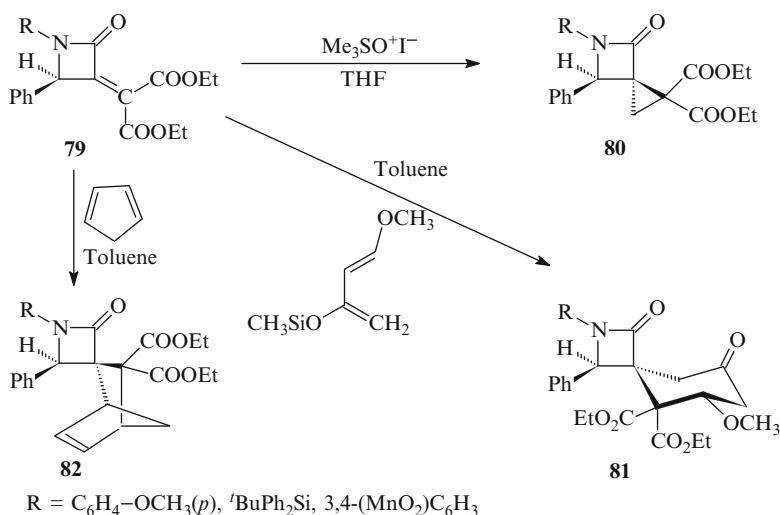
Scheme 19 Synthesis of 4-spirocyclopropylazetidin-2-one via photocycloaddition

4-spirocyclopropylazetidin-2-ones **74**, **75** ($\text{R} = \text{Ph}$). However, photochemical reaction of **70** with 2-methylpropene yielded two isomeric thietanes **72** ($\text{R} = \text{Me}$) and **73** both of which produced the spiro- β -lactam **75** ($\text{R} = \text{Me}$) 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**.



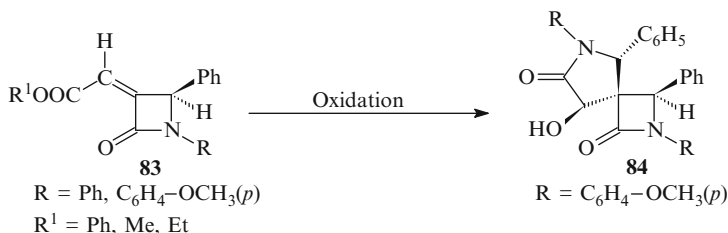
Scheme 20 Preparation of spiro-β-lactams using addition reactions to exocyclic double bond



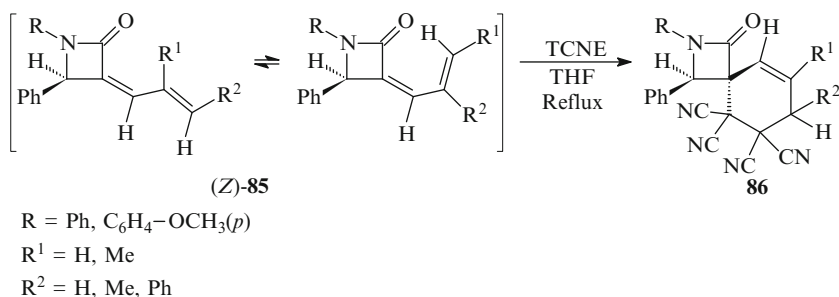
Scheme 21 Use of *Diels-Alder* reaction in synthesis of spiro-β-lactams

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



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



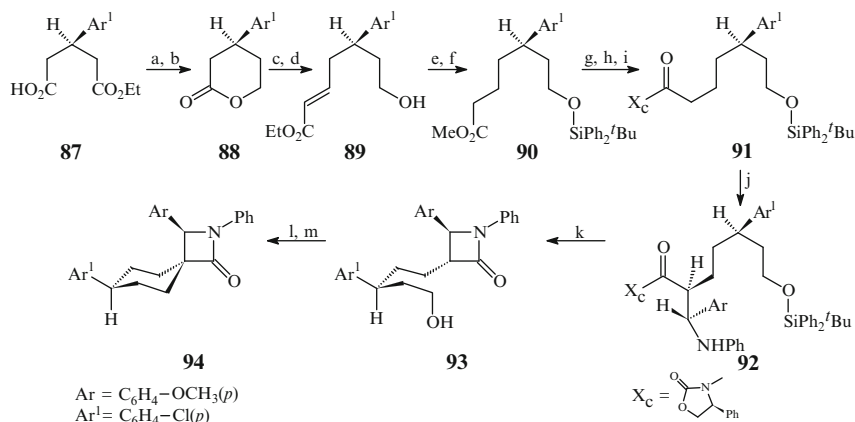
Scheme 23 Incorporation of 3-(prop-2-enylidene)azetidin-2-one for the synthesis of spiro- β -lactams via *Diels-Alder* reactions

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 *Danishesky'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 monocoxylates 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**.



Reagents: a) LiBH_4 , b) PhCH_3 , H^+ , c) DIBALH , d) $t\text{-BuLi}$, (EtO) $_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, e) Mg/MeOH , f) $t\text{-BuPh}_2\text{SiCl}$, g) LiOH , h) $(\text{COCl})_2$, i) $\text{X}_\text{C}\text{-H}$, j) TiCl_4 , ArCH=NPh , k) BSA , TBAF , l) CBr_4 , Ph_3P , m) LDA

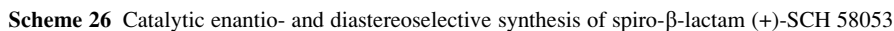
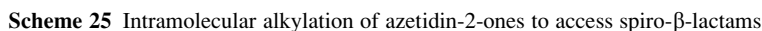
Scheme 24 Enantioselective synthetic route to cholesterol absorption inhibitor spiro- β -lactams

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.

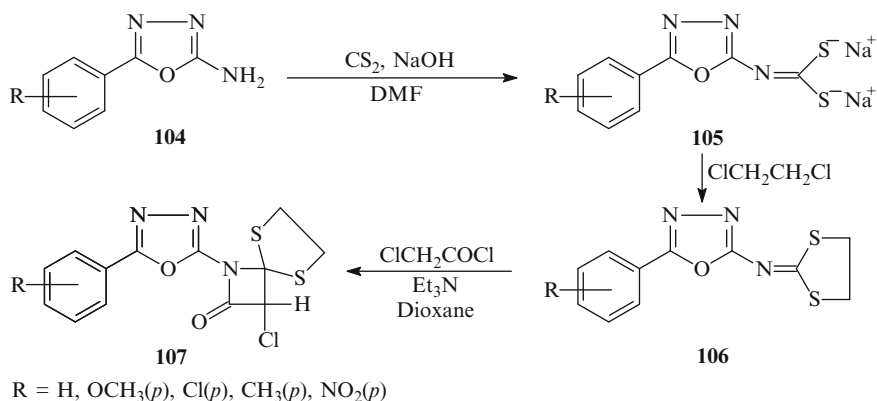
Spiro- β -lactams (+)-SCH 54016 **94** have been found to exhibit CAI activity, therefore an efficient synthetic route for these spiro- β -lactams for continuing biological evaluation was of great interest. Chen et al. [45] have reported an efficient and highly enantioselective synthetic route to spiro-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



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



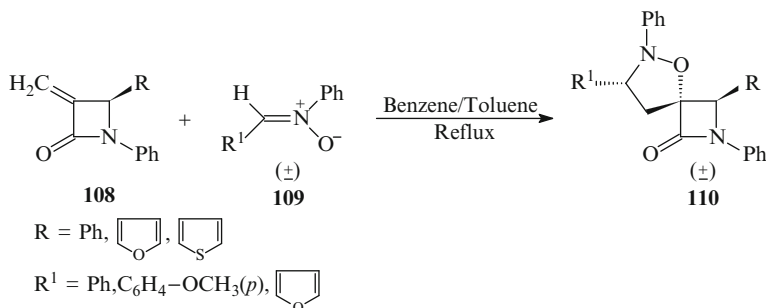
Scheme 27 Efficient synthetic route to antimicrobial spiroazetidin-2-ones

aldol condensation was constructed and followed by $n\text{-Bu}_4\text{NF}$ 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 $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ and subsequently NaOH/PTC . Addition of Grignard reagent to this compound **102**, followed by selective debenzoylation produced spiro- β -lactam (+)-SCH 58053 **103** in 99.5% chemical purity and 99.5% ee.

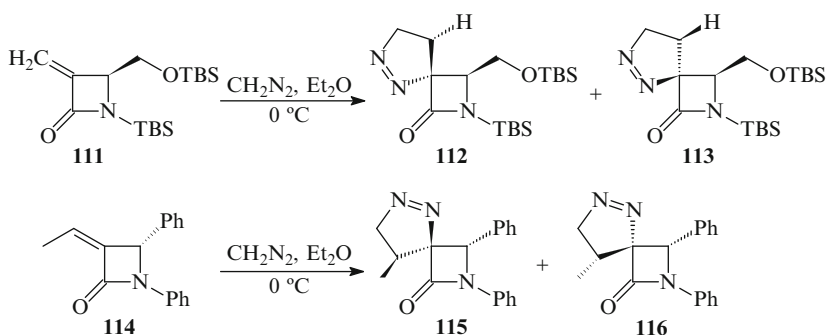
Hussain and Nizamuddin have synthesized 1, 3-dithiolane substituted spiro- β -lactams (Scheme 27) since 1, 3-dithiolane derivatives exhibit various biological activities like fungicidal, bactericidal, and insecticidal [97]. The starting thiadiazoles **104** were treated with sodium hydroxide and carbon 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 nitronc cycloaddition. Keeping this in mind, Basak et al. have carried an enantiospecific 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 diazo-methane 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 nitron cycloaddition

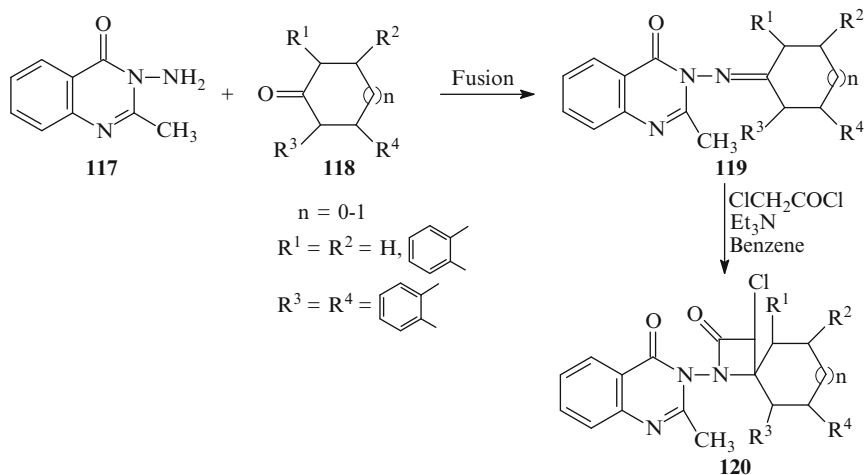


Scheme 29 Synthesis of optically active spiro- β -lactams using α -alkylidene- β -lactams

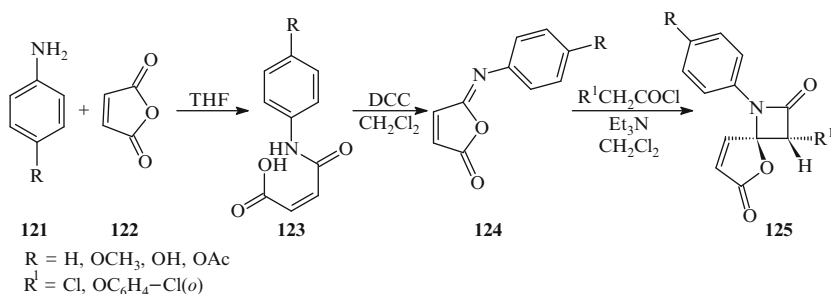
resulted into spiro products **115**, **116** (d.r. 82:18, 97%). The diastereomers were obtained in pure form by column chromatography. The CH_2OTBS moiety found in the spiro- β -lactams **112**, **113** offers the possibility of establishing tricyclic system related to the carbapenam series [6].

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

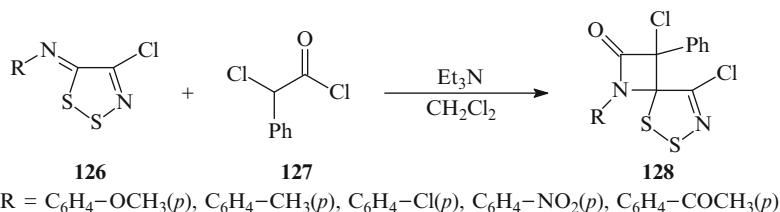


Scheme 31 Preparation of *N*-aryl-substituted spiro-β-lactams via Studinger cycloaddition

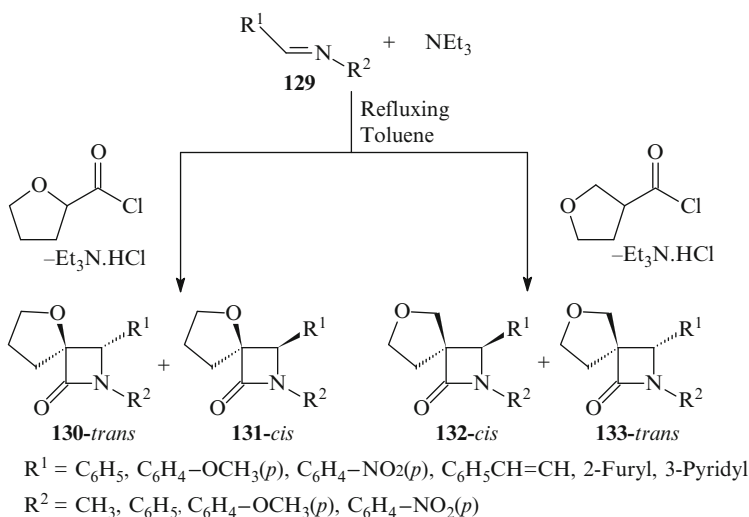
these spiro-β-lactams **125** was established by NOE experiments and X-ray diffraction analysis. The molecular perspective of these compounds nearly show a planner arrangement for the β-lactam ring and the *N*-phenyl group.

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).



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

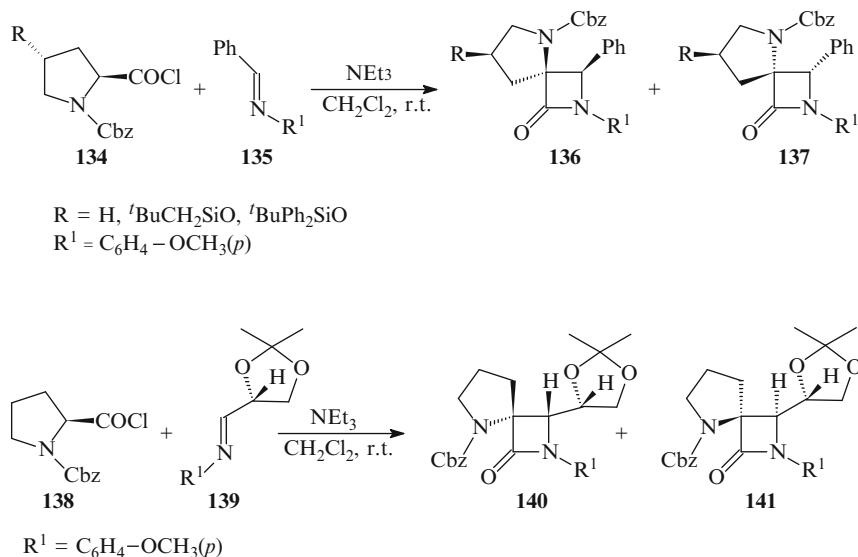


Scheme 33 Synthesis of *cis*- and *trans*-spiro- β -lactams using unsymmetrical ketenes

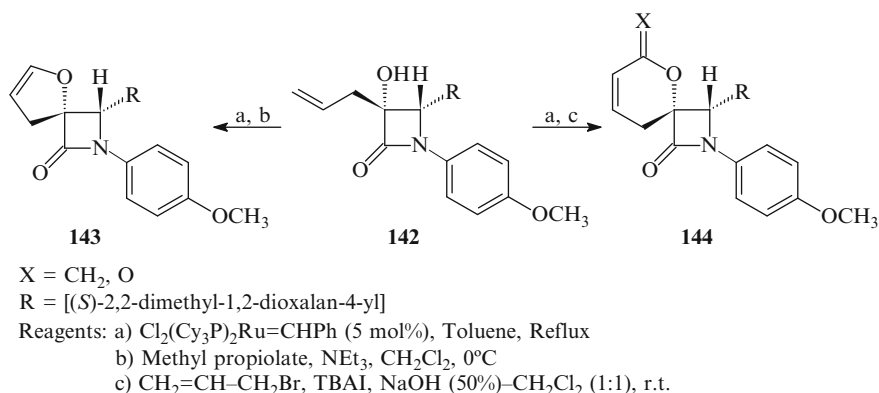
The ratio of *cis/trans* reported, is to be strongly influenced by two factors: the position of oxygen on acyl chloride precursor and the electronic nature of substituents R^1 and R^2 on the imine. Thus, the reaction of 2-tetrahydrofuroyl chloride with imine is more stereoselective than that of 3-tetrahydrofuroyl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



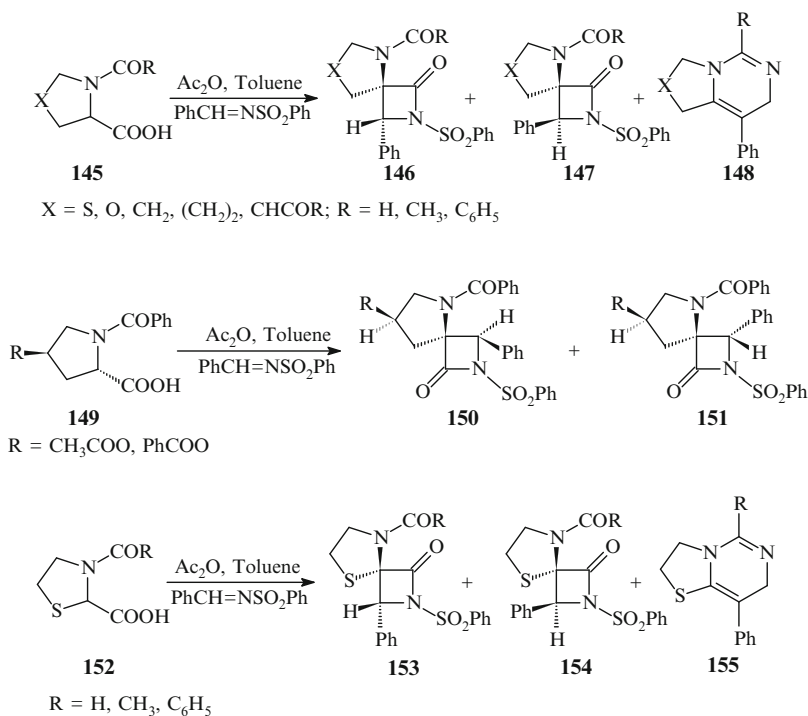
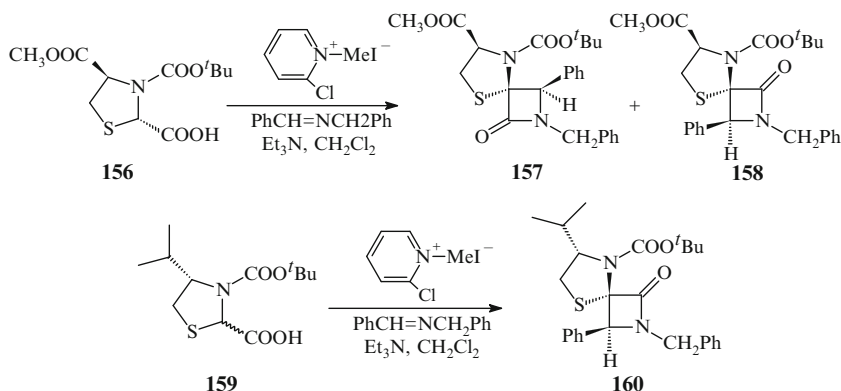
Scheme 34 Preparation of spiro- β -lactams using unsymmetrical cyclic ketenes



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 benzyloxy-*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.

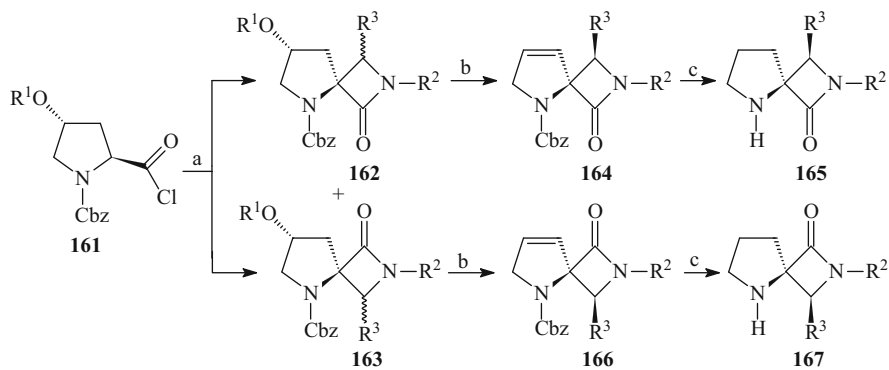
In connection with these results, and as an extension of their studies toward the reactivity of new bicyclic mesoionic compounds and their usefulness in the synthesis of condensed heterocycles, they further reported the stereoselective synthesis of spiro- β -lactams **153**, **154** (Scheme 36) by reactions of imines with mesoionic compounds or ketenes generated from *N*-acyl-thiazolidine-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*-*tert*-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 ¹H 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 K₂CO₃/MeOH and



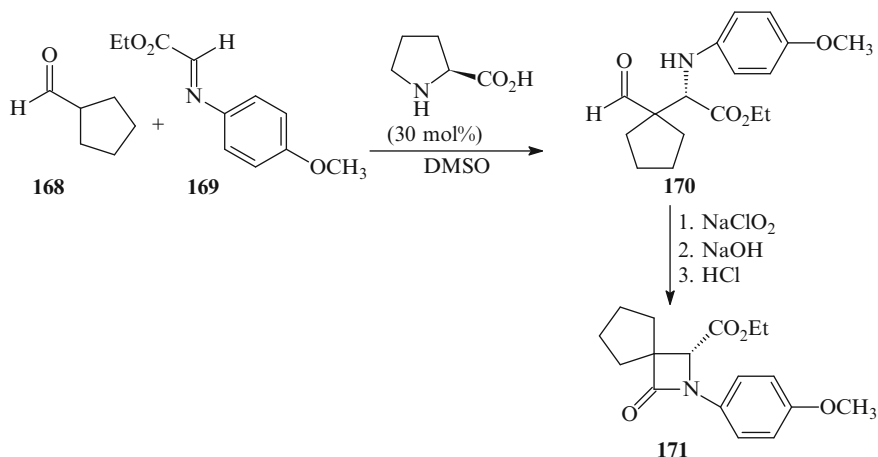
Reagents: a) $E-R^3CH=NR^2$, Et_3N , CH_2Cl_2 b) K_2CO_3 , $MeOH$, c) H_2 , 10% Pd/C , $EtOH$

$R^1 = Ms, Ts, Ns$

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

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

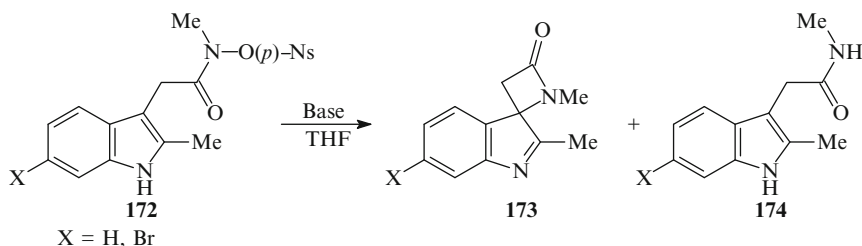
Scheme 38 Asymmetric synthesis of proline-derived spiro- β -lactams



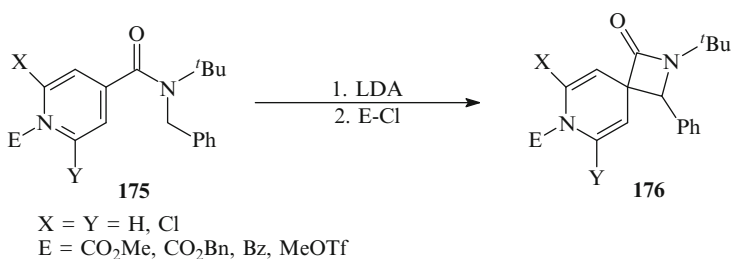
Scheme 39 Proline-catalyzed Mannich reaction furnishing spiro- β -lactams

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 substituent 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



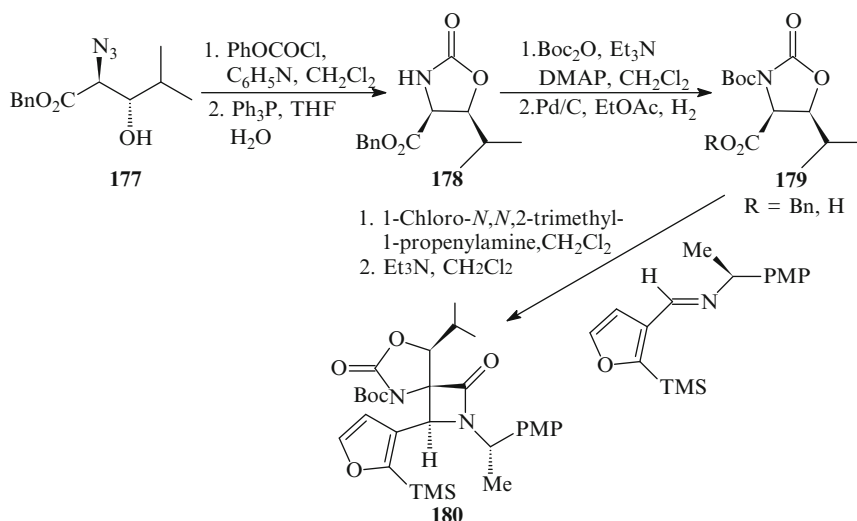
Scheme 41 Synthesis of spiro- β -lactams via cyclization of lithiated pyridine and quinoline carboxamides

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

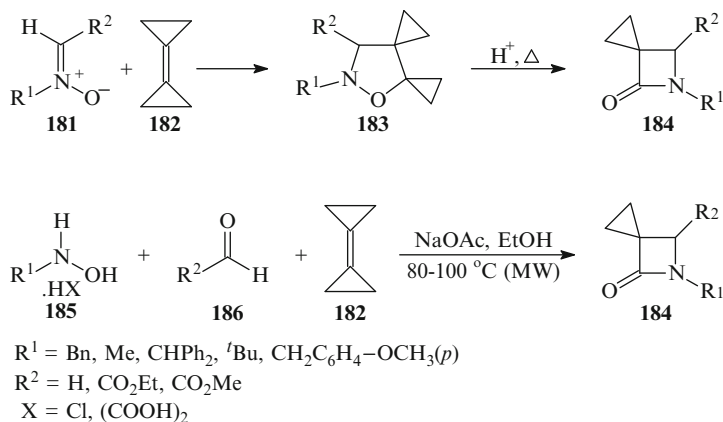
anions, which underwent intramolecular attack on the pyridine or quinoline ring either directly or on activation of the ring by *N*-acylation.

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].

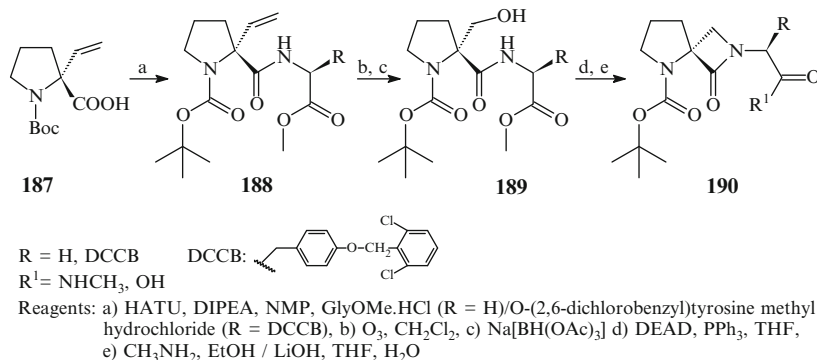
The alcohol **177** was converted to starting substrates oxazolidinone **178** by acylation followed by reduction of the azide function along with cyclization. Oxazolidinone **178** was protected with *t*-butylpyrocarbonate-4-(dimethylamino)pyridine (DMAP) and triethylamine, which was further subjected 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 cycloadducts **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**,



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

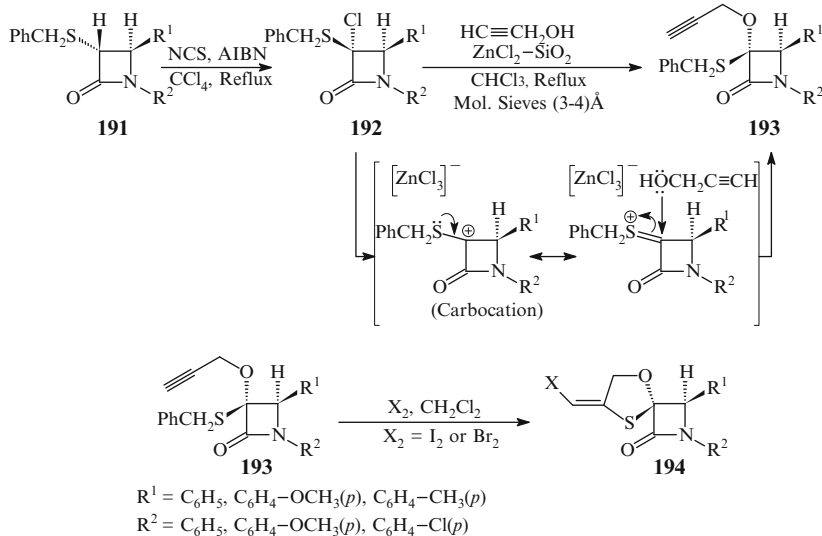


Scheme 44 Chiroselective synthesis of spiro- β -lactams serving as efficient β -turn nucleators

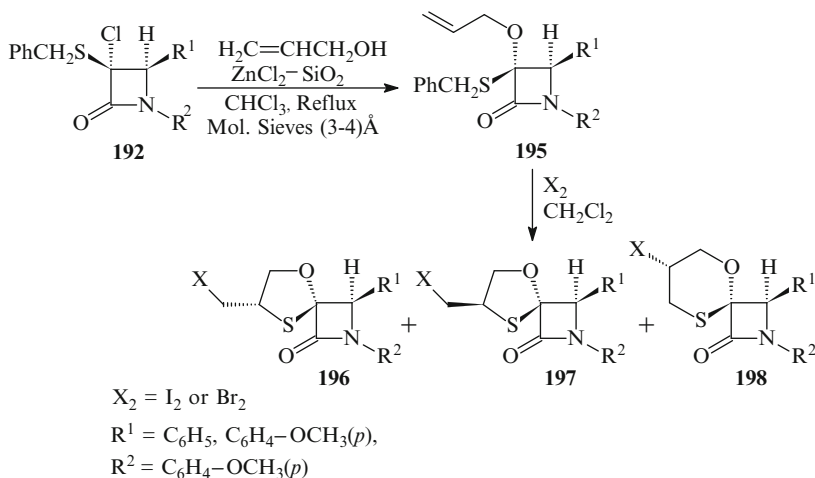
aldehydes **186**, and bicyclopentadiene **182** in the presence of sodium acetate and ethanol under microwave irradiation furnished the desired spiro- β -lactams **184** after 30–120 min in single operation. The time required for the completion of this reaction was never more than 2 h, whereas, with 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 $\text{Na}[\text{BH}(\text{OAc})_3]$ provided the hydroxymethyl-substituted derivative **189** in



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



Scheme 46 Extended halogen-mediated intrasulfonyl 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

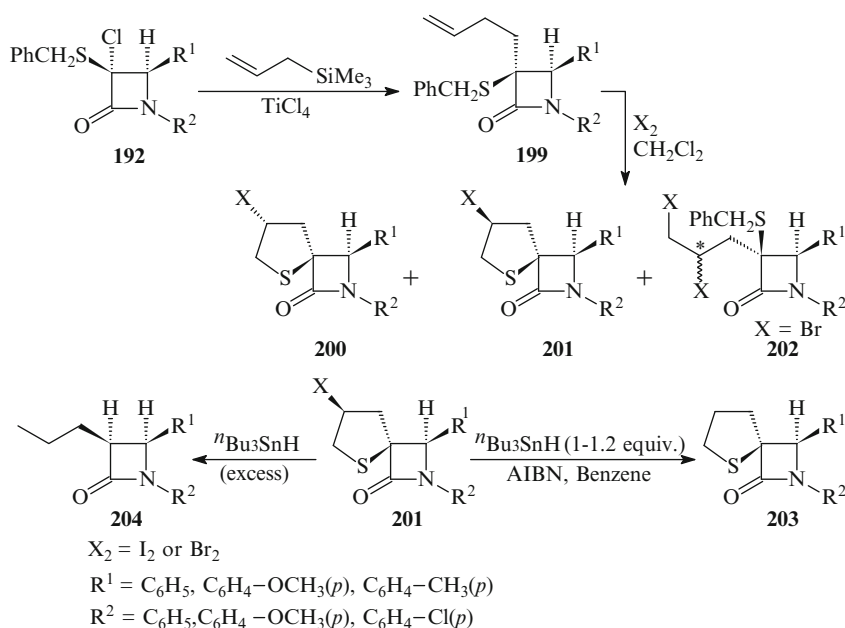
192 for the synthesis of novel azetidin-2-ones and their C-3 functionalizations [122–127].

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 $\text{ZnCl}_2/\text{SiO}_2$ 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 intrasulfonyl 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 ^1H 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 intrasulfonyl 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 intrasulfonyl 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.



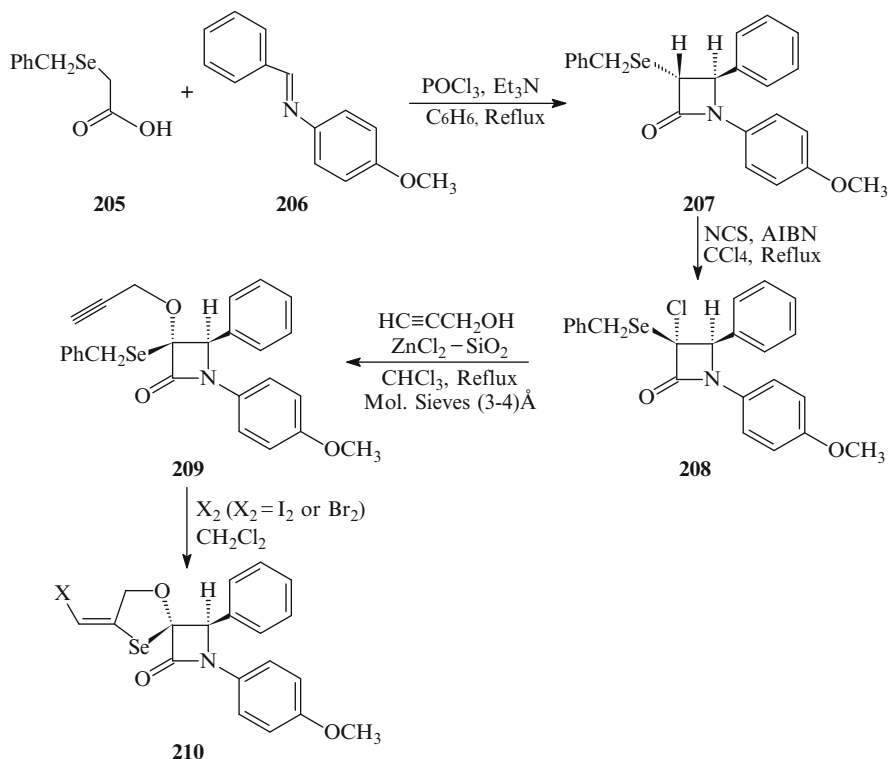
Scheme 47 Synthesis of spiro- β -lactams using 3-allyl-3-benzylthio- β -lactams

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-benzyl-selenoethanoic 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,

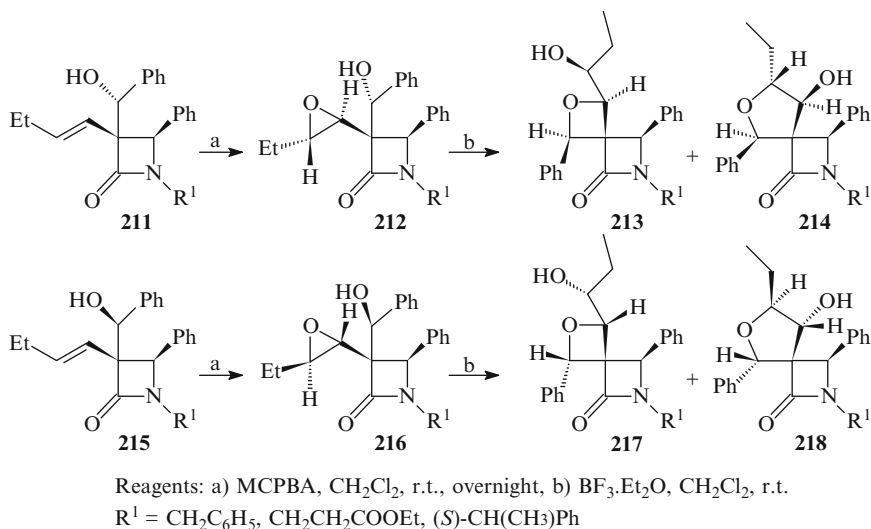


Scheme 48 Facile synthesis of new class of spiro seleno- β -lactams

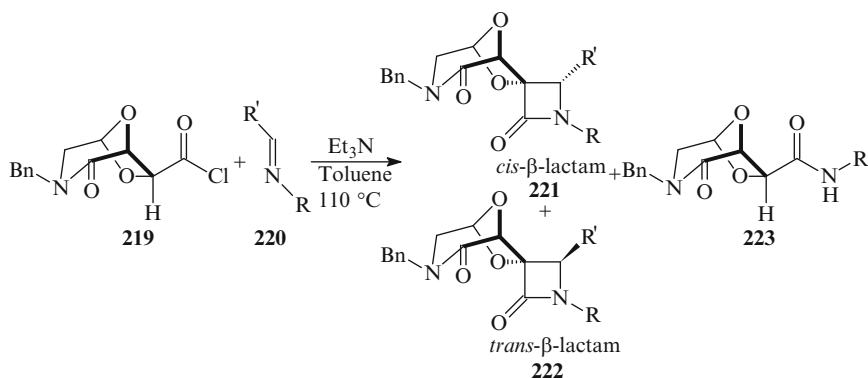
cis-3-chloro-3-benzylseleno- β -lactam **208** using *N*-chlorosuccinimide and AIBN. The *cis*-3-chloroseleno- β -lactam **208** was successfully converted to *cis*-3-benzylseleno-3-(prop-2-ynoxy)- β -lactam **209**, which served as potential substrate for undergoing halogen-mediated intraselenyl cyclization 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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



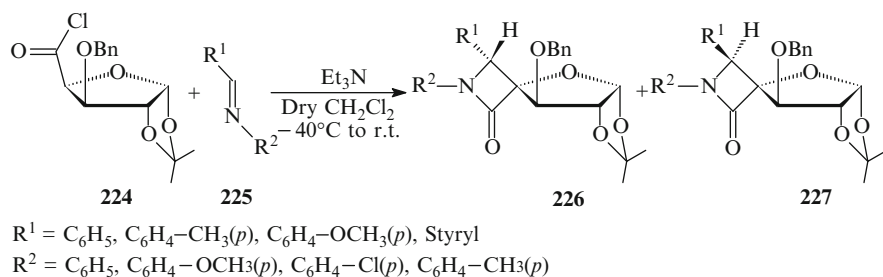
Scheme 49 A synthetic route to four- and five-membered hydroxyl-spiro- β -lactams



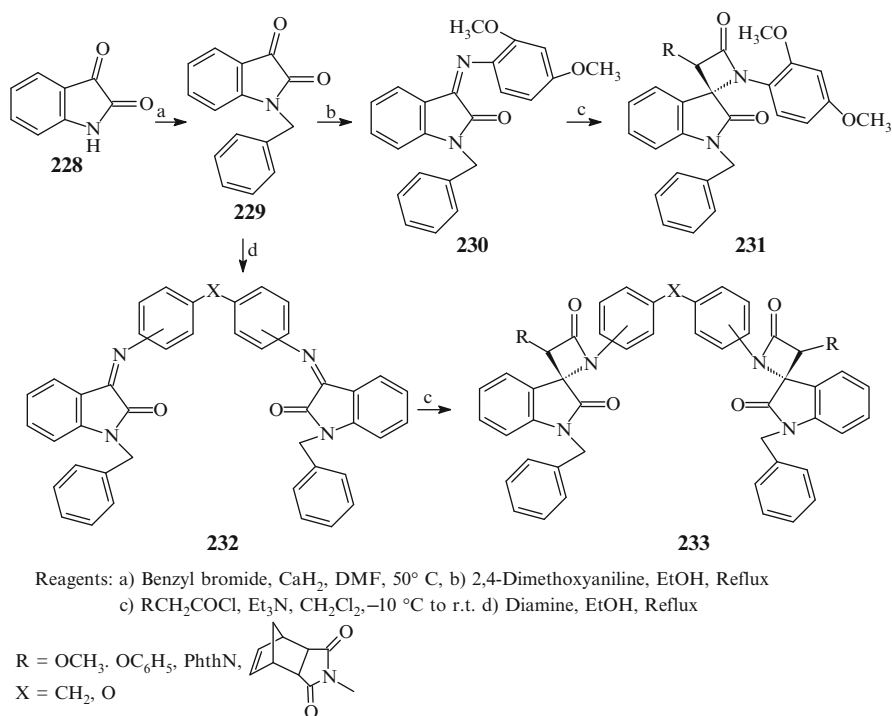
Scheme 50 Diastereoselective synthesis of spiro- β -lactams using unsymmetrical bicyclic ketene

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.

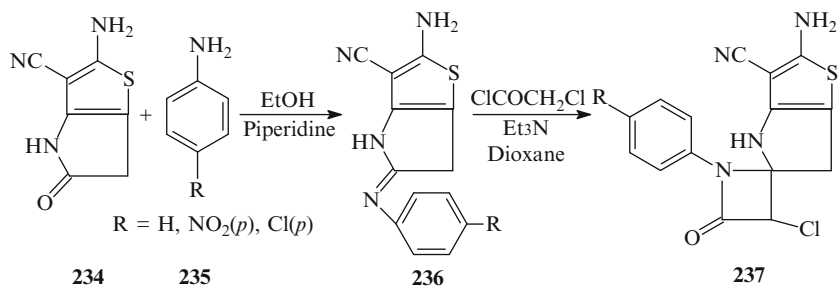


Scheme 51 Stereoselective synthesis of spiro- β -lactams using D-(+)-glucose derived chiral ketenes



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 benzyllisatin **229** (Scheme 52). The starting substrate, benzyllisatin **229** was prepared by reaction of isatin **228** with benzyl bromide and calcium chloride in DMF. The benzyllisatin 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 benzyllisatin **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

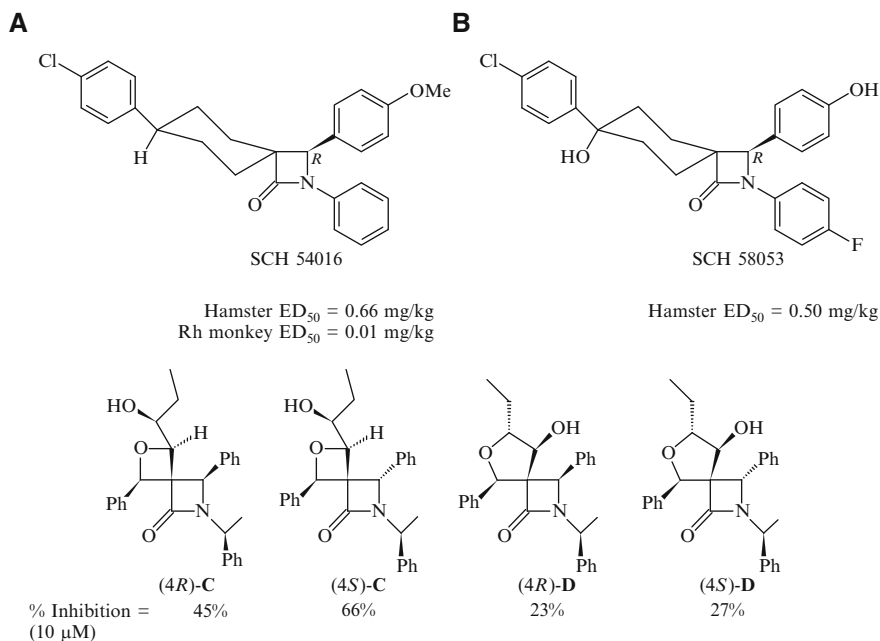


Fig. 6 Potent cholesterol absorption inhibiting spiro- β -lactams

CAI activity with an $ED_{50} = 0.66 \text{ mg kg}^{-1}$ 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 ($ED_{50} = 0.01 \text{ mg kg}^{-1}$) 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 ($IC_{50} = 12 \text{ }\mu\text{M}$ from the literature data, $IC_{50} = 16.8 \text{ }\mu\text{M}$ when concurrently tested) with enzymatic assays performance 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 ($IC_{50} = 20 \text{ }\mu\text{g mL}^{-1}$) [47]. Besides this, it also inhibited HLE ($IC_{50} = 0.4 \text{ }\mu\text{g mL}^{-1}$) as well as Cathepsin G ($IC_{50} = 4.0 \text{ }\mu\text{g mL}^{-1}$).

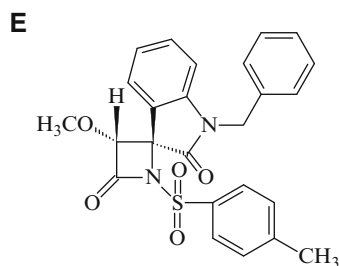


Fig. 7 Antiviral spiro- β -lactam

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. viridans*, *S. hemolyticus*, 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

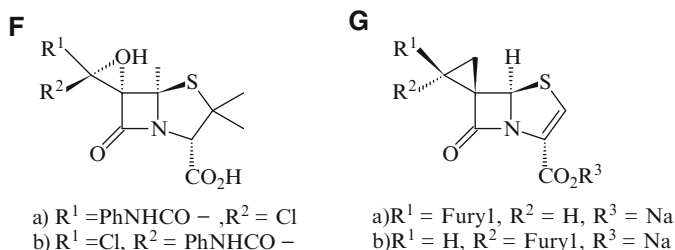


Fig. 8 β -Lactamase inhibiting and antibacterial spiro- β -lactams

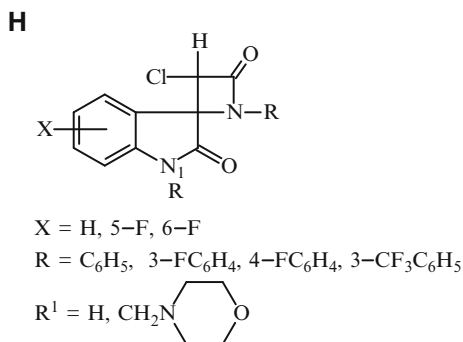
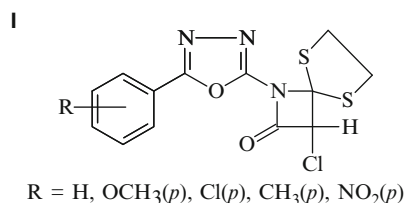


Fig. 9 Antibacterial spiro- β -lactams

Fig. 10 Antimicrobial spiro- β -lactams

bacteria (zone of inhibition between 10–17 mm in diameter), maximum against *S. hemolyticus*. 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**.

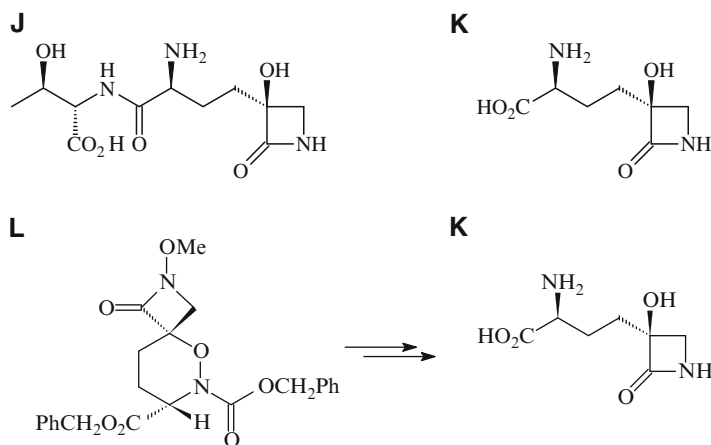


Fig. 11 Spiro- β -lactam: precursor for tabtoxin

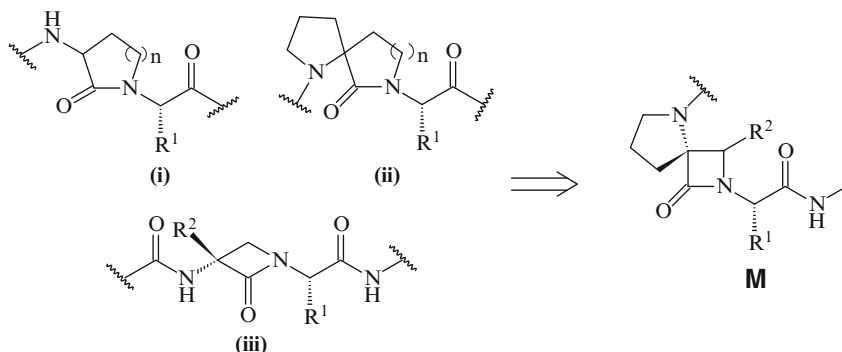


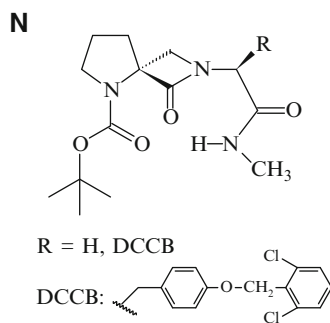
Fig. 12 Spiro- β -lactams as β -turn mimics

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 **N** 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 chiroselective 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.

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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, Haeggeli 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 ME Jr, 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, Rodriguez-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. Uchtyl TF, Durbin RD (1980) *Experientia* 36:301
143. Thomas MD, Langston-Unkefer PJ, Uchtyl 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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β -Lactams

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